UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA REABILITAÇÃO

Gustavo dos Santos Ribeiro

Ventilação periódica durante o exercício: análise de diferentes critérios de diagnóstico e de intervenções sobre a morbimortalidade e respostas ao exercício

Porto Alegre
2022

Gustavo dos Santos Ribeiro

Ventilação periódica durante o exercício: análise de diferentes critérios de diagnóstico e de intervenções sobre a morbimortalidade e respostas ao exercício

Tese submetida ao Programa de Pós-Graduação em Ciências da Reabilitação da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Doutor em Ciências da Reabilitação.

Orientador: Prof. Dr. Marlus Karsten

Porto Alegre

2022

Catalogação na Publicação

Ribeiro, Gustavo dos Santos
Ventilação periódica durante o exercício : análise de diferentes critérios de diagnóstico e de intervenções sobre a morbimortalidade e respostas ao exercício / Gustavo dos Santos Ribeiro. -- 2022.
175 f. : il., graf., tab. ; 30 cm.

Tese (doutorado) -- Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Ciências da Reabilitação, 2022.

Orientador(a): Marlus Karsten.

1. Insuficiência Cardíaca. 2. Teste de Esforço. 3. Respiração Periódica. 4. Reabilitação Cardíaca. 5. Exercício Físico. I. Título.

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

Ventilação periódica durante o exercício: análise de diferentes critérios de diagnóstico e de intervenções sobre a morbimortalidade e respostas ao exercício

BANCA AVALIADORA

_____

Prof. Dr. Maurício Milani
Programa de Pós-Graduação em Ciências da Reabilitação
Universidade de Brasília

_____

Prof. Dr. Rodrigo Della Méa Plentz
Programa de Pós-Graduação em Ciências da Reabilitação
Universidade Federal de Ciências da Saúde de Porto Alegre

_____

Prof. Dr. Michel Silva Reis
Programa de Pós-Graduação em Cardiologia
Universidade Federal do Rio de Janeiro

Porto Alegre
2022

Dedico este trabalho à minha esposa Cristine, minha maior incentivadora e musa inspiradora, às minhas filhas Giovana e Maria Eduarda, que a cada dia me ensinam um novo significado de amor e felicidade, aos meus pais Aníbal e Lígia, pelo apoio em todas as minhas escolhas, e aos meus amigos e familiares que estiveram juntos nessa caminhada.

AGRADECIMENTOS

Agradeço a todos que de alguma forma estiveram presentes e compreenderam a minha ausência em alguns momentos neste processo de formação acadêmica.

... A Deus, por guiar o meu caminho com sabedoria e proteção.

... À minha família, pelo apoio e amor incondicional, em especial aos meus pais, por serem meus exemplos, pessoas éticas, responsáveis e dedicadas, pois sem eles nada seria possível. A minha irmã, que desde o meu nascimento esteve ao meu lado me protegendo.

... À minha esposa Cristine, por seu amor e compreensão nos momentos em que precisei me ausentar, por aguentar meu mau humor sem reclamar, por mostrar que a vida pode ser simples e bela quando se está com quem se ama, por me entender em uma troca de olhar.

... Às minhas filhas Giovana e Maria Eduarda, que me enlouquecem diariamente com a alegria e a felicidade de cada descoberta, me ensinando diferentes formas de expressar, dar carinho e amor.

... Ao meu orientador Prof. Dr. Marlus Karsten, por acreditar no meu potencial e por permitir que em nossa convivência eu pudesse aprender ainda mais a partir dos seus conhecimentos, dando liberdade às minhas escolhas.

... Aos colegas Prof. Dr. Luís Fernando Deresz e Prof. Dr. Thomas Beltrame pelo acolhimento, paciência e oportunidade de aprendizado.

... A todos os colaboradores que tive a oportunidade de conhecer nessa jornada, em especial ao Prof. Dr. Dominique Hansen (Bélgica), ao Prof. Dr. Piergiuseppe Agostoni e à Dra. Elisabetta Salvioni (Itália).

... E a todos que tive a felicidade de conhecer ao longo da vida.

MUITO OBRIGADO

“O êxito da vida não se mede pelas vitórias que conquistamos, mas pelas dificuldades que superamos ao longo do caminho.”

(Autor desconhecido)

RESUMO

Introdução: A ventilação periódica durante o exercício (EOV) é uma alteração caracterizada por oscilações na ventilação minuto (VE), frequentemente vista na insuficiência cardíaca. Seu diagnóstico é baseado na interação entre amplitude, comprimento do ciclo e duração da oscilação. Entretanto, não há consenso sobre a definição de EOV mais indicada. Sua complexidade e diversidade limita o uso deste marcador na prática clínica. Além disso, quantificar a variabilidade da VE (vVE) pode contribuir na identificação precoce do fenômeno e o exercício físico pode amenizar as oscilações observadas no padrão ventilatório. **Objetivos**: (*E1*) Desenvolver uma ferramenta para auxiliar e padronizar a identificação da EOV. (*E2*) Caracterizar o perfil clínico dos pacientes utilizando três definições distintas do fenômeno, comparando a prevalência, a sensibilidade e especificidade para desfechos adversos em dois anos. (*E3*) Analisar a vVE, testar sua sensibilidade e especificidade para desfechos adversos a médio prazo, comparando-a com a abordagem dicotômica. (*E4*) Verificar o efeito do exercício na reversão da EOV. **Métodos**: (*E1*) Cinco definições dicotômicas, duas abordagens alternativas, uma técnica para suavizar o sinal e estatísticas básicas foram incorporadas em uma interface desenvolvida no LabVIEW. Dois avaliadores independentes testaram a confiabilidade da ferramenta. (*E2*) Dados de 233 pacientes foram analisados retrospectivamente para identificar a presença de EOV utilizando as definições de Ben-Dov, Corrà e Leite. Os dados foram agrupados em EOV-positivo ou negativo e, posteriormente, analisados por testes apropriados para determinar a prevalência, perfil clínico, sensibilidade e especificidade para predizer desfechos adversos em dois anos. (*E3*) Dados de 233 pacientes foram usados para calcular a vVE durante o teste cardiopulmonar de esforço. O ponto de corte para triagem de risco, sensibilidade e especificidade para eventos adversos foi determinada pela curva ROC. Os dados foram agrupados em alta e baixa vVE. O perfil clínico e a taxa de sobrevida foi analisada por testes apropriados. Em seguida, os dados foram agrupados e analisados utilizando a abordagem cruzada. (*E4*) Uma busca de alta sensibilidade foi realizada adotando os critérios: (P) pacientes com EOV, (I) exercício físico, (C) *single-arm* e (O) reversão de EOV. Os estudos elegíveis foram selecionados e sintetizados por revisores independentes. **Resultados**: (*E1*) A ferramenta desenvolvida apresentou alta reprodutibilidade para identificar EOV ($\kappa > 0,83$). (*E2*) A prevalência de EOV foi maior nas definições de Ben-Dov e Corrà comparada à Leite (17,2% vs 9,4%). Os casos positivos identificados por Corrà exibiram um risco 3x maior de resultados adversos. Ben-Dov apresentou risco 2x maior. (*E3*) A vVE demonstrou maior sensibilidade para predizer eventos adversos a médio prazo que a abordagem dicotômica (94,3 vs 37,1). Pacientes com baixa vVE e EOV exibiram um risco 3 e 7x maior de desfechos adversos que pacientes com baixa ou alta variabilidade sem EOV. (*E4*) O exercício físico mostrou-se eficaz para reverter casos de EOV (~70% dos casos). **Conclusão**: A definição de Corrà foi a única definição clássica que previu eventos adversos a médio prazo. A vVE apresentou resultados similares à abordagem dicotômica, sugerindo ser uma técnica promissora para ser incorporada à prática clínica. O exercício físico foi efetivo para reverter casos de EOV.

Palavras-chave: Insuficiência Cardíaca; Teste de Esforço; Respiração Periódica; Prognóstico; Reabilitação Cardíaca; Exercício Físico.

ABSTRACT

Background: Exercise oscillatory ventilation (EOV) is an alteration characterized by fluctuations in minute ventilation (VE), often seen in heart failure. Its diagnosis is based on the interaction between amplitude, cycle length and duration of the oscillation. However, there is no consensus on the most appropriate definition of EOV. Its complexity and diversity impair the use of this marker in clinical practice. In addition, quantifying the VE variability (vVE) can contribute to the early phenomenon identification and exercise can alleviate the oscillations observed in the ventilatory pattern. **Aims**: (E1) Develop a tool to assist and standardize the EOV identification. (E2) To characterize the clinical profile of patients using three different definitions of the phenomenon, comparing the prevalence, sensitivity, and specificity for adverse outcomes in 2-years. (E3) To analyze vVE, test sensitivity and specificity for adverse outcomes in the middle term, comparing it with the dichotomous approach. (E4) Check the effect of the exercise on the EOV reversal. **Methods**: (E1) Five dichotomous definitions, two alternative approaches, a technique to smooth the signal and basic statistics were incorporated into an interface developed in the LabVIEW. Two independent reviewers tested the tool's reliability. (E2) Data from 233 patients were analyzed retrospectively to identify the EOV presence using the definitions of Ben-Dov, Corrà and Leite. Data were pooled into EOV-positive or negative, and subsequently analyzed by appropriate tests to determine the prevalence, clinical profile, sensitivity, and specificity to predict adverse outcomes at 2-years. (E3) Data from 233 patients were used to calculate vVE during cardiopulmonary exercise testing. The cut-off point for risk screening, sensitivity and specificity for adverse events was determined by the ROC curve. Data were grouped into high and low vVE. The clinical profile and survival rate were analyzed by appropriate tests. Then, the data were pooled and analyzed using the cross-over approach. (E4) A high-sensitivity search was performed adopting the following criteria: (P) EOV patients, (I) exercise, (C) single-arm, and (O) EOV reversal. Eligible studies were selected and synthesized by independent reviewers. **Results**: (E1) The developed tool showed high reproducibility to identify EOV ($\kappa > 0.83$). (E2) The EOV prevalence was higher in the definitions of Ben-Dov and Corrà compared to Leite (17.2% vs 9.4%). The positive cases identified by Corrà exhibited a 3x greater risk of adverse outcomes. Ben-Dov had a 2x greater risk. (E3) The vVE showed greater sensitivity to predict adverse events in the middle term than the dichotomous approach (94.3 vs 37.1). Patients with low vVE and EOV exhibited a 3 and 7x greater risk of adverse outcomes than patients with low or high variability without EOV. (E4) Exercise proved to be effective in reversing EOV cases (~70% of cases). **Conclusion**: Corrà's definition was the only classic definition that predicted adverse events in the middle follow-up. The vVE showed similar results to the dichotomous approach, suggesting that it is a promising technique to be incorporated into clinical practice. The exercise was effective to reverse the EOV cases.

Keywords: Cardiology; Cardiovascular Diseases; Exercise Test; Periodic Breathing; Prognosis, Cardiac Rehabilitation.

LISTA DE FIGURAS

Referencial teórico

Artigo 1

Artigo 2

Artigo 3

Artigo 4

LISTA DE TABELAS

Referencial teórico

Artigo 1

Artigo 2

Artigo 3

Artigo 4

LISTA DE ABREVIATURAS E SIGLAS

BNP	*B-type natriuretic peptide* (peptídeo natriurético tipo B)
$C_{a-v}O_2$	Diferença arteriovenosa de oxigênio
CI	*Cardiac index* (índice cardíaco)
DDVE	Diâmetro diastólico do ventrículo esquerdo
EOV	*Exercise oscillatory ventilation* (ventilação periódica durante o exercício)
FEVE	Fração de ejeção do ventrículo esquerdo
h	Amplitude do ciclo
HR	*hazard ratio* (razão de risco)
IAH	índice apneia-hipopneia
IC	insuficiência cardíaca
ICC	Coeficiente de correlação intraclasse
κ	Coeficiente de correlação kappa
LV_1	Primeiro limiar ventilatório
LV_2	Segundo limiar ventilatório
MD	*Mean difference* (diferença média)
NT-proBNP	*N-terminal pro b-type natriuretic peptide* (fragmento amino-terminal do pró-peptídeo natriurético cerebral)
NYHA	*New York Heart Association*
O_2	Oxigênio
$PaCO_2$	Pressão de dióxido de carbono arterial
PAD	Pressão atrial direita
PAM	Pressão arterial média
PaO_2	Pressão de oxigênio arterial
PAP	Pressão da artéria pulmonar
PCP	Pressão capilar pulmonar
PDE5	Fosfodiesterase-5
PSVD	Pressão sistólica do ventrículo direito
RM	Repetições máximas
RMSSD	Raiz quadrada da média do quadrado das diferenças
ROC	*Receiver operating characteristic* (característica de operação do

	receptor)
RR	Risco relativo
SDNN	Desvio padrão dos intervalos
SNA	Sistema nervoso autônomo
TCPE	Teste cardiopulmonar de esforço
VDI	*Ventilation dispersion index* (índice de dispersão da ventilação)
VE	Ventilação minuto
VE/VCO_2	Produção de dióxido de carbono por ventilação
VO_2	Consumo de oxigênio
VO_{2PICO}	Consumo de oxigênio de pico
vVE	Variabilidade da ventilação minuto
Δt	Período oscilatório total
$\Delta VO2/\Delta WR$	*Work rate relationship* (relação da taxa de trabalho)
λ	Comprimento do ciclo

SUMÁRIO

1 CONTEXTUALIZAÇÃO

Caracterizada por oscilações na ventilação minuto (VE), a ventilação periódica durante o exercício (EOV) é um fenômeno anormal e típico no padrão ventilatório de pacientes com insuficiência cardíaca (IC) exibindo forte impacto prognóstico (Agostoni *et al*., 2017). Dados recentes indicam risco quatro vezes maior de pacientes com EOV terem eventos cardiovasculares adversos que seus pares sem EOV (Vainshelboim *et al*., 2017). Entretanto, ainda não há consenso sobre quais critérios seriam adequados para confirmar sua ocorrência.

Atualmente, seu diagnóstico é confirmado por meio da inspeção visual da curva ventilatória obtida durante o teste cardiopulmonar de esforço (TCPE). Variáveis como consumo de oxigênio (VO_2) e eficiência ventilatória (VE/VCO_2 *slope*) são marcadores amplamente aceitos na prática clínica devido à forte associação com desfechos duros (Cornelis *et al.*, 2015b). Contudo, a EOV tem evidenciado melhor capacidade preditiva que estes dois marcadores (Guazzi *et al.*, 2007; Guazzi *et al.*, 2008). Ainda assim, é preciso facilitar e padronizar sua identificação para viabilizar seu uso na prática clínica.

Além da abordagem clássica ou dicotômica (EOV-positivo ou EOV-negativo), novas estratégias foram desenvolvidas para quantificar o fenômeno. Soma-se os primeiros relatos de reversão da EOV, abrindo novas possibilidades de investigação. Estes fatos levaram ao desenvolvimento de quatro estudos para compor a tese, intitulados:

- *Software development to standardize the clinical diagnosis of the exercise oscillatory ventilation in heart failure.*
- *Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients.*
- *Ventilatory variability alone or in association with a dichotomous diagnostic definition of exercise oscillatory ventilation in predicting heart failure adverse outcomes: An exploratory study.*
- *Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis.*

Estes estudos visam descrever o desenvolvimento de uma ferramenta gratuita para identificar as características da EOV de forma padronizada (artigo 1); comparar a sensibilidade das definições clássicas para desfechos adversos (artigo 2); comparar a sensibilidade da abordagem dicotômica e quantitativa para prever eventos adversos (artigo 3); e demonstrar os efeitos e a segurança do treinamento físico como recurso terapêutico para pacientes com EOV (artigo 4).

1.1 Respiração periódica

Caracterizada por oscilações cíclicas na ventilação minuto (VE), a respiração periódica é um fenômeno anormal e típico no padrão ventilatório de pacientes com IC (Dhakal e Lewis, 2016). Sua presença foi documentada em pacientes acordados (respiração de *Cheyne-Stokes*), dormindo (apneia central do sono) e durante o esforço (Dhakal e Lewis, 2016; Agostoni *et al.*, 2017). Quando este fenômeno ocorre durante o exercício é denominado ventilação periódica durante o exercício ou EOV (*exercise oscillatory ventilation*). De acordo com Vainshelboim *et al*. (2017), três fatores podem ser determinantes para caracterizar o padrão ventilatório do fenômeno:

1) Amplitude (h): definida pela diferença entre o pico da VE e a distância média entre dois nadires consecutivos (depressão ou ponto mais baixo na base da oscilação). Normalmente é expressa em litros por minuto ($L.min^{-1}$).
2) Comprimento (λ): distância entre dois nadires ou depressões consecutivas que formam a base de uma oscilação (tríade nadir-pico-nadir). Usualmente é expressa em segundos (s).
3) Duração (Δt): período oscilatório total sendo formado por dois ou mais ciclos subsequentes. Esta variável também é expressa em segundos (s).

A interação entre estes fatores indica a presença do fenômeno ventilatório. A Figura 1 ilustra o padrão ventilatório característico de um paciente com EOV e seus respectivos parâmetros: amplitude (h), comprimento (λ) e duração (Δt).

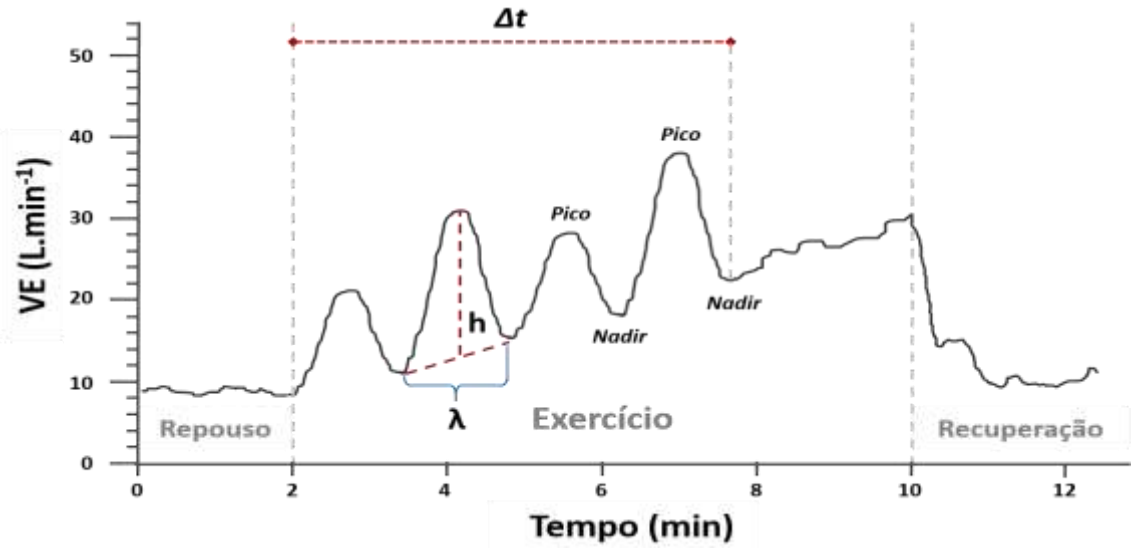


Figura 1. Padrão ventilatório característico de um paciente com EOV durante o teste cardiopulmonar de esforço. VE, ventilação minuto. *h*, amplitude. *λ*, comprimento do ciclo. ∆*t*, duração da oscilação. Fonte: Elaborada pelo autor.

1.2 Mecanismos fisiopatológicos

Embora o padrão oscilatório característico deste fenômeno seja conhecido, os fatores que ocasionam o seu desencadeamento ainda não foram elucidados (Agostoni *et al.*, 2017; Agostoni e Salvioni, 2019). O modelo desenvolvido para explicar a sua fisiopatologia é baseado em pesquisas envolvendo pacientes com apneia central do sono e respiração de *Cheyne-Stokes* – outras manifestações de respiração periódica – sem que houvesse uma amostra específica de pacientes EOV, considerado uma característica da amostra ou desfecho secundário.

O modelo com maior aceitabilidade para elucidar o fenômeno é embasado em quatro alterações fisiológicas adjacentes e complementares: (1) atraso circulatório; (2) congestão pulmonar; (3) hiperatividade quimioceptora; e (4) exacerbação ergorreflexa (Dhakal e Lewis, 2016; Agostoni *et al.*, 2017; Agostoni e Salvioni, 2019). De fato, estes mecanismos fazem parte da fisiopatologia da IC (Dhakal e Lewis, 2016) e podem estar relacionados com o surgimento da EOV. No entanto, não está claro até que ponto eles poderiam influenciar no surgimento e agravamento do fenômeno.

O atraso circulatório seria o principal fator envolvido nesta resposta devido ao menor débito cardíaco observado em pacientes com IC, causando aumento no tempo de circulação pulmonar e, consequentemente, *feedback* tardio e alterações no *drive* ventilatório para tentar manter o equilíbrio ácido-base durante o esforço (Yajima *et al.*, 1994; Mortara *et al.*, 1999; Koike *et al.*, 2003; Agostoni *et al.*, 2008). Esta hipótese foi confirmada em modelos experimentais (Lahiri *et al.*, 1985) e pesquisas clínicas com pacientes em repouso (Yajima *et al.*, 1994; Koike *et al.*, 2003).

O segundo fator do modelo, com forte contribuição na fisiopatologia da EOV, é a congestão pulmonar. Em síntese, o incremento no gradiente de pressão no ventrículo esquerdo aumentaria a pressão alveolar, estimulando os receptores J em resposta à distensão das fibras C (Guazzi *et al.*, 2012; Dhakal e Lewis, 2016). Este mecanismo estimularia o *drive* ventilatório. Entretanto, haveria hiperventilação superficial em resposta a menor complacência pulmonar, reduzindo a pressão de dióxido de carbono arterial ($PaCO_2$), podendo causar apneia (Guazzi *et al.*, 2008; Dhakal e Lewis, 2016).

Os efeitos citados acima seriam incrementados pela instabilidade do *drive* ventilatório causada tanto pela resposta ergorreflexa exacerbada, observada nos músculos periféricos de pacientes com IC (Pardaens *et al.*, 2014), como também pela maior atividade quimioceptora durante o exercício, devido à hiperatividade simpática (Francis *et al.*, 2000). Estes mecanismos potencializariam os efeitos dos outros fatores. O modelo proposto para explicar o mecanismo causador da EOV está sintetizado na Figura 2.

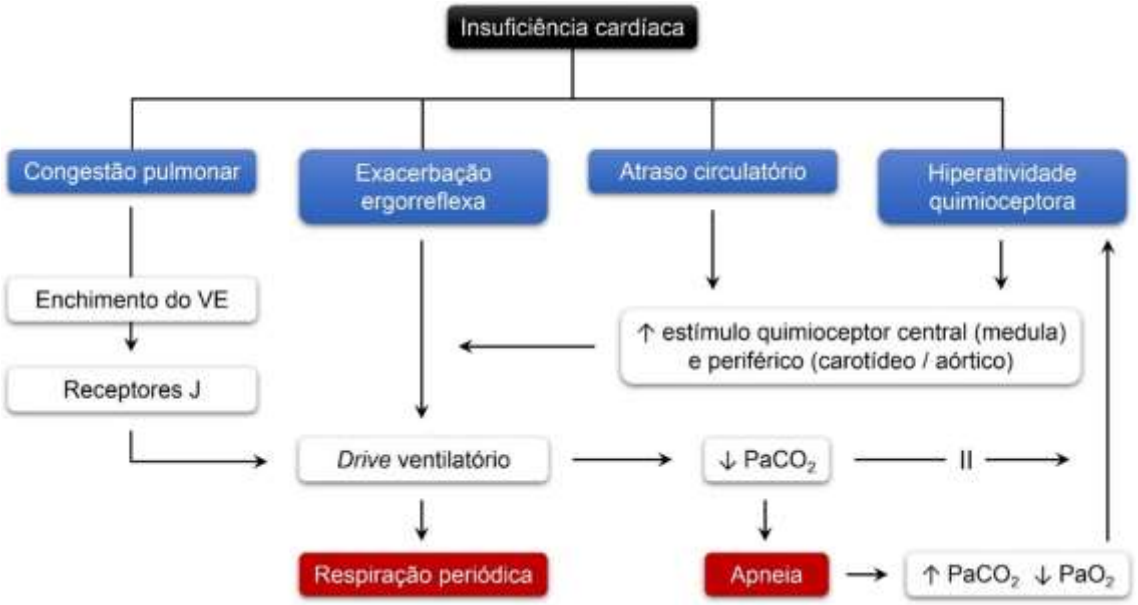


Figura 2. Modelo proposto para explicar o mecanismo da ventilação periódica durante o exercício. $PaCO_2$, pressão de dióxido de carbono arterial. PaO_2, pressão de oxigênio arterial. VE, ventrículo esquerdo. Fonte: Adaptado de Dhakal e Lewis (2016).

Embora as evidências atuais indiquem o atraso circulatório como principal fator desencadeante, grande parte dos estudos aferiram pacientes em repouso (respiração de *Cheyne-Stokes*), dormindo (apneia central do sono) ou sem diagnóstico de EOV. Curiosamente, apenas um estudo utilizou a amostra exclusiva de pacientes com EOV para investigar com maior propriedade a etiologia do fenômeno. Com desenho experimental robusto, Murphy *et al.* (2011) conduziram a principal pesquisa na área, considerada por muitos pesquisadores o grande divisor de águas no tema.

Os autores analisaram por gasometria arterial marcadores de atraso circulatório, congestão pulmonar, *drive* ventilatório e oxigenação sistêmica, tanto em repouso como em exercício. A amostra foi composta por 25 pacientes com diagnóstico de EOV (EOV-positivo) e 31 sem diagnóstico (EOV-negativo). Todos com disfunção sistólica (fração de ejeção do ventrículo esquerdo – FEVE < 40%) e sintomas crônicos de classe II a IV da *New York Heart Association* (NYHA). Um terceiro grupo sem disfunção sistólica (n = 19) foi avaliado para determinar até que ponto as variáveis hemodinâmicas e gasométricas de indivíduos com e sem EOV diferiam de indivíduos pareados por idade sem disfunção sistólica.

Durante o procedimento experimental foram aferidas a pressão arterial média (PAM), a pressão atrial direita (PAD), a pressão da artéria pulmonar (PAP), a pressão capilar pulmonar (PCP), o pH arterial, a diferença arteriovenosa de oxigênio ($C_{a-v}O_2$) e o índice cardíaco (CI – *cardiac index*). A título informativo, a $C_{a-v}O_2$ foi determinada pela quantidade de O_2 arterial e pulmonar mensurada em seus respectivos cateteres. Curiosamente, a EOV foi identificada mesclando critérios de duas definições clássicas usadas para o seu diagnóstico (Ben-Dov *et al.*, 1992; Corrà *et al.*, 2002).

Os principais achados do estudo mostraram que pacientes EOV-positivo tinham pior função hemodinâmica em repouso e exercício do que seus pares EOV-negativo, além de maior comprometimento do ventrículo direito e menor VO_{2PICO}. Os autores observaram correlação inversa entre atraso circulatório e as características do padrão oscilatório (amplitude e comprimento do ciclo), indicando o prejuízo hemodinâmico como principal gatilho do fenômeno. Em contrapartida, a amplitude e o comprimento do ciclo não se mostraram associados às medidas de $PaCO_2$ e PaO_2, minimizando a influência da oxigenação sistêmica como gatilho do fenômeno. A Figura 3 sintetiza as correlações observadas no estudo.

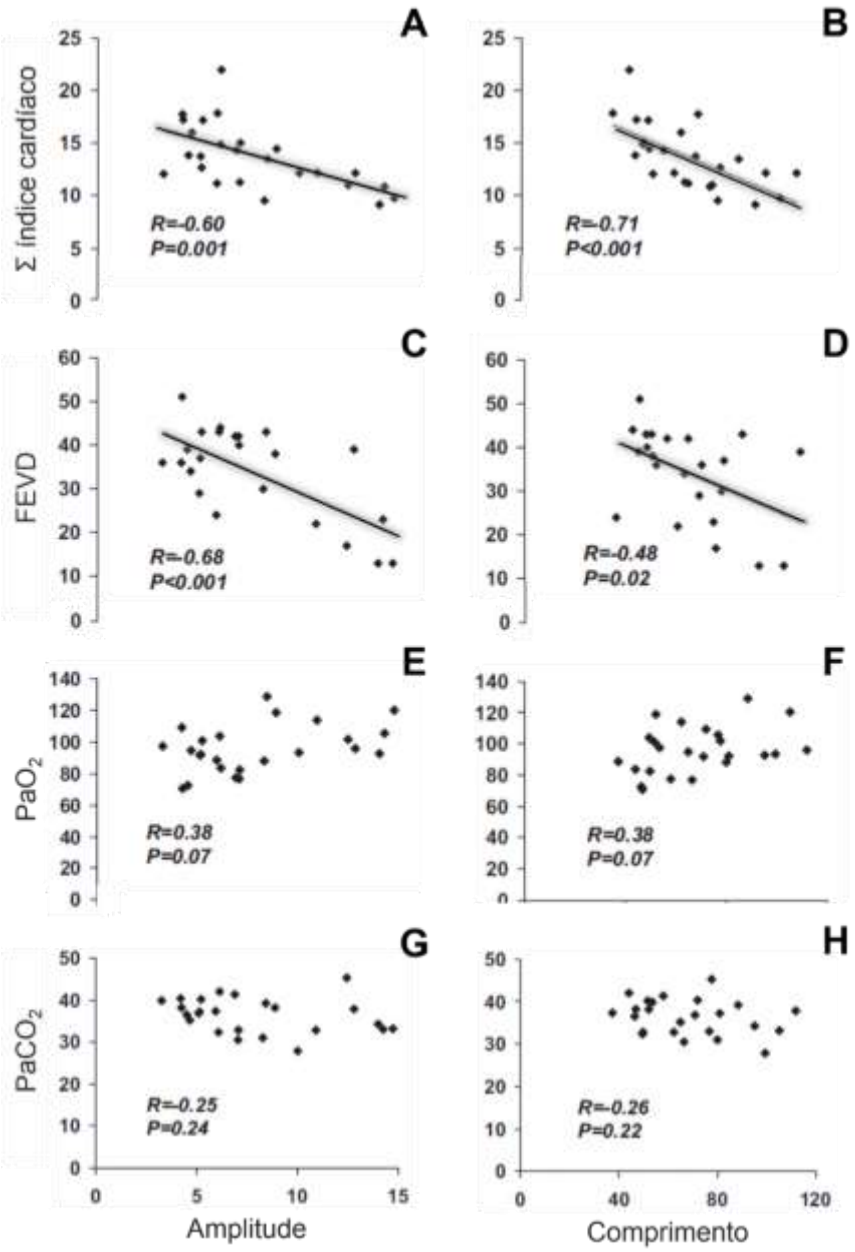


Figura 3. Correlação entre marcadores de função cardíaca (A, B, C e D), oxigenação sistêmica (E, F, G e H) e padrão oscilatório (amplitude e comprimento). FEVD, fração de ejeção do ventrículo direito. PaO_2, pressão de oxigênio arterial. $PaCO_2$, pressão de dióxido de carbono arterial. Fonte: Adaptado de Murphy *et al.* (2011).

Outro dado que chamou atenção foram os valores mais altos de PAP e PCP no grupo EOV-positivo, tanto em repouso como em exercício. Por serem marcadores de congestão pulmonar, Murphy *et al.* (2011) randomizaram 30 pacientes em dois grupos para investigar a influência desta manifestação clínica na etiologia da EOV. O grupo controle recebeu placebo como tratamento e o

grupo intervenção recebeu 25 a 75 mg de inibidor de fosfodiesterase-5, via oral, três vezes ao dia, durante 12 semanas. A Figura 4 ilustra o comportamento ventilatório de um paciente submetido ao tratamento.

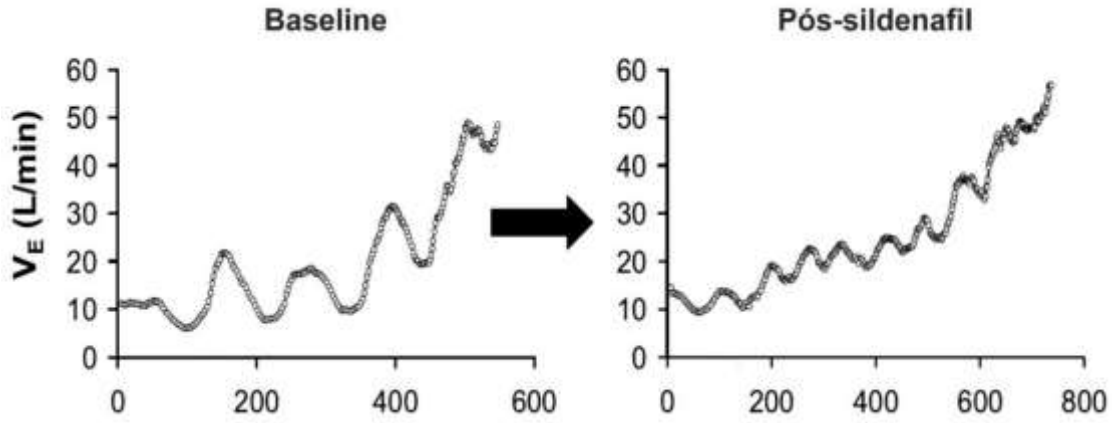


Figura 4. Efeito do tratamento com sildenafil em variáveis do padrão oscilatório. VE, ventilação minuto. Fonte: Adaptado de Murphy *et al.* (2011).

Observou-se redução média na amplitude (7,8 ±1,3 vs 6,3 ± 1,4 $L.min^{-1}$; $p<0,05$) e comprimento dos ciclos (70 ± 8 vs 57 ± 4s; $p<0,05$) após o tratamento com sildenafil. O percentual de melhora em cada variável mostrou-se inversamente relacionado às mudanças no índice cardíaco (r = 0,64 e 0,72), o qual exibiu incremento de aproximadamente 18,6% durante o exercício (maior velocidade circulatória). Entretanto, estas alterações não se correlacionaram com medidas de oxigenação sistêmica (PaO_2) e *drive* ventilatório ($PaCO_2$), indicando papel secundário da congestão pulmonar na etiologia da EOV.

Portanto, os dados Murphy *et al.* (2011) indicam que o maior comprometimento hemodinâmico evidenciado pelo aumento nas pressões de enchimento do ventrículo direito e esquerdo, com redução da pressão arterial sistólica e do índice cardíaco é o principal mecanismo para o surgimento da EOV, com possível influência da congestão pulmonar nesta resposta. Os autores descartaram a influência do *drive* ventilatório e da oxigenação sistêmica como gatilho deste fenômeno, ainda que possam ter papel secundário na amplificação das oscilações.

Um fato que não pode ser desconsiderado é a coexistência de IC e hipertensão pulmonar. Sabe-se que o remodelamento cardíaco visto na IC diastólica causaria um estreitamento vascular devido ao maior espessamento e enrijecimento das paredes do ventrículo direito, aumentando a resistência pulmonar e a redução progressiva do débito cardíaco (Franco, 2012). Spruijt *et al.* (2015) mencionam que pacientes com hipertensão pulmonar apresentam ineficiência na contratilidade do ventrículo direito durante o esforço, causando maior atraso circulatório.

Ainda que os mecanismos centrais expliquem a etiologia da EOV, uma teoria sobre fatores periféricos vem sendo sugerida por alguns pesquisadores. A influência de fatores centrais (pulmonar e cardiovascular) foi o foco de inúmeras pesquisas para explicar o surgimento e/ou reversão da EOV. De fato, as evidências atuais apontam para este caminho (Agostoni *et al.*, 2017). No entanto, existem indícios sugerindo que o lactato possa ter papel secundário na fisiopatologia da EOV por promover a acidose local precoce durante o exercício (Zurek *et al.*, 2012; Yamauchi *et al.*, 2016).

Ainda não existem dados que comprovam esta hipótese. De acordo com Prado *et al.* (2016), pacientes com IC exibem um comportamento hemodinâmico associado a diminuição no transporte convectivo de oxigênio para musculatura ativa, aumentando a participação da glicólise anaeróbia para suprir a demanda energética. Este fato proporcionaria maior produção de metabólitos (ex.: lactato) que, consequentemente, poderiam afetar a sensibilidade dos ergorreceptores intramusculares (Zurek *et al.*, 2012; Yamauchi *et al.*, 2016). A acidose ativaria os quimiorreceptores periféricos, sendo um gatilho adicional para a hiperventilação.

Considerando a hiperatividade quimioceptora e exacerbação ergorreflexa como mecanismos adjacentes da EOV, esta hipótese tem diversos pontos favoráveis à sua comprovação. Recentemente, Ribeiro *et al.* (2020) observaram menor relação entre oferta e extração de oxigênio em pacientes EOV-positivo do que nos pacientes sem diagnóstico de EOV ($\Delta VO2/\Delta WR$ *slope* 9,5 [8,5 - 10,6] vs 11,6 [11,3 - 12,1] $ml.min^{-1}W^{-1}$; $p<0,001$), sugerindo comprometimento adicional a nível periférico. De acordo com Agostoni *et al.* (2017), a maior oferta de oxigênio para músculos periféricos implicaria em redução de trabalho respiratório.

1.3 Implicações clínicas

Diversos estudos têm evidenciado pior prognóstico em pacientes EOV-positivo em comparação àqueles sem a presença do fenômeno (Leite *et al.*, 2003; Guazzi *et al.*, 2007; Guazzi *et al.,* 2008; Cornelis *et al.,* 2015b; Vainshelboim *et al.,* 2017; Rovai *et al.*, 2019). Morte cardiovascular, tempo de hospitalização, necessidade de implante de dispositivo de assistência ventricular esquerda e realização de transplante cardíaco urgente são alguns desfechos que foram relacionados à presença de EOV.

Leite *et al.* (2003) foram pioneiros ao investigar o impacto clínico da EOV na mortalidade de pacientes com indicação ao transplante cardíaco. Foram avaliados 84 pacientes com IC e monitorados até que o óbito fosse registrado (seguimento de 49,7 meses). Os autores observaram menor sobrevida a curto (1 ano) e médio prazo (2 anos) entre os pacientes EOV-positivo, observando risco de óbito três vezes maior. A Figura 5A exemplifica os achados deste estudo, que originou uma das definições clássicas para identificar a EOV (Leite *et al.*, 2003). A Figura 5B ilustra os achados de Vainshelboim *et al.* (2017). Estes autores acompanharam 89 pacientes com IC ao longo de 60 meses, propondo um algoritmo de triagem para identificar a EOV a partir da definição de Leite *et al.* (2003) modificada.

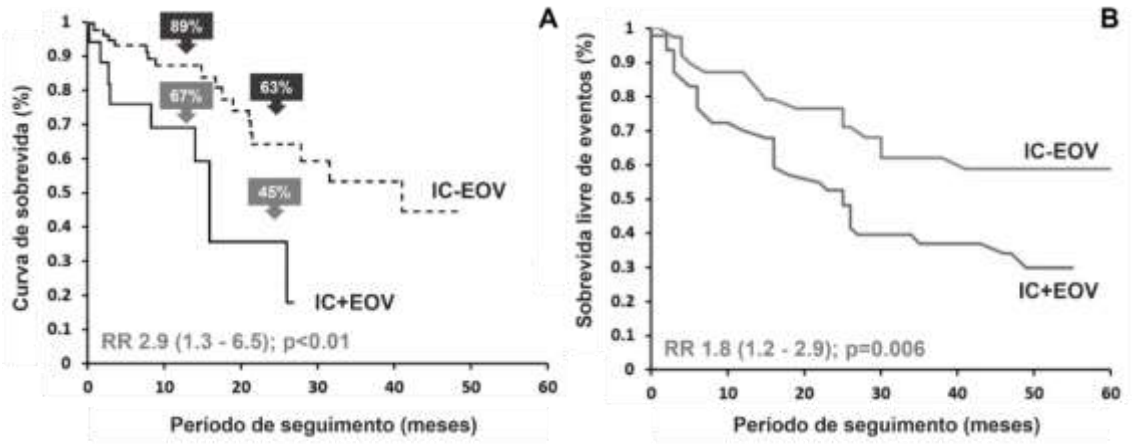
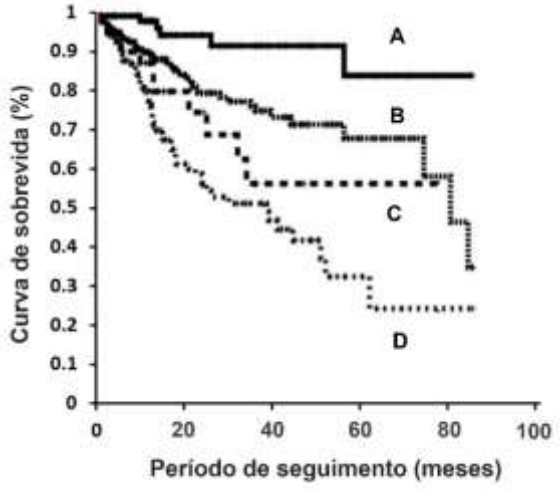


Figura 5. Curva de sobrevida (A) e sobrevida livre de eventos (B) de pacientes com EOV-positivo e EOV-negativo. RR, risco relativo. Fonte: adaptado de Leite *et al.* (2003) e Vainshelboim *et al.* (2017).

Vainshelboim *et al.* (2017) identificaram melhor capacidade preditiva da EOV frente à VE/VCO_2 *slope* (HR 2,2 [1,2 a 4,1] vs 1,1 [1,0 a 1,1]) quando três critérios do algoritmo eram confirmados. Após ajustar o desfecho final para idade, VO_{2PICO} e VE/VCO_2 *slope*, a EOV foi a única variável que permaneceu associada a eventos cardíacos adversos (HR 2,0 [1,1 a 3,7]; p = 0,035).

Guazzi *et al.* (2007) fomentaram a discussão ao avaliarem 156 pacientes com IC sistólica ao longo de 50 meses, estratificando os óbitos por falha de bomba ou morte súbita. Os autores observaram que a EOV estava presente em 100% dos casos de morte súbita e aproximadamente 50% dos casos de falha na bomba. Variáveis como VO_{2PICO} e VE/VCO_2 *slope* também foram analisadas. O principal fator de predição para todas as causas de morte foi a EOV seguida da VE/VCO_2 *slope* e do VO_{2PICO}. Estes valores foram ainda mais expressivos para predizer morte súbita.

