

Exercise Oscillatory Ventilation: A Potential New Risk Factor for Sudden Cardiac Death in Hypertrophic Cardiomyopathy

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Abstract

Other than the traditional risk factors for sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) - detected by means of anamnesis, Holter monitoring, exercise testing, echocardiography and cardiac magnetic resonance imaging - exercise oscillatory ventilation (EOV), detected by cardiopulmonary exercise testing (CPET), has recently been observed in patients with HCM. EOV is considered as one of the most important independent risk factors for morbidity, mortality and SCD in patients with reduced, as well as with preserved ejection fraction. Considering HCM as a prototype of heart failure with preserved ejection fraction, we would like to present a short, specific review concerning EOV as a potential new risk factor for SCD in HCM.

Keywords: Exercise oscillatory ventilation; Hypertrophic cardiomyopathy; Heart failure

Introduction and Pathophysiology of Exercise Oscillatory Ventilation (EOV)

The pathomechanism of EOV is in essence based on a disturbed feedback loop between the pulmonary system, peripheral chemoreceptors in the carotid arteries, and the central respiratory receptors in the medulla oblongata. This implies that instability in any of these regulatory factors leading to an unstable ventilatory regulation can give rise to breathing oscillation pattern.

The study from Corra et al showed that EOV is not present in healthy individuals; EOV was observed only in cardiovascular disease (CVD) patients and in those with depressed left ventricular ejection fraction (LVEF) [1].

This kind of instability may be caused by 1) delay in circulation; 2) system damping reduction; or 3) an increase in controller gain [2-4].

As described by Dhakal et al in patients with heart failure, a reduced cardiac output prolongs circulation time “from lungs to chemoreceptors and respiratory centers” and leads to a consequential delay of feedback signals from respiratory chemoreceptors, which leads to ventilatory instability [5].

Increase in controller gain refers to an increased sensitivity of the peripheral and central receptors responding to changes in arterial partial pressure of arterial carbon dioxide (PaCO_2) and partial pressure of arterial oxygen (PaO_2), which also leads to a pathological ventilatory regulation [5].

The study by Pardaens et al demonstrated that ergoreflex activity gives rise to hyperventilation in patients with recent heart failure decompensation or active heart failure symptoms. Output oscillations originating from neurologic triggering within the medullary vasomotor center are considered the primary cause of the disappearance of respiratory oscillations found at rest or at low levels during intense exercise [6].

Furthermore, delay of respiratory and pulmonary blood flow during exercise, in comparison to fluctuations in patients with reduced LVEF, also attenuates delayed circulation, leading to changes in respiratory feedback mechanisms [7]. Moreover, based on recent studies, chest wall conformation influences ventilatory oscillations. Specifically, patients with pectus excavatum exhibit reduced mechanical capacity for oscillatory breathing. If so, this anatomic variation may give rise to attenuated EOV and

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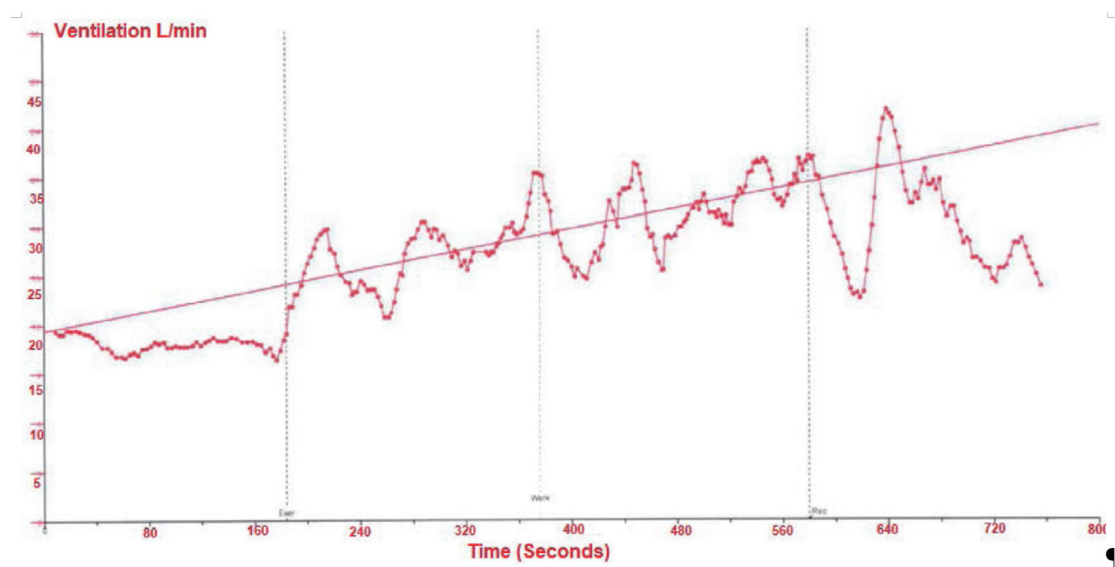


