European Journal of Preventive Cardiology (2022) **29**, e233–e236
https://doi.org/10.1093/eurjpc/zwab195

RESEARCH LETTER
Cardiac Rehabilitation

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

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Received 25 August 2021; revised 14 October 2021; editorial decision 3 November 2021; accepted 5 November 2021; online publish-ahead-of-print 26 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) pretraining 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

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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

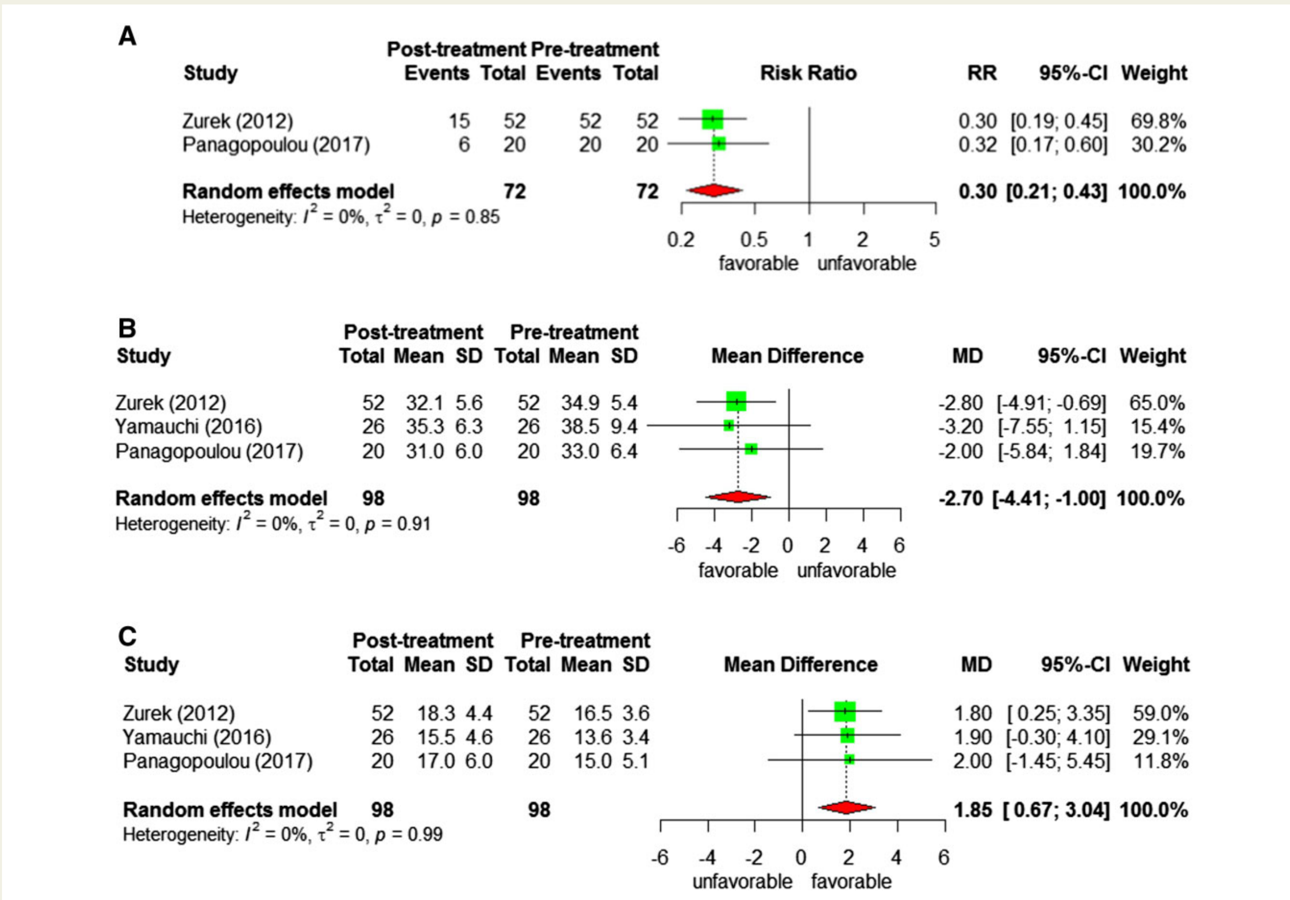

Figure 1 Forest plot of likelihood to improve exercise oscillatory ventilation (*A*), and mean difference on VE/VCO_2 slope (*B*), and VO_{2PEAK} ($mL.kg^{-1}.min^{-1}$) (*C*) in chronic heart failure patients with exercise oscillatory ventilation.

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.

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