Ainda que o remodelamento cardiovascular na IC sistólica e diastólica sejam distintos, Guazzi *et al.* (2008) constataram resultados similares entre as etiologias, isto é, maior valor preditivo da EOV comparada ao VO_{2PICO} e VE/VCO_2 *slope*. A presença deste marcador representou risco duas vezes maior de eventos fatais que o segundo melhor preditor. Além disso, a prevalência de EOV entre as etiologias mostrou-se similar (IC sistólica 31% vs 35% IC diastólica). Estes dados reforçam o alto valor preditivo do fenômeno. A Figura 6 resume os achados destes dois estudos.



A curva de sobrevida é menor em todos as etiologias de IC na presença de EOV

Etiologia	n	Eventos	Sobrevida
(A) IC diastólica sem EOV	103	5	95.1%
(B) IC sistólica sem EOV	263	44	83.3%
(C) IC diastólica com EOV	48	12	75.0%
(D) IC sistólica com EOV	142	55	61.3%

Análise de Kaplan-Meyer ($p < 0.001$).

Figura 6. Análise de sobrevida de pacientes com insuficiência cardíaca de origem sistólica e diastólica. IC, insuficiência cardíaca. EOV, ventilação periódica durante o exercício. Fonte: adaptado de Guazzi *et al.* (2008).

Diferente dos estudos supracitados, que investigaram o impacto clínico da EOV em pacientes com IC, Cornelis *et al.* (2015b) realizaram uma revisão sistemática para avaliar a relação entre EOV e outras variáveis prognósticas. Após a triagem e seleção dos estudos, os autores observaram que pacientes EOV-positivo apresentavam menor VO_{2PICO} (MD −2,86 ml.kg.min^{-1} [−3,17 a −2,54]; $p < 0,001$) e maior VE/VCO_2 *slope* (MD 5,89 [4,59 a 7,19]; $p < 0,001$) que os pacientes sem diagnóstico de EOV. Estas variáveis são marcadores clássicos de mau prognóstico para pacientes com IC.

1.4 Prevalência

Uma das principais divergências atreladas à EOV é a prevalência de casos. Os dados disponíveis mostram forte discrepância entre os estudos publicados. A Tabela 1 descreve os dados de prevalência e os principais achados clínicos relacionados à EOV. Informações compiladas dos estudos de Dhakal e Lewis (2016) e Agostoni *et al.* (2017). É possível observar variação de 6,7 a 58% dependendo do tipo de ergômetro (Guazzi *et al.*, 2008), analisador de gases (Cornelis *et al.*, 2015a), tratamento de dados (Cornelis *et al.*, 2015a) e definição de EOV utilizada (Ingle *et al.*, 2009).

Tabela 1. Prevalência e principais achados relacionados a ventilação periódica durante o exercício.

Estudo	N	Idade	FEVE	VO_{2PICO}	VE/VCO_2	Prevalência	Definição	Desfecho
Corrà (2002)	323	57 ± 9	24 ± 8	14 ± 3	32 ± 8	11,8%	Corrà	↑ mortalidade (30%)
Leite (2003)	84	47 ± 11	34 ± 7[a]	13 ± 3[a]	49 ± 7[a]	29,4%	Leite	↑ risco de morte (3x)
Corrà (2006)	133	58 ± 10	23 ± 7	15 ± 4	34 ± 10	21,1%	Corrà	↑ mortalidade isolada (17%) ↑ mortalidade associada a IAH > 30/h (54%)
Guazzi (2007)	156	61 ± 9	35 ± 11	17 ± 5	35 ± 8	33,0%	Leite	Melhor preditor de morte
Guazzi (2008)	405	56 ± 13	25 ± 8	12 ± 4[b]	40 ± 9[b]	35,1%	Corrà *	Melhor preditor de morte
Guazzi (2008)	151	59 ± 13	48 ± 8	12 ± 4[c]	37 ± 7[c]	31,8%	Corrà *	Melhor preditor de morte
Arena (2008)	154	49 ± 14	30 ± 14	15 ± 5	36 ± 9	35,7%	Corrà	↓ sobrevida em três anos
Ingle (2009)	240	59 ± 13	34 ± 6	21 ± 5	35 ± 9	30,8% 25,0%	Leite Corrà	↑ mortalidade (58%) ↑ mortalidade (50%)
Corrà (2009)	631	58 ± 10	29 ± 8	16 ± 4	32 ± 7	6,7%	Kremser	Melhor preditor de morte
Sun (2010)	580	64 ± 12	26 ± 7	12 ± 4	35 ± 17	50,8%	Sun	↑ risco de morte associado a VE/VCO_2 slope
Murphy (2011)	56	59 ± 2	30 ± 1	12 ± 1	39	45,0%	Ben-Dov *	Correlação com menor débito cardíaco e maior pressão de enchimento ventricular.
Scardovi (2012)	370	74 [71 – 78]	41 [34 – 50]	12 [10 – 14]	34 [30 – 39]	58,0%	Leite	Melhor preditor de morte
Matsuki (2013)	46	66 ± 17[d]	41 ± 16	12 ± 3[d]	36 ± 7[d]	43,5%	Corrà	↑ níveis de NT-proBNP

Vainshelboim (2017)	89	57 ± 8	47 ± 12	15 ± 6	37 ± 9	53,9%	Leite *	Preditor de eventos adversos
Rovai (2019)	4482	62 [53 – 69]	28 ±7	14 ± 5	32 [28 – 38]	17,1%	Corrà	↓ sobrevida associada com FE reduzida
Rovai (2019)	1239	65 [54 – 74]	44 ± 3	16 ± 6	30 [27 – 34]	16,4%	Corrà	↓ sobrevida associada com FE preservada

FEVE, fração de ejeção do ventrículo esquerdo, em porcentagem. VO_{2PICO}, consumo de oxigênio pico, em ml/kg/min. VE/VCO_2, produção de dióxido de carbono por ventilação. IAH, índice de apneia-hipopneia. NT-proBNP, fragmento amino-terminal do pró-peptídeo natriurético cerebral. * modificada. [a] EOV-positivo (n = 24). [b] EOV-positivo (n = 142). [c] EOV-positivo (n = 48). [d] EOV-positivo (n = 20). Valores apresentados como média e desvio padrão ou mediana e intervalo interquartil. Fonte: adaptado de Dhakal e Lewis (2016) e Agostoni *et al.* (2017).

1.5 Métodos de diagnóstico

O diagnóstico clássico de EOV é realizado pela interpretação visual da curva ventilatória durante o TCPE considerando algumas características citadas anteriormente (h, λ e Δt). Entretanto, não existe consenso sobre o melhor método para identificar o fenômeno. Cornelis *et al.* (2015a) mencionam a existência de pelo menos nove subdivisões para o diagnóstico da EOV. Os autores agruparam as técnicas em definições originais, modificadas, métodos computacionais, quantificações, métodos vagamente descritos e indefinidos.

Esta pesquisa demonstra a diversidade conceitual que dificulta a aplicabilidade e disseminação deste marcador na prática clínica. Por exemplo, Corrà *et al.* (2002) preconizam que um teste deve apresentar oscilações durante 60% do tempo total com amplitude superior à 15% da VE mensurada em repouso. Por outro lado, Ben-Dov *et al.* (1992) afirmam que a presença de apenas dois ciclos consecutivos com magnitude maior ou igual a 25% caracteriza um caso de EOV. As definições mais usuais e suas características conceituais são descritas na Tabela 2.

Tabela 2. Definições e critérios para ventilação periódica durante o exercício.

Autor	Amplitude	Comprimento	Duração
Ben-Dov	≥ 25% da VE média do ciclo	30 à 60s	≥ 2 ciclos consecutivos
Corrà	> 15% da VE de repouso	-	> 60% do exercício
Leite	≥ 5 $L.min^{-1}$	-	≥ 3 ciclos regulares*

* um ciclo é regular se o desvio-padrão de três ciclos consecutivos ou mais for menor que 20% da média observada. VE, ventilação minuto. Fonte: Ben-Dov *et al.* (1992), Corrà *et al.* (2002) e Leite *et al.* (2003).

Existem diversas variações na literatura além das definições clássicas, como aplicar os conceitos de Ben-Dov *et al.* (1992) com magnitude superior a 30% (Sun *et al.*, 2010), usar apenas a amplitude maior que 5 $L.min^{-1}$ para caracterizar uma oscilação (Reis *et al.*, 2018) ou considerar flutuações na VE em repouso que persistam por pelo menos 50% do período total do exercício (Passino *et al.*, 2008).

Estes exemplos mostram a dificuldade de se chegar a um consenso sobre qual a equação ou critério mais adequado para avaliar o fenômeno. Ainda que a *American Heart Association* indique a definição de Corrà, não há consenso sobre sua utilização (Agostoni *et al.*, 2017). A dificuldade de interpretar cada conceito é outro fator a ser considerado.

Neste sentido, a definição de Leite *et al.* (2003) apresenta a maior complexidade por preconizar a presença de três ou mais oscilações regulares durante o teste de esforço para confirmar o diagnóstico de EOV. Além disso, não está claro como o desvio padrão do comprimento dos ciclos, que deve ser inferior a 20% da média observada, é calculado. Certamente, este fato causou adaptações do conceito original (ex.: Reis *et al.,* 2018). O mesmo princípio vale para outras definições. A Figura 7 ilustra o padrão ventilatório de um paciente com EOV identificado a partir de três definições clássicas.

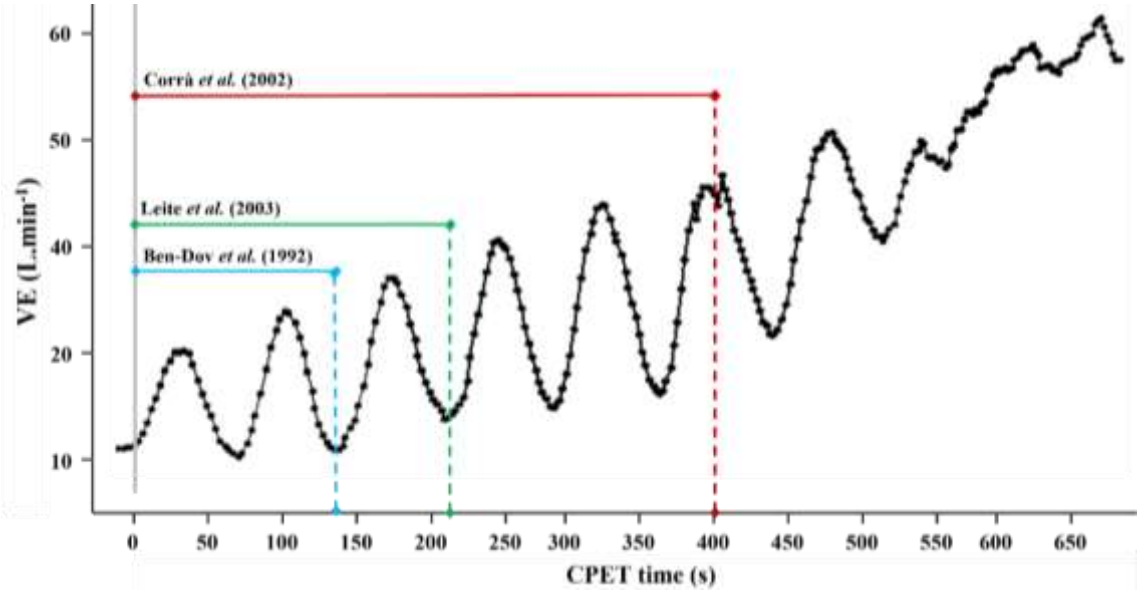


Figura 7. Padrão ventilatório característico de um paciente com EOV identificado a partir de três definições clássicas. VE, ventilação minuto. CPET, teste de cardiopulmonar de esforço. Fonte: elaborado pelo autor.

A discussão sobre a aplicabilidade das definições é recorrente. Normalmente, são adaptadas de acordo com a *expertise* de cada centro e pouco se discute sobre o processamento de dados (Brawner *et al.*, 2018). Ingle *et al.* (2009) foram pioneiros ao investigar a reprodutibilidade do diagnóstico utilizando as definições de Corrà *et al.* (2002) e Leite *et al.* (2003). Entretanto, o estudo não

relata como a análise foi realizada (interpretação visual, manipulação de dados ou outro método). Ingle *et al.* (2009) apenas citaram que a reprodutibilidade foi superior aplicando a definição de Corrà (ICC = 0,86 [0,82 a 0,89]) comparada à de Leite (ICC = 0,78 [0,73 a 0,83)].

Em contrapartida, Brawner *et al.* (2018) observaram baixa (κ = 0,24 [0,20 a 0,27]) e moderada (κ = 0,47 [0,44 a 0,50]) reprodutibilidade quando utilizaram intervalos médios de 10 e 30s como método de pré-processamento do sinal para determinar a presença de EOV, respectivamente. Brawner *et al.* (2018) afirmam que a ausência do detalhamento das técnicas torna a interpretação subjetiva.

1.6 Abordagens quantitativas

Castro *et al.* (2017) descreveram uma abordagem inovadora para quantificar a EOV com base na variabilidade da VE. Até então, a EOV era interpretada de forma dicotômica: EOV-positivo ou EOV-negativo. Embora tradicional, a abordagem dicotômica não considera a hipótese de haver uma classificação de gravidade dentro do fenótipo EOV-positivo. Portanto, o uso de métodos lineares para inferir a influência do sistema nervoso autonômico (SNA) no padrão ventilatório de pacientes com EOV poderia trazer informações adicionais ao tema.

A análise no domínio do tempo faz uso de alguns índices matemáticos para inferir a influência do SNA na modulação da variável de interesse. Dentre os principais índices no domínio do tempo, destacam-se o desvio padrão de todos os intervalos RR normais gravados em um intervalo de tempo (SDNN) e a raiz quadrada da média do quadrado das diferenças entre intervalos RR normais adjacentes em um intervalo de tempo (rMSSD) (Tarvainen *et al.*, 2014).

Para testar a aplicabilidade da abordagem, Castro *et al.* (2017) analisaram 18 voluntários do sexo masculino (atletas e sedentários). Os autores calcularam o SDNN e o RMSSD da VE e os normalizaram pelo número de ciclos respiratórios registrados durante o teste para amenizar a influência da duração na interpretação do resultado. Não está claro se os ciclos respiratórios se referem a todos os ciclos registrados ou apenas aqueles que exibiam um comportamento oscilatório.

Os dados do estudo não indicaram diferença entre atletas do sexo masculino e sedentários para o rMSSD normalizado. Entretanto, Castro *et al.*

(2017) observaram que indivíduos sedentários exibiam maior variabilidade da VE que atletas, sugerindo que este marcador poderia ser modificado pelo exercício. Embora não tenha avaliado pacientes com IC e o impacto desta nova ferramenta na morbimortalidade, este estudo apresentou uma abordagem diferenciada para quantificar o fenômeno.

Corroborando com o raciocínio dos autores supracitados, Brawner *et al.* (2018) descreveram outro método para mensurar de forma objetiva e quantificável a EOV. A principal justificativa para seu desenvolvimento era a subjetividade do modelo dicotômico e a ausência de um padrão de referência para disseminar o uso deste marcador na prática clínica. O índice de dispersão ventilatória (*ventilation dispersion index,* VDI) avalia a interação entre a amplitude e frequência das oscilações durante o exercício. Embora complexo, os autores disponibilizaram uma planilha online para utilizar este novo marcador (http://links.lww.com/MSS/B36).

Seguramente esta abordagem é a que apresenta maior complexidade conceitual e matemática. Entretanto, exibi um desenho experimental consistente. Brawner *et al.* (2018) enviaram dados brutos e gráficos padronizados para seis cardiologistas determinarem a presença de EOV de acordo com três definições do fenômeno (Kremser *et al.*, 1987; Corrà *et al.*, 2002; Leite *et al.*, 2003). Os cardiologistas deveriam indicar se o teste era positivo, negativo ou inconclusivo. Apenas casos com concordância superior a quatro opiniões foram determinados como positivo ou negativo. Caso contrário, eram inconclusivos.

O ponto de corte para o VDI foi determinado a partir da área sob a curva ROC utilizando as medidas de sensibilidade e especificidade para identificar o escore com maior equilíbrio para diagnosticar casos positivos. Brawner *et al.* (2018) identificaram o valor de 0,924 como o ponto de equilíbrio, sugerindo utilizá-lo como ponto de corte para identificar a presença do fenômeno. Valores acima deste ponto foram associados ao fenótipo EOV-positivo. A Figura 8 ilustra a representação gráfica do método, além de apresentar a equação desenvolvida para o cálculo do VDI.

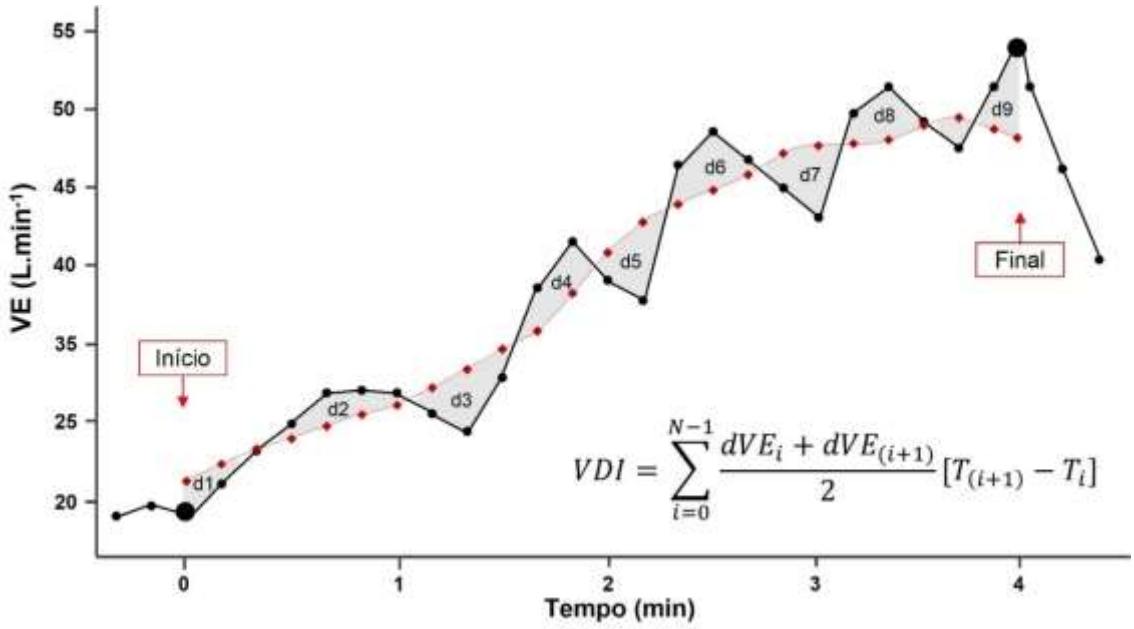


Figura 8. Representação gráfica do *Ventilation Dispersion Index*. Marcadores pretos representam a média móvel de 30s da VE em intervalos de 10s. Os pontos vermelhos representam a VE média estimada com base nos 30s prévios e posteriores. As áreas sombreadas demarcadas com a letra *d* representam a dispersão entre VE e VE média. A área de dispersão total é obtida pela soma d1 + d2 ··· d9. VE, ventilação minuto. VDI, *ventilation dispersion index*. d, dispersão. T, tempo do teste. Fonte: adaptado de Brawner *et al.* (2018).

1.7 Recursos tecnológicos

A diversidade conceitual e a complexidade técnica no processamento dos dados (limpeza do sinal e aplicação das definições diagnósticas) tendem a limitar a aplicabilidade deste marcador na prática clínica. De fato, alguns critérios demandam conhecimentos básicos de estatística. Entretanto, existem recursos que facilitam sua aplicabilidade. Além da planilha eletrônica mencionada anteriormente, uma interface gráfica vem sendo desenvolvida para auxiliar na identificação do fenômeno de forma automatizada (Cornelis *et al.,* 2017).

O VOdEX-tool é uma interface gráfica que deve ser incorporada ao analisador de gases da Cortex®. Foi desenvolvida para padronizar a amostragem de dados com filtros uniformes, permitindo a detecção automática e padronizada das características ventilatórias (h, λ e Δt). A premissa para seu desenvolvimento é que somente a inspeção visual da curva ventilatória poderia causar um forte viés no diagnóstico de EOV, por não conseguir aplicar corretamente os critérios

preconizados. Neste sentido, o VOdEX-tool busca identificar automaticamente os parâmetros de EOV (h, λ e Δt) e sinalizar a presença do fenômeno de acordo com cinco definições.

Para desenvolver a interface, Cornelis *et al.* (2017) testaram diferentes métodos de filtragem utilizando dados *breath-by-breath.* Então, encaminharam para que estudantes de engenharia avaliassem se o método era muito forte e filtrava dados reais, muito fraco e não excluía ruídos, ou era adequado com equilíbrio entre exclusão de ruídos e manutenção do sinal verdadeiro. Após analisarem os filtros, os pesquisadores concluíram que a transformação do tipo *wavelet* era adequada para suavizar o sinal, sem haver perda de informação.

Cornelis *et al.* (2017) incorporaram o método na interface juntamente com as quatro definições de EOV mais usuais: Ben-Dov *et al.* (1992), Corra *et al.* (2002), Leite *et al.* (2003) e Sun *et al.* (2010). Os autores sugerem a realização de um protocolo padronizado com coleta de gases no modo *breath-by-breath* para otimizar o uso da interface (3 min de repouso, 8 a 12 min de exercício e 3 min de recuperação – protocolo de rampa).

Embora a ferramenta possa facilitar o diagnóstico de EOV, os autores destacam que é preciso testar sua validade e confiabilidade. Esta ferramenta está em fase final de implementação e, possivelmente, só poderá ser usada no analisador de gases da Cortex®. A interface parece ser uma ferramenta simples, permitindo a análise deste fenômeno respiratório e melhorando a avaliação diagnóstica e prognóstica dos pacientes com IC.

1.8 Recursos terapêuticos

Diversos estudos têm apontado a EOV como forte preditora de mortalidade e desfechos adversos (Guazzi *et al.,* 2008; Vainshelboim *et al.,* 2017; Rovai *et al.*, 2019), tornando essencial o tratamento para reverter ou amenizar a sua fisiopatologia. Dada a complexidade deste fenômeno, diversas alternativas têm sido investigadas como opção de tratamento para pacientes com EOV. Protocolos com exercício físico (Zurek *et al.*, 2012; Yamauchi *et al.*, 2016; Panagopoulou *et al.*, 2017), auto servo-ventilação (Kazimierczak *et al.*, 2011; Joho *et al.*, 2013) e inibidor de fosfodiesterase-5 (Guazzi *et al.*, 2012) têm demonstrado resultados promissores. Ainda assim, as pesquisas no campo da reabilitação mostram-se incipientes.

1.8.1 Exercício físico

Castro *et al.* (2010) foram os primeiros autores a relatarem um caso de reversão da EOV utilizando o treinamento físico como método de reabilitação. Neste estudo de caso, um homem de 58 anos com cardiomiopatia hipertensiva, disfunção sistólica, FEVE < 20% e classe funcional NYHA III, foi submetido a um programa de treinamento durante quatro meses (60 min, três vezes por semana). Foram realizadas 48 sessões de treinamento aeróbio com intensidade entre o primeiro limiar ventilatório (LV_1) e 10% abaixo do segundo limiar ventilatório (LV_2). A intensidade da sessão era monitorada pela percepção subjetiva de esforço. Ao final do programa de reabilitação observou-se reversão do quadro clínico (EOV-positivo), incremento de performance e função cardiorrespiratória.

Fomentando a discussão, Zurek *et al.* (2012) observaram reversão em 71% dos casos EOV-positivo após três meses de reabilitação. O protocolo era composto por 45 min de exercício aeróbio em cicloergômetro em intensidade correspondente à 60 - 80% do VO_{2PICO}, seguido de exercícios calistênicos (duas vezes por dia). Além disso, os autores relataram que os pacientes participavam de uma reunião informativa por semana (não está claro o que era abordado nestas sessões). Deste modo, totalizaram 36 sessões de treinamento e 12 sessões informativas. Embora não tenham detalhado como ocorreu o ajuste de cargas, Zurek *et al.* (2012) confirmaram o efeito positivo do protocolo de treinamento na reversão da EOV.

Yamauchi *et al.* (2016) ampliaram as evidências sobre o treinamento físico na reabilitação de pacientes com EOV ao avaliarem retrospectivamente 3.933 pacientes admitidos em um centro de referência cardiovascular. Os autores identificaram 26 casos EOV-positivo (< 1% da amostra). O programa de reabilitação foi composto por 30 min de exercício aeróbio em intensidade correspondente ao LV_1, além de exercício resistido (três vezes por semana). Após os cinco meses de intervenção, observou-se redução de 51% os níveis plasmáticos de BNP, além de correlação positiva entre BNP e amplitude do ciclo (r = 0,615; p = 0,007). Embora os autores não tenham relatado o percentual de reversão, evidenciaram diminuição na amplitude do ciclo (18,6 ± 11,9 vs 12,1 ± 5,2 $L.min^{-1}$; p = 0,009).

Corroborando com estes achados, Panagopoulou *et al.* (2017) avaliaram o efeito do treinamento intervalado de alta intensidade e resistido na sintomatologia da EOV. Pacientes com IC foram aleatorizados em dois grupos: 40 min de treinamento intervalado de alta intensidade (30s a 100% VO_{2PICO} por 60s de repouso passivo) ou 20 min do mesmo protocolo com mais quatro exercícios resistidos (55-65% de 2-RM). Observou-se reversão em 70% dos casos de EOV após as 36 sessões de reabilitação, melhorando aproximadamente 17% a potência máxima e 13% o VO_{2PICO}. Além disso, Panagopoulou *et al.* (2017) constataram redução no período de oscilações sem que houvesse distinção entre protocolos.

Curiosamente, nenhum dos estudos citados relatou se houve ajuste nas cargas de treino. Fato que pode ter gerado um subaproveitamento dos benefícios advindos com o treinamento físico. Ainda assim, os achados mostram-se promissores e abrem diferentes perspectivas de atuação profissional. Contudo, as evidências sobre o efeito do treinamento físico na reversão da EOV e suas implicações na morbimortalidade seguem limitadas. Os dados disponíveis são procedentes de um estudo de caso, um estudo retrospectivo multicêntrico, um estudo de braço único (sem grupo controle) e um estudo randomizado que acabou sendo combinado no final, totalizando menos de 100 pacientes avaliados.

1.8.2 Suporte ventilatório

Os dispositivos de servo-ventilação tornaram-se alvo de investigações devido à similaridade da EOV com outras formas de respiração periódica (ex.: apneia central do sono). Entretanto, apenas dois estudos investigaram o recurso. Kazimierczak *et al.* (2011) analisaram dados ecocardiográficos, cardiorrespiratórios e a polisonografia de pacientes com apneia central do sono e respiração de *Cheyne-Stokes*, identificando 12 casos de EOV-positivo na amostra. O suporte ventilatório foi utilizado como terapia para pacientes com índice apneia-hipopneia (IAH) moderado e grave (acima de 15 e 30 eventos por hora, respectivamente) durante três meses.

Ao final do tratamento os autores observaram reversão em 87,5% dos casos e melhora na FEVE, pulso de oxigênio, IAH e concentração de NT-proBNP. Entretanto, não houve alterações no VO_{2PICO}, VE/VCO_2 *slope*,

saturação de oxigênio e outros marcadores. Kazimierczak *et al.* (2011) não explicaram o motivo de quatro pacientes terem sido excluídos da análise. Por fim, eles citam que a EOV pode ser revertida com suporte ventilatório, mas não explicam o mecanismo que respaldaria esse desfecho.

Em outro estudo, com desenho semelhante, Joho *et al.* (2013) realizaram três meses de tratamento com suporte ventilatório em pacientes com IC e apneia central do sono. O protocolo era composto por sessões diárias usando o dispositivo AutoSet CS2 (tempo médio de uso de 3,6 ± 2,2 horas/noite). Ao final do tratamento, Joho *et al.* (2013) identificaram reversão em 77,8% dos casos de EOV, redução de 42,2% na amplitude do ciclo, além de melhora no VO_{2PICO} e na VE/VCO_2 *slope*. Curiosamente, os resultados de EOV não eram nítidos por ser um desfecho secundário e a amostra não estar estratificada em grupos EOV-positivo e EOV-negativo.

1.8.3 Fármacos

Dada a complexidade do fenômeno, Guazzi *et al.* (2012) investigaram o uso do inibidor de fosfodiesterase-5 (PDE5) como recurso terapêutico no tratamento da EOV. A principal justificativa seria a suposta relação entre os mecanismos fisiopatológicos do fenômeno com a hipertensão pulmonar. Em outras palavras, o aumento na pressão alveolar como resposta à vasoconstrição pulmonar ocasionaria instabilidade no *drive* ventilatório, podendo causar o atraso circulatório que desencadearia a EOV. O inibidor de PDE5 auxiliaria na vasodilatação pulmonar, melhorando o suprimento de oxigênio, atenuando o prejuízo circulatório (Guazzi *et al.*, 2012; Dupuis e Guazzi, 2015).

Para investigar o efeito do medicamento, Guazzi *et al.* (2012) randomizaram 32 pacientes com EOV e hipertensão pulmonar. O grupo intervenção recebeu 50 mg de sildenafil três vezes ao dia. Guazzi *et al.* (2012) avaliaram diversos marcadores de hipertensão pulmonar e função cardiorrespiratória (incluindo os parâmetros de EOV), observando que o tratamento farmacológico resultava em melhora do débito cardíaco, VO_{2PICO}, eficiência ventilatória (VE/VCO_2 *slope*) e nos parâmetros de EOV, indicando a reversão de 87% dos casos diagnosticados em seis meses e de 93% em 12 meses.

Guazzi *et al.* (2012) citaram que o fosfodiesterase é uma enzima abundante na musculatura lisa do pulmão, principalmente em pacientes com hipertensão pulmonar (Humbert e Ghofrani, 2016). A inibição da PDE5 aumenta a expressão de óxido nítrico endotelial, estimulando a vasodilatação pulmonar (Andersson, 2018). De acordo com Guazzi *et al.* (2004), a vasodilatação pulmonar melhoraria a difusão alveolar devido à menor resistência pulmonar, proporcionando melhor distribuição do fluxo sanguíneo. Entretanto, parece que os benefícios advindos com o uso desta droga são verdadeiros apenas para os pacientes com baixa eficiência ventilatória, não para pacientes com eficiência ventilatória moderada (Murphy *et al.*, 2011; Guazzi *et al.*, 2012).

Curiosamente, Murphy *et al.* (2011) já haviam observado resultados positivos com o uso deste medicamento após 12 semanas de tratamento (Figura 4). O período de intervenção resultou na diminuição da amplitude (7,8 ± 1,3 para 6,3 ± 1,4 $L.min^{-1}$) e do comprimento dos ciclos (70 ± 8 para 57 ± 4 s), como também no atraso circulatório (18,6 ± 6%). Os autores observaram ainda correlação inversa entre características do padrão oscilatório (amplitude e comprimento do ciclo) com atraso circulatório (*cardiac index*) conforme ilustrado anteriormente (Figura 3). A Tabela 3 resume os principais achados e tratamentos para pacientes com EOV.

Tabela 3. Protocolos de tratamento e principais achados.

Estudo	Tratamento	Frequência	Principais achados
Castro (2010)	Exercício	48 sessões	Reversão da EOV
		3x por semana	↑ VO_{2PICO}
Panagopoulou	Exercício	36 sessões	Reversão de 70% dos casos
(2017)		3x por semana	↑ Eficiência ventilatória
Yamauchi	Exercício	60 sessões	↓ 51% nos níveis de BNP
(2016)		3x por semana	↓ 35% na amplitude do ciclo
Zurek (2012)	Exercício	36 sessões	Reversão de 71% dos casos
		3x por semana	↑ Eficiência ventilatória
Kazimierczak	ASV	7x por semana	Reversão de 87% dos casos
(2011)		12 semanas	↓ 36% nos níveis de BNP
Murphy (2011)	PDE-5	7x por semana	↓ 18% *delay* circulatório
		12 semanas	
Guazzi (2012)	PDE-5	7x por semana	Reversão de 93% dos casos
		12 meses	↑ Eficiência ventilatória

EOV, ventilação periódica durante o exercício. VO_{2PICO}, pico do consumo de oxigênio. BNP, peptídeo natriurético do tipo B. ASV, auto servo-ventilação. PDE-5, inibidor de fosfodiesterase-5. Fonte: elaborada pelo autor.

1.9 Justificativa

A EOV é uma manifestação atípica no padrão ventilatório de pacientes com IC, caracterizada por breves períodos de oscilação na VE, cerca de 60 a 180s, que podem perdurar por todo o exercício. Embora a sua fisiopatologia não seja completamente compreendida, as evidências atuais indicam que prejuízos hemodinâmicos são a principal explicação para seu surgimento. Entretanto, as diferentes definições diagnósticas podem dificultar a interpretação e inviabilizam a sua aplicabilidade na prática clínica.

Não está claro se as definições caracterizam o mesmo perfil de pacientes, se apresentam a mesma sensibilidade para predizer desfechos adversos, se são sensíveis a diferentes tratamentos ou se novas abordagens trariam informações relevantes ao tema. O entendimento destas questões permitirá a escolha de condutas mais assertivas para as especificidades dos pacientes, além de auxiliar na disseminação do uso desse poderoso marcador prognóstico.

2 OBJETIVOS

2.1 Objetivo geral

Comparar a capacidade preditiva entre as definições dicotômico e a variabilidade da ventilação minuto para predizer eventos adversos em pacientes com EOV e testar sua responsividade ao treinamento físico.

2.2 Objetivo – Artigo 1

- Desenvolver uma ferramenta semiautomática para auxiliar no diagnóstico da EOV e facilitar a inclusão deste marcador na prática clínica.

2.3 Objetivo – Artigo 2

- Caracterizar o perfil clínico dos pacientes com EOV por meio de definições que priorizam características distintas do fenômeno (amplitude vs duração);
- Comparar a prevalência de EOV aplicando as definições de Ben-Dov, Corrà e Leite em um mesmo banco de dados;
- Comparar a sensibilidade e a especificidade entre as definições de Ben-Dov, Corrà e Leite para predizer desfechos adversos em um seguimento de dois anos.

2.4 Objetivo – Artigo 3

- Avaliar a variabilidade da ventilação minuto em pacientes com insuficiência cardíaca;
- Analisar a sensibilidade e a especificidade da variabilidade da ventilação minuto para predizer desfechos adversos em um seguimento de dois anos;
- Comparar a sensibilidade e a especificidade entre a abordagem dicotômica e a variabilidade da ventilação minuto para predizer desfechos adversos em um seguimento de dois anos.

2.5 Objetivo – Artigo 4

- Verificar o efeito do treinamento físico na reversão da EOV e outros fatores prognósticos de pacientes com EOV.

REFERÊNCIAS

AGOSTONI, P.; APOSTOLO, A.; ALBERT, R. K. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. **Chest,** v. 133, n. 1, p. 197-203, 2008.

AGOSTONI, P.; CORRA, U.; EMDIN, M. Periodic breathing during incremental exercise. **Ann Am Thorac Soc,** v. 14, n. Supplement_1, p. S116-s122, 2017.

AGOSTONI, P. et al. Exercise hyperpnea in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. **J Appl Physiol,** v. 92, n. 4, p. 1409-16, 2002.

AGOSTONI, P.; SALVIONI, E. Exertional periodic breathing in heart failure: mechanisms and clinical implications. **Clin Chest Med,** v. 40, n. 2, p. 449-457, 2019.

ANDERSSON, K. E. PDE5 inhibitors - pharmacology and clinical applications 20 years after sildenafil discovery. **Br J Pharmacol,** v. 175, n. 13, p. 2554-2565, 2018.

ARENA, R. et al. Prognostic value of timing and duration characteristics of exercise oscillatory ventilation in patients with heart failure. **J Heart Lung Transplant,** v. 27, n. 3, p. 341-7, 2008.

BEN-DOV, I. et al. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. **Am Rev Respir Dis,** v. 145, n. 4 Pt 1, p. 776-81, 1992.

BRAWNER, C. A. et al. Exercise oscillatory ventilation: interreviewer agreement and a novel determination. **Med Sci Sports Exerc,** v. 50, n. 2, p. 369-374, 2018.

CASTRO, R. et al. Reversal of periodic breathing after aerobic training in heart failure. **Eur Respir J,** v. 35, n. 6, p. 1409-11, 2010.

CASTRO, R. et al. Minute-ventilation variability during cardiopulmonary exercise test is higher in sedentary men than in athletes. **Arq Bras Cardiol,** v. 109, p. 185-190, 2017.

CORNELIS, J. et al. An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation--a systematic review. **Int J Cardiol,** v. 190, p. 161-9, 2015a.

CORNELIS, J. et al. Development of a clinical applicable graphical user interface to automatically detect exercise oscillatory ventilation: The VOdEX-tool. **Int J Cardiol,** v. 240, p. 291-296, 2017.

CORNELIS, J. et al. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis. **Int J Cardiol,** v. 182, p. 476-86, 2015b.

CORRA, U. et al. Exercise haemodynamic variables rather than ventilatory efficiency indexes contribute to risk assessment in chronic heart failure patients treated with carvedilol. **Eur Heart J,** v. 30, n. 24, p. 3000-6, 2009.

CORRÀ, U. et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. **Circulation,** v. 113, n. 1, p. 44-50, 2006.

CORRA, U. et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. **Chest,** v. 121, n. 5, p. 1572-80, 2002.

DHAKAL, B.; LEWIS, G. Exercise oscillatory ventilation: Mechanisms and prognostic significance. **World J Cardiol,** v. 8, n. 3, p. 258-266, 2016.

DUPUIS, J.; GUAZZI, M. Pathophysiology and clinical relevance of pulmonary remodelling in pulmonary hypertension due to left heart diseases. **Can J Cardiol,** v. 31, n. 4, p. 416-429, 2015.

FRANCIS, D. et al. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. **Circulation,** v. 102, n. 18, p. 2214-21, 2000.

FRANCO, V. Right ventricular remodeling in pulmonary hypertension. **Heart Fail Clin,** v. 8, n. 3, p. 403-12, 2012.

GUAZZI, M. et al. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. **Eur Heart J,** v. 29, n. 22, p. 2751-9, 2008.

GUAZZI, M. et al. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. **J Am Coll Cardiol,** v. 50, n. 4, p. 299-308, 2007.

GUAZZI, M. et al. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. **J Am Coll Cardiol,** v. 44, n. 12, p. 2339-48, 2004.

GUAZZI, M.; VICENZI, M.; ARENA, R. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. **Eur J Heart Fail,** v. 14, n. 1, p. 82-90, 2012.

HUMBERT, M.; GHOFRANI, H.-A. The molecular targets of approved treatments for pulmonary arterial hypertension. **Thorax,** v. 71, n. 1, p. 73-83, 2016.

INGLE, L. et al. Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure. **Eur J Cardiovasc Prev Rehabil,** v. 16, n. 4, p. 451-6, 2009.

JOHO, S. et al. Adaptive servo-ventilation improves exercise oscillatory ventilation and ventilatory inefficiency in patients with heart failure and central sleep apnea. **IJC Metab Endoc,** v. 1, p. 20-26, 2013.

KAZIMIERCZAK, A. et al. Resolution of exercise oscillatory ventilation with adaptive servoventilation in patients with chronic heart failure and Cheyne-Stokes respiration: preliminary study. **Kardiol Pol,** v. 69, n. 12, p. 1266-71, 2011.

KOIKE, A. et al. Relation between oscillatory ventilation at rest before cardiopulmonary exercise testing and prognosis in patients with left ventricular dysfunction. **Chest,** v. 123, n. 2, p. 372-9, 2003.

KREMSER, C. B.; O'TOOLE, M. F.; LEFF, A. R. Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. **Am J Cardiol,** v. 59, n. 8, p. 900-5, 1987.

LAHIRI, S. et al. Peripheral chemoreceptors in respiratory oscillations. **J Appl Physiol,** v. 58, n. 6, p. 1901-8, 1985.

LEITE, J. et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. **J Am Coll Cardiol,** v. 41, n. 12, p. 2175-81, 2003.

LORENZI-FILHO, G. et al. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. **Eur Respir J,** v. 19, n. 1, p. 37-40, 2002.

MATSUKI, R. et al. Characteristics of patients with severe heart failure exhibiting exercise oscillatory ventilation. **Clin Exp Hypertens,** v. 35, n. 4, p. 267-72, 2013.

MORTARA, A. et al. Association between hemodynamic impairment and Cheyne-Stokes respiration and periodic breathing in chronic stable congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. **Am J Cardiol,** v. 84, n. 8, p. 900-4, 1999.

MURPHY, R. et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. **Circulation,** v. 124, n. 13, p. 1442-51, 2011.

PANAGOPOULOU, N. et al. Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure. **Eur J Prev Cardiol,** v. 24, n. 8, p. 825-832, 2017.

PARDAENS, S. et al. Activation of the ergoreceptors in cardiac patients with and without heart failure. **J Card Fail,** v. 20, n. 10, p. 747-54, 2014.

PASSINO, C. et al. **Exertional periodic breathing is frequent in heart failure patients: correlation with clinical status and neuro-hormonal activation**. ESC Congress 2008. Germany: European Heart Journal. 29**:** 553-553 p. 2008.

PRADO, D. et al. Effect of exercise training on ventilatory efficiency in patients with heart disease: a review. **Braz J Med Biol Res,** v. 49, 2016.

REIS, H. et al. Association of oscillatory ventilation during cardiopulmonary test to clinical and functional variables of chronic heart failure patients. **Braz J Cardiovasc Surg,** v. 33, p. 176-182, 2018.

RIBEIRO, G. S. et al. Exercise oscillatory ventilation impairs oxygen delivery/extraction in male patients with chronic heart failure. **Eur J Prev Cardiol,** v. 27, n. 1_suppl, p. S85, 2020.

ROVAI, S. et al. Exercise oscillatory ventilation and prognosis in heart failure patients with reduced and mid-range ejection fraction. **Eur J Heart Fail,** v. 21, n. 12, p. 1586-1595, 2019.

SCARDOVI, A. et al. A case for assessment of oscillatory breathing during cardiopulmonary exercise test in risk stratification of elderly patients with chronic heart failure. **Int J Cardiol,** v. 155, n. 1, p. 115-9, 2012.

SOLIN, P. et al. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. **Circulation,** v. 99, n. 12, p. 1574-9, 1999.

