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INVITED EDITORIAL

Exercise oscillatory ventilation in heart failure and brain–lung–heart–muscle crosstalk

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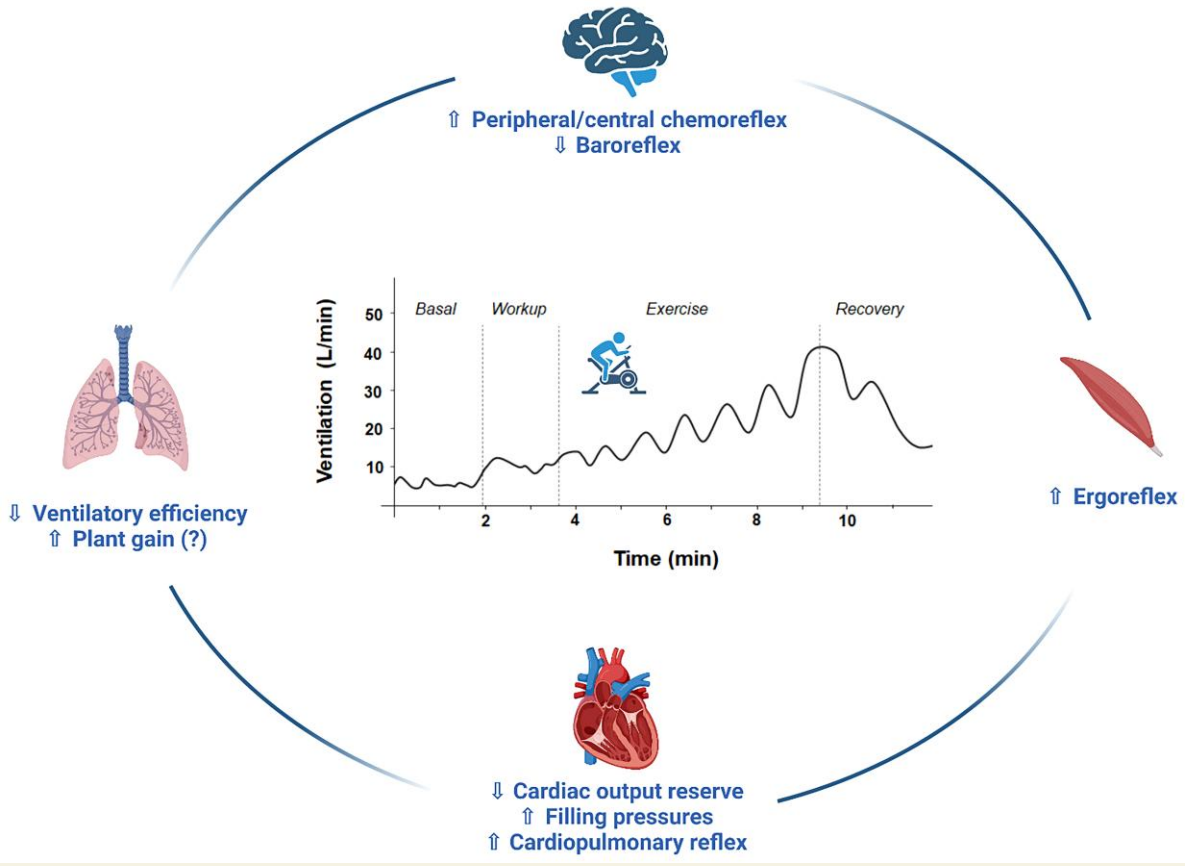
Graphical Abstract



Pathophysiological determinants of exercise oscillatory ventilation (EOV). While the pathophysiological determinants of EOV have been poorly investigated so far, the several similarities with Cheyne–Stokes respiration suggest a possible role for increased peripheral/central chemoreflex sensitivity, increased plant gain, and circulatory delay. Furthermore, an increased ventilatory response to the mechano- and/or metaboreceptors within the skeletal muscle (i.e. the ergoreflex) could contribute as well. Finally, the incapacity to adapt the cardiovascular performance to the growing energetic requests may promote EOV persistence throughout the whole exercise. *Created with BioRender.com.*

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This editorial refers to 'Exercise oscillatory breathing in heart failure with reduced ejection fraction: clinical implication' by C. da Luz Goulart *et al.*, https://doi.org/10.1093/eurjpc/zwac116.