Figure 1. Exercise oscillatory ventilation (EOV). The length of an oscillation cycle in ventilation is defined as the time between two oscillations nadirs. Furthermore, oscillation amplitude is the difference between the peak ventilation of oscillation and the nadirs [19].

correspondingly lower risk of SCD [8]. Investigating whether thoracic morphology modulates the prevalence or severity of EOV could refine the predictive value of cardiopulmonary exercise testing (CPET) in hypertrophic cardiomyopathy (HCM).

Definition

The length of an oscillation cycle in ventilation is defined as the time between two oscillations nadirs. Furthermore, oscillation amplitude is the difference between the peak ventilation of oscillation and the nadirs (Fig. 1) [9]. Several definitions exist, which are summarized in Table 1 [2, 10-14].

Reversibility of EOV

Few small studies have demonstrated the reversibility of EOV with various therapeutic measures. Ribeiro et al [15] noticed

reversibility of EOV with a phosphodiesterase-3 inhibitor. Furthermore, Castro et al [16] showed EOV reversal as well as improvement in New York Heart Association (NYHA) class with exercise training, although there was no improvement in LVEF. Moreover, in a study by Marcus et al, using pacing-induced chronic heart failure (CHF) rabbit models, denervation of chemoreceptor in carotid bodies reduced oscillatory breathing patterns [17].

Heart Rate Variability (HRV) and Respiratory Variability

HRV is known to be related to average heart rate (HR) and respiratory rate. Any alterations of these two important parameters may give rise to changes in HRV [18]. The study by Gasior et al demonstrated that respiratory rate and HR influence HRV; however, the influence of breathing rate is HR-dependent. The correction of HRV for the HR decreases

Table 1. Criteria for EOV

Ben-Dov et al, 1992 [13]	Three or more consecutive regular oscillations in VE with oscillation amplitude > 25% of average VE and cycle length 30 - 60 s
Kremser et al, 1987 [11], and Corra et al, 2006 [12]	Oscillations in VE with a cycle length of approximately 1 min, amplitude > 15% of resting VE, and duration > 60% (> 66%) of exercise duration
Sun et al, 2010 [10]	Three or more consecutive cyclic fluctuations in VE, amplitude > 30% of concurrent mean VE, oscillation of ≥ 3 gas exchange variables, cycle length of 40 - 140 s
Leite et al, 2003 [2]	Three or more cycles of regular oscillation in VE with standard deviation of 3 consecutive cycle lengths within 20% of the average and minimal average amplitude of oscillation > 5 L/min
American Heart Association (AHA) consensus, 2010 [14]	EOV pattern that persists for at least 60% of the exercise test at amplitude 15% or more of the average resting value

EOV: exercise oscillatory ventilation; VE: minute ventilation.

the association between respiratory rate and HRV [18].

And so, HR appears to be a main leading factor of reproducibility of HRV [18].

EOV in HCM and Future Aspects

As aforementioned, EOV has been investigated in patients with systolic and diastolic heart failure and is recognized as an independent risk factor for cardiovascular death. Parallely, HCM is considered as a prototypical substrate for diastolic heart failure [19].

The retrospective study by Sakellaropoulos et al identified, to our knowledge for the first time, the presence of exercise oscillatory gas exchange kinetics in HCM, with a prevalence of 5%. It is associated with overt heart failure, peak $\text{VO}_2 \leq 9.1 \text{ mL/kg/min}$, as well as an enlarged left atrial diameter, indexed with a cutoff of 25 mm/m^2 [9].

We highly recommend that further larger studies should be conducted in order to investigate the potential role of EOV in the assessment of SCD in patients with HCM. Other than the traditional risk factors for the implantation of implantable cardioverter defibrillator (ICD) as a primary prophylaxis for SCD, we support CPET to be performed routinely, in order to evaluate HCM patients due to its highly prognostic and predictive power.

Concerning treatment, studies on myosin inhibitors demonstrate excellent results in the treatment of HCM [20], and an investigation on EOV could be a very promising and productive field of research.

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Conflict of Interest

None to declare.

Author Contributions

SGS and AM have contributed to the article concerning article design, providing clinical expertise to revise critically. MM, PS, MA, AP, IP, EK, BSS and CR have equally contributed to the article concerning literacy search.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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