SPRUIJT, O. et al. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. **Am J Respir Crit Care Med,** v. 191, n. 9, p. 1050-7, 2015.

SUN, X. G. et al. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. **J Am Coll Cardiol,** v. 55, n. 17, p. 1814-23, 2010.

TARVAINEN, M. P. et al. Kubios HRV: heart rate variability analysis software. **Comput Methods Programs Biomed,** v. 113, n. 1, p. 210-20, 2014.

VAINSHELBOIM, B. et al. A method for determining exercise oscillatory ventilation in heart failure: Prognostic value and practical implications. **Int J Cardiol,** v. 249, p. 287-291, 2017.

YAJIMA, T. et al. Mechanism of periodic breathing in patients with cardiovascular disease. **Chest,** v. 106, n. 1, p. 142-6, 1994.

YAMAUCHI, F. et al. Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure. **Heart Vessels,** v. 31, n. 10, p. 1659-68, 2016.

ZUREK, M. et al. Exercise training reverses exertional oscillatory ventilation in heart failure patients. **Eur Respir J,** v. 40, n. 5, p. 1238-44, 2012.

3 ARTIGO 1

A SEMIAUTOMATED SOFTWARE TO ASSIST THE CLINICAL DIAGNOSIS OF THE EXERCISE OSCILLATORY VENTILATION: DEVELOPMENT AND RELIABILITY OF EASY-EOV TOOL

Submetido ao periódico *Journal of Medical Systems* – Percentil 94 (*Scopus*), Fator de Impacto 4,920

Software Development to Standardize the Clinical Diagnosis of Exercise Oscillatory Ventilation in Heart Failure

Gustavo dos Santos Ribeiro[1], Thomas Beltrame[2], Luís Fernando Deresz[3], Dominique Hansen[4], Piergiuseppe Agostoni[5], Marlus Karsten[1,6]

[1] Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil.

[2] Departamento de Fisioterapia, Universidade Federal de São Carlos (UFSCAR), São Carlos, Brazil.

[3] Departamento de Educação Física, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, Brazil.

[4] Hasselt University (UHASSELT), Faculty of Rehabilitation Sciences, BIOMED/REVAL, Hasselt, Belgium / Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium.

[5] Centro Cardiologico Monzino, IRCCS, Milan, Italy. Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Milano, Italy.

[6] Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Florianópolis, Brazil. Programa de Pós-Graduação em Fisioterapia, UDESC, Florianópolis, Brazil.

Corresponding author

Marlus Karsten, Centro de Ciências da Saúde e do Esporte, Universidade do Estado de Santa Catarina (UDESC), Rua Pascoal Simone 358, CEP 88080-350, Florianópolis, SC, Brazil. E-mail: marlus.karsten@udesc.br

Statements and Declarations

Conflict of Interest/Ethics declarations: The authors declare that there is no conflict of interest.

Abstract

Background: Exercise oscillatory ventilation (EOV) is characterized by periodic oscillations of minute ventilation during cardiopulmonary exercise testing (CPET). Despite its prognostic value in chronic heart failure (HF), its diagnosis is complex due to technical limitations. An easier and more accurate way of EOV identification can contribute to a better approach and clinical diagnosis. This study aims to software development to standardize the EOV diagnosis from CPET's raw data in heart failure patients.

Methods: The software was developed in the "drag-and-drop" G-language using LabVIEW®. Five EOV definitions (Ben-Dov, Corrà, Kremser, Leite, and Sun definitions), two alternative approaches, one smoothing technique, and some basic statistics were incorporated into the interface which provides the visualization of four charts of the ventilatory response. EOV identification was based on a set of criteria verified from the interaction between amplitude, cycle length, and oscillation time. Two raters analyzed the datasets. In addition, repeated measurements were verified after six months using about 25% of the initial data. Cohen's kappa coefficient (κ) was used to investigate the reliability.

Results: Overall, 391 tests were analyzed in duplicate (inter-rater reliability) and 100 tests were randomized for new analysis (intra-rater reliability). High inter-rater ($\kappa > 0.80$) and intra-rater ($\kappa > 0.80$) reliability of the five EOV diagnoses were observed.

Conclusion: The present study proposes novel semi-automated software to detect EOV in HF, with high inter and intra-rater agreements. The software project and its tutorial are freely available for download.

Keywords

Cardiology, Cardiovascular Diseases, Cardiopulmonary Exercise Test, Periodic Breathing, Prognosis

Introduction

Exercise oscillatory ventilation (EOV) is a phenomenon originally described in chronic heart failure (HF) patients, characterized by periodic oscillations of the minute ventilation (VE) during exercise testing [1-3]. Current evidence suggests that HF patients with EOV have a four-fold increased risk of adverse cardiovascular events, and deterioration in all prognostic parameters from the cardiopulmonary exercise test (CPET) [4]. Agostoni and Salvioni [1] claimed that EOV can be considered as an independent marker of worse prognosis, with better prognostic predictability than peak oxygen consumption ($\dot{V}O_{2.peak}$) and ventilatory efficiency ($VE/\dot{V}CO_2$ slope) [5, 6].

Although the prognostic value is clinically relevant, this marker is not commonly used in clinical practice due to the absence of consensus on the best EOV definition [2, 4, 7], and the lack of standardized data processing techniques. Cornelis et al. [7] highlighted at least nine conceptual variations to identify EOV by the combination of different characteristics of the VE response during CPET: amplitude (h), cycle length (λ), and oscillation time (∆t). Furthermore, the EOV identification depends on the manual data calculation or visual interpretation of the VE response, impacting the diagnosis reliability due to the inter-rater variability [7].

Cornelis et al. [8] developed a graphical interface to automatically detect the ventilatory pattern characteristic of EOV. Different smoothing techniques were applied to remove noise from the breath-by-breath VE signals and the four most common EOV definitions were included in this interface [9-12]. The EOV diagnosis has become faster and less affected by the inter-rater variation. Even though this was a precursor initiative for standardizing EOV identification, it is not clear whether this tool will be made available to all types of gas analyzers, or if it will be available for a broader application.

To better incorporate the EOV assessment into clinical practice and spread its applicability, we believe that it is necessary to simplify its analysis and improve the inter-rater agreement. Therefore, this study aims to develop a semi-automated tool to standardize the identification of EOV from the CPET exported raw data. We hypothesize that our tool will be able to support the EOV

identification and show a good inter-rater agreement improving the evaluation and follow-up of EOV patients.

Methods

Study design

This cross-sectional study based on retrospective data was approved by the local ethics committee (referee 3.516.801/2019 and 4.558.550/2021). Data from 500 CPETs performed in a specialized center were used to test the tool's reliability. Figure 1 illustrates the study design. All procedures were done according to current ethical recommendations to ensure data confidentiality and privacy of the individuals. The consent term to use of retrospective data was provided by the Centro Cardiologico Monzino.

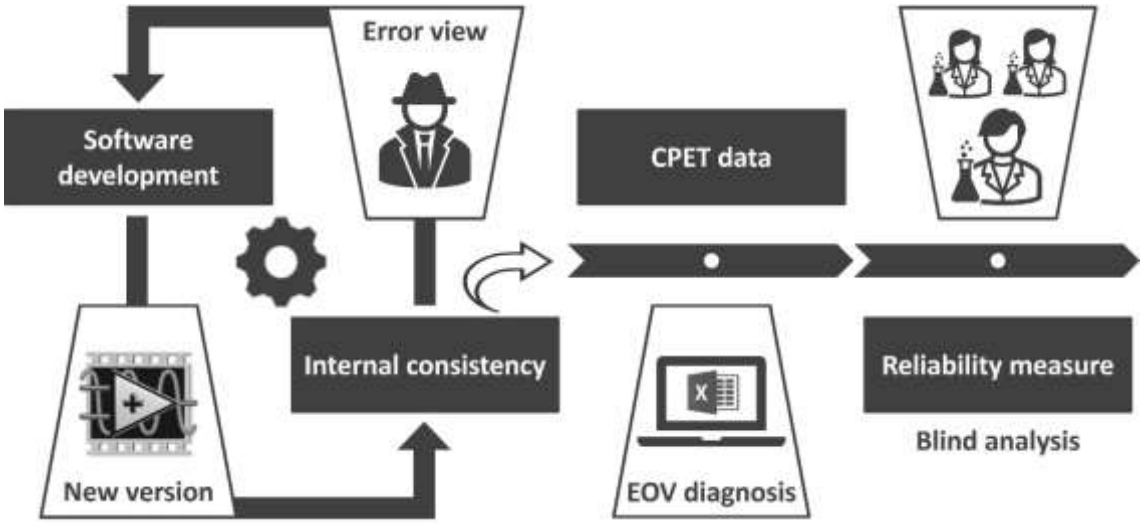


Fig. 1 Experimental study design. CPET, cardiopulmonary exercise test. EOV, exercise oscillatory ventilation

Software development

The software was developed in the "drag-and-drop" G-language using the LabVIEW® 2014 (National Instruments Corp®, Texas, US). The system was updated whenever an inconsistency in the simulated tests was observed. The following virtual instruments were inserted to feasible the EOV assessment:

- Graphic visualization of the ventilatory pattern – at rest and exercise
- Data smoothing technique
- EOV diagnosis in a semi-automated way

- Alternative approaches to assessing EOV
- Statistics to automate all calculations
- Field to export the data to further analysis
- Other features (refer to Table 3)

Ventilatory pattern

Four charts were available in the system to view full VE response, just exercise time and resting period, besides the amplitude's borderline of each cycle. Only the main chart (exercise time) allows the ventilatory pattern characteristics to be demarcated. Figure 2 illustrates a typical EOV pattern, and its main characteristics [2, 3, 7], including:

- Amplitude (*h*): the difference between the VE cycle´s peak and its baseline (a line between two consecutive nadirs).
- Cycle length (*λ*): distance between two consecutive nadirs.
- Oscillation time (∆*t*): total oscillation period during the CPET.

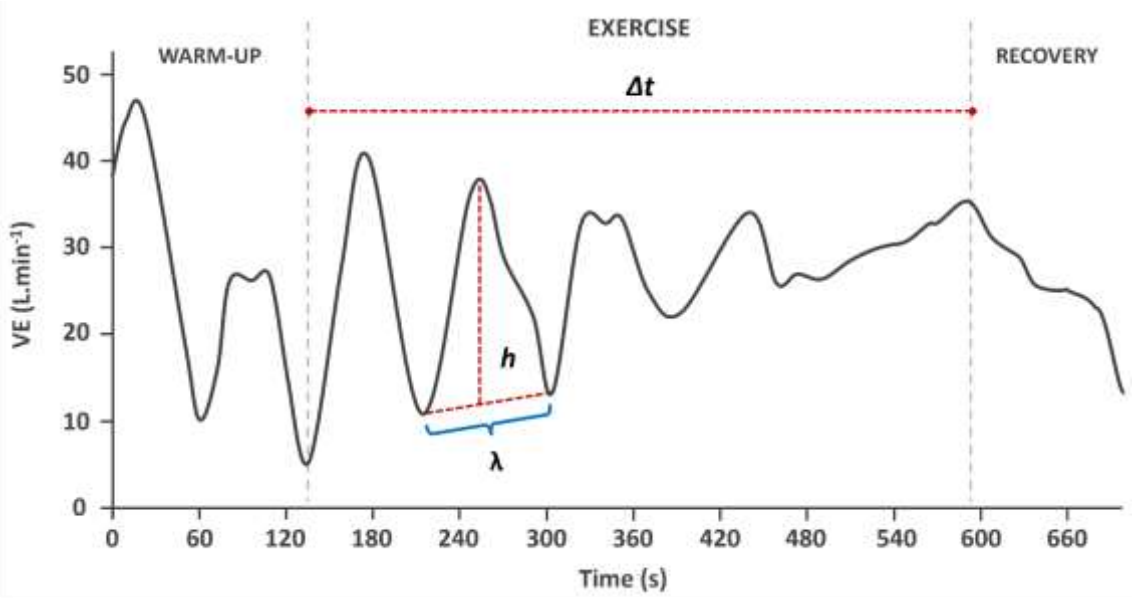


Fig. 2 Minute-ventilation response of exercise oscillatory ventilation case during the cardiopulmonary exercise test. VE, minute ventilation. h, cycle´s amplitude. λ, cycle´s length. ∆t, and oscillation time

Smoothing technique

Moving average filter (MAF) is a consolidated data pre-processing method to reduce the high-frequency noise influences over the VE data [13], facilitating the cycle identification. The MAF window size can be selected by the user according to guidelines or center expertise (e.g., 5 to 30 breaths).

$$MAF = \left(\dot{V}E_{(i)} + \dot{V}E_{(i+1)} + \cdots + \dot{V}E_{(i+M)}\right) \div M \quad (1)$$

where $\dot{V}E_{(i)}$ is initial data of minute ventilation and M is the number of points in the average. In this research, a 7-breaths filter was adopted.

EOV identification

The EOV identification was based on a set of criteria verified from the interaction between h, λ and ∆t [9-12]. The EASY-EOV tool automatically calculates the h, λ and ∆t. The user needs to mark the beginning, peak, and end of each cycle manually (nadir-peak-nadir triad) in the exercise chart (Figure 4). The algorithm classifies periodic ventilation following the definition of Corrà [12], Kremser [14], Ben-Dov [9], Leite [10], and Sun [11]. These criteria are summarized in Table 1.

Table 1. Criteria adopted in the five main definitions to diagnose exercise oscillatory ventilation

Author	Criteria
Ben-Dov et al. [8]	Two or more consecutive cycles with the VE average ≥ 25% cycle and 30 to 60s of length.
Corrà et al. [11]	At least 60% oscillation in total CPET time with amplitude > 15% of VE at rest.
Kremser et al. [14]	At least 66% of total exercise time with amplitude > 15% of the VE at rest.
Leite et al. [9]	Three or more regular oscillations with SD length < 20% of cycle average and amplitude above 5 $L.min^{-1}$.
Sun et al. [10]	Three or more consecutive cycles with the VE average ≥ 30% cycle and 40 to 140s of length. Positive oscillations in at least three other CPET variables.

VE, minute ventilation. CPET, cardiopulmonary exercise test. SD, standard deviation.

Alternative approaches

In an alternative way to the binary analysis (EOV-positive or negative), the Ventilation Dispersion Index (VDI) and the VE variability (vVE) were implemented in the system. The VDI combines the cycle´s h with the oscillation frequency during the CPET [15], whereas the vVE analyses the VE response through time-domain linear methods, as the standard deviation of VE (SDNN) and its relativized form (SDNN/n) to reduce the influence of the number of observations registered [16].

$$\mathrm{VDI} = \sum_{i=0}^{N-1} \frac{dVE_{(i)} + dVE_{(i+1)}}{2} \times \left[T_{(i+1)} - T_{(i)}\right] \qquad (2)$$

where VDI is Ventilation Dispersion Index, dVE is the absolute difference between the VE and the mean VE every 30s, T is the exercise time in seconds, and "*i*" is the data interval starting at 70s of exercise (*i* = 0) through the second to last exercise interval (*i* = N – 1).

$$vVE = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n-1}} \div number\ of\ cycles \quad (3)$$

where vVE is the minute ventilation variability, x_i is VE standard deviation, x is the mean standard deviation of VE, n is the total of standard deviations.

Measurement properties

According to the COSMIN taxonomy, the principal domains that determine the quality of an instrument are reliability, validity, and responsiveness [17]. The reliability of the measures (inter-rater and intra-rater agreement) was assessed by Cohen's kappa coefficient (κ), adopting k ≥ 0.80 as an adequate measure [18]. The validity of the measures and their internal consistency (a reliability domain) were assessed using the CPETs data from the HF patients.

Internal consistency

Throughout the development phase, the software version was updated when the rater identified some conflict or error between the automatic EOV identification by the system and its manual identification following the same criteria. Some CPETs were used to stress the software algorithms during the development phase (only HF patient's data). No conflict was observed after the last update (on May 15th, 2021).

Inter-rater agreement

Two independent raters used the software interface and visually labelled the beginning and end of the VE cycles during the CPET. The EASY-EOV tool automatically indicated the EOV presence following the EOV definitions (Table 1), besides calculating the VDI and vVE. Standardized recommendations of how to use the software were given to both researchers. All notes were sent to the principal researcher for agreement analysis.

Intra-rater agreement

The intra-rater agreement was verified after six months of the first screening. An online service (https://www.randomizer.org/) was used to randomize a subset of 100 CPETs [17]. All notes were sent to the principal researcher to evaluate the agreement.

Results

The software project in National Instruments proprietary format and the tutorial are freely available for download from the Mendeley Data repository under Creative Commons licenses (CC BY-NC-SA 4.0). Repository number: *[Blinded]*. An example of code used in LabView programming is shown in figure 3.

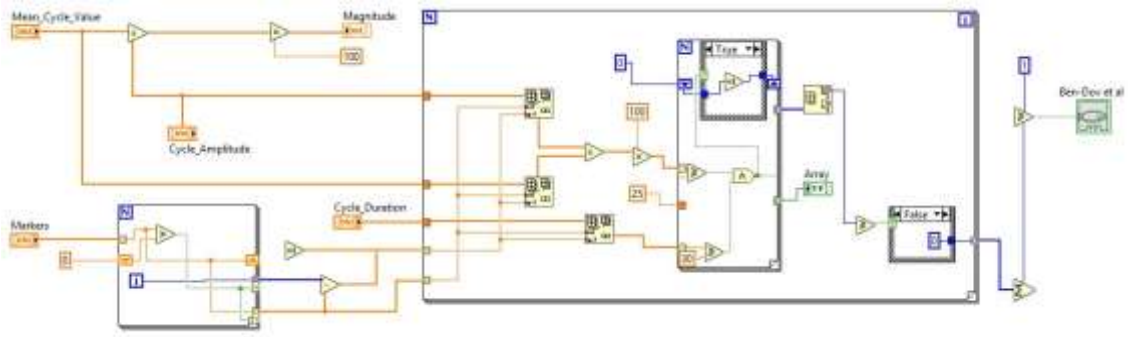


Fig. 3 Code sample used for Ben-Dov definition on the LabView

Reliability

One hundred and nine CPETs were excluded: one test did not include the VE response, 57 files did not correspond to HF patients, and 51 records did not analyze values at resting making the application of two definitions unfeasible. Therefore, 391 tests were analyzed in duplicate (inter-rater reliability) and 100 were randomized for new analysis (intra-rater reliability). Table 2 presents the inter and intra-rater reliability measures for each EOV definition.

Table 2. Reliability measure for the exercise oscillatory ventilation identification

Definition	Inter-rater (κ)	Intra-rater (κ)
Ben-Dov et al. [8]	0.92 ± 0.03	0.87 ± 0.07
Corrà et al. [11]	0.83 ± 0.04	0.89 ± 0.06
Kremser et al. [14]	0.85 ± 0.05	0.82 ± 0.09
Leite et al. [9]	0.86 ± 0.05	0.82 ± 0.12
Sun et al. [10]	0.97 ± 0.03	0.90 ± 0.10

Cohen's kappa coefficient (κ).

Software testing, user case, and graphical interface

Five EOV definitions [9-12, 14], two alternative approaches [15, 16], one smoothing technique [13], and some basic statistics were incorporated into this user-friendly interface which provides the visualization of four charts (resting, exercise, entire CPET response, and cycle's amplitude). The main functions are described in Table 3.

Table 3. Available features in the EASY-EOV tool

Function	Description
Controls	
Open file	Path indicating the file to be imported (txt file accepted).
Channel selection	Field to change the data input according to the original data source.
Channel descriptions	File heather. Available data for analysis and reference channels to use.
Export data	Button to copy/export data (basic stats, vVE, and cycle markers).
Clear data	Button to clear all insert data of the oscillatory cycles (nadir-peak-nadir).
Legends	Caption for the chart markings (main window and VE peak limit).
Chart	
Full data	Top left chart for visualization of all available data.
Exercise time	Main chart for the VE response visualization during exercise.
Resting data	Top chart for the VE response visualization at rest.
Standard unit	Button to fix the graph´s scale (80 $L.min^{-1}$ vs 600 sec).
Change the unit	Button to change the main chart unit ($L.min^{-1}$ or $mL.min^{-1}$).
Adjust rest data	Field to adjust the beginning and end of the resting period (top window).
Adjust exercise data	Field to adjust the beginning and end of exercise (main window).
VE peak limit	Chart displaying the amplitude boundaries used to identify EOV.
Smoothing	
MAF	Button to activate the MAF function.
MAF window	Field to select the MAF length (e.g., 7-cycles or other).
Results	
EOV definition	Displays the identification of EOV according to each definition.

CPET, cardiopulmonary exercise test. EOV, exercise oscillatory ventilation. MAF, moving average filter. VE, minute ventilation. vVE, minute ventilation variability. SD, standard deviation.

Briefly, the raw data must be imported (txt file tab-separated) and the input channels adjusted to select the VE and workload channels accordingly to txt file columns. Afterward, the user must select the MAF window size, and the CPET main data window (incremental exercise). Data processing methods were implemented to identify the EOV features. Figure 4 illustrates the software interface.

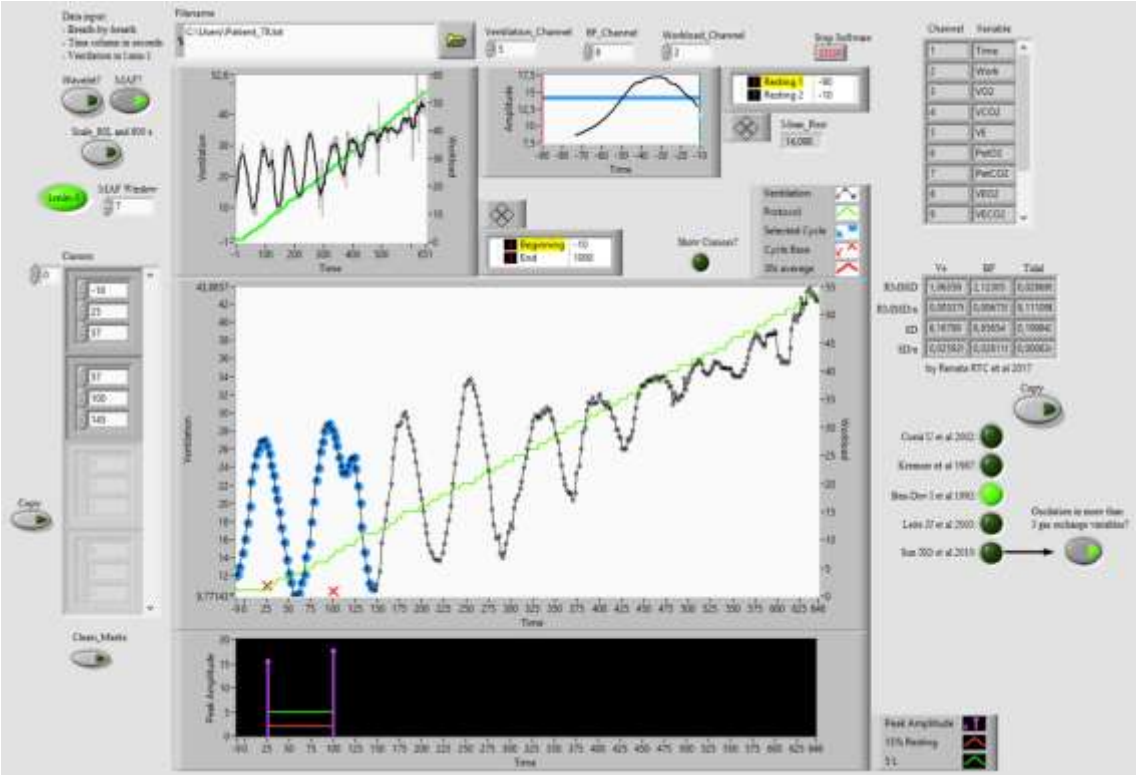


Fig. 4 EASY-EOV tool interface

Discussion

This is the first study that developed a freely available semi-automated tool to standardize the clinical diagnosis of EOV in HF. The EASY-EOV tool automatically calculates the h, λ, and ∆t, and our data indicate high inter-rater and intra-rater agreement for EOV diagnosis. This offers new resources and possibilities for professionals to use this prognostic marker in clinical practice.

To automate EOV analysis, Cornelis et al. [8] developed a graphical interface that can be incorporated exclusively on a gas analyzer from a research partner company. The premise was that only visual inspection could cause a strong diagnostic bias, so the authors observed that the wavelet transformation

smoothed the signal without any data loss, incorporating it into the interface with the four most usual EOV definitions [9-12]. They concluded that their approach could make the EOV diagnosis faster and more rater independent.

Although this resource appears to be robust, the authors [8] pointed out that it is still necessary to test the validity and reliability. In addition, Cornelis et al.'s approach was developed for a specific gas analyzer, which limits its use with data from other analyzers.

Brawner et al. [15] investigated the clinical reliability of the EOV diagnosis. The authors sent worksheets from 243 CPET data to six cardiologists to diagnose EOV according to three definitions [10, 14, 19]. They had to answer whether the tests were positive, negative, or inconclusive for EOV. Agreement between raters was low (κ <0.47). In contrast, Ingle et al. [20], applying the Corrà and Leite definitions in 240 CPETs of HF patients and found an intraclass correlation of 0.86 (0.82-0.89) and 0.78 (0.73-0.83), respectively. Studies evaluating the inter-rater reliability were not identified.

The lack of a gold standard definition to aid in the diagnosis of this phenomenon contributes to high intra- and inter-rater variability since each specialized center applies a protocol according to local expertise producing numerous conceptual variations [7]. Nevertheless, our study showed a high intra- and inter-rater reliability using a semi-automated system. The EASY-EOV tool also mitigates the methodological bias and standardizes assessment protocols. In addition, this tool allows analyzing the data of any test and analyzer, regardless of the automated system that was obtained. Our perspective is that it can be improved over the years and, through new guidelines and software improvements, contribute to the implementation of this important prognostic marker in clinical practice.

In the β version, we provide five classic definitions to identify the EOV cases [9-12, 14], two alternative techniques to quantify the fluctuations in the ventilatory pattern [15, 16], as well as other resources that allow to automatically calculate different parameters and to export the report to a database. Even so, the software has some limitations, such as the need for raters' training to identify the cycles, spreadsheets dependency to enter the correct data into the system, the CPET time conversion may be needed, and the LabVIEW® license is needed.

Conclusion

We describe the development of semi-automated software to standardize the clinical diagnosis of EOV, showing high inter-and intra-rater agreement. This user-friendly interface allows greater use of this prognostic marker in clinical practice, improving EOV detection and follow-up. As it is an open-source resource it is possible to incorporate new features into the tool, besides automating the entire process of detecting oscillatory cycles. These improvements can be developed by several users, benefiting all health professionals.

References

1. Agostoni P, Salvioni E (2019) Exertional periodic breathing in heart failure: mechanisms and clinical implications. Clin Chest Med 40(2):449-457.
2. Ribeiro GS, Deresz LF, Salvioni E, Hansen D, Agostoni P, Karsten M (2022) Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients. Int J Cardiol.
3. Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M (2022) Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis. Eur J Prev Cardiol 29(6):e233-e236.
4. Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D (2015) Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis. Int J Cardiol 182:476-486.
5. Guazzi M, Myers J, Peberdy M, Bensimhon D, Chase P, Arena R (2008) Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. Eur Heart J 29(22):2751-2759.
6. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga, et al (2007) Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. J Am Coll Cardiol 50(4):299-308.
7. Cornelis J, Beckers P, Vanroy C, Volckaerts T, Vrints C, Vissers D (2015) An overview of the applied definitions and diagnostic methods to assess

exercise oscillatory ventilation - a systematic review. Int J Cardiol 190:161-169.

8. Cornelis J, Denis T, Beckers P, Vrints C, Vissers D, Goossens M (2017) Development of a clinical applicable graphical user interface to automatically detect exercise oscillatory ventilation: The VOdEX-tool. Int J Cardiol 240:291-296.
9. Ben-Dov I, Sietsema K, Casaburi R, Wasserman K (1992) Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. Am Rev Resp Dis 145(4):776-781.
10. Leite J, Mansur A, Freitas H, Chizola P, Bocchi E, Terra-Filho, et al (2003) Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. J Am Coll Cardiol 41(12):2175-2181.
11. Sun X, Hansen J, Beshai J, Wasserman K (2010) Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol 55(17):1814-1823.
12. Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats A, et al (2002) Oscillatory ventilation during exercise in patients with chronic heart failure: Clinical correlates and prognostic implications. Chest 121(5):1572-1580.
13. Smith S (2003) Digital signal processing. A practical guide for engineers and scientists. Burlington, Newnes Elsevier.
14. Kremser C, O'Toole M, Leff A (1987) Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. Am J Cardiol 59(8):900-905.
15. Brawner C, Ehrman J, Myers J, Chase P, Vainshelboim B, Farha S, et al (2018) Exercise oscillatory ventilation: interreviewer agreement and a novel determination. Med Sci Sports Exerc 50(2):369-374.
16. Castro R, Lima S, Sales A, Nobrega A (2017) Minute-ventilation variability during cardiopulmonary exercise test is higher in sedentary men than in athletes. Arq Bras Cardiol 109(3):185-190.
17. Mokkink L, Prinsen C, Bouter L, Cecilia A, Bouter L, Vet H, Terwee C (2016) The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and how to select an outcome measurement instrument. Braz J Phys Ther 20:105-113.

18. McHugh M. Interrater reliability: the kappa statistic (2012) Biochem Med 22(3):276-282.
19. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, et al (2012) Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 126(18):2261-2274.
20. Ingle L, Isted A, Witte KK, Cleland J, Clark A (2009) Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 16(4):451-456.

4 ARTIGO 2

SENSITIVITY AND SPECIFICITY OF DIFFERENT EXERCISE OSCILLATORY VENTILATION DEFINITIONS TO PREDICT 2-YEAR MAJOR ADVERSE CARDIOVASCULAR OUTCOMES IN CHRONIC HEART FAILURE PATIENTS

Publicado no periódico *International Journal of Cardiology* (ANEXO A)

Percentil 83 (*Scopus*), Fator de Impacto 4,164

Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients

Gustavo dos Santos Ribeiro[1], Luís Fernando Deresz[2], Elisabetta Salvioni[3], Dominique Hansen[4], Piergiuseppe Agostoni[3,5], Marlus Karsten[1,6,7]

[1] Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil.
[2] Departamento de Educação Física, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, Brazil.
[3] Centro Cardiologico Monzino, IRCCS, Milan, Italy.
[4] Hasselt University (UHASSELT), Faculty of Rehabilitation Sciences, BIOMED/REVAL, Hasselt, Belgium / Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium.
[5] Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Milano, Italy.
[6] Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Florianópolis, Brazil.
[7] Programa de Pós-Graduação em Fisioterapia, UDESC, Florianópolis, Brazil.

Authorship statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Correspondence author

Marlus Karsten, Centro de Ciências da Saúde e do Esporte, Universidade do Estado de Santa Catarina (UDESC), Rua Pascoal Simone 358, CEP 88080-350, Florianópolis, SC, Brazil.
E-mail: marlus.karsten@udesc.br

Funding

This study was financed in part by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Keywords

Cardiology, Cardiovascular Diseases, Cardiopulmonary Exercise Test, Periodic Breathing, Prognosis.

Sample CRediT author statement

Gustavo Ribeiro: Conceptualization, Methodology, Formal analysis, Writing - Original draft preparation. **Luís Fernando Deresz**: Conceptualization, Methodology, Writing - Original draft preparation. **Elisabetta Salvioni**: Resources, Writing - Review & Editing. **Dominique Hansen**: Writing - Review & Editing, Supervision. **Piergiuseppe Agostoni**: Resources, Writing - Review & Editing, Supervision. **Marlus Karsten**: Conceptualization, Methodology, Writing - Review & Editing, Project administration.

Highlights

- Exercise oscillatory ventilation is a phenomenon associated with a worse prognosis.
- There is no consensus on the best EOV definition to be applied.
- EOV prevalence is higher when Ben-Dov or Corrà definitions are applied.
- BNP levels are associated with amplitude and cycle length.
- Corrà definition has the better capacity to predict 2-year mortality

Abstract

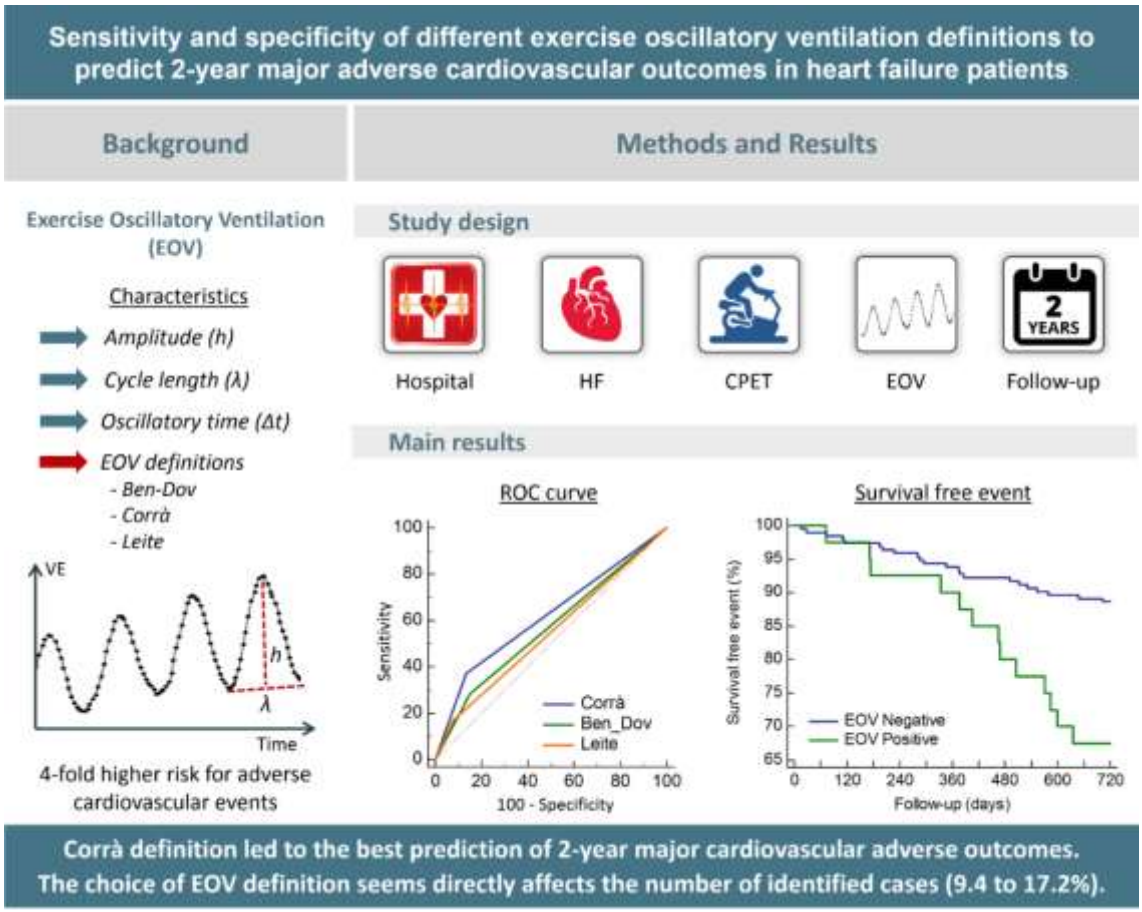
Background: Exercise oscillatory ventilation (EOV) shows a four-fold greater risk of adverse events. This study aims to analyze the sensibility and specificity of three EOV diagnostic definitions to predict adverse outcomes at a 2-year follow-up and to compare its EOV prevalence and relations with the patient's profile.

Methods: Cardiopulmonary exercise tests from 233 heart failure patients were analyzed. Two blinded reviewers used a semiautomated software to identify EOV cases pattern according to the definitions of Ben-Dov, Corrà, and Leite. Data were grouped in EOV-positive or EOV-negative according to each definition. Baseline characteristics, EOV prevalence, relative risk, sensitivity, and specificity to predict 2-years of major adverse cardiovascular outcomes were analyzed.

Results: The Corrà definition led to the best prediction of 2-year major cardiovascular adverse outcomes (HR 2.46 [1.16 to 5.25]; p = 0.019, AUC = 0.618; p = 0.007). EOV prevalence was 17.2%, 17.2%, and 9.4% applying Ben-Dov, Corrà, and Leite definition, respectively. The main clinical differences between EOV-positive and EOV-negative patients were: MECKI score and VE/VCO2 slope (all definitions), and BNP levels (Ben-Dov and Leite). BNP levels were correlated with amplitude (rho = 0.255; p = 0.033) and cycle length (rho = 0.388; p = 0.002).

Conclusion: Corrà definition was the only one that exhibited the capacity to predict major adverse cardiovascular outcomes at a 2-year follow-up. Regardless of its definition, EOV was more often prevalent in patients with a greater MECKI score and VE/VCO2 slope values.

Graphical abstract



1. Introduction

Exercise oscillatory ventilation (EOV) is an abnormal ventilatory pattern observed in chronic heart failure (HF) patients and associated with disease severity and worse prognosis [1-3]. Cornelis *et al*. [4] found a four-fold greater risk of adverse cardiovascular events in HF EOV-positive patients compared to their counterparts without EOV. Rovai *et al*. [5] highlighted in a large sample size population that EOV is associated with lower survival of HF patients with reduced or mid-range left ventricular ejection fraction in a 2-year follow-up regardless of age and gender.

Although current evidence reinforces its predictive value, the EOV prevalence is still controversial. Cornelis *et al*. [6] identified nine subgroups of EOV definitions based on EOV length and amplitude. It is not surprising that these differences reflect the wide range of EOV reported incidence, from 7 to 58% of HF patients [2, 6].

Even if the American Heart Association has indicated the Corrà definition to screening the EOV cases [2], there is no consensus on the best definition to be applied [4, 7]. Ingle *et al*. [8] were the first to evaluate the impact of different definitions on the prevalence and prognostic of EOV patients. A similar prevalence between Corrà and Leite definitions was observed (25 vs. 31%). However, EOV cases identified by Corrà definition exhibited a higher hazard ratio (HR 6.3 [1.6 to 25.2]) to all-cause death in 12-month than EOV cases identified by Leite definition (HR 4.9 [2.6 to 18.2]).

The use of different options to determine the EOV due to the lack of standardization compromises EOV clinical applicability. Albeit likely, it is unclear whether and to what extent the different definitions exhibit distinct sensitivities and specificities to detect EOV and predict adverse outcomes. Among all the definitions available, we chose to compare Ben-Dov, Corrà, and Leite because these definitions have different conceptual criteria in their development (e.g., high amplitude vs. longer duration) and have been frequently utilized in studies on EOV. These features may be linked to the HF aetiology (e.g., left or right HF) or clinical markers of hemodynamic impairment.

Therefore, this study aims to analyse the sensibility and specificity to predict major adverse cardiovascular outcomes in a 2-year follow-up in HF

patients, using three diagnostic definitions that apply distinct criteria to screen this phenomenon, and to compare the EOV prevalence and the clinical profile.

2. Methods

2.1 Study design

The present study is characterized as longitudinal research with analysis of retrospective anonymized single centre data. Data from 500 cardiopulmonary exercise tests (CPETs) performed between 2011 and 2014 were analyzed. This study was approved by the Research Ethics Committee from the main author (referee 3.516.801/2019) according to current ethical standards.

2.2 Data sampling

CPETs of HF patients aged 40 to 90 years old were included. Data from patients who performed a short CPET, < 6 minutes [9, 10], with a too-short registration (< 90 seconds) of the minute ventilation (VE) values at rest, or tests that do not would allow applying the EOV definitions (corrupted file) were excluded. Patients with a follow-up < 2 years were also excluded.

2.3 Exercise test protocol

CPETs followed the hospital routine [11]. Briefly, a personalized ramp protocol was performed on an electronically braked cycle ergometer (Erg 800S; Sensor Medics, Yorba Linda, CA) [5, 12]. All subjects were instructed to perform a maximal effort (exercise peak near to10 min). The tests were stopped when patients reported fatigue or in the presence of any cardiac abnormalities. The breath-by-breathy data were collected and analysed using the 20-s smoothing average (Vmax® 12-3A Series, CareFusion, Yorba Linda, CA).

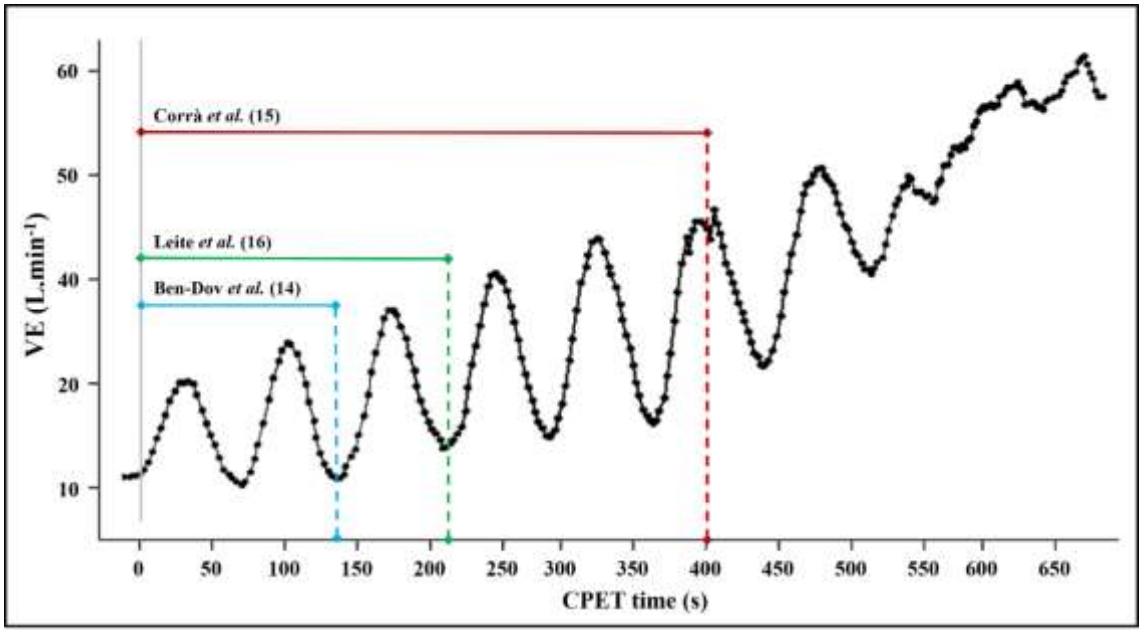
The highest 20-s averaged oxygen uptake (VO_2) value registered determined the VO_{2PEAK}. The VE/VCO_2 slope, a marker of ventilatory efficiency, was measured applying the V-slope method, which is defined by the linear relationship between VE and carbon dioxide production (VCO_2) excluding the first minute of exercise and the period above the respiratory compensation point [5]. All measures were done following the hospital's expertise.