Exercise oscillatory ventilation (EOV) is defined as an abnormal respiratory pattern, characterized by a cyclic fluctuation of ventilation and respiratory gases, which can be observed during cardiopulmonary exercise test (CPET) in a significant subset of heart failure (HF) patients.[1]

Exercise oscillatory ventilation has been long considered an ominous sign, being associated with worse clinical severity and increased risk of mortality.[1,2] However, both the determinants and the pathophysiological consequences of EOV are still poorly understood.[3] Furthermore, the clinical presentation of EOV is not homogenous: while in some patients, EOV may persist throughout the whole performance; in others, it disappears with the increase of physical effort.[4] In addition, the clinical correlates and the consequences of such a variability have not been investigated until now.

In the present Issue of the Journal, da Luz Goulart *et al.* examined for the first time the clinical and prognostic implications of EOV persistence vs. disappearance during CPET in 315 stable patients with HF and reduced ejection fraction (HFrEF).[5] At the baseline recording, most patients ($n = 202$, 64%) showed EOV, which persisted up to the peak of exercise in 70 patients (i.e. 22% of the whole cohort). Exercise oscillatory ventilation persistence was associated with a worse clinical profile, systolic function, and exercise performance, and, at a 35-month follow-up was associated with a higher risk of mortality and hospitalization. Of note, peak oxygen consumption and ventilatory efficiency (expressed as VE/VCO2 slope) maintained an additive prognostic power also in this high-risk patients' subset.[5]

The authors should be commented on the conceptualization of this study, whose findings highlight the critical role of analysing cardiorespiratory interactions in HF patients to optimize risk stratification and, eventually, therapeutic algorithms. What remains to be clarified are the pathophysiological determinants of EOV and of its persistence or disappearance during effort.

Considering the similarities between EOV and Cheyne–Stokes respiration (CSR), it has been proposed that the same mechanisms may underlie both phenomena. Indeed, although CSR has been long considered a sleep-related breathing disorder, it is now clear that it may be observed also in awake and upright patients, further aggravating outcomes.[6,7] As hypothesized through mathematical modelling, and recently confirmed in HF patients, increased chemoreflex sensitivity, increased plant gain, and circulatory delay are the main pathophysiological determinants of CSR.[8] Unfortunately, the contribution of such factors to EOV has been scarcely investigated so far.

On the other hand, the beneficial effects of beta-blockers,[9] sacubitril–valsartan,[10] cardiac resynchronization therapy,[11] and rehabilitation[12] on reducing EOV incidence may suggest some roles for autonomic dysregulation, reduced cardiac output, and physical deconditioning. In this regard, a disproportionate ventilatory response to exercise from either peripheral or central mechano- and/or metaboreceptors may explain the persistence of EOV in more compromised patients.[13]

In line with this hypothesis, the incapacity to adequate cardiac performance to the growing exercise load may sustain the mismatch between peripheral energetic requests and supply, fostering EOV and ventilatory inefficiency. Interestingly, the integration of echocardiography with CPET (i.e. e-CPET), allowing a deeper study of the interplay between ventilatory and hemodynamic parameters, may offer the opportunity of shedding light on these critical mechanisms both at baseline recording and during different exercise phases.[14] In particular, it might unravel a differential behaviour in terms of contractile (ejection fraction; global longitudinal strain) and flow reserve (cardiac output, evaluated by velocity–time integral on left ventricular outflow tract), as well as of right ventricular performance/coupling.[15] At the same time, e-CPET allows the evaluation of other possible determinants of EOV, such as valvular reserve (mitral insufficiency) and interstitial congestion, whose increase during exercise may favour ventilatory instability by triggering cardiopulmonary reflex systems. Finally, by extrapolation from universal Fick's equation, peripheral oxygen extraction capacity can be derived, portending a scenario of HF patients who are either good or poor extractors.[15]

Considering the clinical and prognostic significance of EOV in HF patients, as further confirmed by da Luz Goulart *et al.*[5] a more accurate comprehension of the underlying mechanisms is warranted to optimize therapeutic strategies. To do so, studying the interplay between central/peripheral chemo-, baro-, and ergoreflex systems, haemodynamic and ventilatory response to exercise is a promising path to be pursued (*Graphical Abstract*).

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