2.4 Clinical profile and MECKI score

The clinical variables were obtained directly from the hospital's medical record. Data about body mass index, New York Heart Association (NYHA) functional classification, left ventricular eject fraction (LVEF), right ventricular systolic pressure (RVSP), hemoglobin, and B-type natriuretic peptide (BNP) levels were recorded. The MECKI score was used for calculating the risk of chronic systolic heart failure, estimated from six independent predictors (% of VO_{2PEAK} predict, VE/VCO_2 slope, hemoglobin, sodium, left ventricular ejection fraction, and modification of diet in renal disease [MDRD]) [13].

2.5 EOV definitions

The EOV was determined by the combined characteristics of the ventilatory pattern (amplitude, cycle length, and/or oscillatory time) according to the definitions of Ben-Dov [14], Corrà [15], and Leite [16]. Figure 1 shows the EOV-positive ventilatory pattern and the synthesis of the EOV definitions and illustrates the minimum of oscillatory cycles or duration recommended for each definition.



EOV definition	Oscillations during exercise	Amplitude of the oscillations	Cycle length of the oscillations
Ben-Dov *et al.*	≥ 2 consecutive cyclic fluctuations	≥ 25% of the average VE cycle	30 to 60s
Corrà *et al.*	> 60% of the total exercise time	> 15% of the average VE at rest	-
Leite *et al.*	≥ 3 consecutive cyclic fluctuations	≥ 5 $L.min^{-1}$	SD < 20% of the average

Fig. 1. EOV-positive ventilatory pattern. EOV, exercise oscillatory ventilation. VE, minute ventilation. CPET, cardiorespiratory exercise test. SD, standard deviation.

2.6 EOV identification

Two blinded reviewers used semiautomated tool to identify EOV cases in a standardized way. The software EASY-EOV tool 1.0 is an open-access application developed to allow the EOV analysis from CPET raw data of any system (LabVIEW, National Instruments, US). In their validation study, high intra-rater ($k \geq 0.82$) and inter-rater ($k \geq 0.83$) reliability was observed (unpublished data).

2.7 Follow-up data

Follow-up data were recorded by the hospital service from the CPET time until the registration of the death or cardiovascular event – limited to 2-years for all patients. Subjects who had too short (< 1 year) or no clinical follow-up after CPET were excluded. Cardiovascular death, an urgent heart transplant or left ventricular assist device (LVAD) were included as major adverse cardiovascular outcomes.

2.8 Statistical analysis

Data were grouped in EOV-positive or EOV-negative according to each definition. To measure normality, we used the Kolmogorov–Smirnov test. Baseline characteristics were compared by the Mann-Whitney test or Fisher's exact test (EOV-positive vs EOV-negative) and Kruskal-Wallis' test (EOV-positive between Ben-Dov, Corrà, and Leite). Cochran's Q test and the McNemar post hoc were applied to compare the prevalence among definitions. Furthermore, the interaction between EOV characteristics (amplitude, cycle length, and total oscillation time) and BNP levels was assessed by Spearman's correlation (*rho*).

All patients were followed for 2 years. The risk of major adverse cardiovascular outcomes was calculated for each definition. The sensitivity and specificity to predict major adverse cardiovascular outcomes were estimated by the Receiver-Operating Characteristic (ROC) curve. All baseline variables were inserted as possible predictors in the univariate model (removed variable if $p > 0.1$ or collinearity > 0.3) [8]. The multivariable Cox proportional-hazards regression was used with the backward method to identify de better predictive model (entered variable if $p < 0.05$).

3. Results

Among 500 patients who performed the CPET, 443 were HF patients. Of them, sixty-one records with data register at rest minor than 90 seconds and 149 patients with too short or no clinical follow-up after CPET were excluded leading to a study population of 233 cases. Table 1 shows the sample characteristics. EOV prevalence was 17.2% (Ben-Dov), 17.2% (Corrà), and 9.4% (Leite). Ben-Dov and Corrà definitions identified 40 EOV cases each. Both definitions exhibited higher prevalence than EOV cases identified by Leite ($p < 0.01$).

Table 1. Clinical characteristics stratified by EOV definition

Variable/Definition	Ben-Dov (14)		Corrà (15)		Leite (16)	
	EOV-positive	EOV-negative	EOV-positive	EOV-negative	EOV-positive	EOV-negative
Sample, n (%)	40 (17.2)	193 (82.9)	40 (17.2)	193 (82.9)	22 (9.4)	211 (90.6)
Male gender, n (%)	35 (87.5)	156 (80.8)	31 (77.5)	160 (82.9)	21 (95.5)	170 (80.6)
Age, years	69 [66 – 72]	68 [67 – 70]	74 [69 – 76]*	68 [66 – 69]	69 [63 – 75]	68 [67 – 70]
Body mass index, kg/m²	24.8 [23.8 – 27.4]	26.6 [25.4 – 27.2]	24.8 [24.2 – 27.0]	26.6 [25.4 – 27.3]	24.2 [22.3 – 27.0]*	26.6 [25.4 – 27.3]
NYHA class III-IV, n (%)	22 (55.0)*	67 (34.7)	22 (55.0)*	67 (34.7)	13 (59.1)*	76 (36.0)
LVEF, %	32.9 [30.2 – 36.4]	32.7 [32.0 – 35.2]	32.8 [29.2 – 37.3]	32.9 [32.0 – 35.0]	31.9 [24.7 – 36.4]	33.0 [32.1 – 35.2]
RVSP, mmHg	36.0 [33.0 – 46.0]	35.0 [32.0 – 37.0]	39.0 [31.0 – 46.0]	35.0 [33.0 – 37.0]	42.0 [31.0 – 49.0]	35.0 [33.0 – 37.0]
MECKI score, %	8.1 [6.0 – 11.5]*	3.7 [2.9 – 4.8]	7.4 [4.8 – 12.6]*	3.8 [3.1 – 4.9]	11.1 [3.1 – 16.1]*	4.0 [3.3 – 5.2]
Hemoglobin, mg/dL	13.9 [12.7 – 14.7]	13.9 [13.7 – 14.3]	13.6 [12.8 – 14.2]	14.0 [13.7 – 14.3]	13.9 [12.6 – 14.8]	13.6 [13.7 – 14.2]
BNP, pg/mL	550 [372 – 737]*	263 [200 – 322]	330 [272 – 549]	272 [221 – 398]	514 [282 – 987]*	275 [224 – 379]
CPET time, s	533 [486 – 572]	532 [517 – 562]	492 [477 – 572]	539 [521 – 563]	538 [470 – 652]	530 [515 – 556]
VO_{2PEAK}, ml.kg.min^{-1}	12.7 [11.0 – 14.7]*	14.0 [13.4 – 14.8]	12.2 [11.1 – 13.5]*	14.3 [13.5 – 15.0]	12.6 [9.8 – 14.9]	14.0 [13.2 – 14.8]
VE/VCO_2 slope	36.3 [32.9 – 40.3]*	29.6 [28.8 – 30.6]	36.0 [32.0 – 40.0]*	30.0 [28.8 – 31.0]	37.6 [32.0 – 42.7]*	30.0 [29.0 – 31.0]
Maximal workload, w	61 [46 – 80]*	69 [64 – 75]	48 [37 – 64]*	71 [68 – 79]	56 [33 – 80]*	70 [64 – 74]
Major adverse outcome, n (%)	10 (25.0)	25 (13.0)	13 (32.5)**	22 (11.4)	6 (27.3)	29 (13.7)

Continuous data are expressed as median [95% confidence interval (CI)] and categorical data as absolute (n) and relative (%) frequencies. EOV, exercise oscillatory ventilation. EOV-positive, patients with a confirmed diagnosis. EOV-negative, patients with a negative diagnosis. NYHA, New York Heart Association. LVEF, left ventricular eject fraction. RVSP, right ventricular systolic pressure. BNP, B-type natriuretic peptide. CPET, cardiopulmonary exercise test. VO_{2PEAK}, peak oxygen uptake. VE/VCO_2, minute ventilation-carbon dioxide production. *$p < 0.05$ Mann-Whitney Test (EOV-positive vs EOV-negative). **$p < 0.01$ Fisher's exact test (EOV-positive vs EOV-negative).

EOV patients had a worse functional class, MECKI score, ventilatory efficiency (VE/VCO_2 slope), and lower maximal workload regardless of definition. There was no difference in clinical characteristics among EOV-positive groups from Ben-Dov, Corrà and Leite ($p > 0.05$). EOV cases identified by Ben-Dov and Leite presented higher levels of BNP than HF patients without EOV screened by the same definition. Spearman's analysis indicated a low to moderate correlation between BNP levels, amplitude (*rho* = 0.255; $p = 0.033$), and cycle length (*rho* = 0.388; $p = 0.002$). No association with total oscillation time was observed (*rho* = -0.104; $p = 0.229$).

Among all EOV cases, 16 patients were exclusively identified by Corrà and 12 by Ben-Dov definition. Both shared 22 EOV cases. Leite's definition shared 15 positive cases with Corrà and 19 with Ben-Dov. Only one EOV patient was identified just by Leite. The overlap of EOV cases is presented in the Figure 1S. Regarding isolated diagnosis, BNP levels were higher when EOV was identified by Ben-Dov than by Corrà (720 [411 to 1,067] vs. 260 [80 to 677] pg/mL; $p = 0.019$).

The relative risk for 2-year major adverse cardiovascular outcomes was significant applying Corrà (2.9 [1.6, 5.2]; $p < 0.001$), and Ben-Dov definitions (1.9 [1.0, 3.7]; $p = 0.047$). However, Corrà definition was the only one that showed a significant capacity to predict 2-year major adverse cardiovascular outcomes (Table 2).

Table 2. Sensitivity and specificity to predict 2-year major cardiovascular adverse outcomes.

Definition	AUC	95% CI	p-value	Sensitivity	Specificity
Ben-Dov	0.567	0.487 to 0.647	0.100	28.57	84.85
Corrà	0.618	0.533 to 0.702	0.007	37.14	86.36
Leite	0.545	0.479 to 0.611	0.179	17.14	91.92

EOV, exercise oscillatory ventilation. AUC, area under the ROC curve. CI, confidence interval.

Supplemental Table 1S shown the potential predictors for major adverse cardiovascular outcomes (univariate analysis). Four variables were entered in the predictive model after multivariate Cox analysis (R^2-adjusted = 0.184; $p < 0.001$). Only two had significant predictive values: Corrà (HR 2.46 [1.16 to 5.25]; $p = 0.019$) age (HR 1.07 [10.3 to 1.12]; $p = 0.002$).

4. Discussion

The number of HF patients identified as EOV-positive ranged from 9.4 to 17.2% according to the applied definition. There was no difference between Ben-Dov and Corrà prevalence, 40 cases each. Of these 40 cases identified by Ben-Dov and Corrà criteria, only 22 cases were identified by both criteria, while the other 18 cases were identified exclusively by Ben-Dov or by Corrà criteria. Moreover, the Corrà definition allowed us to identify EOV cases with the highest 2-years major adverse cardiovascular outcomes. In contrast, the BNP levels were higher in cases identified exclusively by Ben-Dov. Furthermore, a low-moderate correlation between BNP levels, amplitude, and cycle length was observed.

To our knowledge, Ingle *et al*. [8] were the only ones that investigate the impact of different EOV diagnostic definitions on prognostic power. They evaluated 240 HF patients applying Corrà and Leite definitions. There was no difference in EOV prevalence in both definitions (Corrà 25% and Leite 31%). However, Ingle *et al*. [8] observed that EOV cases identified by Corrà were associated with a higher hazard rate to all-cause mortality at 1-year (HR 5.2 [2.8 to 9.9]; $p < 0.001$) in comparison to the cases identified by the Leite definition (HR 4.8 [2.8 to 8.8]; $p < 0.001$).

In the present study population, we found a lower EOV prevalence in all definitions (mostly using Leite), as well as lower sensitivity to predict adverse outcomes applying Corrà criteria, in comparison with other studies [8, 16]. Furthermore, Ben-Dov and Leite's definitions did not show sensitivity to predict major adverse cardiovascular outcomes in 2-year. We highlight some points that can justify this difference: baseline characteristics (our sample was older and with lower VO_{2PEAK}), the difference in follow-up time (24 vs 12 months), and the use of a semiautomated tool to identify EOV cases rather than manual scoring and/or visual interpretation (less subjectivity).

Our findings differ from other studies that used Leite's definition to identify EOV cases. In the original study, Leite *et al*. [16] observed a 30% EOV prevalence and 3-times greater risk to death at 2-year in patients with heart transplantation indications (RR 2.97 [1.34 to 6.54]; $p < 0.01$). Similarly, Vainshelboim *et al*. [17] found a higher prevalence rate (54%) and hazard ratio for major cardiac-related events at 5-year (HR 2.2 [1.2 to 4.1]; $p = 0.011$) applying Leite-modified criteria.

Regarding Corrà, the results are contradictory. The original study reported a prevalence slightly lower than our – 12% [15]. Nevertheless, Guazzi *et al*. [18] found a higher EOV prevalence in reduced (35%) and preserved ejection fraction HF patients (32%), beyond the greater hazard rate to overall mortality at 4-years (HR 2.0 [1.3 to 3.1]; $p < 0.001$ and 5.9 [2.1 to 16.9], $p < 0.001$). It should be noted that the exercise tests were performed both on a treadmill and cycle ergometer, making further inferences unfeasible since the specificity can produce different physiological responses. In this sense, Guazzi *et al*. [18] observed 25% EOV cases among tests performed on a cycle ergometer and 41% among tests done on a treadmill.

Another point to be considered is the use of dichotomous outcomes: EOV-positive or EOV-negative. As the EOV pathophysiology remains unknown [1, 3, 17], it is plausible to consider that the amplitude and/or length of each cycle differs from one patient to another, even with a confirmed EOV diagnosis for two or three definitions (by Corrà and Ben-Dov, for example). The clinical impact of this variation yet is unknown. It seems that the cycle amplitude would be related to hemodynamic impairments such as circulatory delay [19], lower ventilatory efficiency [20], and higher plasma BNP levels [20]. Thus, higher amplitudes would be related to worse outcomes in EOV patients. Nonetheless, this hypothesis yet needs to be investigated.

Our data show the EOV patients diagnosed by Ben-Dov and Leite definitions have higher BNP levels than those identified by Corrà, albeit lower mortality. Yamauchi *et al*. [20] also found a positive correlation between cycle amplitude and BNP levels when applying Leite definition ($r = 0.615$; $p = 0.007$). However, they did not report any hypothesis able to explain this finding. An essential factor that may have influenced BNP levels is the right ventricular impairment, commonly seen in HF plus pulmonary hypertension. Leuchte *et al*.

[21] found that high BNP levels were directly related to pulmonary capillary wedge pressure, pulmonary vascular resistance, and right atrial pressure, beyond inversely correlated with cardiac index and VO_{2PEAK}. Indeed, Murphy *et al*. [19] had already observed association between right ventricular eject fraction and both amplitude (r = -0.68; p < 0.001) and cycle length (r = -0.48; p = 0.02), suggesting that these parameters would be related to worse hemodynamic function in EOV patients.

This is the first study that investigated the predictive capacity of three definitions with totally different conceptual characteristics: Ben-Dov, Corrà, and Leite. Indeed, Ben-Dov proposed as criteria to EOV diagnosis the presence of two consecutive cycles with 30-60s of length and cycle magnitude of near to 25% of the average VE [14]. Corrà indicated that the oscillation would need to be present at least 60% of total exercise time with amplitude above 15% of the VE at rest [15], a longer exercise time albeit less pronounced amplitude. Finally, Leite proposed that EOV would be characterized by at least three regular oscillations with minimal amplitude above 5 L/min [16].

In brief, Ben-Dov and Leite's definitions imply a shorter oscillation time, but a larger amplitude compared to the Corrà definition. It is unknown how these definitions are related to the patient hemodynamic impairment, albeit it is possible to speculate that a higher ventilation amplitude suggests a greater hemodynamic impairment [19, 20]. Nevertheless, the oscillation time seems to have a greater influence to predict adverse outcomes, which possibly would justify the better sensitivity shown by the Corrà definition. Accordingly, the reasons behind the cessation of EOV during exercise, albeit at present unknown, are of major importance. The idea that EOV ceased during exercise due to the capability to improve cardiac output or to divert more blood to the exercising muscles both leading to an improved peripheral oxygen delivery which in its turn allows reducing the metabo and chemoreflex sites of activation are attractive and maybe the link between the observed difference in EOV prognosis and definition.

4.1 Limitations

The present study has a few limitations which need to be acknowledged. Firstly, our sample size was small as limited in the number of major adverse cardiovascular outcomes, which may be related to the optimal treatment offered

in a high-level cardiology centre. In this regard, bigger studies with a larger HF population that includes different phenotypes are definitively essential. Secondly, we reanalyzed CPET previously done in a single centre with mainly a low-ejection fraction HF phenotype. Therefore, our data should not be applied to different HF populations as in mid-range or preserved ejection fraction patients [5].

5. Conclusion

The Corrà definition was the only one that exhibited the capacity to predict major adverse cardiovascular outcomes at a 2-year follow-up. The choice of EOV definition seems to affect the number of identified cases (ranging from 9.4 to 17.2%). Regardless of the definition, EOV was more often prevalent in patients with a greater MECKI score and VE/VCO_2 slope values. There were no differences in the clinical characteristics among EOV-positive groups. The positive correlation of BNP levels with amplitude and cycle length, the main features of the Ben-Dov and Leite definitions, suggests a link between these features with a clinical impairment marker.

References

[1] Agostoni P, Salvioni E. Exertional periodic breathing in heart failure: Mechanisms and clinical implications. Clin Chest Med. 2019;40:449-57.

[2] Agostoni P, Corra U, Emdin M. Periodic Breathing during Incremental Exercise. Ann Am Thorac Soc. 2017;14:S116-s22.

[3] Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M. Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis. Eur J Prev Cardiol. 2021.

[4] Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis. Int J Cardiol. 2015;182:476-86.

[5] Rovai S, Corra U, Piepoli M, Vignati C, Salvioni E, Bonomi A, et al. Exercise oscillatory ventilation and prognosis in heart failure patients with reduced and mid-range ejection fraction. Eur J Heart Fail. 2019;21:1586-95.

[6] Cornelis J, Beckers P, Vanroy C, Volckaerts T, Vrints C, Vissers D. An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation--a systematic review. Int J Cardiol. 2015;190:161-9.

[7] Panagopoulou N, Karatzanos E, Dimopoulos S, Tasoulis A, Tachliabouris I, Vakrou S, et al. Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure. Eur J Prev Cardiol. 2017;24:825-32.

[8] Ingle L, Isted A, Witte K, Cleland JG, Clark A. Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2009;16:451-6.

[9] Hansen D, Bonné K, Alders T, Hermans A, Copermans K, Swinnen H, et al. Exercise training intensity determination in cardiovascular rehabilitation: Should the guidelines be reconsidered? Eur J Prev Cardiol. 2019;26:1921-8.

[10] Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R, et al. Work-rate affects cardiopulmonary exercise test results in heart failure. Eur J Heart Fail. 2005;7:498-504.

[11] Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. Int J Cardiol. 2019;288:107-13.

[12] Campodonico J, Mapelli M, Spadafora E, Ghilardi S, Agostoni P, Banfi C, et al. Surfactant proteins changes after acute hemodynamic improvement in patients with advanced chronic heart failure treated with Levosimendan. Respir Physiol Neurobiol. 2018;252-253:47-51.

[13] Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, et al. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. Int J Cardiol. 2013;167:2710-8.

[14] Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. Am Rev Respir Dis. 1992;145:776-81.

[15] Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJS, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: Clinical correlates and prognostic implications. Chest. 2002;121:1572-80.

[16] Leite J, Mansur A, De Freitas H, Chizola P, Bocchi E, Terra-Filho M, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. J Am Coll Cardiol. 2003;41:2175-81.

[17] Vainshelboim B, Amin A, Christle JW, Hebbal S, Ashley EA, Myers J. A method for determining exercise oscillatory ventilation in heart failure: Prognostic value and practical implications. Int J Cardiol. 2017;249:287-91.

[18] Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. Eur Heart J. 2008;29:2751-9.

[19] Murphy R, Shah R, Malhotra R, Pappagianopoulos P, Hough S, Systrom D, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. Circulation. 2011;124:1442-51.

[20] Yamauchi F, Adachi H, Tomono J, Toyoda S, Iwamatsu K, Sakuma M, et al. Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure. Heart Vessels. 2016;31:1659-68.

[21] Leuchte HH, Holzapfel M, Baumgartner RA, Ding I, Neurohr C, Vogeser M, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. J Am Coll Cardiol. 2004;43:764-70.

Supplemental materials

2. Methods

All analyses were performed in RStudio version 1.4.1106 (RStudio Inc., Boston, US). We summarize below all package's requirements and the command line used for each analysis.

2.1 Packages required

```
library("car")
library("DescTools")
library("dplyr")
library("ggplot2")
library("gmodels")
library("psych")
library("qqplotr")
library("rcompanion")
library("rstatix")
library(“devtools”)
library(“ggpubr”)
library(“tidyverse”)
library(“gtsummary”)
library(“ModelGood”)
library(“readxl”)
library(“RVAideMemoire”)
library(“survival”)
library(“survminer”)
```

2.2 Prevalence and Cochran's Q test

```
Step 1  Data$Definition = factor (Data$Definition, levels = c("Corrà", "Ben_Dov", "Leite"))
Step 2  cochran.qtest (EOV ~ Definition | Patient, data = Data)
Step 3  PTpairwiseMcnemar(EOV~Definition|Patient,data=Data, test="mcnemar", method="fdr",digits=3)
Step 4  cldList (p.adjust ~ Comparison, data = PT, threshold  = 0.05)
```

2.3 Relative risk

```
Step 1  Table = xtabs (~ Exitus + Definition, data = Data)
Step 2  RR <- (Table [2,2]/(Table [2,2]+Table [1,2]))/(Table [2,1]/(Table [2,1]+Table [1,1]))
Step 3  R <- sqrt(1/Table [2,2]+1/Table [2,1]-1/(Table [2,2]+Table [1,2])-1/(Table [2,1]+Table [1,1]))
Step 4  RR
Step 5   exp(log(RR)-1.96*R)
Step 6   exp(log(RR)+1.96*R)
Step 7  2*pnorm (q = (log(RR)/R), lower.tail=FALSE)
```

2.4 Sensitivity and specificity

Step 1 with(Data, Sensitivity (Definition, Exitus))

Step 2 with(Data, Specificity (Definition, Exitus))

2.5 ROC Curve

Step 1 pROC::roc (Exitus ~ Definition, data=Data, ci=TRUE)

Step 2 roc <- Roc (Exitus ~ Definition, data=Data)

Step 3 plot(roc, auc=TRUE)

Step 4 roc <- Roc(list(Corrà=Exitus ~ Corrà, Ben_Dov=Exitus ~Ben_Dov, Leite=Exitus ~ Leite), data=Data)

Step 5 plot(roc,auc=TRUE)

2.6 Univariate COX Regression

Step 1 CR.cox <- coxph (Surv (Follow, Exitus) ~ Variable, data = Data)

Step 2 summary (CR.cox)

2.7 Multivariate COX Regression

Step 1 mod.a <- step (lm (Exitus ~ Variable 1 + Variable 2 + … , data = Data), direction = "backward")

Step 2 summary (mod.a)

Step 3 res.cox <- coxph (Surv (Follow, Exitus) ~ Corrà + Age + BNP + MECKI, data = Data)

Step 4 summary(res.cox)

2.8 Normality test

Step 1 dat %>%
group_by(Definition) %>%
summarise(`W Stat` = shapiro.test(variable)$statistic, p.value = shapiro.test(variable)
$p.value)

2.9 Fisher's test

Step 1 table = xtabs (~ Definition + variable, data = Data)

Step 2 fisher.test (table, alternative = "two.sided")

2.10 Mann-Whitney U test

Step 1
```
dat %>% select(variable) %>% group_by(dat$Definition) %>%
summarise(n = n(),
mean = mean(variable, na.rm = TRUE),
sd = sd(variable, na.rm = TRUE),
LCL = mean - qt(1 - (0.05 / 2), n - 1) * stderr,
UCL = mean + qt(1 - (0.05 / 2), n - 1) * stderr,
median = median(variable, na.rm = TRUE),
LCLmed = MedianCI(variable, na.rm=TRUE)[2],
UCLmed = MedianCI(variable, na.rm=TRUE)[3])
```

2.11 Spearman's correlation test

Step 1
```
AMP <- cor.test (dat$BNP, dat$Amplitude, method = "spearman",
alternative = "greater")
```
Step 2 AMP

Step 3
```
LEN <- cor.test (dat$BNP, dat$Lenght, method = "spearman",
alternative = "greater")
```
Step 4 LEN

Step 5
```
TIME <- cor.test (dat$BNP, dat$P_CPX, method = "spearman",
alternative = "greater")
```
Step 6 TIME

3. Results

Supplemental Table 1S shows univariate analysis of potential predictors for major adverse cardiovascular outcomes. Among all the variables, Corrà definition showed the best hazard ratio for cardiovascular adverse outcomes in 2 years followed by haemoglobin and VO2PEAK. Ben-Dov and Leite did not show positive results.

Table 1S. Univariate analysis for 2-year adverse outcome

Variable	HR	95%CI	p-value
Corrà	3.11	1.57 – 6.18	0.001
Ben-Dov	2.04	0.98 – 4.24	0.058
Leite	2.15	0.89 – 5.18	0.088
VE/VCO_2 slope	1.08	1.04 – 1.13	< 0.001
Age	1.08	1.04 – 1.13	< 0.001
MECKI score	1.03	1.01 – 1.04	< 0.001
PAPS	1.03	1.00 – 1.05	< 0.001
BNP levels	1.00	1.00 – 1.00	< 0.001
Maximal workload	0.96	0.95 – 0.98	< 0.001
BMI	0.92	0.84 – 1.00	0.054
VO_{2PEAK}	0.81	0.73 – 0.90	< 0.001
Hb	0.79	0.65 – 0.96	0.021

HR, hazard ratio. CI, confidence interval.

Figure 1S shows the overlap of EOV cases. Overall, 59 EOV cases were identified. Only 13 cases filled the criteria of all definitions. Corrà was the definition with the highest number of isolated cases (n = 16), followed by Ben-Dov (n = 12) and Leite (n = 1).

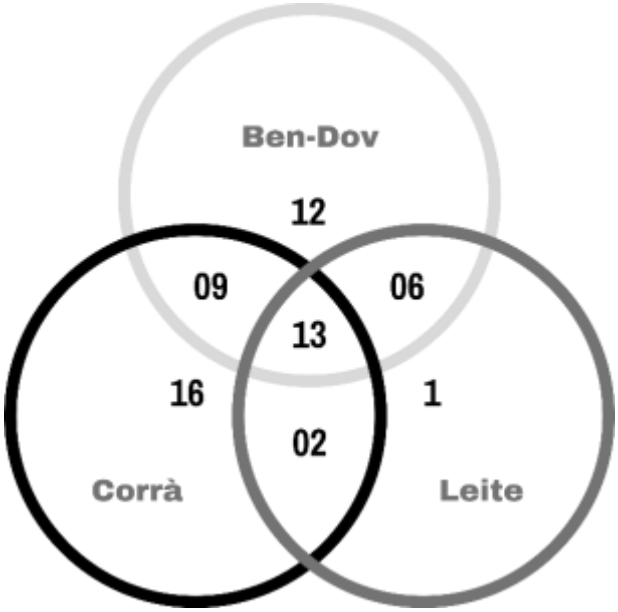


Figure 1S. Venn diagram of the overlap of EOV cases.

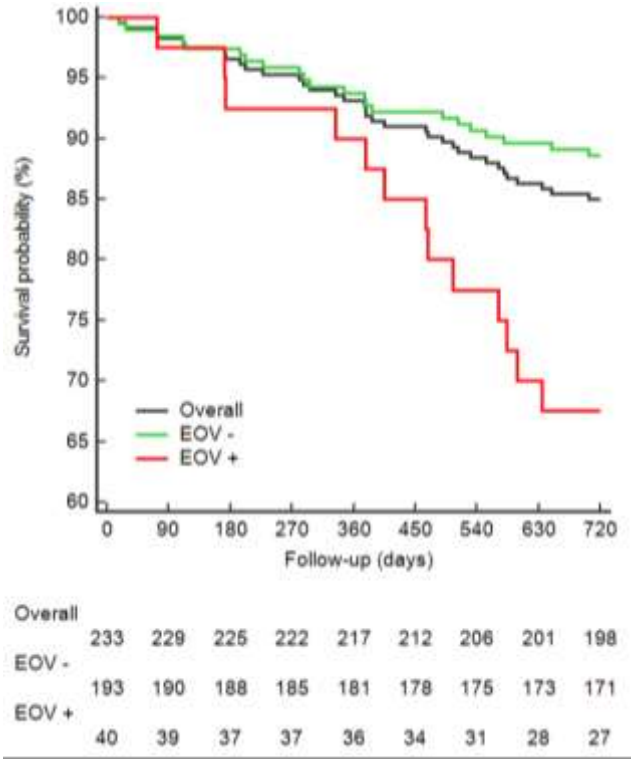


Figure 2S. Kaplan-Meier survival analysis. EOV, exercise oscillatory ventilation. EOV -, negative diagnosis by Corrà definition. EOV +, positive diagnosis by Corrà definition.

5 ARTIGO 3

VENTILATORY VARIABILITY ALONE OR IN ASSOCIATION WITH A DICHOTOMOUS DIAGNOSTIC DEFINITION OF EXERCISE OSCILLATORY VENTILATION IN PREDICTING HEART FAILURE ADVERSE OUTCOMES: AN EXPLORATORY STUDY

Formatado conforme normas do periódico *Heart Failure Reviews* – Percentil 84 (*Scopus*), Fator de Impacto 4,654

Ventilatory variability alone or in association with a dichotomous diagnostic definition of exercise oscillatory ventilation in predicting heart failure adverse outcomes: An exploratory study

Gustavo dos Santos Ribeiro[1], Luís Fernando Deresz[2], Elisabetta Salvioni[3], Dominique Hansen[4], Piergiuseppe Agostoni[3,5], Marlus Karsten[1,6,7]

[1] Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil.
[2] Departamento de Educação Física, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, Brazil.
[3] Centro Cardiologico Monzino, IRCCS, Milan, Italy.
[4] Hasselt University (UHASSELT), Faculty of Rehabilitation Sciences, BIOMED/REVAL, Hasselt, Belgium / Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium.
[5] Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Milano, Italy.
[6] Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Florianópolis, Brazil.
[7] Programa de Pós-Graduação em Fisioterapia, UDESC, Florianópolis, Brazil.

Correspondence author
Marlus Karsten, Centro de Ciências da Saúde e do Esporte, Universidade do Estado de Santa Catarina (UDESC), Rua Pascoal Simone 358, CEP 88080-350, Florianópolis, SC, Brazil.
E-mail: marlus.karsten@udesc.br

Funding
This study was financed in part by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Conflict of Interest Statement
The authors declare that there is no conflict of interest.

Abstract

Purpose: to analyze the accuracy of the minute-ventilation variability (vVE) alone or in association with a dichotomous definition of exercise oscillatory ventilation to predict adverse outcomes at 2-year in chronic heart failure (CHF) patients.

Methods: 500 cardiopulmonary exercise tests were analyzed. Breath-by-breath data were used to calculate time-domain vVE. EOV was identified according to Corrà's definition. Cardiovascular death, urgent heart transplant, and left ventricular assist device implantation were the adverse endpoints monitored until 2-years after cardiopulmonary assessment. All analyses were done in MedCalc Software with appropriate tests to the data nature ($p<0.05$)

Results: Thirty-five deaths were registered, and 40 EOV cases were identified. ROC curve indicated a vVE < 54.9 L.breath-1.min-1 as the better cut-off to predict adverse outcomes. The vVE alone had greater sensitivity to predict 2-year adverse events than the dichotomic definition (94.3 vs 37.1). Relative risk and hazard ratios were 4.0 (1.3 to 12.5) and 2.7 (1.3 to 5.6) for the low vVE, and 2.9 (1.6 to 5.2) and 4.8 (1.9 to 11.9) for the EOV-positive, respectively. Patients with low vVE and EOV presented about 3- and 7-times more risk of adverse outcomes than patients without EOV with low [2.6 (1.4 to 4.6); p=0.002] or high vVE (7.1 [2.2 to 23.2]; p=0.001), respectively.

Conclusion: CHF patients with low vVE or EOV-positive presented similar risk of 2-year adverse events. However, the vVE showed greater sensitivity in predicting adverse events. CHF patients with low vVE and EOV-positive had worse prognostic than those with EOV-negative and low or high vVE.

Introduction

The cardiopulmonary exercise test (CPET) is the reference procedure to assess cardiovascular, metabolic, and respiratory responses during exercise (1). Chronic heart failure (CHF) patients may exhibit an atypical oscillatory pattern in the minute-ventilation (VE) response during the entire exercise or limited to the first part of it. This phenomenon known as exercise oscillatory ventilation (EOV) is a strong predictor of adverse outcomes in CHF (2) exhibiting a four-fold greater risk of adverse events (1).

Despite its prognostic value, there are still disagreements about which criteria should be used to detect it. The main definitions require the visual interpretation of the ventilatory curve and mathematical calculations of each oscillatory cycle to determine the presence of the phenomenon in a dichotomized way (3). This approach may neglect the intermediate stages of the disease if we consider that the EOV is the advanced stage of the disease. Furthermore, the absence of a gold standard definition makes the use of this marker in clinical practice unfeasible.

Minute ventilation variability (vVE) data could add relevant information to evaluate and treat CHF patients, identifying changes in the ventilatory pattern before the phenomenon became more severe. Castro et al. (3, 4) claim that some patients may present VE oscillations without reaching the recommended criteria for the EOV diagnosis. In this sense, the continuous approach could assist in risk stratification and disease evolution follow-up. Time-domain indexes are the most basic measurements for biological signals analysis (5).

However, we did not find studies that evaluated the prognostic value of this marker in clinical practice. The only information available about the CHF patients showed an inverse correlation between left ventricular ejection fraction (LVEF) and vVE (6), indicating a new path to be explored. Thus, this study aims to analyze the accuracy of the vVE to predict 2-year adverse outcomes in CHF patients.

Methods

Study design

A retrospective data from 500 patients admitted to a single center between 2011 and 2014 were analyzed. Only CHF patients' data were included in the final sample. This study was part of the research "*Exercise oscillatory ventilation in patients with heart failure: analysis of different diagnostic criteria and their implications on morbimortality*". This project was approved by the Research Ethics Committee according to current ethical standards and Helsinki Declaration (referee 3.516.801/2019).

Data sampling

All procedures were done as previously described (7). Briefly, CPET files with a time lower than six min (8, 9), without recording the VE at rest, or without follow-up data were excluded.

Cardiopulmonary exercise test

A personalized ramp protocol on an electronically braked cycle ergometer (Erg 800S; Sensor Medics, Yorba Linda, CA) with gas exchange analysis (Vmax® 12-3A Series, CareFusion, Yorba Linda, CA) was performed according to hospital routine (10, 11). The VO_{2PEAK} and VE/VCO_2 slope were determined using the highest 20-s average from oxygen uptake and the linear relationship between VE and carbon dioxide production according to the hospital's expertise, respectively (10, 11).

VE variability

Breath-by-breath data from beginning to peak exercise were used to automatically calculate time-domain ventilatory variability in the software EASY-EOV tool (LabVIEW, National Instruments, US). To minimize the influence of exhaustion and exercise time on this parameter, the vVE was defined by the standard deviation (SD) of VE normalized by the number of respiratory cycles (SD/n) – multiplied by 10^3 (3).

EOV diagnosis

The classic EOV diagnosis was determined by the combined characteristics of the ventilatory pattern according to the Corrà definition (12).

Two blinded reviewers used the software EASY-EOV tool (LabVIEW, National Instruments, US) to identify positive cases, as previously detailed (7).

Clinical profile and follow-up data

Clinical variables were measured according to the hospital routine and obtained directly from the electronic medical record. The MECKI score was estimated from six predictors available in the database (13). Follow-up data were monitored until 2-years after cardiopulmonary assessment. Cardiovascular death, urgent heart transplant, and left ventricular assist device (LVAD) were the adverse endpoints.

Statistical analysis

All analyses were done in MedCalc Statistical Software version 19 (MedCalc Software bvba, Ostend, BE). Firstly, the vVE cut-off to predict 2-year adverse endpoints, as well as its sensitivity and specificity, was estimated by the Receiver-Operating Characteristic (ROC) curve. Then, data were grouped in low or high vVE to calculate the relative risk (RR) and the Kaplan-Meier survival analysis at 2 years. Afterwards, baseline characteristics were explored by the Kolmogorov–Smirnov (normality), Mann-Whitney (continuous variables), and Fisher's exact tests (dichotomous data), besides Spearman's correlation when appropriated.

Finally, we performed a cross-analysis combining the EOV diagnosis (EOV-positive) with vVE (high and low) to better know and stratify the risk of these patients. The patients were categorized into four groups: low vVE + EOV-positive (LV-EOV); low vVE + EOV-negative (LV-CHF); high vVE + EOV-positive (HV-EOV); and high vVE + EOV-negative (HV-CHF). All analyses adopted a 5% of significance ($p < 0.05$).

Results

Figure 1S illustrates the flowchart of data selection. The CPET of two hundred thirty-three CHF patients were analyzed. Thirty-five death was registered in follow-up. Furthermore, 40 EOV cases were screened by Corrà definition (dichotomic approach). A vVE less than 54.9 $L.breath^{-1}.min^{-1}$ was indicated as the better cutoff to predict adverse outcomes at 2 years (quantitative

approach). All values and coordinates, including the ROC curve's chart (Figure 2S), are available in the supplementary material. Table 1 describes the sample characteristics according to ventilatory variability level (high and low).

Table 1. Sample characteristics (clinical profile)

	Overall (n = 233)	High vVE (n = 63)	Low vVE (n = 170)	EOV-positive (n = 40)	High vs Low (*p*-value)	Low vVE vs EOV (*p*-value)
Male gender, n (%)	191 (82.0)	63 (100)	128 (75.3)	31 (77.5)	< 0.001	0.840
Age, years	69 [67 – 70]	62 [59 – 66]	70 [69 – 72]	74 [69 – 76]	< 0.001	0.151
Body mass index, kg/m²	26.1 [25.3 – 27.0]	26.6 [25.3 – 27.5]	26.0 [24.9 – 27.2]	24.8 [24.2 – 27.0]	0.596	0.181
NYHA class III-IV, n (%)	89 (38.2)	12 (19.1)	77 (45.3)	22 (55.0)	< 0.001	0.294
LVEF, %	32.9 [30.1 – 36.4]	35.2 [32.5 – 37.6]	32.3 [31.1 – 33.9]	32.8 [29.2 – 37.3]	0.065	0.948
RVSP, mmHg	35.0 [33.0 – 37.0]	34.0 [29.0 – 37.0]	35.0 [33.0 – 39.0]	39.0 [31.0 – 46.0]	0.359	0.500
MECKI score, %	4.45 [3.59 – 5.66]	2.32 [1.48 – 3.59]	5.95 [4.06 – 7.04]	7.4 [4.8 – 12.6]	< 0.001	0.125
Hemoglobin, mg/dL	13.9 [13.7 – 14.2]	14.5 [13.7 – 15.2]	13.7 [13.4 – 14.0]	13.6 [12.8 – 14.2]	0.005	0.666
BNP, pg/mL	292 [252 – 396]	171 [96 – 396]	348 [272 – 458]	330 [272 – 549]	0.010	0.975
CPET time, s	532 [517 – 556]	556 [513 – 579]	527 [507– 547]	492 [477 – 572]	0.294	0.248
VO_{2PEAK}, ml.kg.min^{-1}	13.9 [13.2 – 14.5]	18.7 [17.2 – 20.1]	12.7 [12.0 – 13.4]	12.2 [11.1 – 13.5]	< 0.001	0.307
VE/VCO_2 slope	30.2 [29.4 – 31.9]	28.2 [27.0 – 32.0]	30.6 [29.6 – 32.0]	36.0 [32.0 – 40.0]	0.031	0.006
Maximal workload, w	69 [62 – 74]	110 [98 – 117]	59 [53 – 63]	48 [37 – 64]	< 0.001	0.038
EOV-positive, n (%)	40 (17.2)	4 (6.3)	36 (21.2)	40 (100)	0.006	-
Adverse events, n (%)	35 (15.0)	3 (4.8)	32 (18.8)	13 (32.5)	0.014	0.084

Continuous data are expressed as median [95% confidence interval (CI)] and categorical data as absolute (n) and relative (%) frequencies. vVE, minute-ventilation variability. NYHA, New York Heart Association. LVEF, left ventricular eject fraction. RVSP, right ventricular systolic pressure. BNP, B-type natriuretic peptide. CPET, cardiopulmonary exercise test. VO_{2PEAK}, peak oxygen uptake. VE/VCO_2, minute ventilation-carbon dioxide production. EOV, exercise oscillatory ventilation. EOV cases identified by Corrà definition.

Briefly, the patients with low vVE are older and show worse clinical profile and cardiorespiratory function than high vVE patients, besides a greater number of adverse events. Among baseline variables, only the VO_{2PEAK} and maximal workload exhibited an association with vVE (Figure 1A and 1B, respectively). Regarding the dichotomous analysis, the EOV-positive group had lower ventilatory efficiency and maximal workload than the low vVE patients. Lastly, EOV patients had lower vVE indices than non-EOV patients (37.6 ± 18.1 vs 46.1 ± 22.0 $L.breath^{-1}.min^{-1}$; $p = 0.021$).

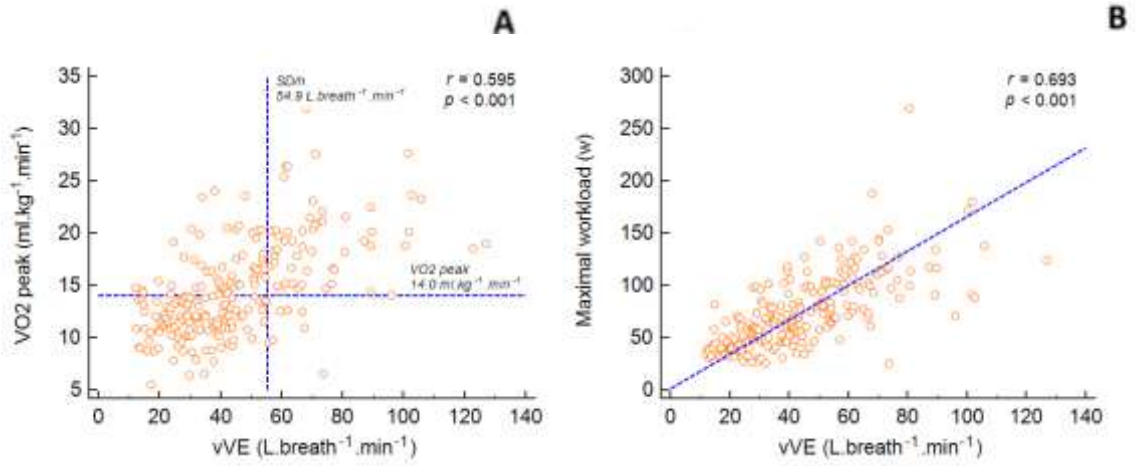


Figure 1. Correlation between minute-ventilation variability (vVE), VO_{2PEAK} (A) and maximal workload (B). VO_{2PEAK}, peak oxygen uptake.

Relative risk to adverse endpoints was 4.0 (1.3 to 12.5) and 2.9 (1.6 to 5.2) in the quantitative (vVE) and dichotomic (EOV) approaches, respectively. Figure 2 features the Kaplan-Meier analyses. Both sensitivity and specificity analyses to predict adverse outcomes at 2 years are available in the supplementary material (Table 1S).

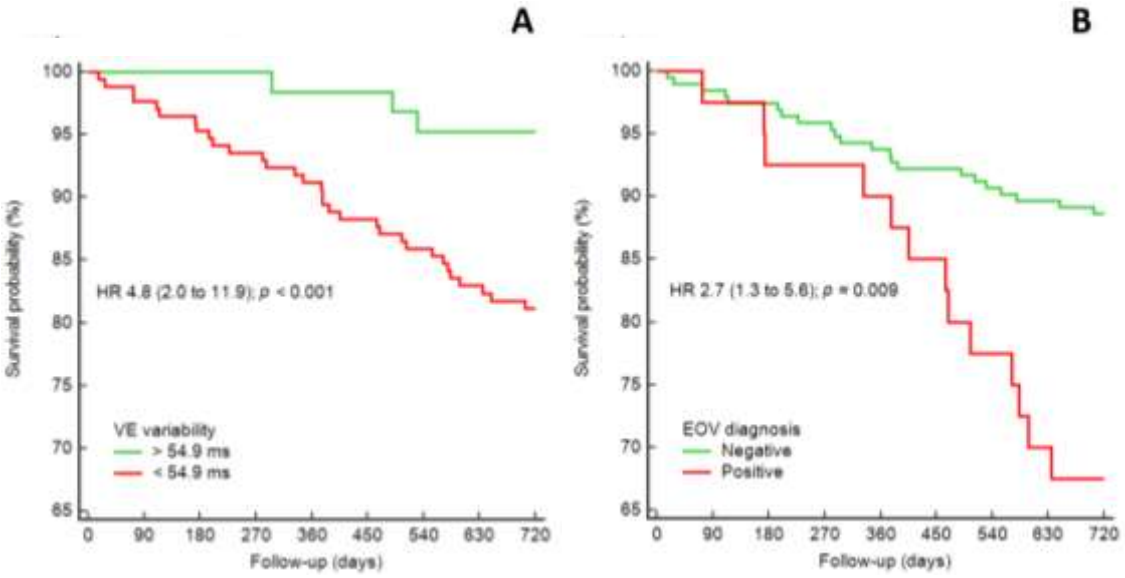


Figure 2. Survival analysis for minute-ventilation variability (A) and EOV diagnosis [dichotomic approach] (B). HR, hazard ratio. VE, minute ventilation. EOV, exercise oscillatory ventilation.

Table 2 shows the clinical profile stratified according the cross-analysis. Briefly, LV-EOV patients exhibited higher cardiovascular risk, worse VO_{2PEAK}, VE/VCO_2 slope, and maximal workload than HV-CHF patients. It was observed similar cardiovascular risk, oxygen uptake, and maximal workload between LV-EOV and LV-CHF groups. The LV-EOV group had more adverse events at 2-year than LV-CHF (p = 0.007) and HV-CHF (p < 0.001) groups. There was no difference in recorded adverse endpoints between LV-CHF and HV-CHF groups (p = 0.086). Lastly, the HV-CHF group had a lower prevalence of NYHA class III-IV patients than the LV-EOV (p < 0.001) and LV-CHF (p = 0.002) groups. Few cases of HV-EOV were recorded, making other inferences unfeasible.

Table 2. Clinical profile stratified by the cross-approach.

	LV-EOV	LV-CHF	HV-EOV	HV-CHF	*p*-value
Sample size, n (%)	36 (15.5)	134 (57.6)	4 (1.7)	59 (25.3)	< 0.001
Male gender, n (%)	27 (75.0)	101 (75.4)	4 (100)	59 (100)	< 0.001
Age, years	73.5 ± 10.5	70.0 ± 10.0	73.5 ± 10.5	61.0 ± 12.0	< 0.001
Body mass index, kg/m²	24.8 ± 5.0	26.6 ± 6.3	24.4 ± 1.9	26.6 ± 4.4	0.265
NYHA class III-IV, n (%)	21 (58.3)	56 (41.8)	1 (25.0)	11 (18.6)	< 0.001
LVEF, %	32.6 ± 13.2	32.2 ± 9.0	35.8 ± 6.0	35.2 ± 9.2	0.274
RVSP, mmHg	39.0 ± 15.0	35. ± 15.5	39.0 ± 20.8	34.0 ± 16.2	0.607
MECKI score, %	8.4 ± 11.6	4.8 ± 8.2	2.2 ± 11.0	2.3 ± 4.3	< 0.001
Hemoglobin, mg/dL	13.6 ± 2.1	13.7 ± 2.3	13.0 ± 1.4	14.5 ± 2.2	0.018
BNP, pg/mL	310 ± 359	354 ± 590	549 ± 432	122 ± 455	0.024
CPET time, s	492 ± 138	532 ± 139	480 ± 93	563 ± 99	0.259
VO_{2PEAK}, $ml.kg.min^{-1}$	12.1 ± 3.6	13.1 ± 4.1	19.8 ± 5.0	18.6 ± 5.8	< 0.001
VE/VCO_2 slope	36.0 ± 11.4	30.2 ± 7.6	36.0 ± 9.1	28 ± 7.7	< 0.001
Maximal workload, w	47 ± 32	61 ± 33	94 ± 27	112 ± 36	< 0.001
Adverse events, n (%)	13 (36.1)	19 (14.2)	0 (0.0)	3 (5.1)	< 0.001

Continuous data are expressed as median [95% confidence interval (CI)] and categorical data as absolute (n) and relative (%) frequencies. EOV, exercise oscillatory ventilation. LV, low minute-ventilation variability. HV, high minute-ventilation variability. CHF, chronic heart failure (without EOV). NYHA, New York Heart Association. LVEF, left ventricular eject fraction. RVSP, right ventricular systolic pressure. BNP, B-type natriuretic peptide. CPET, cardiopulmonary exercise test. VO_{2PEAK}, peak oxygen uptake. VE/VCO_2, minute ventilation-carbon dioxide production

Regarding adverse outcomes, patients from the LV-EOV group had 3- and 7-times more risk of adverse outcomes at 2 years than patients from the LV-CHF (2.6 [1.4 to 4.6]; p = 0.002) and HV-CHF (7.1 [2.2 to 23.2]; p = 0.001) groups. Figure 3S shows the Kaplan-Meier analysis of the combined groups. Briefly, the LV-EOV group exhibited a worse hazard ratio for adverse endpoint compared to HV-CHF and LV-CHF groups (HR 8.2 [2.8 to 24.4] and HR 2.8 [1.0 to 7.4], respectively). An algorithm for risk screening was developed based on these data (Figure 3).

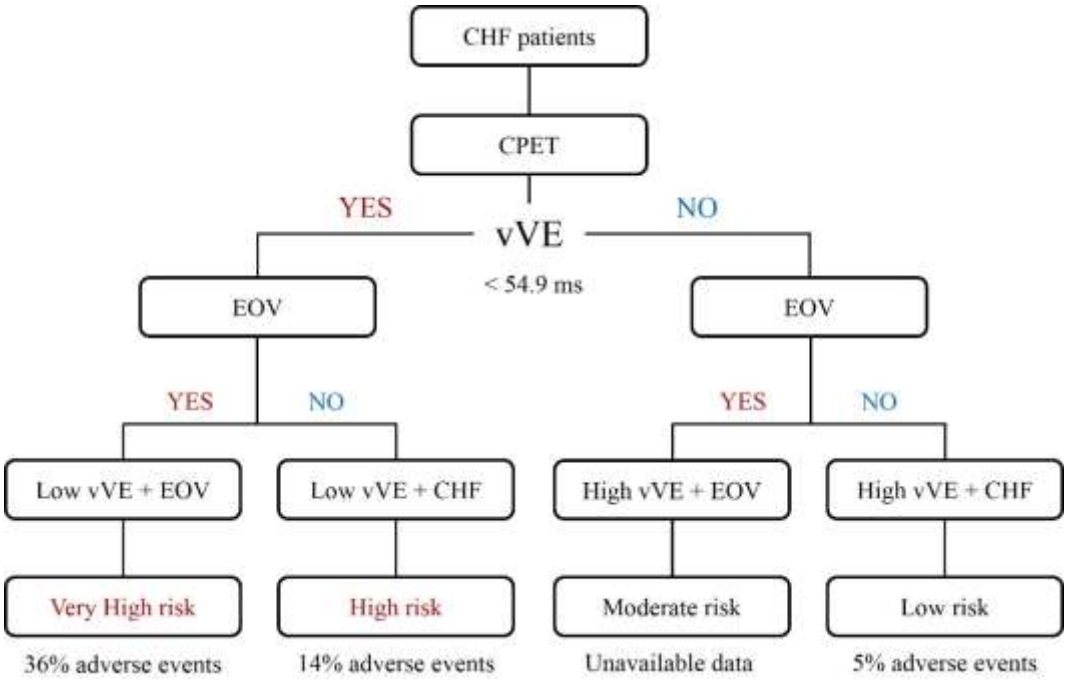


Figure 3. Algorithm proposal for screening the risk of adverse events in EOV patients. CHF, chronic heart failure. EOV, exercise oscillatory ventilation. vVE, minute-ventilation variability.

Discussion

This is the first study to investigate the use of vVE to predict adverse events in CHF patients. Our data indicate similar performance between the dichotomic approach to diagnose the EOV and the minute-ventilation variability, a quantitative approach to identify changes in the ventilatory pattern. However, the quantitative method showed greater sensitivity to predicting adverse events over 2-year. Adverse outcomes risk was about 4-times greater in patients with low vVE compared to their high vVE peers, and 3-times greater in EOV-positive patients, diagnosed by the dichotomous approach. Regarding the clinical profile, patients with low vVE had worse prognostic markers and lower exercise capacity than patients with high vVE, besides 90% of EOV cases diagnosed by the classic method.

We found only three studies that applied a proposal like ours. Interestingly all are from the same research group. Castro et al. (3) compared the ventilatory variability of 18 male volunteers during the incremental test (9 healthy adults and 9 high-performance athletes). The authors observed that sedentary individuals exhibited higher vVE than athletes (97.5 ± 7.7 vs 71.6 ± 1.6 L.breath $^{-1}$, respectively). However, the normalized index from both groups is higher than the cut-off presented in this study to stratify high-risk cases (< 54.9 L.breath^{-1}.min^{-1}). Based on those data, Castro et al. (3) concluded that the vVE could be a conditioning variable responsive to exercise training.

To test this hypothesis, Castro et al. (4) randomized 24 healthy adults into an intervention and control group. Individuals in the intervention group underwent an individualized hypocaloric diet with a deficit near 500 kcal.day^{-1} and participated in a supervised physical training program for 12 weeks (three weekly sessions of 60 min). The exercise protocol consisted of stretching, aerobic and resistance training, with intensity adjustment every week. Participants in the control group received only advice about the importance of a healthy lifestyle. The authors observed no difference in vVE after the intervention period (64.6 ± 5.1 vs 77.7 ± 8.1 L.breath^{-1}). However, claimed a 15% reduction in the respiratory rate in the intervention group.

The physiological basis behind these responses is still unclear. It appears that vVE is secondary to breathing rate in healthy adults while the response in athletes is secondary to tidal volume fluctuations (14). The higher tidal volume

provided by the pulmonary adaptations to exercise training reflects in the lower breathing rate of high-performance athletes during submaximal efforts (15, 16). Castro et al. (4) corroborate showing that the breathing rate of healthy adults is responsive to a healthy lifestyle (exercise and a diet). The authors mention that a healthy lifestyle can reduce ventilatory variability as it reflects less instability in the ventilatory drive. In addition, vVE can be used as a marker of pulmonary adaptation to exercise (4).

Furthermore, we observed that patients with low vVE exhibit lower survival and worse clinical profile than patients with high vVE, especially when the stratified approach was used. A possible explanation for this finding is the physiological adaptations to exercise. While athletes have a good cardiorespiratory function and adapt to different demands, increasing VE to reduce its variability, CHF patients exhibit less adaptability and ability to adjust the system, increasing VE to meet the new metabolic demand. A fact that could support this hypothesis is the total VE amplitude during CPET of an athlete (124.0 $L.min^{-1}$) and an EOV-positive patient (43.7 $L.min^{-1}$), previously evaluated in our laboratory (unpublished data).

Another empirically observed fact that could contribute to the hypothesis mentioned above is the VE numbers recorded during the incremental test of an EOV-positive and negative patient. Analyzing the ventilatory pattern and comparing the amount of VE in a standardized sample (e.g., 100s), we may observe that an EOV-positive patient had higher respiratory rate than an EOV-negative patient (Figure 4S). This fact would support the lower vVE, possibly due to the inability to adapt to their cardiorespiratory function. However, the facts mentioned above are just speculations that still need to be investigated further.

We did not find data in the literature that could explain the vVE behavior in heart failure. The only study in the area showed an inverse correlation between LVEF and vVE (r = -0.531; p = 0.034) (6). However, our data did not indicate this association (r = 0.099; p = 0.065). However, we observed a positive correlation between vVE with VO_{2PEAK} and maximal workload, unlike the finding. It is possible that the sample size (17 vs 233), LVEF (23 ± 6% vs 34 ± 8%), and patients age (59 ± 9 vs 67 ± 10 years) may have some influence on this divergence. Nonetheless, these are just suppositions since the study design does not allow

further inferences. The mechanisms related to vVE modulation in CHF patients remain unexplained.

Pathophysiology suggested for EOV also modulates vVE by sympathetic hyperactivity in response to variations in arterial carbon dioxide partial pressure (17). In this sense, changes in vVE would appear before the phenomenon became more severe, being a continuous and gradual process (3, 4). Goulart et al. (18) reinforce this assumption by observing two distinct patterns of EOV, persistent and disappearing during incremental exercise. The authors noted that patients with EOV persistent had a worse clinical profile, and a higher risk of mortality and hospitalization compared to cases of EOV disappeared. This finding corroborates the hypothesis that vVE anticipates the emergence of more severe EOV cases (3, 4).

However, other mechanisms seem to intervene in vVE behavior. The cardiorespiratory coupling reflects the interaction between the cardiovascular and respiratory systems in search of mutual synchronism, where breathing can influence the heart rate and vice versa. Lin et al. (19) demonstrated that it is possible to modulate the heart rate by manipulating the respiratory rate. However, the influence of autonomic modulation on vVE is a field that still needs to be explored, even more so if we consider the strong association of heart rate variability (a well-known indicator of autonomic control) with poor prognosis in heart failure (20), and the (controversial) influence of β-blockers in the EOV reversal (21).

Limitations

Although the prognostic value of vVE has been observed, it is necessary to recognize some limitations in the study. The analyzed data come from a reference single-centre that may not reflect the reality of other places. Furthermore, this study is characterized as retrospective cross-sectional research. It is necessary to consider that the patients treated at the respective institution may have received different interventions or not have adhered to the treatment. Data on nutritional status and exercise were not recorded. Finally, the clinical profile of the patients (e.g., reduced left ventricular ejection fraction) and the limited number of adverse outcomes suggest caution for the generalization of the findings.

Conclusion

Although the EOV is a powerful predictor of adverse outcomes in CHF, the quantitative analysis of the minute-ventilation variability may allow early identification of changes in the ventilatory pattern before the CHF reaches more advanced stages. It is a measure independent of the evaluator's expertise, which does not require manual selection of respiratory cycles (amplitude and length) or the fulfillment of pre-established criteria by the dichotomic definitions, proving to be a versatile alternative for evaluating CHF patients. Furthermore, it could be used to stratify the vVE by risk zones.

References

1. Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis. Int J Cardiol. 2015;182:476-86.
2. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S, et al. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. J Am Coll Cardiol. 2007;50:299-308.
3. Castro R, Lima S, Sales A, Nóbrega A. Minute-ventilation variability during cardiopulmonary exercise test is higher in sedentary men than in athletes. Arq Bras Cardiol. 2017;109:185-90.
4. Castro R, Sales A, Nóbrega A. Lifestyle interventions reduce exercise ventilatory variability in healthy individuals: a randomized intervention study. Future Cardiol. 2020;16:439-46.
5. Ambaye G. Time and frequency domain analysis of signals: review. Int J Eng Res Technol. 2020;12:1-6.
6. Castro R, Antunes-Correa L, Ueno L, Rondon M, Negrão C, Nobrega A. Ventilation variability inversely correlates to ejection fraction in heart failure. Eur Respir J. 2010;36:1482-3.
7. Ribeiro G, Deresz L, Salvioni E, Hansen D, Agostoni P, Karsten M. Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients. Int J Cardiol. 2022;360:39-43.

8. Hansen D, Bonné K, Alders T, Hermans A, Copermans K, Swinnen H, et al. Exercise training intensity determination in cardiovascular rehabilitation: Should the guidelines be reconsidered? Eur J Prev Cardiol. 2019;26:1921-8.
9. Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R, et al. Work-rate affects cardiopulmonary exercise test results in heart failure. Eur J Heart Fail. 2005;7:498-504.
10. Rovai S, Corra U, Piepoli M, Vignati C, Salvioni E, Bonomi A, et al. Exercise oscillatory ventilation and prognosis in heart failure patients with reduced and mid-range ejection fraction. Eur J Heart Fail. 2019;21:1586-95.
11. Agostoni P, Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. Int J Cardiol. 2019;288:107-13.
12. Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats A, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: Clinical correlates and prognostic implications. Chest. 2002;121:1572-80.
13. Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, et al. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. Int J Cardiol. 2013;167:2710-8.
14. Castro R, Magini M, Pedrosa S, Sales AR, Nóbrega AC. Principal components analysis to evaluate ventilatory variability: comparison of athletes and sedentary men. Med Biol Eng Comput. 2011;49:305-11.
15. Harrison O, Russell B, Pattinson K. Perceptual and ventilatory responses to hypercapnia in athletes and sedentary individuals. Front Physiol. 2022;13:820307.
16. Myrianthefs P, Baltopoulos G. A higher tidal volume may be used for athletes according to measured FVC. Sci World J. 2013;2013:526138.
17. Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M. Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis. Eur J Prev Cardiol. 2022;29:e233-e236.
18. Goulart C, Agostoni P, Salvioni E, Kaminsky LA, Myers J, Arena R, et al. Exercise oscillatory breathing in heart failure with reduced ejection fraction: clinical implication. Eur J Prev Cardiol. 2022.

19. Lin W, Fu T, Huang S, Tsai C, Lin W, Lin K. Influence of heart rate variability in healthy subjects with respiratory manipulation. Int Conf Bioinformatics Biomed. 2015:1706-1708.
20. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, et al. Short-Term Heart Rate Variability Strongly Predicts Sudden Cardiac Death in Chronic Heart Failure Patients. Circulation. 2003;107:565-70.
21. Belli-Marin JFC, Bocchi EA, Ayub-Ferreira S, Junior NC, Guimarães GV. Effects of β-blocker therapy on exercise oscillatory ventilation in reduced ejection fraction heart failure patients: A case series study. Biomed Pharmacother. 2022; 156:113106.

.

SUPPLEMENTARY MATERIAL

Manuscript: Ventilatory variability alone or in association with a dichotomous definition of exercise oscillatory ventilation in predicting adverse outcomes in heart failure patients. An exploratory study

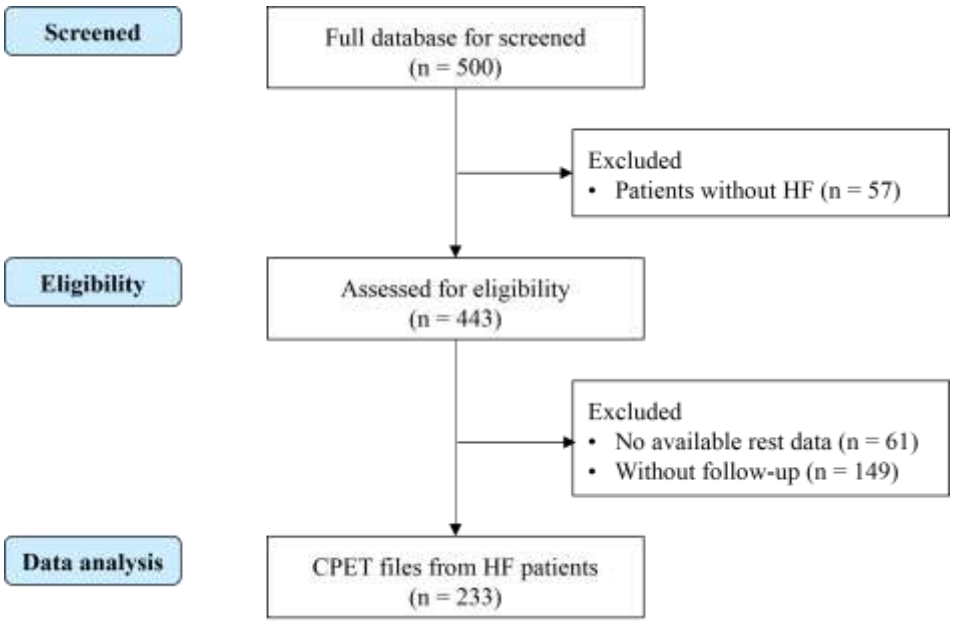


Figure 1S. Flowchart of data selection. CPET, cardiopulmonary exercise test. HF, heart failure.

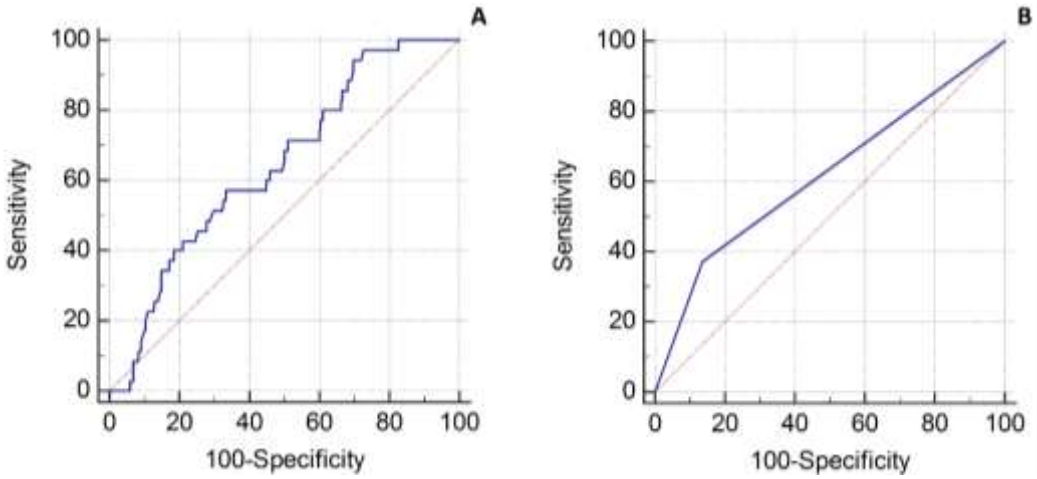


Figure 2S. ROC curve of the minute-ventilation variability (A) and EOV definition [dichotomic approach] (B).

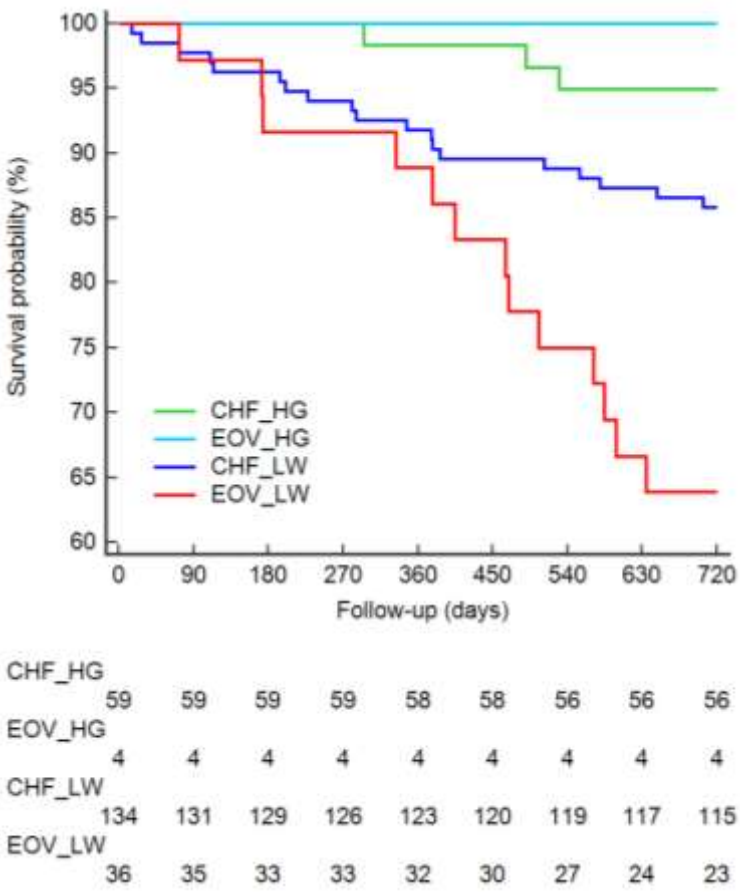


Figure 3S. Survival analysis of the cross-approach. EOV, exercise oscillatory ventilation. HV, high minute-ventilation variability. LV low minute-ventilation variability.

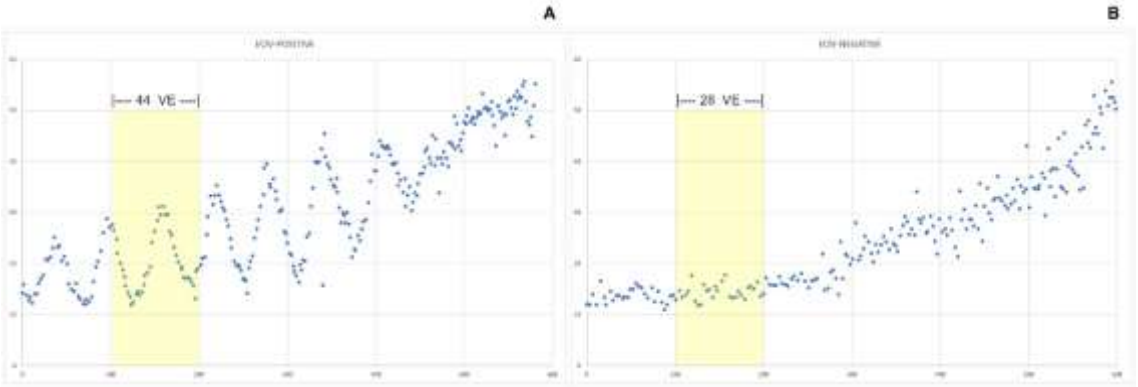


Figure 4S. Ventilatory pattern of one EOV patient (A) and non-EOV (B).VE, minute-ventilation. Yellow zone, standardized sampling of 100-s.

ROC curve

Variable	vVE
Classification variable	Adverse outcomes
Sample size	233
Positive group [a]	35 (15.02%)
Negative group [b]	198 (84.98%)

[a] Adverse outcomes = 1; [b] Adverse outcomes = 0.

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.643
Standard Error [a]	0.0467
95% Confidence interval [b]	0.578 to 0.704
z statistic	3.058
Significance level P (Area=0.5)	0.0022

[a] DeLong et al., 1988. [b] Binomial exact.

Youden index

Youden index J	0.2459
Associated criterion	≤ 54.9
Sensitivity	94.29
Specificity	30.30

Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<12.1	0.00	0.0 - 10.0	100.00	98.2 - 100.0		1.00
≤16	0.00	0.0 - 10.0	93.94	89.7 - 96.8	0.00	1.06
≤16.6	2.86	0.07 - 14.9	93.94	89.7 - 96.8	0.47	1.03
≤17.2	2.86	0.07 - 14.9	92.93	88.4 - 96.1	0.40	1.05
≤18.1	8.57	1.8 - 23.1	92.93	88.4 - 96.1	1.21	0.98
≤18.9	8.57	1.8 - 23.1	91.92	87.2 - 95.3	1.06	0.99
≤19.5	11.43	3.2 - 26.7	91.41	86.6 - 94.9	1.33	0.97
≤19.7	11.43	3.2 - 26.7	90.91	86.0 - 94.5	1.26	0.97
≤20	14.29	4.8 - 30.3	90.91	86.0 - 94.5	1.57	0.94
≤20.4	17.14	6.6 - 33.6	89.90	84.8 - 93.7	1.70	0.92
≤21.4	17.14	6.6 - 33.6	89.39	84.2 - 93.3	1.62	0.93
≤21.5	20.00	8.4 - 36.9	89.39	84.2 - 93.3	1.89	0.89
≤22.2	22.86	10.4 - 40.1	88.89	83.7 - 92.9	2.06	0.87
≤23.2	22.86	10.4 - 40.1	87.37	81.9 - 91.7	1.81	0.88
≤23.3	25.71	12.5 - 43.3	86.87	81.4 - 91.2	1.96	0.86
≤23.7	25.71	12.5 - 43.3	85.86	80.2 - 90.4	1.82	0.87
≤24	28.57	14.6 - 46.3	85.35	79.6 - 90.0	1.95	0.84

≤24.5	28.57	14.6 - 46.3	84.85	79.1 - 89.5	1.89	0.84
≤24.6	34.29	19.1 - 52.2	84.85	79.1 - 89.5	2.26	0.77
≤26	34.29	19.1 - 52.2	82.83	76.8 - 87.8	2.00	0.79
≤26.1	37.14	21.5 - 55.1	82.83	76.8 - 87.8	2.16	0.76
≤26.9	37.14	21.5 - 55.1	81.31	75.2 - 86.5	1.99	0.77
≤27.4	40.00	23.9 - 57.9	81.31	75.2 - 86.5	2.14	0.74
≤27.9	40.00	23.9 - 57.9	78.79	72.4 - 84.3	1.89	0.76
≤28.1	42.86	26.3 - 60.6	78.79	72.4 - 84.3	2.02	0.73
≤29.2	42.86	26.3 - 60.6	75.25	68.6 - 81.1	1.73	0.76
≤29.6	45.71	28.8 - 63.4	74.75	68.1 - 80.6	1.81	0.73
≤30.5	45.71	28.8 - 63.4	72.22	65.4 - 78.3	1.65	0.75
≤30.6	48.57	31.4 - 66.0	72.22	65.4 - 78.3	1.75	0.71
≤31.8	48.57	31.4 - 66.0	71.21	64.4 - 77.4	1.69	0.72
≤32	51.43	34.0 - 68.6	70.20	63.3 - 76.5	1.73	0.69
≤33	51.43	34.0 - 68.6	67.68	60.7 - 74.1	1.59	0.72
≤33.8	54.29	36.6 - 71.2	67.17	60.2 - 73.7	1.65	0.68
≤34.1	54.29	36.6 - 71.2	66.67	59.6 - 73.2	1.63	0.69
≤34.5	57.14	39.4 - 73.7	66.67	59.6 - 73.2	1.71	0.64
≤39.5	57.14	39.4 - 73.7	55.05	47.8 - 62.1	1.27	0.78
≤40	60.00	42.1 - 76.1	55.05	47.8 - 62.1	1.33	0.73
≤40.4	60.00	42.1 - 76.1	54.04	46.8 - 61.1	1.31	0.74
≤40.7	62.86	44.9 - 78.5	54.04	46.8 - 61.1	1.37	0.69
≤41.8	62.86	44.9 - 78.5	50.51	43.3 - 57.7	1.27	0.74
≤42.1	65.71	47.8 - 80.9	50.00	42.8 - 57.2	1.31	0.69
≤42.4	68.57	50.7 - 83.1	50.00	42.8 - 57.2	1.37	0.63
≤42.5	68.57	50.7 - 83.1	48.99	41.8 - 56.2	1.34	0.64
≤42.7	71.43	53.7 - 85.4	48.99	41.8 - 56.2	1.40	0.58
≤47.1	71.43	53.7 - 85.4	39.90	33.0 - 47.1	1.19	0.72
≤47.3	74.29	56.7 - 87.5	39.90	33.0 - 47.1	1.24	0.64
≤48.2	74.29	56.7 - 87.5	39.39	32.5 - 46.6	1.23	0.65
≤48.6	77.14	59.9 - 89.6	39.39	32.5 - 46.6	1.27	0.58
≤49.1	77.14	59.9 - 89.6	38.89	32.1 - 46.1	1.26	0.59
≤50.1	80.00	63.1 - 91.6	38.89	32.1 - 46.1	1.31	0.51
≤52.2	80.00	63.1 - 91.6	33.84	27.3 - 40.9	1.21	0.59
≤52.6	82.86	66.4 - 93.4	33.84	27.3 - 40.9	1.25	0.51
≤53.4	82.86	66.4 - 93.4	33.33	26.8 - 40.4	1.24	0.51
≤53.6	85.71	69.7 - 95.2	33.33	26.8 - 40.4	1.29	0.43
≤53.8	85.71	69.7 - 95.2	31.82	25.4 - 38.8	1.26	0.45
≤54	88.57	73.3 - 96.8	31.82	25.4 - 38.8	1.30	0.36
≤54.1	88.57	73.3 - 96.8	30.81	24.5 - 37.7	1.28	0.37
≤54.6	91.43	76.9 - 98.2	30.30	24.0 - 37.2	1.31	0.28

≤54.9	94.29	80.8 - 99.3	30.30	24.0 - 37.2	1.35	0.19
≤57.4	94.29	80.8 - 99.3	27.78	21.7 - 34.6	1.31	0.21
≤57.5	97.14	85.1 - 99.9	27.27	21.2 - 34.0	1.34	0.10
≤66.7	97.14	85.1 - 99.9	17.17	12.2 - 23.2	1.17	0.17
≤66.8	100.00	90.0 - 100.0	17.17	12.2 - 23.2	1.21	0.00
≤126.8	100.00	90.0 - 100.0	0.00	0.0 - 1.8	1.00	

Table 1S. Sensitivity and specificity to predict adverse endpoints at 2-year.

Criteria	AUC	95% CI	*p*-value	Sensitivity	Specificity
EOV-positive	0.618	0.532 to 0.680	0.007	37.1	86.4
vVE	0.643	0.578 to 0.704	0.002	94.3	30.3

AUC, area under the ROC curve. EOV, exercise oscillatory ventilation by Corrà definition. vVE, minute ventilation variability < 54.9 $L.breath^{-1}.min^{-1}$.

6 ARTIGO 4

EXERCISE TRAINING EFFECTS ON METABOLIC AND VENTILATORY CHANGES IN HEART FAILURE PATIENTS WITH EXERCISE OSCILLATORY VENTILATION: SYSTEMATIC REVIEW AND META-ANALYSIS

Publicado no periódico *European Journal of Preventive Cardiology* (ANEXO B)
Percentil 90 (*Scopus*), Fator de Impacto 7,804

Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis

Gustavo S Ribeiro, MSc[1], Camila Cargnin, MSc[1], Pedro Dal Lago, PT, ScD[1,2], Dominique Hansen, PT, PhD, FESC[3], Piergiuseppe Agostoni, MD, PhD, FESC[4,5] and Marlus Karsten, PT, PhD[1,6,7]

[1] Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil.

[2] Departamento de Fisioterapia, UFCSPA, Porto Alegre, Brazil.

[3] Hasselt University (UHASSELT), Faculty of Rehabilitation Sciences, BIOMED/REVAL, Hasselt, Belgium / Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium.

[4] Centro Cardiologico Monzino, IRCCS, Milano, Italy.

[5] Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Milano, Italy.

[6] Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Florianópolis, Brazil.

[7] Programa de Pós-Graduação em Fisioterapia, UDESC, Florianópolis, Brazil.

Short title: Exercise in EOV patients: a systematic review

Conflict of interest: None declared

Corresponding author

Marlus Karsten, Centro de Ciências da Saúde e do Esporte, Universidade do Estado de Santa Catarina, Rua Pascoal Simone 358, 88080-350, Florianópolis, SC, Brazil.

Email: marlus.karsten@udesc.br

Manuscript word count: 1050 words

Exercise oscillatory ventilation (EOV) is a phenomenon characterized by cyclic oscillations in the ventilatory pattern observed during the cardiopulmonary exercise test (EOV characteristics: Figure 1S). It is considered an independent predictor for death and adverse cardiovascular events in chronic heart failure (CHF) patients[1]. A recent meta-analysis showed that EOV-positive patients exhibited a worse peak oxygen uptake (VO_{2PEAK}) and ventilatory efficiency (VE/VCO_2 slope)[2]. Although the EOV pathophysiology is not fully understood, current evidence suggests that circulatory delay, pulmonary congestion, high chemosensitivity, and exacerbated ergoreflex signalling are the main triggering factors[1, 3].

Several treatments were investigated to alleviate EOV symptomatology and thereby improve the patient's prognosis (e.g., adaptive servo-ventilation, phosphodiesterase 5 inhibition, exercise training and levosimendan infusion). Although the evidence regarding exercise training as EOV treatment is limited, there is also no effective pharmacological treatment for EOV. Thus, targeting EOV by exercise intervention is highly relevant. This systematic review aims to verify the exercise training effect on EOV reversal, and other prognostic factors in CHF patients and EOV coexistence.

This study followed the recommendations of the PRISMA statement and was registered at PROSPERO: CRD42021254587. The search was performed in several databases from inception to 30th July 2021, with no language restriction. Inclusion criteria followed the PICOT question: (P) EOV patients; (I) exercise training; (C) pre-training values in EOV group – single arm; (O) EOV reversal [primary], VO_{2PEAK} and VE/VCO_2 slope [secondary]; and (T) clinical trial – randomized, non-randomized, or uncontrolled trials. Full methods' description is available as supplementary material.

Nine potentially eligible studies were identified, and three trials met the eligibility criteria (PRISMA flowchart; Figure 2S). Zurek *et al*.[4] assessed two non-randomized groups composed of EOV-positive patients (intervention and control group). Panagopoulou *et al*.[5] analysed two groups who performed the exercise training (EOV-positive and EOV-negative; uncontrolled trial), and Yamauchi *et al*.[6] evaluated a single group (uncontrolled trial). Only data referring to the EOV-positive intervention groups were analyzed. The characteristics of the included

studies and the methodological quality are shown in Table S1 and S2, respectively.

All studies (Table 1) included aerobic exercise three times per week: 30 or 40-min of cycling at the anaerobic threshold[5, 6], or 45-min cycling at 60-80% of VO_{2PEAK} (twice daily)[4]. One study analysed two protocols[5], 40-min of high-intensity interval training (HIIT) on a cycle ergometer or 20-min of HIIT plus four resistance exercises (3-sets of 10 to 12 repetitions at 55 to 65% of 2-RM). Besides, resistance training was proposed in the other two studies (3 to 4-exercises)[4, 6]. These protocols agree with current guidelines for cardiovascular rehabilitation of CHF patients[7]. No study reported adverse events, major complications, or sample loss during the follow-up.

Table 1 Characteristics of treatments and main findings

Study (year)	Treatment	Frequency	Intensity	Main findings
Panagopoulou 2017	40-min of HIIT (30-sec of effort follow 60-sec of passive rest) on cycle ergometers or 20-min of HIIT protocol plus four resistance exercises: leg extension, leg curls, arm curls, and lateral arm abduction (3-sets of 10 to 12 repetitions)	3-times per week (36 sessions)	AT: >100% of VO_{2PEAK} RT: 55 to 65% of 2-RM	Improvement of cardiopulmonary efficiency and functional capacity, besides reducing the EOV duration. EOV disappeared in 70% of the cases.
Yamauchi 2016	30-min of aerobic training plus resistance training	3-times per week (60 sessions)	Anaerobic threshold level	A 5-month cardiac rehabilitation program reduces 51% plasma BNP levels and 35% EOV amplitude. There were correlations between EOV amplitude and BNP levels (r=0.615), and EOV amplitude and VE/VCO_2 slope (r=0.625).
Zurek 2012	45-min twice day of aerobic training performed on a cycle ergometer and callisthenic exercises.	3-times per week (36 sessions)	AT: 60-80% of VO_{2PEAK}	EOV disappeared in 71.2% out of patients after training; ventilatory efficiency (VE/VCO_2 slope) and the central hemodynamic during exercise ($PETCO_2$ at RCP) were improved.

AT, aerobic training. BNP, B-type natriuretic peptide. EOV, exercise oscillatory ventilation. HIIT, high-intensity interval training. $PETCO_2$, partial pressure of end-tidal carbon dioxide. RCP, respiratory compensation point. RT, resistance training. VE/VCO_2 slope, minute ventilation-carbon dioxide production slope. VO_{2PEAK}, peak oxygen uptake. 2-RM, 2-repetition maximum.

VO_{2PEAK} and VE/VCO_2 slope values were available in three trials[4-6] (98 patients), and EOV reversal in two trials (72 patients)[4, 5]. A random-effects model with a 95% confidence interval (95% CI) was applied to assess the relative likelihood for EOV reversal, as well as to measure the exercise effect on VO_{2PEAK} and VE/VCO_2 slope [standardized mean difference (SMD)]. The mean difference (MD) analysis was also performed. The meta-analysis (Figure 1) showed a moderate effect on VO_{2PEAK} (SMD 0.43 [0.15, 0.71]; p=0.003), and VE/VCO_2 slope (SMD -0.44 [-0.72, -0.15]; p=0.003), beyond a relevant EOV reversal (RR 0.30 [0.21, 0.43]; p<0.001). No heterogeneity in EOV reversal, VE/VCO_2 slope and VO_{2PEAK} were observed (p>0.05). In summary, exercise training was effective in reversing EOV, as well as improving aerobic capacity and ventilatory efficiency.

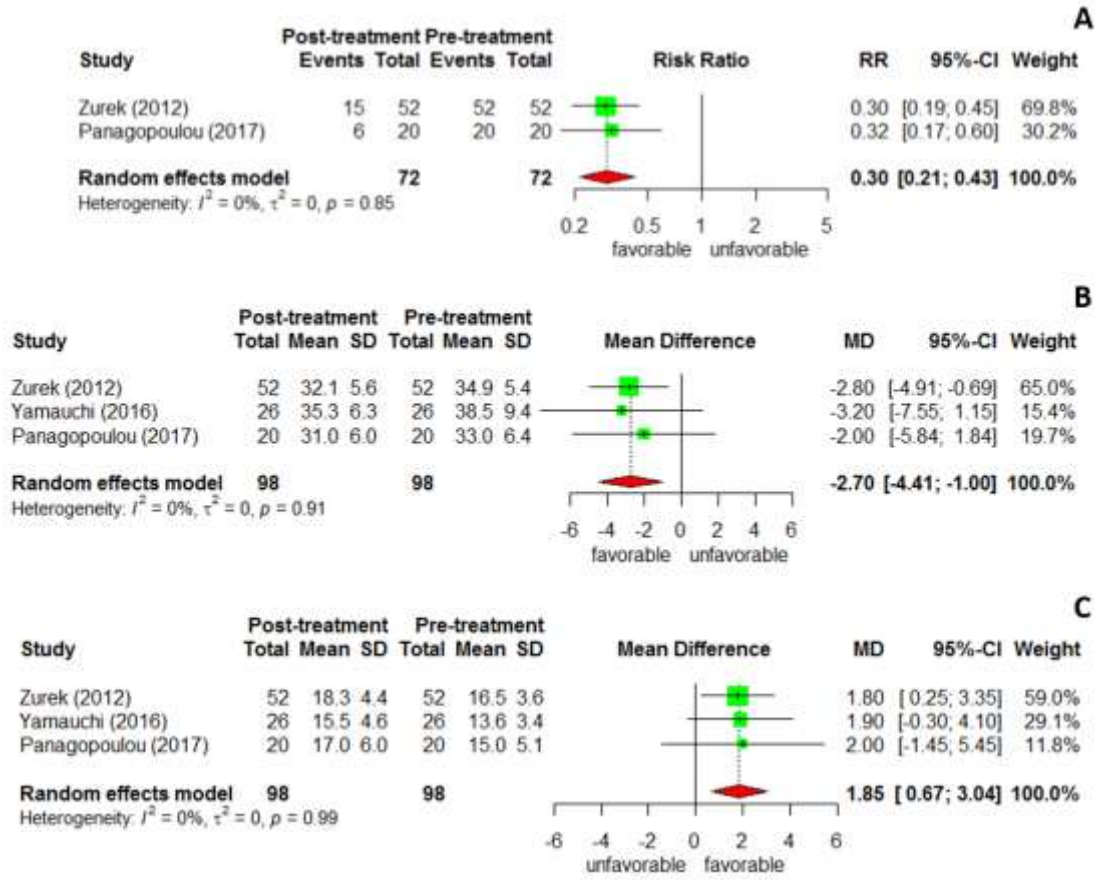


Figure 1. Forest plot of likelihood to improve EOV (A), and mean difference on VE/VCO_2 slope (B), and VO_{2PEAK} ($mL.kg^{-1}.min^{-1}$) (C) in CHF patients with EOV.

The main finding of this review was an EOV reversal near to 70% of the patient cases after a 6-month exercise-training program. Aerobic power and ventilatory efficiency were also improved. Exercise training stimulates mitochondrial biogenesis, hereby optimizing oxidative metabolism in peripheral muscles, as well improving endothelial function and neural control of breathing pathways[5]. This may explain the observed improvement in cardiorespiratory function.

Three factors seem to have a pivotal role in EOV pathophysiology: (1) hyperventilation, (2) circulatory delay (lower cardiac output), and (3) CO_2 cerebrovascular reactivity[1]. Hyperventilation is related to sympathetic hyperactivity and leads to a significant $PaCO_2$ reduction below the respiratory threshold. A pause in the central impulses to respiratory muscles occurs, stopping respiratory movements, followed by a $PaCO_2$ increase and another hyperventilation period. This instability would be further potentiated by circulatory delay and cerebrovascular reactivity to CO_2 impairment, which contributes to the ventilatory central control misalignment[1].

EOV reversal could be promoted by two opposite groups of mechanisms, i.e., by hyperventilation further increase or by hyperventilation mitigation. The former has been demonstrated by the disappearance of EOV if external dead space is added[8] or if patients breathe a gas mixture with added CO_2[9]. On the other hand, hyperventilation mitigation is possible through an improved oxygen delivery to the working muscles, which inhibits metabolites' accumulation[10], a potential trigger to EOV due to intramuscular ergo-receptors impairment[6]. Besides that, exercise training provides improvements in $PaCO_2$ and PaO_2 chemosensitivity and in circulatory time[5], which potentiate the attenuation of the ventilatory drive instability.

Indeed, patients with Cheyne-Stokes respiration exhibit a longer circulation time between lung and chemoreceptors than those without Cheyne-Stokes respiration[11]. This study also suggested that the interaction between chemoreflex gain (change in minute ventilation/change in end-tidal CO_2 partial pressure ratio) and the plant gain (variance in end-tidal CO_2 partial pressure/variance in minute ventilation ratio) may stimulate growing cycles of oscillation (main EOV feature), with plant gain predicting the severity of Cheyne-

Stokes respiration at daytime and a combination of chemoreflex gain and plant gain at night.

Another factor that corroborates to EOV reversal is the ventilatory efficiency improvement. Similar to VO_{2PEAK}, the factors responsible for this improvement have not been elucidated yet in EOV-positive patients. However, Guazzi *et al*.[12] showed that exercise training increases lung diffusion capacity and alveolar-capillary conductance, softening the pulmonary pressure gradients, providing an improvement in ventilatory efficiency. Nevertheless, greater oxygen delivery to the peripheral muscles would imply a reduction in respiratory work (less hyperventilation)[1].

The present analysis has some limitations. Firstly, criteria for VE/VCO_2 slope definitions are possibly different among studies. Secondly, EOV may be present during the entire exercise or may be limited to the first part of the test. This condition also can have influenced the identification of the VE/VCO2 slope and VO2peak.

In conclusion, exercise training is effective for (partly) reversing EOV and improving aerobic capacity (VO_{2PEAK}) and ventilatory efficiency (VE/VCO_2 slope). However, no study evaluated whether the EOV reappeared after detraining.

References

1. Agostoni P and Salvioni E. Exertional Periodic Breathing in Heart Failure: Mechanisms and Clinical Implications. *Clin Chest Med* 2019; 40: 449-457. DOI: 10.1016/j.ccm.2019.02.016.
2. Cornelis J, Taeymans J, Hens W, et al. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis. *Int J Cardiol* 2015; 182: 476-486. DOI: 10.1016/j.ijcard.2015.01.029.
3. Agostoni P, Corrà U and Emdin M. Periodic Breathing during Incremental Exercise. *Annals of the American Thoracic Society* 2017; 14: S116-s122. DOI: 10.1513/AnnalsATS.201701-003FR.
4. Zurek M, Corrà U, Piepoli MF, et al. Exercise training reverses exertional oscillatory ventilation in heart failure patients. *Eur Respir J* 2012; 40: 1238-1244. DOI: 10.1183/09031936.00167011.

5. Panagopoulou N, Karatzanos E, Dimopoulos S, et al. Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure. *Eur J Prev Cardiol* 2017; 24: 825-832. DOI: 10.1177/2047487317695627.
6. Yamauchi F, Adachi H, Tomono J, et al. Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure. *Heart Vessels* 2016; 31: 1659-1668. DOI: 10.1007/s00380-015-0782-x.
7. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020: 2047487320913379. DOI: 10.1177/2047487320913379.
8. Agostoni P, Apostolo A and Albert R. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. *Chest* 2008; 133: 197-203. 2008/01/12. DOI: 10.1378/chest.07-1439..
9. Apostolo A, Agostoni P, Contini M, et al. Acetazolamide and inhaled carbon dioxide reduce periodic breathing during exercise in patients with chronic heart failure. *J Card Fail* 2014; 20: 278-288. 2014/01/15. DOI: 10.1016/j.cardfail.2014.01.007.
10. Aimo A, Saccaro LF, Borrelli C, et al. The ergoreflex: how the skeletal muscle modulates ventilation and cardiovascular function in health and disease. *Eur J Heart Fail* 2021; 23: 1458-1467. DOI: 10.1002/ejhf.2298.
11. Giannoni A, Gentile F, Navari A, et al. Contribution of the Lung to the genesis of Cheyne-Stokes respiration in heart failure: plant gain beyond chemoreflex gain and circulation time. *J Am Heart Assoc* 2019; 8: e012419. DOI: 10.1161/jaha.119.012419.
12. Guazzi M, Reina G, Tumminello G, et al. Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol (1985)* 2004; 97: 1866-1873. DOI: 10.1152/japplphysiol.00365.2004.

Supplementary material

Material and methods

Study design

This systematic review followed the recommendations of the PRISMA statement[1] and was formerly registered on PROSPERO: CRD42021254587.

Eligibility criteria

The following PICOT was adopted: (P) EOV patients; (I) exercise training; (C) pre-training values in EOV group – single arm; (O) EOV reversal, VO_{2PEAK}, or VE/VCO_2 slope; and (T) clinical trial – randomized, non-randomized, or uncontrolled trials. No language restriction was applied. Conference abstract, editorials, case reports, and reviews were excluded.

Data sources and search strategy

Standardized terms were used to perform a high-sensibility search in different databases (PubMed, Embase, Scopus, Web of Knowledge, PEDro, Cochrane Library, and Lilacs) on 30th July 2021. The main terms used were “heart failure”, “exercise oscillatory ventilation”, “therapeutics”, “rehabilitation”, “physical therapy”, “exercise”, and similar terms.

- ***Biblioteca Virtual em Saúde***: ((tw:(heart failure)) AND (tw:(oscillatory ventilation)) OR (tw:(periodic breathing)) AND (tw:(exercise)) OR (tw:(rehabilitation))) AND (db:("IBECS" OR "LILACS")).
- ***Cochrane Central***: ("oscillatory ventilation" OR "periodic breathing") AND ("heart failure") AND ("exercise" OR "revers*" OR "rehab*").
- ***Embase***: (('heart disease'/exp OR 'heart failure'/exp) AND ('exercise'/exp OR 'rehabilitation'/exp) AND ('oscillatory ventilation' OR 'periodic breathing'/exp)).
- ***PEDro Databases***: #1 Search: (“periodic breathing”); #2 Search: (“oscillatory ventilation”).
- ***PubMed***: (heart failure[tiab] OR heart failure[mh]) AND (“oscillatory ventilation”[tiab] OR “periodic breathing”[tiab] OR “oscillatory breathing”[tiab])

AND (“exercise” OR “rehabilitation” OR “physical therapy modalities” OR “therapeutics” OR “revers$”).

- ***Scopus***: TITLE-ABS-KEY ("oscillatory ventilation" OR "periodic breathing") AND TITLE-ABS-KEY (exercise OR "rehabilitation" OR "physical therapy modalities" OR "therapeutics" OR "cardiac rehabilitation") AND TITLE-ABS-KEY ("heart failure" OR "cardiac heart failure").
- ***Web of Science***: ((TS=("heart failure" OR "cardiac heart failure")) AND TS=("oscillatory ventilation" OR "periodic breathing")) AND TS=(exercise OR "rehabilitation" OR "physical therapy modalities" OR "therapeutics" OR "revers$" OR "cardiac rehabilitation").

Study selection

Two reviewers (GR and CC) assessed independently the titles and the abstracts. The screening was carried out in a references management’s software (EndNote X7, Thomson Reuters, US). All potentially eligible studies were read in full. Disagreements were resolved by the third author (PL). The κ coefficient was used to measure the agreement level[2].

Data extraction

This process was done independently by two authors (GR and CC). The extracted data were: 1) study design; 2) country; 3) EOV criteria; 4) sample size; 5) baseline characteristics; 6) exercise protocol; and 7) outcomes. EOV reversal was the primary outcome. Were considered as secondary outcomes any cardiopulmonary, hemodynamic, metabolic, or functional measures as VO_{2PEAK}, VE/VCO_2 slope, left ventricular ejection fraction, EOV parameters (amplitude, cycle length, and duration), workload and/or inflammatory markers. The authors provided a narrative synthesis describing the exercise protocol, population characteristics, and the main outcomes.

Methodological quality assessment

TESTEX scale was applied to assess the methodological quality of the included studies. This tool was developed to review the exercise training studies[3], assigning 5-point for study quality and 10-point for study reporting. All analysis

was done in duplicate (GR and MK) and disagreements were resolved by a third author (DH).

Data analysis

The random-effect model was applied using the standardized mean difference (SMD) with a 95% confidence interval (95% CI) to measure the exercise effect on $VO2_{PEAK}$ and VE/VCO_2 slope in CHF patients with EOV. An SMD value higher than 0.5 indicated a moderate effect size and higher than 0.8 indicated a large effect size[2]. Subsequently, a mean difference (MD) analysis was also performed. In addition, a random-effect model was applied with 95% CI to assess the relative risk (RR) from EOV reversal. Values above or near 50% of the statistical I^2 were indicative of heterogeneity[2]. Forest plots summarize the results. All analyses were done in RStudio software (RStudio Inc., Boston, US).

1. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71. DOI: 10.1136/bmj.n71.

2. Ribeiro GS, Melo RD, Deresz LF, et al. Cardiac rehabilitation programme after transcatheter aortic valve implantation versus surgical aortic valve replacement: Systematic review and meta-analysis. *Eur J Prev Cardiol* 2017; 24: 688-697. 2017/01/11. DOI: 10.1177/2047487316686442.

3. Smart NA, Waldron M, Ismail H, et al. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. *Int J Evid-Based Health* 2015; 13: 9-18. DOI: 10.1097/xeb.0000000000000020.

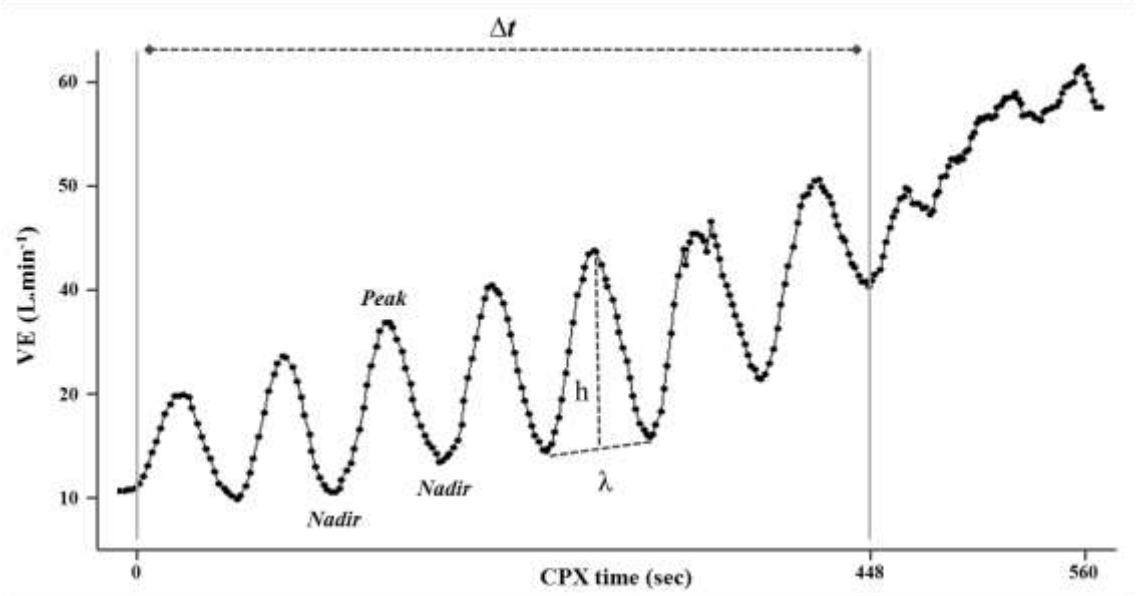


Figure 1S. EOV characteristics in a patient undergoing cardiopulmonary exercise testing. VE, minute ventilation. h, amplitude. λ, cycle length. ∆t, duration. CPX, cardiopulmonary exercise test.

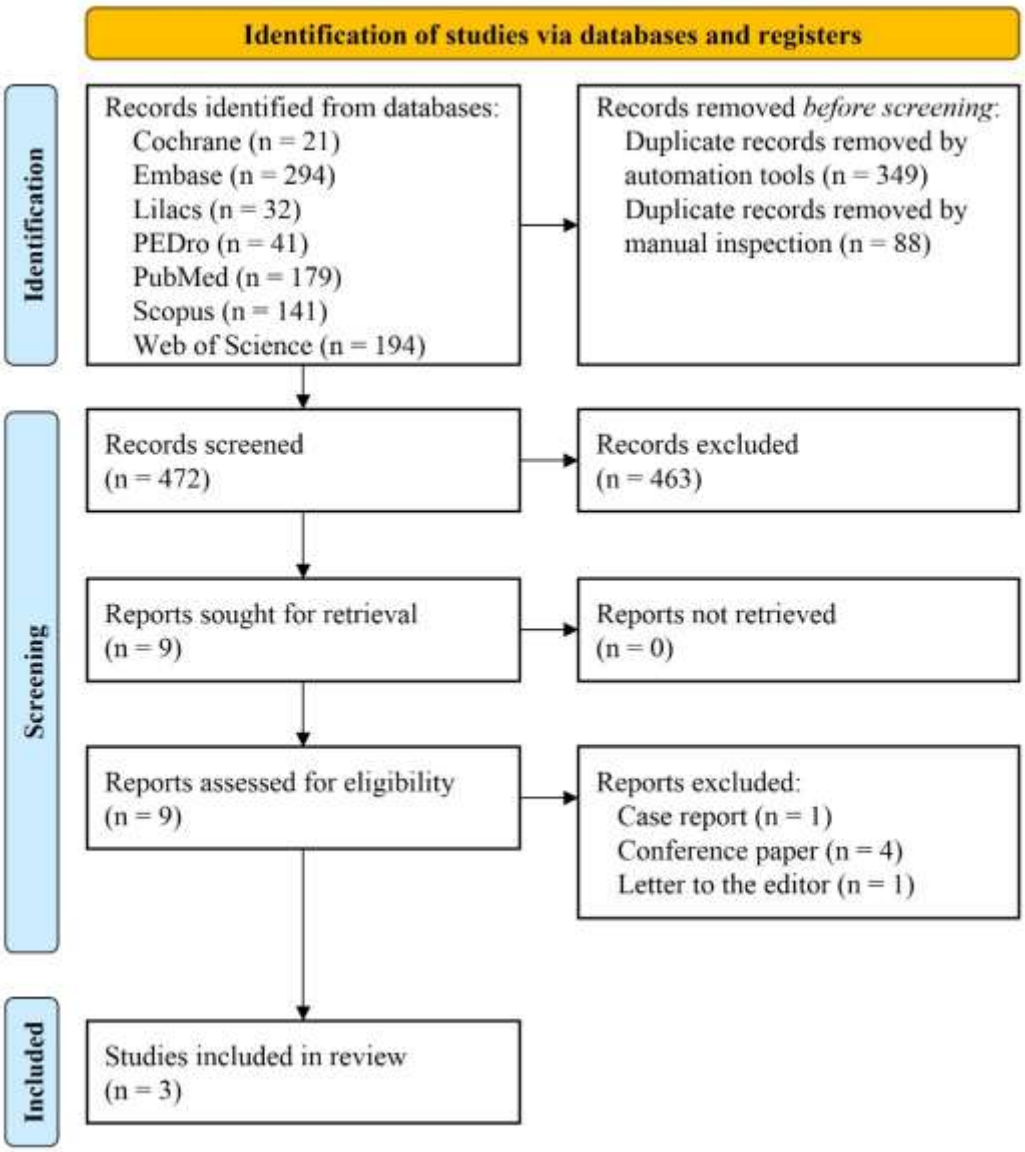


Figure 2S. PRISMA flowchart. EOV, exercise oscillatory ventilation. CPX, cardiopulmonary exercise test.

Table 1S Characteristics of the included studies

Authors (years)	Panagopoulou (2017)	Yamauchi (2016)	Zurek (2012)
Country	Greece	Japan	Switzerland/Italy
EOV criteria	Corrà (2002)	Leite (2003)	Leite (2003)
Sample size, n	20	26	52
Age, years	54 ± 12	62 ± 16	58 ± 10
Gender, male	17 (85)	24 (92)	47 (90)
BMI, kg.m²	26.4 ± 3.9	22 ± 5	26.1 ± 4.6
LVEF, %	32 ± 11	31 ± 13	27 ± 9
Ischemic heart disease	8 (40)	7 (27)	22 (42)
Comorbidities			
Hypertension	NA	16 (62)	NA
Diabetes	NA	7 (27)	NA
Dyslipidaemia	NA	16 (62)	NA
Chronic kidney disease	NA	16 (62)	NA
Atrial fibrillation	NA	6 (23)	13 (25)
Medication			
ACE inhibitors/ARB	16 (80)	17 (65)	52 (100)
β-blockers	17 (85)	20 (77)	47 (90)
Diuretics	18 (90)	25 (96)	42 (81)

EOV, exercise oscillatory ventilation. BMI, body mass index. LVEF, left ventricular eject fraction. NA, not available. ACE, angiotensin-converting enzyme. ARB, angiotensin receptor blocker. Data are expressed as means ± SD or n (%).

Table 2S Testex scale for quality assessment

Criteria / Author (year)	Quality bias					Reporting bias										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Total**
Panagopoulou (2017)	1	1	NR	1	NR	1	NR	NR	1	1	1	1	NR	NR	1	**9**
Yamauchi (2016)	1	NR	NR	NR	1	1	NR	1	1	1	1	1	1	NR	1	**10**
Zurek (2012)	1	NR	NR	1	NR	1	NR	NR	1	1	1	1	1	NR	1	**9**

Quality bias: (1) eligibility criteria specified; (2) randomization method; (3) allocation concealment; (4) groups similar at baseline; and (5) blinded assessor. Reporting bias: (6) study withdrawals reported; (7) adverse events reported; (8) session attendance reported; (9) intention-to-treat analysis; (10) between-group primary analysis; (11) between-group secondary analysis; (12) point measures for all outcomes; (13) activity monitoring controls; (14) relative exercise intensity adjusted; and (15) exercise energy expenditure information reported. NR, not reported.

7 CONCLUSÃO GERAL

A ventilação periódica durante o exercício é um fenômeno anormal e típico no padrão ventilatório de pacientes com insuficiência cardíaca. Sua presença é relacionada ao maior risco de eventos adversos. Entretanto, não há consenso sobre qual a definição com maior sensibilidade para realizar o diagnóstico e se elas apresentam capacidade preditiva similar para predizer desfechos adversos. Além disso, a complexidade conceitual inviabiliza a utilização deste marcador na prática clínica. Questões como métodos alternativos de diagnóstico e o efeito do exercício físico como tratamento carecem de maiores explicações.

Estas indagações nortearam as atividades da presente tese que resultou no desenvolvimento de quatro artigos e um software. O EASY-EOV tool permite analisar as características do padrão ventilatório, como amplitude e comprimento do ciclo, de forma padronizada e semiautomatizada facilitando a identificação do fenômeno. Esta ferramenta será disponibilizada gratuitamente para comunidade científica proporcionando maior inserção deste marcador na prática clínica. Seu desenvolvimento, funcionalidades e alta reprodutibilidade para identificar casos de EOV foram descritos no primeiro artigo desta tese.

De acordo com o que foi descrito no segundo estudo, pode-se observar que as definições priorizam características distintas do padrão ventilatório (ex.: amplitude *vs* duração). Sua escolha parece afetar o número de casos positivos (prevalência) e a sensibilidade para predizer eventos cardiovasculares adversos a curto-médio prazo. Neste cenário, a definição proposta por Corrà mostrou-se mais efetiva para triar casos de maior complexidade (risco de morte) e predizer eventos adversos em nossa amostra. Além disso, nossos dados sugerem que a amplitude do ciclo teria maior relação com comprometimento ventricular.

No terceiro artigo da tese, demonstramos que a variabilidade da VE pode ser uma ferramenta útil para quantificar a EOV e predizer desfechos adversos em magnitude similar a abordagem dicotômica. Sua aferição mostrou-se mais ágil e independente da expertise do avaliador ou das definições dicotômicas. Além disso, análise quantitativa pode identificar alterações no padrão ventilatório antes que a doença atinja estágios mais avançados. Nossos dados sugerem que pacientes com insuficiência cardíaca e baixa variabilidade da VE exibem maior risco de eventos adversos a médio prazo que pacientes com alta variabilidade.

Por fim, o último estudo apresentado na tese investigou o efeito do treinamento físico na reversão da EOV e outros marcadores prognósticos em pacientes EOV-positivo. Após minuciosa revisão sistemática, identificamos um número reduzido de estudos com este enfoque. Os protocolos foram sintetizados e os resultados meta-analisados, mostrando que o treinamento físico é efetivo para reverter os casos de EOV-positivo, melhorar a capacidade aeróbia e a eficiência ventilatória de pacientes com insuficiência cardíaca, além de seguro para ser incorporado ao tratamento conservador.

Concluindo, a definição de Corrà demonstrou melhor capacidade preditiva dentre as definições dicotômicas para predizer desfechos adversos de curto a médio prazo. A variabilidade da VE obteve resultamos superiores a abordagem dicotômica mostrando ser um método promissor para avaliar e acompanhar pacientes EOV. Além disso, o fenômeno mostrou-se responsivo ao exercício físico como método de tratamento.

8 IMPACTOS DO TRABALHO

Ao longo da minha pesquisa tive a oportunidade de investigar diferentes aspectos relacionados à ventilação periódica durante o exercício. Cada estudo desenvolvido abordou uma temática distinta que poderá impactar positivamente na avaliação ou tratamento de pacientes. Destaco algumas contribuições da presente tese: (1) o desenvolvimento de uma ferramenta gratuita para padronizar e disseminar o uso deste marcador na prática clínica; (2) a possibilidade de uso da variabilidade da VE como recurso para avaliar e acompanhar a sintomatologia de pacientes com alterações no padrão ventilatório; (3) a síntese dos protocolos de reabilitação para profissionais da saúde utilizarem no tratamento de pacientes EOV-positivo; e (4) o respaldo à maior sensibilidade da definição de Corrà para predizer, isoladamente e entre as definições dicotômicas, desfechos adversos a médio prazo.

9 ATIVIDADES REALIZADAS DURANTE O DOUTORADO

Durante o desenvolvimento do doutorado pude participar de diversas atividades vinculadas ou não ao projeto de pesquisa, as quais contribuíram direta ou indiretamente para o meu amadurecimento acadêmico. Neste período, ministrei aulas em cursos de especialização, palestrei em eventos científicos, colaborei com outros projetos de pesquisa, auxiliei no desenvolvimento de um software, orientei trabalhos de conclusão e fui revisor de periódicos. Resumo abaixo as principais produções desenvolvidas no período.

9.1 Produção técnico-científica relacionada à pesquisa do doutorado

Em outubro de 2017 fui instigado pelo meu orientador a estudar uma área ainda pouco explorada na literatura: a ventilação periódica durante o exercício. Em meio às discussões e amadurecimento do projeto, desenvolvi a 1ª produção da tese, encaminhada ao EuroPrevent Congress 2019 (Apêndice A), realizado em Lisboa, Portugal. Naquele período, além de participar do evento, realizei visita técnica ao Centro Cardiologico Monzino (Itália), viabilizando a parceria que resultou no desenvolvimento do software (parecer 4.558.550/2021, Anexo C), no estudo da sensibilidade e especificidade das definições clássicas e da variabilidade da VE para prever eventos adversos (parecer 3.516.801/2019, Anexo D), além de outros resumos apresentados em congressos internacionais (Apêndice 2 a 5). Os artigos publicados encontram-se nos Anexos A e B.

Artigo completo publicado em periódico científico

1. Ribeiro GS, Deresz LF, Salvioni E, Hansen D, Agostoni P, Karsten M. Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients. International Journal of Cardiology, v. 360, p. 39-43, 2022.
2. Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M. Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis. European Journal of Preventive Cardiology, v. 26, n. 6, p. e233-e236, 2022.

Capítulo de livro publicado

1. Ribeiro GS, Karsten M. Ventilação periódica durante o exercício em indivíduos com insuficiência cardíaca. In: Associação Brasileira de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva; Martins JA, Karsten M, Dal Corso S, organizadores. PROFISIO Programa de Atualização em Fisioterapia Cardiovascular e Respiratória: Ciclo 8. Porto Alegre: Artmed Panamericana; 2022. p. 9-35.

Resumo publicado em anais de evento

1. Ribeiro GS, Beltrame T, Deresz LF, Hansen D, Agostoni P, Karsten M. EASY-EOV tool: metodologia de construção e análise da reprodutibilidade de um software para detectar casos de ventilação periódica durante o exercício. In: 20º Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva 2022. Florianópolis. Assobrafir Ciência, 2022, v. 7, p. 454. [2° Lugar no Prêmio de Inovação e Tecnologia].
2. Ribeiro GS, Deresz LF, Salvioni E, Hansen D, Agostoni P, Karsten M. Brain natriuretic peptide levels are associated with cycle length average and are different between Ben-Dov and Corrà exercise oscillatory ventilation definitions in heart failure patients. In: ESC Preventive Cardiology 2022, Ljubljana. European Journal of Preventive Cardiology, 2020, v. 29, p. i20.
3. Ribeiro GS, Deresz LF, Salvioni E, Hansen D, Agostoni P, Karsten M. Would be the minute ventilation variability an alternative to the dichotomous diagnosis of exercise oscillatory ventilation? In: ESC Preventive Cardiology 2022, Prague. European Journal of Preventive Cardiology, 2020, v. 29, 304.
4. Ribeiro GS, Deresz LF, Dal Lago P, Hansen D, Agostoni P, Karsten M. Exercise oscillatory ventilation impairs oxygen delivery/extraction in male patients with chronic heart failure. In: ESC Preventive Cardiology, 2020, Malaga. European Journal of Preventive Cardiology, 2020, v. 27, p. S85.
5. Ribeiro GS, Cargnin C, Dal Lago P, Hansen D, Agostoni P, Karsten M. Effects of pharmacological and non-pharmacological treatments on cardiorespiratory parameters in chronic heart failure patients with exercise oscillatory ventilation: a systematic review. In: European Congress on

Preventive Cardiology, 2019, Lisbon. European Journal of Preventive Cardiology, 2019. v. 26. p. S42-S43.

Curso de aperfeiçoamento

Além das atividades de pesquisa, realizei alguns cursos complementares para qualificar minha atuação acadêmica. Destacando-se os cursos:

1. Metanálise utilizado o software R: Ensaios clínicos (HTANALYZE 2019).
2. Revisão sistemática e metanálise em rede (HTANALYZE 2019).
3. Revisão sistemática e meta-análise (UNICAMP 2020).

Edital de pesquisa

Em 2019 desenvolvi um projeto para concorrer a uma bolsa de doutorado sanduíche no exterior concedida pela CNPJ. Participei efetivamente de todos os processos do edital. Embora a proposta “Avaliação da oxigenação dos músculos respiratórios e periféricos em pacientes com ventilação periódica em exercício submetidos à infusão de levosimendan” tenha recebido uma boa avaliação (9,40 pontos), acabou ficando abaixo da linha de corte dos recursos disponíveis.

Visitas de técnicas no exterior

Em abril de 2019 tive a oportunidade de visitar dois centros de referência no tratamento de pacientes com insuficiência cardíaca: o Heart Centre Hasselt (Bélgica) e o Centro Cardiologico Monzino (Itália). Em ambos os locais, vivenciei a rotina de avaliação dos pacientes e os protocolos de reabilitação sob a tutoria dos professores Dr. Dominique Hansen e Dr. Piergiuseppe Agostoni. Momentos de muito aprendizado que estreitaram a relação entre os grupos. A possibilidade de vivenciar o dia a dia de uma equipe multiprofissional em um ambiente clínico que desenvolve pesquisa foi um diferencial para ampliar minha visão acadêmica.

9.2 Produção técnico-científica não relacionada à pesquisa de doutorado

Durante o doutorado pude participar de projetos de outros grupos de pesquisa. Estas vivências complementaram minha formação técnico-científica e resultaram em algumas publicações na área. Além disso, tive a oportunidade de contribuir com a formação de acadêmicos de diferentes áreas do conhecimento da Universidade do Estado de Santa Catarina (UDESC), Universidade do Estado

do Amazonas (UEA), Escola Bahiana de Medicina e Saúde Pública, Faculdade SOGIPA de Educação Física e Instituto Sul-Brasileiro de Cursos e Qualificações. Destaco algumas produções realizadas neste período:

Artigo completo publicado em periódico científico

1. Vieira A, Martins E, Althoff A, Rech D, Ribeiro GS, Matte D, Karsten M. Application and measurement properties of the talk test in cardiopulmonary patients: a systematic review. Reviews in Cardiovascular Medicine, v. 23, n. 7, p. 225, 2022.
2. Dubal A, Portela M, Ribeiro GS, Lopes A. Efeito do agachamento com carga equalizada na potência de membros inferiores de judocas de alto rendimento. Revista Brasileira de Prescrição e Fisiologia do Exercício, v.13, n. 86, p. 1076-1083, 2020.
3. Lopes A, Rodriguez J, Santos P, Ribeiro GS, Carteri R. Which variable best explains the adaptations of strength training? FIEP Bulletin, v. 90, p. 75-85, 2020.
4. Gross J, Lopes A, Krüger R, Ribeiro GS, et al. Efeito da crioterapia de imersão sobre níveis de força e potência muscular. Revista Brasileira de Fisiologia do Exercício, v. 19, n. 4, p. 283-291, 2020.
5. Ribeiro GS, Fragoso E, Nunes R, Lopes A. Erro técnico de medida em antropometria: análise de precisão e exatidão em diferentes plicômetros. Revista de Educação Física, v. 88, n. 2, p. 810-817, 2019.
6. Ribeiro GS, Neves V, Deresz LF, Melo R, Dal Lago P, Karsten M. Can RR intervals editing and selection techniques interfere with the analysis of heart rate variability? Brazilian Journal of Physical Therapy, v. 22, n. 5, p. 383-390, 2018.
7. Pereira U, Ribeiro GS, Lopes A. Can heart rate variability predict the second metabolic threshold in young soccer players? International Journal of Exercise Science, v. 11, n. 2, p. 1105-1111, 2018.
8. Karsten M, Ribeiro GS, Esquivel M, Matte D. Effects of inspiratory muscle training with linear workload devices on the sports performance and cardiopulmonary function of athletes: A systematic review and meta-analysis. Physical Therapy in Sport, v. 34, p. 92-104, 2018.

9. Vitória M, Lopes A, Garllip D, Ribeiro, GS. Área muscular da coxa não prediz altura do salto vertical em atletas de futebol profissional. Revista Brasileira de Futsal e Futebol, v. 10, n. 40, p. 577-582, 2018.

Carta ao editor publicada em periódico científico

1. Karsten M, Ribeiro GS, Esquivel M, Matte D. Maximizing the effectiveness of inspiratory muscle training in sports performance: A current challenge. Physical Therapy in Sport, 36, p. 68-69, 2019.
2. Matte D, Ribeiro GS, Esquivel M, Karsten M. Regarding: Inspiratory muscle training improves performance of a repeated sprints ability test in professional soccer players. Journal of Bodywork and Movement Therapies, v. 23, n. 3, p. 443-444, 2019.

Livro publicado

1. Lopes A, Petroski CA, Ribeiro GS. Antropometria aplicada à saúde e ao desempenho esportivo: uma abordagem a partir da metodologia ISAK. 2. ed. Porto Alegre: IsulBra, 2018. 210p.

Resumo publicado em anais de evento

1. Martins E, Silveira L, Ribeiro GS, Vieira A, Roque A, Mortimer F, Benetti M, Karsten M. Talk Test Responsiveness after 8-week of exercise training in cardiovascular disease patients. In: European Congress on Preventive Cardiology, 2021. European Journal of Preventive Cardiology, 2021. v. 28. p. i310.
2. Karsten M, Mortimer FM, Silveira L, Ribeiro GS. Exercise test with constant workload versus incremental test in individuals with cardiovascular disease: systematic review and meta analysis. In: European Congress on Preventive Cardiology, 2021. European Journal of Preventive Cardiology, 2021. v. 28. p. i309.
3. Karsten M, Rech D, Vieira A, Silva M, Ribeiro GS, Matte D. Is frailty associated with functional capacity decline in chronic cardiovascular disease patients? A systematic review and meta-analysis. In: European Congress on Preventive Cardiology, 2019, Lisbon. European Journal of Preventive Cardiology, 2019. v. 26. p. S93-S94.

4. Ribeiro GS, Deresz LF, Melo R, Pontes M, Dal Lago P, Karsten M. Heart rate variability quality analysis is a strong 30-day mortality predictor in aortic stenosis patients underwent to valve repair procedure. In: European Congress on Preventive Cardiology, 2019, Lisbon. European Journal of Preventive Cardiology, 2019. v. 26. p. S124-S125.
5. Ribeiro GS, Deresz LF, Melo R, Pontes M, Dal Lago P, Karsten M. Could be the detrended fluctuation analysis an alternative tool to support the heart team to decide between surgical aortic valve replacement or transcatheter aortic valve implantation? In: European Congress on Preventive Cardiology, 2019, Lisbon. European Journal of Preventive Cardiology, 2019. v. 26. p. S126-S127.
6. Ramos T, Fernandes P, Ribeiro G, Lima A. Estado nutricional de escolares do Ensino Fundamental I da cidade de Novo Aripuanã – Amazonas. In: Congresso Internacional de Ciências da Saúde, 2018, Juazeiro do Norte. Journal of Human Growth and Development, 2018. p. 420.
7. Ramos T, Tibao M, Ribeiro G, Lima, A. Curvas de crescimento de escolares do Ensino Fundamental I da cidade de Novo Aripuanã – Amazonas. In: Congresso Internacional de Ciências da Saúde, 2018, Juazeiro do Norte. Journal of Human Growth and Development, 2018. p. 421.
8. Fernandes P, Ramos T, Ribeiro GS, Lima, A. Perfil antropométrico de escolares do Ensino Fundamental I de Novo Aripuanã – Amazonas. In: Congresso Internacional de Ciências da Saúde, 2018, Juazeiro do Norte. Journal of Human Growth and Development, 2018. p. 422.
9. Tibao M, Duarte L, Ribeiro GS, Lima A. Status maturacional de escolares do Ensino Fundamental I da cidade de Novo Aripuanã – Amazonas. In: Congresso Internacional de Ciências da Saúde, 2018, Juazeiro do Norte. Journal of Human Growth and Development, 2018. p. 423.
10. Duarte L, Fontes Junior R, Ribeiro GS, Lima, A. Aptidão física relacionada à saúde de escolares de Novo Aripuanã – Amazonas. In: Congresso Internacional de Ciências da Saúde, 2018, Juazeiro do Norte. Journal of Human Growth and Development, 2018. p. 427.
11. Castro D, Fontes Junior R, Ribeiro GS, Lima A. Desempenho esportivo de escolares de Novo Aripuanã – Amazonas. In: Congresso Internacional de

Ciências da Saúde, 2018, Juazeiro do Norte. Journal of Human Growth and Development, 2018. p. 428.

12. Fragoso E, Nunes R, Guimaraes A, Ribeiro GS, Lima A, Silva R, Garllip D, Castilha F, Lopes A. Analysis of precision and accuracy in anthropometry: a comparative study between different skinfold calipers. In: 35º Congresso Mundial de Medicina do Esporte FIMS, 2018, Rio de Janeiro. Revista Brasileira de Medicina do Esporte. São Paulo: Atha Comunicação e Editora, 2018. v. 24. p. 47-47.
13. Fragoso E, Guimaraes A, Ribeiro GS, Lima A, Nunes R, Silva R, Garllip D, Castilha F, Lopes A. Reliability analysis of the different instruments to measure skinfold thickness. In: 35º Congresso Mundial de Medicina do Esporte FIMS, 2018, Rio de Janeiro. Revista Brasileira de Medicina do Esporte. São Paulo: Atha Comunicação e Editora, 2018. v. 24. p. 57-57.
14. Fragoso E, Zaccani W, Guimaraes A, Ribeiro GS, Lima A, Silva R, Garllip D, Castilha F, Lopes A. Muscle-Bone Index: a new paradigm for the monitoring of athletes performance. In: 35º Congresso Mundial de Medicina do Esporte FIMS, 2018, Rio de Janeiro. Revista Brasileira de Medicina do Esporte. São Paulo: Atha Comunicação e Editora, 2018. v. 24. p. 48-48.
15. Silva A, Fragoso E, Zaccani W, Ribeiro GS, Lopes A. Correlação entre diâmetro do úmero e área muscular do braço: vantagem mecânica para produção de força. In: VII Congresso de Ciências do Esporte da Região Norte - VII CONCENO, 2018, Palmas. Anais do VII Congresso de Ciências do Esporte da Região Norte. Porto Alegre: Colégio Brasileiro de Ciências do Esporte, 2018. v. VII. p. 1-2.
16. Silva A, Fragoso E, Zaccani W, Ribeiro GS, Lopes A. Comprimento da mão em judocas do sexo masculino: uma vantagem mecânica para produção de força. In: VII Congresso de Ciências do Esporte da Região Norte - VII CONCENO, 2018, Palmas. Anais do VII Congresso de Ciências do Esporte da Região Norte. Porto Alegre: Colégio Brasileiro de Ciências do Esporte, 2018. v. VII. p. 1-2.
17. Karsten M, Ribeiro GS, Melo R, Pontes M, Dal Lago P. Muscle quality is lower in frail patients with severe aortic stenosis and is associated to muscle strength, nutritional status and cardiac operative risk. In: Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia

Intensiva, 2018, Manaus. ASSOBRAFIR Ciência. São Paulo: ASSOBRAFIR, 2018. v. 9. p. 51-52. [1° Lugar no Prêmio Fisioterapia Cardiovascular].

18. Karsten M, Rech D, Vieira A, Silva M, Matte D, Ribeiro GS. Fragilidade está associada à maior chance de morte em pacientes com doença cardiovascular crônica: dados preliminares de uma revisão sistemática com meta-análise. In: Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva, 2018, Manaus. ASSOBRAFIR Ciência. Londrina: ASSOBRAFIR, 2018. v. 9. p. 340-341.
19. Mata C, Moraes B, Esquivel M, Ribeiro GS, Karsten M. Impacto do treinamento muscular inspiratório no desmame de pacientes em ventilação mecânica invasiva: meta-análise de ensaios clínicos randomizados. In: Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva, 2018, Manaus. ASSOBRAFIR Ciência. São Paulo: ASSOBRAFIR, 2018. v. 9. p. 415-415.

Cursos de curta duração

1. Especialização em Fisiologia do Exercício e Nutrição Esportiva. Disciplina: Avaliação e prescrição de treinamento para esportes de longa duração – 10h. Instituto Sul-Brasileiro de Cursos e Qualificações: Porto Alegre, 2021.
2. Especialização em Fisiologia do Exercício e Nutrição Esportiva. Disciplina: Avaliação e prescrição de treinamento para esportes de longa duração – 10h. Instituto Sul-Brasileiro de Cursos e Qualificações: Porto Alegre, 2019.
3. Especialização em Fisiologia do Exercício e Nutrição Esportiva. Disciplina: Respostas e adaptações ao treinamento cardiovascular – 20h. Faculdade SOGIPA de Educação Física: Pelotas, 2018.
4. Especialização em Fisiologia do Exercício e Nutrição Esportiva. Disciplina: Respostas e adaptações ao treinamento cardiovascular – 20h. Faculdade SOGIPA de Educação Física: Porto Alegre, 2018.

Orientação, coorientação e colaboração em trabalhos de conclusão

1. Felipe Moreira Mortimer. Teste de exercício com carga constante versus teste de esforço incremental em indivíduos com doenças cardiovasculares:

revisão sistemática e metanálise. 2020. Dissertação (Mestrado em Fisioterapia) - Universidade do Estado de Santa Catarina.

2. Edgar Manoel Martins. Responsividade de um protocolo de teste da fala em esteira ergométrica a um programa de exercícios aeróbios aplicado em indivíduos com doenças cardiovasculares. 2020. Dissertação (Mestrado em Fisioterapia) - Universidade do Estado de Santa Catarina.
3. Patrícia Pinto Fernandes. Curvas de Crescimento de Crianças da Escola Estadual Professor Francisco Sá. 2018. Trabalho de Conclusão de Curso (Graduação em Educação Física) - Universidade do Estado do Amazonas.
4. Taiz Carina Teixeira Ramos. Estado Nutricional de Escolares do Ensino Fundamental I da Cidade de Novo Aripuanã - Amazonas. 2018. Trabalho de Conclusão de Curso (Graduação em Educação Física) - Universidade do Estado do Amazonas.
5. Caroline da Rosa Schüller. Treinamento de força na reabilitação de pacientes com acidente vascular cerebral. 2018. Trabalho de Conclusão de Curso (Especialização em Fisiologia do Exercício e Nutrição Esportiva) - Faculdade SOGIPA de Educação Física.
6. Lizia Villeroy Schneider. Aspectos neuromusculares do treinamento de força: fatores intervenientes na produção de força. 2018. Trabalho de Conclusão de Curso (Especialização em Fisiologia do Exercício e Nutrição Esportiva) - Faculdade SOGIPA de Educação Física.
7. Márcio Vitória. Relação entre área muscular de coxa e altura do salto vertical em atletas de futebol profissional. 2018. Trabalho de Conclusão de Curso (Especialização em Fisiologia do Exercício e Nutrição Esportiva) - Faculdade SOGIPA de Educação Física.
8. Victor Manoel Corrêa Freitas. Influência do anticoncepcional oral no ganho de massa magra em mulheres praticantes de treinamento de força. 2018. Trabalho de Conclusão de Curso (Especialização em Fisiologia do Exercício e Nutrição Esportiva) - Faculdade SOGIPA de Educação Física.
9. Bruno Silva de Oliveira e Ieda Conceição Brandão. Treinamento muscular inspiratório melhora a força muscular inspiratória e reduz o tempo de permanência hospitalar de pacientes submetidos a cirurgia cardiovascular: Revisão sistemática com meta-análise. 2017. Trabalho de Conclusão de

Curso (Especialização em Fisioterapia Hospitalar) - Escola Bahiana de Medicina e Saúde Pública.

Palestras ministradas

1. Antropometria aplicada à detecção de jovens talentos. Centro Universitário do Norte (UNINORTE): Manaus, 2020
2. Fisiologia do exercício aplicada ao treinamento de atletas de voleibol em formação. In: Curso de Treinadores Nível II. Federação Gaúcha de Voleibol (FGV): Porto Alegre, 2019
3. Fisiopatologia da obesidade. In: XVII Jornada Nacional de Atividade Física. Universidade Luterana do Brasil (ULBRA): Cachoeira do Sul, 2017.

Participação em bancas de qualificação

1. Gabriela Leopoldino e José Luís Rodrigues. Perfil clínico e funcional de idosos frágeis e não frágeis submetidos à cirurgia cardíaca. 2022. Trabalho de Conclusão de Curso (Residência Multiprofissional em Saúde) - Instituto de Cardiologia do Rio Grande do Sul.
2. Amanda Althoff. Teste da fala como ferramenta de prescrição da intensidade de exercício aeróbio na reabilitação cardiovascular. 2021. Banca de qualificação do Trabalho de Conclusão de Curso (Graduação em Fisioterapia) - Universidade do Estado de Santa Catarina.

Participação em projetos de pesquisa

1. Análise de recursos para triagem e diagnóstico de fragilidade e sarcopenia em pacientes com câncer. Coordenação: Prof. Dr. Marlus Karsten. Aluna: Eduarda Borges Mendonça.
2. Responsividade de um protocolo de teste da fala em esteira ergométrica a um programa de exercícios aeróbios aplicado em indivíduos com doenças cardiovasculares. Coordenação: Prof. Dr. Marlus Karsten. Aluno: Edgar Manoel Martins.
3. Impacto da fragilidade em desfechos clínicos, funcionais e fisiológicos de indivíduos com doença cardiorrespiratória crônica. Coordenação: Prof. Dr. Marlus Karsten. Aluna: Daiana Aparecida Rech.

4. Validação do teste da fala em esteira para avaliação cardiorrespiratória de adultos com ou sem doença cardiovascular. Coordenação: Prof. Dr. Marlus Karsten. Aluna: Ariany Marques Vieira.
5. Avaliação multiparamétrica e reabilitação cardiopulmonar de pacientes com coexistência de insuficiência cardíaca crônica e doença pulmonar obstrutiva crônica. Projeto desenvolvido pelo Grupo de Pesquisa em Saúde Cardiovascular e Exercício. Universidade do Estado de Santa Catarina. Coordenação: Prof. Dr. Marlus Karsten.
6. Síndrome Sarcopênica - Função Física, Fenótipo e Qualidade de vida em idosos com e sem Estilo de Vida Sedentário. Universidade do Estado do Amazonas. Coordenação: Prof. Me. Alex Barreto de Lima.
7. Aptidão física, composição corporal, estado nutricional, qualidade de vida e imagem corporal de escolares na faixa etária dos 07 aos 17 anos do município de Tonantins, Amazonas. Universidade do Estado do Amazonas. Coordenação: Prof. Me. Alex Barreto de Lima.
8. Estudo das características antropométricas, dermatoglificas, nutricionais, níveis de aptidão física, atividade física, qualidade de vida, estilo de vida e percepção da imagem corporal de crianças e adolescentes das escolas de Novo Aripuanã, Amazonas, Brasil. Universidade do Estado do Amazonas. Coordenação: Prof. Me. Alex Barreto de Lima.

Revisor de periódico

Outra atividade ministrada durante meu período de doutorado foi a revisão de artigos encaminhados para publicação. Neste período fui convidado para ser revisor ad-hoc dos periódicos: *Clinical Rehabilitation, Clinics, Journal of Exercise Rehabilitation, Scientia Medica, International Journal of Sports Physiology and Performance*, Revista Brasileira de Geriatria e Gerontologia, Revista Brasileira de Educação Física e Esporte.

APÊNDICES

APÊNDICE 1

Resumo apresentado no EuroPrevent Congress 2019

Effects of pharmacological and non-pharmacological treatment on cardiorespiratory parameters in chronic heart failure patients with exercise oscillatory ventilation: a systematic review

Ribeiro GS[1], Cargnin C[1], Dal Lago P[1], Hansen D[3], Agostoni P[4], Karsten M[5]

Background: Exercise oscillatory ventilation (EOV), described as ventilatory oscillation cycles with or without interposed apnea, is associated with worse prognosis in chronic heart failure (CHF) patients. Studies show a 4-fold higher risk for adverse cardiovascular events in patients with EOV.

Purpose: To synthesize the effects of pharmacological and non-pharmacological treatments on oxygen uptake (VO_2 peak), ventilatory efficiency (VE/VCO_2 slope), and EOV parameters in CHF patients with EOV.

Methods: Searches were performed on several databases. There was no restriction on study design, but only studies published after 2008 were selected. Inclusion criteria: adult patients (40 years old or older) with EOV diagnosis concomitant to CHF. Intervention: all non-invasive therapies designed to improve symptomatology and prognostic factors for a period longer than 6-weeks. Outcomes: cardiopulmonary and EOV parameters. A meta-analysis of treatment effect on oxygen uptake and ventilatory efficiency was done.

Results: One case study, one cohort study and four clinical trials were identified. Overall, 123 EOV patients were evaluated: 16 patients in pharmacological treatment and 111 patients in non-pharmacological treatment. Briefly, the pharmacological therapy (phosphodiesterase 5 inhibition) was done per 12-month, the adaptive servo-ventilation treatment was done per 12-weeks, and exercise was done per 15 ± 1 weeks. The studies characteristics and the main findings are presents in Table 1. Meta-analysis shown that the pharmacological and non-pharmacological treatments were associated with a significant improvement in Peak VO_2 (SMD 0.50 [0.75, 0.25], $p<0.001$) and VE/VCO_2 slope (SMD -0.63 [-0.13, -1.14], $p=0.01$).

Conclusions: Pharmacological and non-pharmacological treatments improve cardiorespiratory and EOV parameters, leading to improvement in the symptoms and prognostic factors in CHF patients with EOV. Besides that, exercise intervention is so effective as pharmacologic treatment to reduce EOV.

Table 1. Studies characteristics and main findings

Study (year)	Treatment	n	Follow-up	Main findings
Guazzi (2012)	PDE5	16	12-months	Reversal in 93% of EOV cases
Kazimierczak (2011)	ASV	08	12-weeks	Reversal in 86% of EOV cases
Castro (2010)	Exercise	1	16-weeks	Reversal of EOV
Zurek (2012)	Exercise	52	12-weeks	Reversal in 71% of EOV cases
Yamauchi (2016)	Exercise	26	20-weeks	Decrease of EOV amplitude
Panagopoulou (2017)	Exercise	20	12-weeks	Decrease of EOV duration

PDE5, phosphodiesterase 5 inhibition. EOV, exercise oscillatory ventilation. ASV, adaptive servo-ventilation.

APÊNDICE 2

Resumo apresentado no ESC Preventive Cardiology 2020

Exercise oscillatory ventilation impairs oxygen delivery/extraction in male patients with chronic heart failure

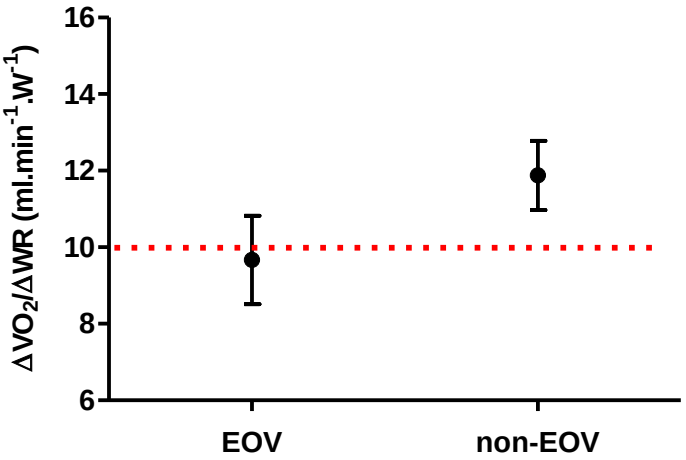
Ribeiro GS[1], Deresz LF[2], Dal Lago P[1], Hansen D[3], Agostoni P[4], Karsten M[5]

Background: Exercise oscillatory ventilation (EOV) is a common phenomenon among chronic heart failure (CHF) patients, being considered an independent predictor of death. The oxygen uptake/work rate (VO_2/WR) slope is a parameter of the efficiency of the muscle oxygen delivery and/or oxygen extraction obtained in the cardiopulmonary exercise test (CPX).

Purpose: To compare oxygen delivery/extraction in CHF male elderly patients with EOV and without EOV.

Methods: A convenience sample composed of CPX data from 30 male CHF patients (15 EOV and 15 non-EOV) was randomly selected from an Italian cardiology specialized centre. CPX was done in cycle-ergometer (personalized incremental ramp protocol) with gas exchange analysed breath-by-breath. $\Delta VO_2/\Delta WR$ slope ($ml.min^{-1}.W^{-1}$) was estimated by linear regression between work rate and oxygen uptake, excluding data preceding 10W of workload. The Mann-Whitney test was used to compare the work efficiency (one-tailed, $p<0.05$), and the Wilcoxon signed rank test was applied to compare the metabolic efficiency of the EOV and non-EOV groups with theoretical cut-off ($10\ ml.min^{-1}.W^{-1}$). Data are showed as median and interquartile range [25%; 75%].

Results: EOV group had lower metabolic efficiency than non-EOV group (9.5 [8.5; 10.6] vs 11.6 [11.3; 12.1] $ml.min^{-1}.W^{-1}$; $p<0.001$). Furthermore, regarding $\Delta VO_2/\Delta WR$ slope theoretical cut-off, EOV group was similar ($p=0.283$) and the non-EOV group was higher ($p<0.0001$) than it.



Work efficiency from EOV and non-EOV patients

Conclusion: These preliminary data suggest that CHF+EOV patients present worse oxygen delivery/extraction, indicating possible EOV-related metabolic impairment at peripheral level.

APÊNDICE 3

Resumo apresentado no ESC Preventive Cardiology 2022

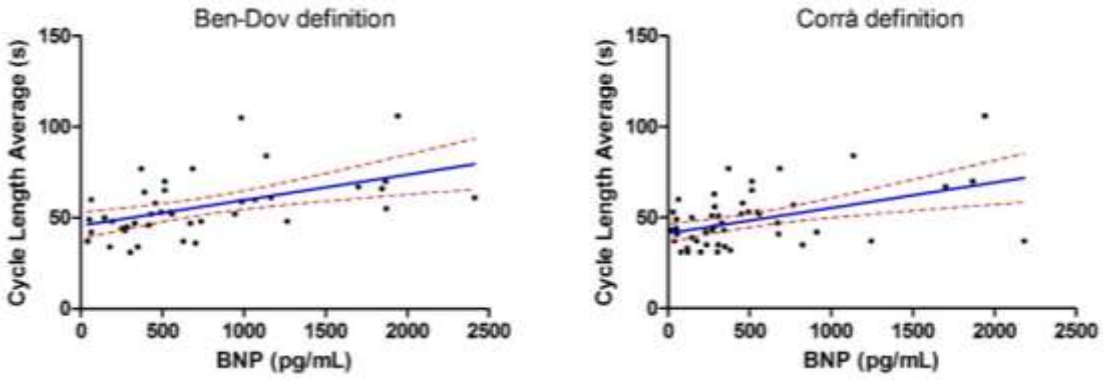
Brain natriuretic peptide levels are associated with cycle length average and are different between Ben-Dov and Corrà exercise oscillatory ventilation definitions in heart failure patients

Ribeiro GS[1], Deresz LF[2], Salvioni E[3], Hansen D[4], Agostoni P[5], Karsten M[6]

Background: The brain natriuretic peptide (BNP) is a marker of ventricular dysfunction related to severity and prognosis in heart failure patients. Exercise oscillatory ventilation (EOV) is a phenomenon in the ventilatory pattern associated with a worse prognosis in heart failure patients. EOV diagnosis is defined by the interaction among amplitude, cycle length, and the total time of the oscillations. Ben-Dov and Corrà definitions are used to identify EOV-positive cases by different criteria, which may stratify EOV patients with distinct clinical characteristics.
Purpose: To assess the BPN levels in heart failure patients and to test BNP level correlation with amplitude, cycle length, and total oscillation time according to Ben-Dov and Corrà definitions.
Methods: Data from 242 cardiopulmonary exercise tests (CPETs) performed between 2011 and 2014 at an Italian heart centre were screened for EOV identification. CPETs were done in a cycle-ergometer with gas exchange analysed breath-by-breath. EOV cases were identified according to the definitions of Ben-Dov and Corrà. Mann-Whitney test was applied to compare BPN levels between the EOV-positive and negative in each definition and between EOV-positive from Ben-Dov and Corrà definitions. Spearman coefficient (r_s) evaluated the association between amplitude and length average of the oscillatory cycle, percentage of total oscillation time, and BNP levels in each EOV definition. The BNP levels from EOV-positive identified by Corrà or Ben-Dov definition alone, and from patients who have met the criteria of both definitions were compared by the Kruskal-Wallis test.
Results: Sixty-seven patients were identified as EOV-positive. From them, 19 were identified exclusively by the Ben-Dov and 26 by Corrà. Twenty-two met the criteria for both definitions. Overall, no difference in EOV prevalence between Ben-Dov and Corrà definitions was found (20.4 vs 24.2%, $p = 0.482$). EOV-positive identified by the Ben-Dov definition have higher BNP levels than EOV-negative ($p < 0.01$) and the EOV-positive by Corrà definition ($p = 0.025$) (Table 1). Spearman correlation showed association just between BNP levels and cycle length average from EOV-positive by the Ben-Dov ($r_s = 0.566$; $p < 0.001$) and by Corrà ($r_s = 0.339$; $p = 0.011$) (Figure 1). When analysed by exclusive criteria identification, the BNP levels were higher in EOV-positive identified by Ben-Dov than Corrà (737 [562 to 1,178] vs 276 [221 to 603] pg/mL; $p = 0.009$). BNP levels in the EOV-positive identified by both definitions (475 [347 to 852] pg/mL) were not different from those identified by the Ben-Dov and Corrà definitions alone.

	Ben-Dov *et al.*		**Corrà *et al.***	
	EOV-positive	EOV-negative	EOV-positive	EOV-negative
Sample, n	41	201	48	194
Age, years	72 [69 – 75]	71 [69 – 72]	74 [71 – 76]*	70 [69 – 72]
LVEF, %	34 [30 – 36]	33 [32 – 35]	36 [32 – 38]	32 [31 – 35]
RVSP, mmHg	35 [31 – 44]	37 [34 – 39]	37 [30 – 44]	35 [35 – 39]
BNP, pg/mL	515 [372 – 737]*†	296 [263 – 379]	320 [269 – 493]	346 [265 – 441]

EOV, exercise oscillatory ventilation. LVEF, left ventricular eject fraction. RVSP, right ventricular systolic pressure. BNP, brain natriuretic peptide. Data are shown as median and 95% confidence interval. *p < 0.01 vs EOV-negative group. †p = 0.025 vs EOV-positive group by Corrà.



Conclusion: EOV-positive identified by the Ben-Dov have higher BNP levels than EOV-negative and the EOV-positive identified by Corrà, alone or not. BNP levels also are associated with the cycle length average, with a higher correlation for the Ben-Dov EOV-positive.

APÊNDICE 4

Resumo apresentado no ESC Preventive Cardiology 2022

Would be the minute ventilation variability an alternative to the dichotomous diagnosis of exercise oscillatory ventilation?

Ribeiro GS[1], Deresz LF[2], Salvioni E[3], Hansen D[4], Agostoni P[5], Karsten M[6]

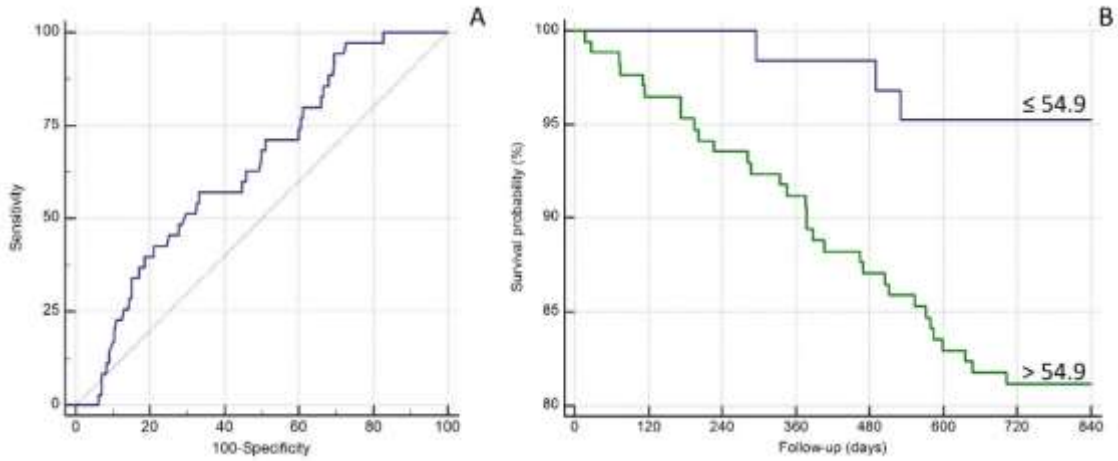
Background: Exercise oscillatory ventilation (EOV) is an abnormal ventilatory phenomenon observed in chronic heart failure (HF) patients usually defined as EOV-positive or EOV-negative based on a dichotomous diagnosis. Minute ventilation variability (vVE) can quantify the presence of these oscillations and assist the prognosis of patients.

Purpose: To analyse the sensitivity and specificity of vVE to predict 2-year all-causes of death in HF patients.

Methods: Data from 233 cardiopulmonary exercise tests from HF patients performed between 2011 and 2014 at an Italian heart centre were analysed. The vVE was defined by the standard deviation (SD) of VE normalized by the number of respiratory cycles (SD/n) during the exercise tests. The cut-off to predict 2-year mortality was determined by the receiver-operating characteristic (ROC) curve.

Results: Thirty-five deaths were registered at 2-years. The ROC curve indicated ≤ 54.9 as the better cut-off for vVE (32 deaths were registered in follow-up). The relative risk was 3.9 (1.3 to 12.4) with a hazard ratio of 2.7 (1.3 to 5.6) for 2-year mortality.

Cut-off	AUC	95% CI	p-value	Sensitivity	Specificity
≤ 54.9	0.643	0.578 to 0.704	0.002	94.3 (80.8 to 99.3)	30.3 (24.0 to 37.2)



Conclusion: The vVE appears to be a sensitive alternative to quantify EOV and stratify high-risk cases from 2-year all-cause mortality.

APÊNDICE 5

20º Simpósio Internacional de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva

EASY-EOV tool: metodologia de construção e análise da reprodutibilidade de um software para detectar casos de ventilação periódica durante o exercício

Introdução: A ventilação periódica durante o exercício (EOV) é uma alteração característica no padrão ventilatório de pacientes com insuficiência cardíaca. Atualmente tem sido apontada como marcador de mau prognóstico. Sua presença é definida pela interação de três fatores: amplitude e comprimento dos ciclos, e tempo total de oscilação durante os testes cardiopulmonares de exercício. Diferentes definições aplicam combinações distintas destes fatores como critérios para identificação da EOV, sendo as mais conhecidas as de Corrà, Kremser, Ben-Dov, Leite e Sun. Dada a elevada complexidade para aplicar estes conceitos durante os testes, a investigação da EOV na prática clínica tem sido pouco aplicada, o que contribui para o subdiagnóstico desta condição grave em pacientes com insuficiência cardíaca.

Objetivo: Desenvolver uma ferramenta semiautomatizada para auxiliar no diagnóstico de EOV e testar a sua reprodutibilidade.

Métodos: Dados de 500 testes cardiopulmonares de exercício realizados em um Centro Cardiológico de excelência internacional foram encaminhados para construção e validação do software. O sistema foi desenvolvido no software LabVIEW, incorporando diferentes recursos como: visualização gráfica das curvas ventilatórias e metabólicas em repouso e no exercício, identificação de cada ciclo (tríade nadir-pico-nadir), técnica de suavização de dados (média móvel), rotina matemática automatizada, indicação de EOV e possibilidade de exportar os dados. Dois avaliadores independentes analisarem os testes de acordo com as cinco definições mais conhecidas. A reprodutibilidade foi avaliada pelo teste kappa de Cohen (κ).

Resultados: O software EASY-EOV tool apresenta a possibilidade de identificação de EOV por meio das cinco definições mais conhecidas, uma técnica de suavização e estatísticas básicas, além da visualização de quatro gráficos (repouso, exercício, resposta completa dos testes cardiopulmonares de exercício e amplitude dos ciclos). A análise de reprodutibilidade indicou alta concordância entre os avaliadores para identificação de EOV aplicando os conceitos de Corrà (0,83 ± 0,04), Kremser (0,85 ± 0,05), Ben-Dov (0,92 ± 0,03), Leite (0,86 ± 0,05) e Sun (0,97 ± 0,03).

Conclusão: O software EASY-EOV tool viabilizou a análise semiautomatizada do fenômeno ventilatório, demonstrando alta concordância entre avaliadores para identificar casos de EOV. O acesso à esta ferramenta está disponível gratuitamente, de acordo com a licença Creative Commons (CC BY-NC-SA 4.0).

Prêmio de Inovação e Tecnologia: 2º lugar

ANEXOS

ANEXO A

Artigo publicado no periódico *International Journal of Cardiology*

Qualis A2, Fator de Impacto 4,164

International Journal of Cardiology 360 (2022) 39–43

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Sensitivity and specificity of different exercise oscillatory ventilation definitions to predict 2-year major adverse cardiovascular outcomes in chronic heart failure patients

Gustavo dos Santos Ribeiro [a], Luís Fernando Deresz [b], Elisabetta Salvioni [c], Dominique Hansen [d,e], Piergiuseppe Agostoni [e,f], Marlus Karsten [a,g,h,*]

[a] Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil
[b] Departamento de Educação Física, Universidade Federal de Juiz de Fora (UFJF), Governador Valadares, Brazil
[c] Centro Cardiologico Monzino, IRCCS, Milan, Italy
[d] Hasselt University (UHASSELT), Faculty of Rehabilitation Sciences, BIOMED/REVAL, Hasselt, Belgium
[e] Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium
[f] Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Milano, Italy
[g] Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Florianópolis, Brazil
[h] Programa de Pós-Graduação em Fisioterapia, UDESC, Florianópolis, Brazil

ARTICLE INFO

Keywords:
Cardiology
Cardiovascular diseases
Cardiopulmonary exercise test
Periodic breathing
Prognosis

ABSTRACT

Background: Exercise oscillatory ventilation (EOV) shows a four-fold greater risk of adverse events. This study aims to analyze the sensitivity and specificity of three EOV diagnostic definitions to predict adverse outcomes at a 2-year follow-up and to compare its EOV prevalence and relations with the patient's profile.

Methods: Cardiopulmonary exercise tests from 233 heart failure patients were analyzed. Two blinded reviewers used a semiautomated software to identify EOV cases pattern according to the definitions of Ben-Dov, Corrà, and Leite. Data were grouped in EOV-positive or EOV-negative according to each definition. Baseline characteristics, EOV prevalence, relative risk, sensitivity, and specificity to predict 2-years of major adverse cardiovascular outcomes were analyzed.

Results: The Corrà definition led to the best prediction of 2-year major cardiovascular adverse outcomes (HR 2.46 [1.16 to 5.25]; $p = 0.019$, AUC = 0.618; $p = 0.007$). EOV prevalence was 17.2%, 17.2%, and 9.4% applying Ben-Dov, Corrà, and Leite definition, respectively. The main clinical differences between EOV-positive and EOV-negative patients were: MECKI score and VE/VCO_2 slope (all definitions), and BNP levels (Ben-Dov and Leite). BNP levels were correlated with amplitude ($rho = 0.255$; $p = 0.033$) and cycle length ($rho = 0.388$; $p = 0.002$).

Conclusion: Corrà definition was the only one that exhibited the capacity to predict major adverse cardiovascular outcomes at a 2-year follow-up. Regardless of its definition, EOV was more often prevalent in patients with a greater MECKI score and VE/VCO_2 slope values.

1. Introduction

Exercise oscillatory ventilation (EOV) is an abnormal ventilatory pattern observed in chronic heart failure (HF) patients and is associated with disease severity and worse prognosis [1–3]. Cornelis et al. [4] reported a four-fold greater risk of adverse cardiovascular events in HF EOV-positive patients compared to their counterparts without EOV. Rovai et al. [5] highlighted that the presence of EOV is associated with a lower 2-year survival in HF patients with reduced or mid-range left ventricular ejection fraction, regardless of age and gender.

Although current evidence reinforces its predictive value, the EOV prevalence in HF is still controversial. Cornelis et al. [6] identified nine different EOV definitions based on EOV length and amplitude. It is not surprising that these different definitions lead to a wide range of EOV

* Correspondence author at: Centro de Ciências da Saúde e do Esporte, Universidade do Estado de Santa Catarina (UDESC), Rua Pascoal Simone 358, CEP 88080-350 Florianópolis, SC, Brazil.
E-mail address: marlus.karsten@udesc.br (M. Karsten).

https://doi.org/10.1016/j.ijcard.2022.05.041
Received 6 April 2022; Received in revised form 17 May 2022; Accepted 18 May 2022
Available online 25 May 2022

reported incidence, from 7 to 58% of HF patients [2,6].

Although the American Heart Association has proposed the Corrà definition to screen for EOV cases [7], there is no consensus on the best EOV definition [4,8]. Ingle et al. [9] were the first to evaluate the impact of different definitions on the prevalence and prognosis within EOV-positive patients. A similar prevalence between the Corrà and Leite definitions was observed (25 vs. 31%). However, EOV cases identified by the Corrà definition exhibited a greater hazard ratio (HR 6.3 [1.6 to 25.2]) to all-cause 12-month death than EOV cases identified by Leite definition (HR 4.9 [2.6 to 18.2]).

The different options to determine the EOV, due to the lack of standardization, compromises the clinical applicability of EOV. Albeit likely, it is unclear whether and to what extent the different definitions exhibit distinct sensitivities and specificities to detect EOV, and predict adverse outcomes. Among all the definitions available, we chose to compare Ben-Dov, Corrà, and Leite definitions because these definitions have different conceptual criteria in their development (e.g., high amplitude vs. longer duration) and have been frequently utilized in studies on EOV. These features may be linked to the HF aetiology (e.g., left or right HF) or clinical markers of hemodynamic impairment.

Therefore, this study aims to analyze the sensitivity and specificity to predict major adverse cardiovascular outcomes in a 2-year follow-up in HF patients, using three diagnostic definitions that apply distinct criteria to screen this phenomenon, and to compare the EOV prevalence and the clinical patient profile.

2. Methods

2.1. Study design

Retrospective anonymized single-centre data from 500 cardiopulmonary exercise tests (CPETs) performed between 2011 and 2014, and with a follow-up of at least 2 years, were analyzed. This study was approved by the Research Ethics Committee from the main author (referee 3.516.801/2019) according to current ethical standards.

2.2. Data sampling

CPETs of HF patients aged 40 to 90 years were included. Data from patients who performed a short CPET (< 6 min [10,11]), with a too short registration (< 90 s) of the minute ventilation (VE) at rest, or tests that did not allow to apply the EOV definitions (corrupted file) were excluded. Patients with a follow-up <2 years were also excluded.

2.3. Exercise test protocol

CPETs followed the hospital routine [12]. Briefly, a personalized ramp protocol was performed on an electronically braked cycle ergometer (Erg 800S; Sensor Medics, Yorba Linda, CA) [5,13]. All subjects were instructed to perform a maximal effort (exercise peak near to10 min). The tests were stopped when patients reported fatigue or in the presence of any cardiac abnormalities. The breath-by-breath data were collected and analyzed using the 20-s smoothing average (Vmax® 12-3A Series, CareFusion, Yorba Linda, CA).

The highest 20-s averaged oxygen uptake (VO_2) value registered was considered as the VO_{2PEAK}. The VE/VCO_2 slope, a marker of ventilatory efficiency, was measured by applying the V-slope method, which is defined as the linear relationship between VE and carbon dioxide production (VCO_2), excluding the first minute of exercise and the period above the respiratory compensation point [5]. All measures were done following the hospital's expertise.

2.4. Clinical profile and MECKI score

The patient's clinical variables were obtained directly from the hospital's medical record. Data on body mass index, New York Heart Association (NYHA) functional classification, left ventricular eject fraction (LVEF), right ventricular systolic pressure (RVSP), blood hemoglobin, and B-type natriuretic peptide (BNP) levels were recorded. All variables were collected on the day of the CPET or within the week before it. The MECKI score was used for calculating the risk of chronic systolic HF, estimated from six independent predictors (% of VO_{2PEAK} predict, VE/VCO_2 slope, blood hemoglobin, sodium, left ventricular ejection fraction, and modification of diet in renal disease [MDRD]) [14].

2.5. EOV definitions

The EOV was determined by the combined characteristics of the ventilatory pattern (amplitude, cycle length, and/or oscillatory time) according to the definitions of Ben-Dov [15], Corrà [16], and Leite [17]. Fig. 1 shows the EOV-positive ventilatory pattern and illustrates the minimum of oscillatory cycles or duration recommended for each definition.

2.6. EOV identification

Two blinded reviewers used a semiautomated tool to identify EOV cases in a standardized way. The software EASY-EOV tool 1.0 is an open-access application developed to allow the EOV analysis from CPET raw data of any system (LabVIEW, National Instruments, US). In a validation study, a high intra-rater ($k \geq 0.82$) and inter-rater ($k \geq 0.83$) reliability was observed (unpublished data).

2.7. Follow-up data

Follow-up data were recorded by the hospital service from the completion of the CPET until the registration of death or a cardiovascular procedure – limited to 2-years for all patients. Cardiovascular death, urgent heart transplantation, or the need for left ventricular assist device implantation were included as major adverse cardiovascular outcomes. Subjects without cardiovascular death or need for cardiac procedures, and who had clinical follow-up less than 1 year after CPET, were excluded.

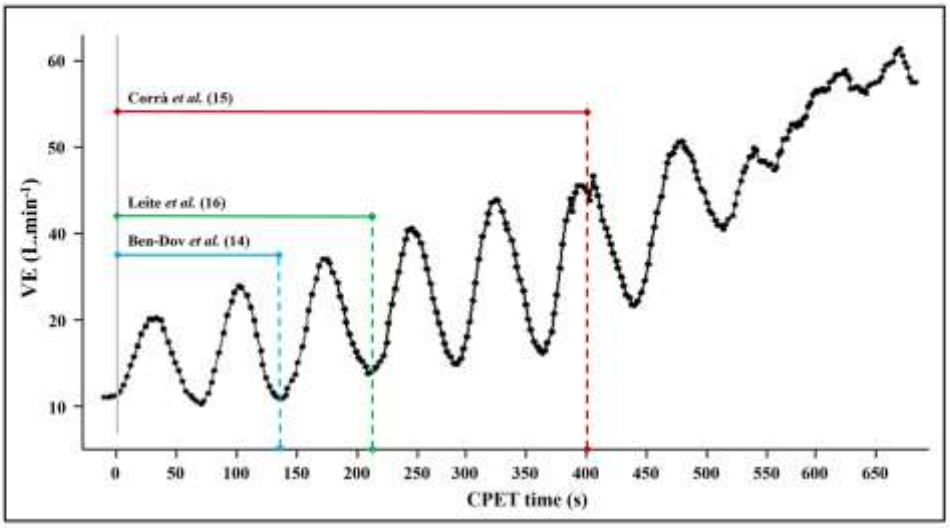
2.8. Statistical analysis

Data were separated in EOV-positive vs. EOV-negative patients according to each definition. To assess normality of data distribution, we used the Kolmogorov–Smirnov test. Baseline characteristics were compared between groups by the Mann-Whitney test or Fisher's exact test (EOV-positive vs EOV-negative) and Kruskal-Wallis test (EOV-positive between Ben-Dov, Corrà, and Leite). Cochran's Q test and the McNemar post hoc were applied to compare the prevalence of EOV across different definitions. Furthermore, the interaction between EOV characteristics (amplitude, cycle length, and total oscillation time) and blood BNP levels was assessed by Spearman's correlations (*rho*).

All patients were followed for two years. The risk of major adverse cardiovascular outcomes was calculated for each EOV definition. The sensitivity and specificity to predict major adverse cardiovascular outcomes were estimated by the Receiver-Operating Characteristic (ROC) curve. All baseline variables were inserted as possible predictors in the univariate model (removed variable if $p > 0.1$ or collinearity >0.3) [9]. Multivariable Cox proportional-hazards regression analysis was used with the backward method to identify the best predictive model (entered variable if $p < 0.05$).

3. Results

Among 500 patients who performed a baseline CPET, 443 were HF patients. Of them, sixty-one records had less than 90 s of VE recording at rest, and 149 patients had too short or no clinical follow-up after CPET:



EOV definition	Oscillations during exercise	Amplitude of the oscillations	Cycle length of the oscillations
Ben-Dov *et al.*	≥ 2 consecutive cyclic fluctuations	≥ 25% of the average VE cycle	30 to 60s
Corrà *et al.*	> 60% of the total exercise time	> 15% of the average VE at rest	-
Leite *et al.*	≥ 3 consecutive cyclic fluctuations	≥ 5 L.min^{-1}	SD < 20% of the average

Fig. 1. EOV-positive ventilatory pattern. EOV, exercise oscillatory ventilation. VE, minute ventilation. CPET, cardiorespiratory exercise test. SD, standard deviation.

these cases were excluded, leading to a study population of 233 cases. Table 1 shows the sample characteristics. EOV prevalence was 17.2% (Ben-Dov), 17.2% (Corrà), and 9.4% (Leite). Ben-Dov and Corrà definitions identified 40 EOV cases each. Both definitions exhibited a greater prevalence than EOV cases identified by Leite ($p < 0.01$).

EOV patients had a worse functional class, MECKI score, ventilatory efficiency (VE/VCO_2 slope), and lower maximal workload, regardless of EOV definition. There was no difference in clinical characteristics among EOV-positive groups when calculated by the definitions of Ben-Dov, Corrà and Leite ($p > 0.05$). EOV-positive cases identified by the definitions of Ben-Dov and Leite presented higher levels of blood BNP than HF patients without EOV. Low to moderate correlations between BNP levels and amplitude ($rho = 0.255$; $p = 0.033$) or cycle length ($rho = 0.388$; $p = 0.002$) were found. No association with total oscillation time was observed ($rho = -0.104$; $p = 0.229$).

Among all EOV cases, 16 patients were exclusively identified by the definition of Corrà and 12 patients by the definition of Ben-Dov. Both definitions shared 22 EOV cases. Leite's definition shared 15 positive cases with Corrà's definition and 19 with Ben-Dov's definition. Only one EOV patient was identified just by the definition of Leite. The overlap of

Table 1
Clinical characteristics stratified by EOV definition.

Variable/Definition	Ben-Dov [15]		Corrà [16]		Leite [17]	
	EOV-positive	EOV-negative	EOV-positive	EOV-negative	EOV-positive	EOV-negative
Sample, n (%)	40 (17.2)	193 (82.9)	40 (17.2)	193 (82.9)	22 (9.4)	211 (90.6)
Male gender, n (%)	35 (87.5)	156 (88.8)	31 (77.5)	160 (82.9)	21 (95.5)	170 (80.6)
Age, years	69 [66–72]	68 [67–70]	74 [69–76]*	68 [66–69]	69 [63–75]	68 [67–70]
Body mass index, kg/m^2	24.8 [23.8–27.4]	26.6 [25.4–27.2]	24.8 [24.2–27.0]	26.6 [25.4–27.3]	24.2 [22.3–27.0]*	26.6 [25.4–27.3]
NYHA class III-IV, n (%)	22 (55.0)*	67 (34.7)	22 (55.0)*	67 (34.7)	13 (59.1)*	76 (36.0)
LVEF, %	32.9 [30.2–36.4]	32.7 [32.0–35.2]	32.8 [29.2–37.3]	32.9 [32.0–35.0]	31.9 [24.7–36.4]	33.0 [32.1–35.2]
RVSP, mmHg	36.0 [33.0–46.0]	35.0 [32.0–37.0]	39.0 [31.0–46.0]	35.0 [33.0–37.0]	42.0 [31.0–49.0]	35.0 [33.0–37.0]
MECKI score, %	8.1 [6.0–11.5]*	3.7 [2.9–4.8]	7.4 [4.8–12.6]*	3.8 [3.1–4.9]	11.1 [3.1–16.1]*	4.0 [3.3–5.2]
Hemoglobin, mg/dL	13.9 [12.7–14.7]	13.9 [13.7–14.3]	13.6 [12.8–14.2]	14.0 [13.7–14.3]	13.9 [12.6–14.8]	13.6 [13.7–14.2]
BNP, pg/mL	550 [372–737]*	263 [200–322]	330 [272–549]	272 [221–398]	514 [282–987]*	275 [224–379]
CPET time, s	533 [486–572]	532 [517–562]	492 [477–572]	539 [521–563]	538 [470–652]	530 [515–556]
VO_{2PEAK}, ml.kg.min^{-1}	12.7 [11.0–14.7]*	14.0 [13.4–14.8]	12.2 [11.1–13.5]*	14.3 [13.5–15.0]	12.6 [9.8–14.9]	14.0 [13.2–14.8]
VE/VCO_2 slope	36.3 [32.9–40.3]*	29.6 [28.8–30.6]	36.0 [32.0–40.0]*	30.0 [28.8–31.0]	37.6 [32.0–42.7]*	30.0 [29.0–31.0]
Maximal workload, w	61 [46–80]*	69 [64–75]	48 [37–64]*	71 [68–79]	56 [33–80]*	70 [64–74]
Major adverse outcome, n (%)	10 (25.0)	25 (13.0)	13 (32.5)**	22 (11.4)	6 (27.3)	29 (13.7)

Continuous data are expressed as median [95% confidence interval (CI)] and categorical data as absolute (n) and relative (%) frequencies. EOV, exercise oscillatory ventilation. EOV-positive, patients with a confirmed diagnosis. EOV-negative, patients with a negative diagnosis. NYHA, New York Heart Association. LVEF, left ventricular eject fraction. RVSP, right ventricular systolic pressure. BNP, B-type natriuretic peptide. CPET, cardiopulmonary exercise test. VO_{2PEAK}, peak oxygen uptake. VE/VCO_2, minute ventilation-carbon dioxide production. *$p < 0.05$ Mann-Whitney Test (EOV-positive vs EOV-negative). **$p < 0.01$ Fisher's exact test (EOV-positive vs EOV-negative).

EOV cases is presented in the Fig. 1S. Regarding isolated diagnosis, blood BNP levels were greater when EOV was identified by the definition of Ben-Dov vs. the definition of Corrà (720 [411 to 1067] vs. 260 [80 to 677] pg/mL; $p = 0.019$).

The relative risk for 2-year major adverse cardiovascular outcomes was significant applying Corrà's definition (2.9 [1.6, 5.2]; $p < 0.001$), and Ben-Dov's definition (1.9 [1.0, 3.7]; $p = 0.047$). However, Corrà's definition was the only one that showed a significant probability to predict 2-year major adverse cardiovascular outcomes (Table 2).

Supplemental Table 1S shows the potential predictors for major adverse cardiovascular outcomes (univariate analysis). Four variables were entered in the predictive model after multivariate Cox analysis (R^2-adjusted = 0.184; $p < 0.001$). Only two variables were significantly predictive: Corrà's definition (HR 2.46 [1.16 to 5.25]; $p = 0.019$) and age (HR 1.07 [10.3 to 1.12]; $p = 0.002$).

4. Discussion

The number of HF patients identified as EOV-positive ranged from 9.4 to 17.2% according to the applied definition. There was no difference in EOV prevalence (40 EOV cases) when applying Ben-Dov's vs. Corrà's definition. Of these 40 cases identified by the Ben-Dov and Corrà criteria, only 22 cases were identified by both criteria, while the other 18 cases were identified exclusively by the Ben-Dov or by Corrà criteria. Moreover, the Corrà definition allowed us to identify EOV cases with the greatest 2-years major adverse cardiovascular outcome rate. In contrast, the blood BNP levels were greater in cases identified exclusively by Ben-Dov's definition. Furthermore, a low-to-moderate correlation between blood BNP levels and amplitude or cycle length was observed.

To our knowledge, Ingle et al. [9] were the only that investigated the impact of different EOV diagnostic definitions on prognosis. They evaluated 240 HF patients applying Corrà and Leite definitions. There was no difference in EOV prevalence in both definitions (Corrà: 25% and Leite: 31%). However, Ingle et al. [9] observed that EOV-positive cases identified by Corrà's definition were associated with a higher all-cause mortality at 1-year (HR 5.2 [2.8 to 9.9]; $p < 0.001$) in comparison to the cases identified by Leite's definition (HR 4.8 [2.8 to 8.8]; $p < 0.001$).

In the present study, we found a lower EOV prevalence by all definitions, as well as a lower sensitivity to predict adverse outcomes applying the Corrà criteria, in comparison with other studies [9,17]. Furthermore, Ben-Dov's and Leite's definitions did not show a sufficient sensitivity to predict 2-year major adverse cardiovascular outcomes. The difference between our and previous study outcomes could be related to: the different baseline characteristics (our sample was older and with lower VO_{2PEAK}), the difference in follow-up time (24 vs 12 months), and the use of a semiautomated tool to identify EOV cases rather than manual scoring and/or visual interpretation (less subjective).

Our findings differ from other studies that used the Leite's definition to identify EOV cases. In the original study, Leite et al. [17] observed a 30% EOV prevalence and a 3-times greater risk for premature death within 2 years in patients with heart transplantation indications (RR 2.97 [1.34 to 6.54]; $p < 0.01$). Similarly, Vainshelboim et al. [18] found a higher prevalence (54%) and hazard ratio for major cardiac-related events at 5 years (HR 2.2 [1.2 to 4.1]; $p = 0.011$) applying Leite's modified criteria.

Table 2
Sensitivity and specificity to predict 2-year major cardiovascular adverse outcomes.

Definition	AUC	95% CI	p-value	Sensitivity	Specificity
Ben-Dov	0.567	0.487 to 0.647	0.100	28.57	84.85
Corrà	0.618	0.533 to 0.702	0.007	37.14	86.36
Leite	0.545	0.479 to 0.611	0.179	17.14	91.92

EOV, exercise oscillatory ventilation. AUC, area under the ROC curve. CI, confidence interval.

Regarding Corrà's methodology, the results are contradictory. The original study reported an EOV prevalence slightly lower than ours (12%) [16]. Nevertheless, Guazzi et al. [19] found a higher EOV prevalence in HF patients with a reduced (35%) and preserved ejection fraction (32%), beyond the greater hazard rate to overall mortality at four years (HR 2.0 [1.3 to 3.1]; $p < 0.001$ and 5.9 [2.1 to 16.9], $p < 0.001$). It should be noted that the exercise tests were performed both on a treadmill and cycle ergometer, making further inferences unfeasible since the specificity of the exercise mode can produce different physiological responses. In this sense, Guazzi et al. [19] observed 25% EOV-positive cases among tests performed on a cycle ergometer and 41% of EOV-positive cases among tests done on a treadmill.

Another point to be considered is the use of dichotomous EOV detection: EOV-positive or EOV-negative. As the EOV pathophysiology remains unknown [1,3,18], it is plausible to consider that the amplitude and/or length of each cycle differs from one patient to another, even with a confirmed EOV diagnosis by two or three definitions (by Corrà and Ben-Dov, for example). The clinical impact of this variation is yet unknown. It seems that the cycle amplitude would be related to hemodynamic impairments such as circulatory delay [20], a lower ventilatory efficiency [21], and higher blood BNP levels [21]. Thus, higher amplitudes would be related to worse outcomes in EOV patients. Nonetheless, this hypothesis yet needs to be confirmed.

Our data show the EOV-positive patients diagnosed by Ben-Dov's and Leite's definition have higher blood BNP levels than those identified by Corrà's definition, albeit with a lower mortality. Yamauchi et al. [21] also found a positive correlation between cycle amplitude and blood BNP levels when applying Leite's definition ($r = 0.615$; $p = 0.007$). However, they did not provide an explanation for this finding. An essential factor that may have influenced blood BNP levels is the right ventricular impairment, commonly seen in HF superimposed by pulmonary hypertension. Leuchte et al. [22] found that high blood BNP levels were directly related to high pulmonary capillary wedge pressures, pulmonary vascular resistance, and right atrial pressure, and were inversely correlated with cardiac index or VO_{2PEAK}. Indeed, Murphy et al. [20] observed an association between right ventricular eject fraction and both amplitude ($r = -0.68$; $p < 0.001$) or cycle length ($r = -0.48$; $p = 0.02$), suggesting that these parameters would be related to a worse hemodynamic function in EOV-positive patients.

This is the first study that investigated the predictive capacity of three definitions for EOV with totally different conceptual characteristics: Ben-Dov, Corrà, and Leite. Indeed, Ben-Dov proposed the presence of two consecutive cycles with 30–60s of length and a cycle magnitude of near to 25% of the average VE for EOV diagnosis [15]. Corrà proposed that the oscillation would need to be present in at least 60% of total exercise time, with an amplitude above 15% of the VE at rest [16]. Finally, Leite proposed that EOV would be characterized by at least three regular oscillations with a minimal amplitude above 5 L/min [17].

In brief, Ben-Dov's and Leite's definitions imply a shorter oscillation time, but a larger amplitude compared to the Corrà's definition. It is unknown how these definitions are related to the patient hemodynamic impairment, albeit it is possible to speculate that a higher ventilation amplitude suggests a greater hemodynamic impairment [20,21]. Nevertheless, the oscillation time seems to have a greater probability to predict adverse outcomes, which possibly would justify the better sensitivity of the Corrà's definition. Accordingly, the reasons behind the cessation of EOV during exercise, albeit at present unknown, are of major importance. The idea that EOV ceased during exercise due to the capability to improve cardiac output, or to divert more blood to the exercising muscles, both leading to an improved peripheral oxygen delivery (which in its turn allows reducing the metabo -and chemoreflex sites of activation) are attractive and maybe the link between the observed difference in EOV prognosis and definition.

At present, the EOV definition described by Corrà [16], i.e., oscillation presence of at least 60% of loaded exercise with a minimal amplitude above 15% of VE at rest, seems to be the best choice to link

EOV to prognosis.

4.1. Limitations

The present study has a few limitations which need to be acknowledged. Firstly, our sample size was small as limited in the number of major adverse cardiovascular outcomes, which may be related to the optimal treatment offered in a high-level cardiology centre. In this regard, bigger studies with a larger HF population that includes different phenotypes are definitively essential. Secondly, we re-analyzed CPET previously done in a single centre with mainly a low-ejection fraction HF phenotype. Therefore, our data should not be applied to different HF populations such as in mid-range or preserved ejection fraction patients [5].

5. Conclusion

The Corrà definition for EOV was the only one that exhibited the capacity to predict major adverse cardiovascular outcomes at a 2-year follow-up. The choice of EOV definition seems to affect the number of identified cases (ranging from 9.4 to 17.2%). Regardless of the definition, EOV was more often prevalent in patients with a greater MECKI score and VE/VCO_2 slope values. There were no differences in the clinical characteristics among EOV-positive groups. The positive correlation of blood BNP levels with amplitude and cycle length, the main features of the Ben-Dov and Leite definitions, suggests a link between these features with a clinical impairment marker.

Authorship statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Funding

This study was financed in part by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brasil) - Finance Code 001.

CRediT authorship contribution statement

Gustavo dos Santos Ribeiro: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Luís Fernando Deresz:** Conceptualization, Methodology, Writing – original draft. **Elisabetta Salvioni:** Resources, Writing – review & editing. **Dominique Hansen:** Writing – review & editing, Supervision. **Piergiuseppe Agostoni:** Resources, Writing – review & editing, Supervision. **Marius Karsten:** Conceptualization, Methodology, Writing – review & editing, Project administration.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.05.041.

References

[1] P. Agostoni, E. Salvioni, Exertional periodic breathing in heart failure: mechanisms and clinical implications, Clin. Chest Med. 40 (2019) 449–457.
[2] P. Agostoni, U. Corrà, M. Emdin, Periodic breathing during incremental exercise, Ann. Am. Thorac. Soc. 14 (2017) S116–s22.
[3] G.S. Ribeiro, C. Cargnin, P. Dal Lago, D. Hansen, P. Agostoni, M. Karsten, Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis, Eur. J. Prev. Cardiol. 29 (2022) e233–e236.
[4] J. Cornelis, J. Taeymans, W. Hens, P. Beckers, C. Vrints, D. Vissers, Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation - a systematic review and descriptive meta-analysis, Int. J. Cardiol. 182 (2015) 476–486.
[5] S. Rivas, U. Corrà, M. Piepoli, C. Vignati, E. Salvioni, A. Bonomi, et al., Exercise oscillatory ventilation and prognosis in heart failure patients with reduced and mid-range ejection fraction, Eur. J. Heart Fail. 21 (2019) 1586–1595.
[6] J. Cornelis, P. Beckers, C. Vanroy, T. Volckaerts, C. Vrints, D. Vissers, An overview of the applied definitions and diagnostic methods to assess exercise oscillatory ventilation–a systematic review, Int. J. Cardiol. 190 (2015) 161–169.
[7] G. Balady, R. Arena, K. Sietsema, J. Myers, L. Coke, G. Fletcher, et al., Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association, Circulation. 122 (2010) 191–225.
[8] N. Papadopoulou, E. Karatzanos, S. Dimopoulos, A. Tasoulis, I. Tachlabouris, S. Vakrou, et al., Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure, Eur. J. Prev. Cardiol. 24 (2017) 825–832.
[9] L. Ingle, A. Isted, K. Witte, J. Cleland, A. Clark, Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure, Eur. J. Cardiovasc. Prev. Rehabil. 16 (2009) 451–456.
[10] D. Hansen, K. Bonné, T. Alders, A. Hermans, K. Copermans, H. Swinnen, et al., Exercise training intensity determination in cardiovascular rehabilitation: should the guidelines be reconsidered? Eur. J. Prev. Cardiol. 26 (2019) 1921–1928.
[11] P. Agostoni, M. Bianchi, A. Moraschi, P. Palermo, G. Cattadori, R. La Gioia, et al., Work-zone affects cardiopulmonary exercise test results in heart failure, Eur. J. Heart Fail. 7 (2005) 498–504.
[12] P. Agostoni, D. Dumitrescu, How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure, Int. J. Cardiol. 288 (2019) 107–113.
[13] J. Crimpodonico, M. Mapelli, E. Spadafora, S. Ghilardi, P. Agostoni, C. Banfi, et al., Surfactant protein changes after acute hemodynamic improvement in patients with advanced chronic heart failure treated with Levosimendan, Respir. Physiol. Neurobiol. 252-253 (2018) 47–51.
[14] P. Agostoni, U. Corrà, G. Cattadori, F. Veglia, R. La Gioia, A.B. Scardovi, et al., Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis, Int. J. Cardiol. 167 (2013) 2710–2718.
[15] I. Ben-Dov, K.E. Sietsema, B. Casaburi, K. Wasserman, Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure, Am. Rev. Respir. Dis. 145 (1992) 776–781.
[16] U. Corrà, A. Giordano, E. Bosimini, A. Mezzani, M. Piepoli, A.J.S. Coats, et al., Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications, Chest. 121 (2002) 1572–1580.
[17] J. Leite, A. Mansur, H. De Freitas, P. Chiavla, E. Bocchi, M. Terra-Filho, et al., Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation, J. Am. Coll. Cardiol. 41 (2003) 2175–2181.
[18] B. Vainshelboim, A. Antin, J.W. Christle, S. Hebbal, E.A. Ashley, J. Myers, A method for determining exercise oscillatory ventilation in heart failure: prognostic value and practical implications, Int. J. Cardiol. 249 (2017) 287–291.
[19] M. Guazzi, J. Myers, M.A. Peberdy, D. Bensimhon, P. Chase, R. Arena, Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights, Eur. Heart J. 29 (2008) 2751–2759.
[20] R. Murphy, R. Shah, R. Malhotra, P. Pappagianopoulos, S. Hough, D. Systrom, et al., Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise, Circulation. 124 (2011) 1442–1451.
[21] F. Yamauchi, H. Adachi, J. Tomono, S. Toyoda, R. Iwamatsu, M. Sakuma, et al., Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure, Heart Vessel. 31 (2016) 1659–1665.
[22] H.H. Leuchte, M. Holzapfel, R.A. Baumgartner, I. Ding, G. Neurohr, M. Vogeser, et al., Clinical significance of brain natriuretic peptide in primary pulmonary hypertension, J. Am. Coll. Cardiol. 43 (2004) 764–770.

ANEXO B

Artigo publicado no periódico *European Journal of Preventive Cardiology*
Qualis A2, Fator de Impacto 4,164

ESC European Society of Cardiology
European Journal of Preventive Cardiology
https://doi.org/10.1093/eurjpc/zwab195

RESEARCH LETTER

Exercise training effects on metabolic and ventilatory changes in heart failure patients with exercise oscillatory ventilation: systematic review and meta-analysis

Gustavo S. Ribeiro [1], Camila Cargnin [1], Pedro Dal Lago [1,2], Dominique Hansen [3,4], Piergiuseppe Agostoni [5,6], and Marlus Karsten [1,7,8]*

[1]Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Rua Sarmento Leite 245, 90050-170 Porto Alegre, Brazil; [2]Departamento de Fisioterapia, UFCSPA, Rua Sarmento Leite 245, 90050-170 Porto Alegre, Brazil; [3]Faculty of Rehabilitation Sciences, Hasselt University (UHASSELT), BIOMED/REVAL, Agoralaan, Building A, 3590 Diepenbeek, Hasselt, Belgium; [4]Heart Centre Hasselt, Jessa Hospital, Jessa Ziekenhuis, Stadsomvaart 11, 3500 Hasselt, Belgium; [5]Centro Cardiologico Monzino, IRCCS, Via Carlo Parea 4, 20138 Milano, Italy; [6]Department of Clinical Sciences of Community Health, Cardiovascular Section, University of Milano, Via Festa del Perdono 7, 20122 Milano, Italy; [7]Departamento de Fisioterapia, Universidade do Estado de Santa Catarina (UDESC), Rua Pascoal Simone 358, 88080-350 Florianópolis, Brazil; and [8]Programa de Pós-Graduação em Fisioterapia, UDESC, Rua Pascoal Simone 358, 88080-350 Florianópolis, Brazil

Received 25 August 2021; revised 14 October 2021; editorial decision 3 November 2021; accepted 5 November 2021

Exercise oscillatory ventilation (EOV) is a phenomenon characterized by cyclic oscillations in the ventilatory pattern observed during the cardiopulmonary exercise test (EOV characteristics: Supplementary material online, *Figure 1S*). It is considered an independent predictor for death and adverse cardiovascular events in chronic heart failure (CHF) patients.[1] A recent meta-analysis showed that EOV-positive patients exhibited a worse peak oxygen uptake (VO_{2PEAK}) and ventilatory efficiency (VE/VCO_2 slope).[2] Although the EOV pathophysiology is not fully understood, current evidence suggests that circulatory delay, pulmonary congestion, high chemosensitivity, and exacerbated ergoreflex signalling are the main triggering factors.[1,3]

Several treatments were investigated to alleviate EOV symptomatology and thereby improve the patient's prognosis (e.g. adaptive servo-ventilation, phosphodiesterase 5 inhibition, exercise training and levosimendan infusion). Although the evidence regarding exercise training as EOV treatment is limited, there is also no effective pharmacological treatment for EOV. Thus, targeting EOV by exercise intervention is highly relevant. This systematic review aims to verify the exercise training effect on EOV reversal, and other prognostic factors in CHF patients and EOV coexistence.

This study followed the recommendations of the PRISMA statement and was registered at PROSPERO: CRD42021254587. The search was performed in several databases from inception to 30th July 2021, with no language restriction. Inclusion criteria followed the PICOT question: (P) EOV patients; (I) exercise training; (C) pre-training values in EOV group — single arm; (O) EOV reversal (primary), VO_{2PEAK} and VE/VCO_2 slope (secondary); and (T) clinical trial: randomized, non-randomized, or uncontrolled trials. Full methods' description is available as Supplementary material online.

Nine potentially eligible studies were identified, and three trials met the eligibility criteria (PRISMA flowchart: Supplementary material online, *Figure 2S*). Zurek *et al.*[4] assessed two non-randomized groups composed of EOV-positive patients (intervention and control group). Panagopoulou *et al.*[5] analysed two groups who performed the exercise training (EOV-positive and EOV-negative; uncontrolled trial), and Yamauchi *et al.*[6] evaluated a single group (uncontrolled trial). Only data referring to the EOV-positive intervention groups were analysed. The characteristics of the included studies and the methodological quality are shown in Supplementary material online, *Tables S1* and *S2*, respectively.

All studies (*Table 1*) included aerobic exercise three times per week: 30 or 40 min of cycling at the anaerobic threshold,[5,6] or 45-min cycling at 60–80% of VO_{2PEAK} (twice daily).[4] One study analysed two protocols,[5] 40 min of high-intensity interval training (HIIT) on a cycle ergometer or 20-min of HIIT plus four resistance exercises (three sets of 10–12 repetitions at 55–65% of 2-repetition maximum). Besides, resistance training was proposed in the other two studies (three to four exercises).[4,6] These protocols agree with current guidelines for cardiovascular rehabilitation of CHF patients.[7] No study reported adverse events, major complications, or sample loss during the follow-up.

VO_{2PEAK} and VE/VCO_2 slope values were available in three trials[4–6] (98 patients), and EOV reversal in two trials (72 patients).[4,5] A random-effects model with a 95% confidence interval was applied to assess the relative likelihood for EOV reversal, as well as to measure the exercise effect on VO_{2PEAK} and VE/VCO_2 slope [standardized mean difference (SMD)]. The mean difference analysis was also performed. The meta-analysis (*Figure 1*) showed a moderate effect on

* Corresponding author. Tel: +55 48 3664-8696, Email: marlus.karsten@udesc.br

Table I Characteristics of treatments and main findings

Study (year)	Treatment	Frequency	Intensity	Main findings
Panagopoulou 2017	40-min of HIIT (30 s of effort follow 60 s of passive rest) on cycle ergometers or 20 min of HIIT protocol plus four resistance exercises: leg extension, leg curls, arm curls, and lateral arm abduction (three sets of 10–12 repetitions)	3 times per week (36 sessions)	AT: >100% of VO_{2PEAK} RT: 55–65% of 2-RM	Improvement of cardiopulmonary efficiency and functional capacity, besides reducing the EOV duration. EOV disappeared in 70% of the cases.
Yamauchi 2016	30 min of aerobic training plus resistance training	3 times per week (60 sessions)	Anaerobic threshold level	A 5-month cardiac rehabilitation programme reduces 51% plasma BNP levels and 35% EOV amplitude. There were correlations between EOV amplitude and BNP levels ($r = 0.615$), and EOV amplitude and VE/VCO_2 slope ($r = 0.625$).
Zurek 2012	45-min twice day of aerobic training performed on a cycle ergometer and callisthenic exercises	3 times per week (36 sessions)	AT: 60–80% of VO_{2PEAK}	EOV disappeared in 71.2% out of patients after training; ventilatory efficiency (VE/VCO_2 slope) and the central haemodynamic during exercise ($PETCO_2$ at RCP) were improved.

AT, aerobic training; BNP, B-type natriuretic peptide; EOV, exercise oscillatory ventilation; HIIT, high-intensity interval training; $PETCO_2$, partial pressure of end-tidal carbon dioxide; RCP, respiratory compensation point; 2-RM, 2-repetition maximum; RT, resistance training; VE/VCO_2 slope, minute ventilation-carbon dioxide production slope; VO_{2PEAK}, peak oxygen uptake.

VO_{2PEAK} [SMD 0.43 (0.15–0.71); $P = 0.003$], and VE/VCO_2 slope [SMD −0.44 (−0.72 to −0.15); $P = 0.003$], beyond a relevant EOV reversal [RR 0.30 (0.21–0.43); $P < 0.001$]. No heterogeneity in EOV reversal, VE/VCO_2 slope, and VO_{2PEAK} were observed ($P > 0.05$). In summary, exercise training was effective in reversing EOV, as well as improving aerobic capacity and ventilatory efficiency.

The main finding of this review was an EOV reversal near to 70% of the patient cases after a 6-month exercise-training programme. Aerobic power and ventilatory efficiency were also improved. Exercise training stimulates mitochondrial biogenesis, hereby optimizing oxidative metabolism in peripheral muscles, as well improving endothelial function and neural control of breathing pathways.[5] This may explain the observed improvement in cardiorespiratory function.

Three factors seem to have a pivotal role in EOV pathophysiology: (i) hyperventilation, (ii) circulatory delay (lower cardiac output), and (iii) CO_2 cerebrovascular reactivity.[1] Hyperventilation is related to sympathetic hyperactivity and leads to a significant $PaCO_2$ reduction below the respiratory threshold. A pause in the central impulses to respiratory muscles occurs, stopping respiratory movements, followed by a $PaCO_2$ increase and another hyperventilation period. This instability would be further potentiated by circulatory delay and cerebrovascular reactivity to CO_2 impairment, which contributes to the ventilatory central control misalignment.[1]

EOV reversal could be promoted by two opposite groups of mechanisms, i.e. by hyperventilation further increase or by hyperventilation mitigation. The former has been demonstrated by the disappearance of EOV if external dead space is added[8] or if patients breathe a gas mixture with added CO_2.[9] On the other hand, hyperventilation mitigation is possible through an improved oxygen delivery to the working muscles, which inhibits metabolites' accumulation,[10] a potential trigger to EOV due to intramuscular ergo-receptors impairment.[6] Besides that, exercise training provides improvements in $PaCO_2$ and PaO_2 chemosensitivity and in circulatory time,[5] which potentiate the attenuation of the ventilatory drive instability.

Indeed, patients with Cheyne–Stokes respiration exhibit a longer circulation time between lung and chemoreceptors than those without Cheyne–Stokes respiration.[11] This study also suggested that the interaction between chemoreflex gain (change in minute ventilation/change in end-tidal CO_2 partial pressure ratio) and the plant gain (variance in end-tidal CO_2 partial pressure/variance in minute ventilation ratio) may stimulate growing cycles of oscillation (main EOV feature), with plant gain predicting the severity of Cheyne–Stokes respiration at daytime and a combination of chemoreflex gain and plant gain at night.

Another factor that corroborates to EOV reversal is the ventilatory efficiency improvement. Similar to VO_{2PEAK}, the factors responsible for this improvement have not been elucidated yet in EOV-positive patients. However, Guazzi *et al.*[12] showed that exercise training

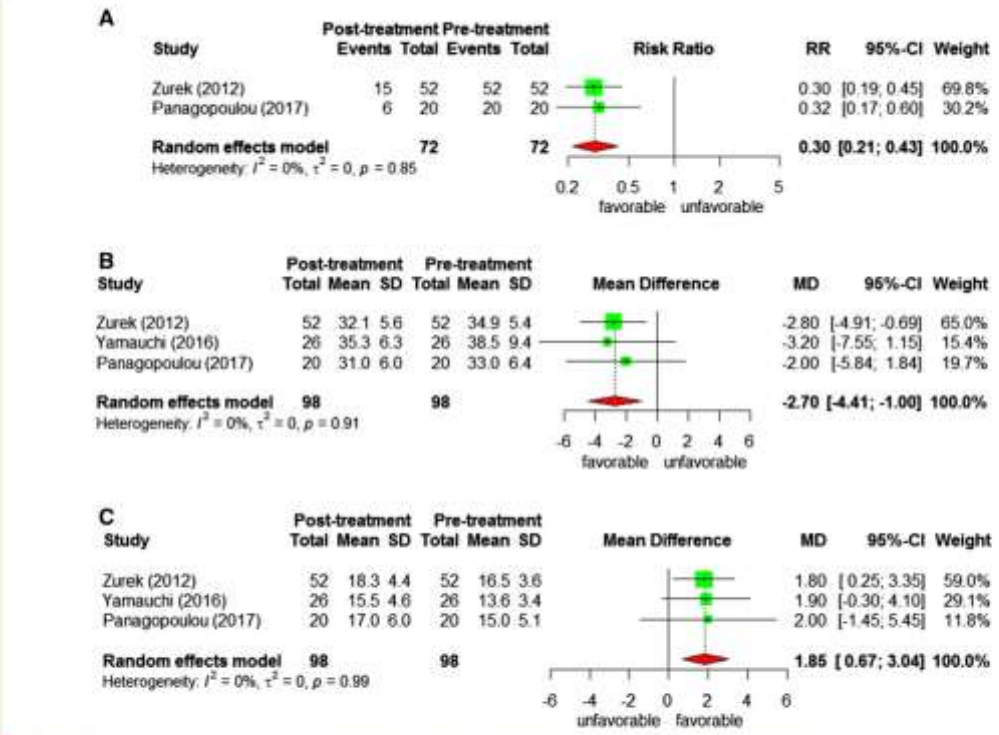


Figure 1 Forest plot of likelihood to improve exercise oscillatory ventilation (*A*), and mean difference on VE/VCO_2 slope (*B*), and VO_{2PEAK} ($mL.kg^{-1}.min^{-1}$) (*C*) in chronic heart failure patients with exercise oscillatory ventilation.

increases lung diffusion capacity and alveolar-capillary conductance, softening the pulmonary pressure gradients, providing an improvement in ventilatory efficiency. Nevertheless, greater oxygen delivery to the peripheral muscles would imply a reduction in respiratory work (less hyperventilation).[1]

The present analysis has some limitations. Firstly, criteria for VE/VCO_2 slope definitions are possibly different among studies. Secondly, EOV may be present during the entire exercise or may be limited to the first part of the test. This condition also can have influenced the identification of the VE/VCO_2 slope and VO_{2PEAK}.

In conclusion, exercise training is effective for (partly) reversing EOV and improving aerobic capacity (VO_{2PEAK}) and ventilatory efficiency (VE/VCO_2 slope). However, no study evaluated whether the EOV reappeared after detraining.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

This study was financed in part by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001.

Conflict of interest: none declared.

References

1. Agostoni P, Salvioni E. Exertional periodic breathing in heart failure: mechanisms and clinical implications. *Clin Chest Med* 2019;**40**:449–457.
2. Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation—a systematic review and descriptive meta-analysis. *Int J Cardiol* 2015; **182**:476–486.
3. Agostoni P, Corra U, Emdin M. Periodic breathing during incremental exercise. *Ann Am Thorac Soc* 2017;**14**:S116–S122.
4. Zurek M, Corrá U, Piepoli MF, Binder RK, Saner H, Schmid J-P. Exercise training reverses exertional oscillatory ventilation in heart failure patients. *Eur Respir J* 2012;**40**:1238–1244.
5. Panagopoulou N, Karatzanos E, Dimopoulos S, Tasoulis A, Tachlabouris I, Vakrou S, Sideris A, Gratziou C, Nanas S. Exercise training improves characteristics of exercise oscillatory ventilation in chronic heart failure. *Eur J Prev Cardiol* 2017;**24**:825–832.
6. Yamauchi F, Adachi H, Tomono J-I, Toyoda S, Iwamatsu K, Sakuma M, Nakajima T, Oshima S, Inoue T. Effect of a cardiac rehabilitation program on exercise oscillatory ventilation in Japanese patients with heart failure. *Heart Vessels* 2016;**31**:1659–1668.
7. Ambrosetti M, Abreu A, Corrá U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-

Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M, Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2021;**28**:460–495.

8. Agostoni P, Apostolo A, Albert R. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. *Chest* 2008;**133**:197–203.
9. Apostolo A, Agostoni P, Contini M, Antonioli L, Swenson ER. Acetazolamide and inhaled carbon dioxide reduce periodic breathing during exercise in patients with chronic heart failure. *J Card Fail* 2014;**20**:278–288.
10. Aimo A, Saccaro LF, Borrelli C, Fabiani I, Gentile F, Passino C, Emdin M, Piepoli MF, Coats AJS, Giannoni A. The ergoreflex: how the skeletal muscle modulates ventilation and cardiovascular function in health and disease. *Eur J Heart Fail* 2021; **23**:1458–1467.
11. Giannoni A, Gentile F, Navari A, Borrelli C, Mirizzi G, Catapano G, Vergaro G, Grotti F, Betta M, Piepoli MF, Francis DP, Passino C, Emdin M. Contribution of the Lung to the genesis of Cheyne-Stokes respiration in heart failure: plant gain beyond chemoreflex gain and circulation time. *J Am Heart Assoc* 2019;**8**:e012419.
12. Guazzi M, Reina G, Tumminello G, Guazzi MD. Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol (1985)* 2004;**97**:1866–1873.

ANEXO C

Parecer 4.558.550/2021 do Comitê de Ética em Pesquisa da Universidade Federal de Ciências da Saúde de Porto Alegre

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EOV Tool: validação e reprodutibilidade de software auxiliar para análise da ventilação periódica durante o exercício

Pesquisador: Marlus Karsten

Área Temática:

Versão: 2

CAAE: 40979620.7.0000.5345

Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.558.550

Apresentação do Projeto:

Os campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram preenchidos com base no documento "PB Informações Básicas do Projeto".

O presente estudo se caracteriza como uma pesquisa transversal fundamentada na análise de dados do teste cardiopulmonar de exercício (TCPE). Os respectivos testes fazem parte da rotina de avaliação dos pacientes encaminhados ao Heart Centre Hasselt (Rehabilitation and Health Center – Jessa Hospital). Os dados serão extraídos por profissional capacitado e compartilhados via plataforma digital com os pesquisadores. Não serão fornecidas informações que possam identificar os indivíduos, contemplando os critérios de privacidade e confidencialidade. Para viabilizar o uso deste material, os pesquisadores irão encaminhar o termo de compromisso para utilização dos dados enquanto o centro participante irá encaminhar o termo de anuência para utilização dos dados.

Posteriormente, um formulário eletrônico será desenvolvido com a ferramenta Google Forms para testar a validade do software. Profissionais com expertise na área serão contatados por e-mail e convidados a participar do estudo. Ao clicarem no link enviado por e-mail será aberto o termo de consentimento livre e esclarecido. Após a leitura do documento, os participantes deverão selecionar o link "aceito participar do estudo" para ter acesso ao formulário que testará a validade do aplicativo. Todas as respostas do participante, assim como a sua anuência serão registradas e

encaminhadas ao centro pesquisador. Procedimento similar será adotado para investigar a aplicabilidade do software usando o Modelo de Aceitação de Tecnologia (TAM). Portanto, todos os sujeitos deverão selecionar o link "aceito participar do estudo" para ter acesso ao vídeo tutorial do aplicativo e ao formulário que testará sua aplicabilidade. A identidade dos participantes não será revelada em nenhuma fase do estudo.

Objetivo da Pesquisa:

Avaliar a reprodutibilidade e a validade do software EOV Tool para identificar casos de EOV em pacientes com insuficiência cardíaca.

Avaliação dos Riscos e Benefícios:

Riscos:

Divulgação indevida de dados pessoais do participante que irá responder o instrumento (quebra de confidencialidade) e um possível desconforto alusivo a digitação.

Benefícios:

o principal benefício do estudo será a comprovação da validade, reprodutibilidade e aplicabilidade do software por profissionais da saúde, facilitando a identificação e disseminando o uso deste marcador na prática clínica.

Comentários e Considerações sobre a Pesquisa:

Trata-se de resposta ao Parecer Consubstanciado No 4.505.323, emitido em 21 de janeiro de 2021.

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos obrigatórios foram apresentados.

Recomendações:

Foram observadas duas inadequações que não apresentam óbices éticos ao desenvolvimento da pesquisa.

As orientações para a resolução dessas inadequações estão discriminadas no campo a seguir.

Conclusões ou Pendências e Lista de Inadequações:

Todas as pendências apontadas no parecer consubstanciado supracitado foram atendidas de maneira adequada.

O CEP/UFCSPA, contudo, solicita a resolução das inadequações abaixo listadas via EMENDA após o

recebimento deste parecer:

1. Substituir, no Termo de Consentimento Livre e Esclarecido (TCLE), a palavra "cópia" por "via", de acordo com a Res. CNS 466/12. Essa alteração deve ser feita também no projeto completo, no apêndice em que se encontra o TCLE;

2. No campo "Resumo" do formulário preenchido na plataforma, o qual gera o documento "PB Informações Básicas", corrigir a informação de que serão utilizados dados coletados entre os anos 2014 e 2017, conforme Carta Resposta encaminhada.

As correções via emenda possibilitam que todos os documentos armazenados na Plataforma Brasil contenham as informações adequadas sobre a pesquisa e em atendimento às normativas vigentes.

O estudo tem cronograma válido até 30/09/2022.

Considerações Finais a critério do CEP:

De acordo com o parecer do Relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situaçã
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1669400.pdf	30/01/2021 12:08:52		Aceito
Outros	CARTA_RESPOSTA_TOOL.pdf	30/01/2021 12:07:01	Gustavo dos Santos Ribeiro	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Projeto_de_Pesquisa_EOV_TOOL_versao_2.pdf	30/01/2021 12:06:43	Gustavo dos Santos Ribeiro	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_de_Pesquisa_EOV_TOOL_versao_2.docx	30/01/2021 12:06:15	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_utilizacao_de_dados_DAL_LAGO.pdf	30/01/2021 12:05:48	Gustavo dos Santos Ribeiro	Aceito
Outros	Termo_de_responsabilidade_visitante_colaborador.pdf	07/12/2020 18:25:54	Gustavo dos Santos Ribeiro	Aceito
Outros	Termo_de_compromisso_para_entrega_de_relatorio.pdf	30/11/2020 14:46:10	Gustavo dos Santos Ribeiro	Aceito
Declaração de	Termo_de_compromisso_de_utilizaca	30/11/2020	Gustavo dos Santos	Aceito

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Continuação do Parecer: 4.558.550

Pesquisadores	o_de_dados_CARGNIN.pdf	14:44:24	Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_utilizacao_de_dados_DERESZ.pdf	30/11/2020 14:44:04	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_utilizacao_de_dados_RIBEIRO.pdf	30/11/2020 14:43:04	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_utilizacao_de_dados_KARSTEN.pdf	30/11/2020 14:42:40	Gustavo dos Santos Ribeiro	Aceito
Declaração de Instituição e Infraestrutura	Consent_term_HASSELT.pdf	30/11/2020 14:42:16	Gustavo dos Santos Ribeiro	Aceito
Folha de Rosto	Folha_de_rosto_EOV_TOOL.pdf	30/11/2020 14:40:18	Gustavo dos Santos Ribeiro	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 25 de Fevereiro de 2021

Assinado por:
Luciane Dalcanale Moussalle
(Coordenador(a))

Endereço: Rua Sarmento Leite ,245
Bairro: Sarmento **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br

ANEXO D

Parecer 3.516.801/2019 do Comitê de Ética em Pesquisa da Universidade Federal de Ciências da Saúde de Porto Alegre

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Ventilação periódica durante o exercício em pacientes com insuficiência cardíaca: análise de diferentes critérios de diagnóstico e suas implicações na morbimortalidade

Pesquisador: Marlus Karsten
Área Temática:
Versão: 1
CAAE: 18718619.4.0000.5345
Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.516.801

Apresentação do Projeto:
O projeto visa a realizar análise retrospectiva baseada em arquivos de dados de testes cardiopulmonares de exercício de três centros especializados, cujos dados serão encaminhados via plataforma digital, em conjunto com dados clínicos, de caracterização e de seguimento dos participantes. Segundo os pesquisadores, essas análises permitirão avaliar e comparar as diferentes definições usadas para diagnosticar a ventilação periódica em exercício, buscando um conceito de maior sensibilidade e especificidade, além de auxiliar no desenvolvimento de software para análise padronizada da presença de EOV.

Objetivo da Pesquisa:
"Avaliar a prevalência da ventilação periódica em exercício (EOV) em pacientes com insuficiência cardíaca (IC), aplicando diferentes conceitos de diagnóstico, e avaliar seu impacto nos índices de mortalidade e tempo de hospitalização. Adicionalmente, busca-se correlacionar a variabilidade da ventilação minuto com medidas ecocardiográficas, hemodinâmicas, taxa de mortalidade e tempo de hospitalização."

Avaliação dos Riscos e Benefícios:
Segundo o projeto, tratam-se de dados previamente coletados, e o único risco seria a divulgação indevida de dados pessoais dos pacientes. Para que isso não ocorra, esses dados não serão incluídos nas informações enviadas ao centro avaliador.

Endereço: Rua Sarmento Leite ,245
Bairro: Sarmento **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Quanto aos benefícios, os resultados poderão contribuir para o melhor entendimento do processo diagnóstico da EOV por meio da identificação de conceito com maior sensibilidade e especificidade diagnóstica e capacidade preditiva de morbimortalidade relacionada à EOV.

Comentários e Considerações sobre a Pesquisa:

A pesquisa visa a realizar análise retrospectiva de dados de pacientes com IC, avançando no estado da arte na área e buscando avaliar conceitos de diagnóstico sobre a prevalência de ventilação periódica em exercício em pacientes com insuficiência cardíaca, buscando chegar a um conceito sensível e específico de diagnóstico, a fim de apurá-lo. Além disso, o desenvolvimento de software de diagnóstico baseado nesse conceito pode representar avanços para a pesquisa na área.

Considerações sobre os Termos de apresentação obrigatória:

Foram submetidos os seguintes documentos:

- termo de compromisso de entrega de relatórios parcial e final;
- termos de compromisso de uso de dados após a aprovação em comitê de ética em pesquisa e de confidencialidade em relação a esses dados assinados por todos os pesquisadores envolvidos;
- folha de rosto assinada pela pró-reitora de pesquisa e de pós-graduação;
- termo de consentimento de uso de dados retrospectivos assinados pelos responsáveis pelos três centros especializados.

Todos os documentos estão adequados.

Recomendações:

-

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Considerações Finais a critério do CEP:

De acordo com o parecer do Relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situaçã
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1357622.pdf	01/08/2019 18:12:54		Aceito
Outros	Termo_de_compromisso_para_entrega_de_relatorio.pdf	01/08/2019 18:12:29	Gustavo dos Santos Ribeiro	Aceito

Endereço: Rua Sarmento Leite ,245
Bairro: Sarmento **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Continuação do Parecer: 3.516.801

Projeto Detalhado / Brochura Investigador	Projeto_de_Pesquisa_EOV_CEP_UFCSPA.docx	31/07/2019 16:23:40	Gustavo dos Santos Ribeiro	Aceito
Declaração de Instituição e Infraestrutura	Consent_term_COSTANTINI.pdf	31/07/2019 12:28:52	Gustavo dos Santos Ribeiro	Aceito
Declaração de Instituição e Infraestrutura	Consent_term_MONZINO.pdf	31/07/2019 12:28:19	Gustavo dos Santos Ribeiro	Aceito
Declaração de Instituição e Infraestrutura	Consent_term_HASSELT.pdf	30/07/2019 23:48:23	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_uso_de_dados_Marlus.pdf	30/07/2019 23:47:46	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_uso_de_dados_Thomas.pdf	30/07/2019 23:47:14	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_uso_de_dados_Luis.pdf	30/07/2019 23:47:02	Gustavo dos Santos Ribeiro	Aceito
Declaração de Pesquisadores	Termo_de_compromisso_de_uso_de_dados_Gustavo.pdf	30/07/2019 23:46:38	Gustavo dos Santos Ribeiro	Aceito
Folha de Rosto	Folha_de_rosto.pdf	30/07/2019 23:42:21	Gustavo dos Santos Ribeiro	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 19 de Agosto de 2019

Assinado por:
Luciane Dalcanale Moussalle
(Coordenador(a))

Endereço: Rua Sarmento Leite ,245
Bairro: Sarmento **CEP:** 90.050-170
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3303-8804 **E-mail:** cep@ufcspa.edu.br