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**Exercise oscillatory ventilation: Mechanisms and prognostic significance**

Dhakal BP *et al*. Exercise oscillatory ventilation

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**Abstract**

Alteration in breathing patterns characterized by cyclic variation of ventilation with a period of approximately one minute known as periodic breathing has been recognized in patients with advanced heart failure for nearly two centuries. Periodic breathing during exercise is a non-invasive parameter that is easily discernible along with other gas exchange parameters during submaximal cardiopulmonary exercise testing. Recent studies have shown that periodic breathing during exercise also known as exercise oscillatory ventilation (EOV) indicates significant impairment in resting and exercise hemodynamic parameters in heart failure (HF) patients. EOV is also an independent risk factor for poor prognosis in HF patients both with reduced and preserved ejection fraction irrespective of other gas exchange variables. Circulatory delay, increased chemosensitivity, pulmonary congestion and increased ergoreflex signaling have been proposed as the mechanisms underlying the generation of EOV in HF patients. There is no proven treatment of EOV but its reversal has been noted with phosphodiesterase inhibitors, exercise training and acetazolamide in relatively small studies. In this review, we discuss the mechanistic basis of periodic breathing during exercise and the clinical implications of recognizing periodic breathing patterns in patients with HF.

**Key words**: Exercise; Oscillatory ventilation; Heart failure

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**Core tip:** Alteration in breathing patterns in patients with advanced heart failure (HF) characterized by cyclic variation of ventilation with a period of approximately one minute is known as periodic breathing. Periodic breathing during exercise, known as exercise oscillatory ventilation (EOV), is an oscillatory pattern during exercise that persists for at least 60% of the exercise test with an amplitude ≥ 15% of the average resting value. Circulatory delay, pulmonary congestion and chemoreceptor sensitivity has been proposed to cause generation of EOV. EOV is an independent predictor of worse outcome irrespective of other gas exchange variables in HF patients.

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**INTRODUCTION**

Heart failure (HF) is a syndrome characterized by impaired cardiac filling or ejection of the blood leading to multiple organ systems dysfunction[1]. Dyspnea on exertion and exercise intolerance are the cardinal manifestations of HF that account for significant disease morbidity. Alteration in breathing patterns secondary to instability in respiratory control has been a recognized feature of HF for almost two centuries[2-4]. Cheyne[2] (1818) first described a severe form of disordered breathing during rest characterized by intervals of apnea with a waxing and waning tidal volume lasting almost a minute in a patient with HF and similar case was described by Stokes three decades later (1854) after which the condition was named Cheyne-Stokes breathing. Other forms of periodic breathing (PB) characterized by cyclic variation of ventilation with or without apnea have been observed both during sleep and during exercise (**Figure 1**). During sleep, HF patients are susceptible to both obstructive and central sleep apnea (CSA). CSA is characterized by nocturnal periodic breathing with intervals of apnea and hypopnea and has been observed in nearly one third of patients with symptomatic HF[5,6].

An unusual crescendo-decrescendo ventilatory response to exercise in patients with heart disease without resting Cheyne-Stokes breathing was initially reported by Weber *et al*[7] and further described by Kremser *et al*[8] in 1987. This phenomenon of periodic oscillatory breathing during exertion without interposed apnea is now known as exercise PB or exercise oscillatory ventilation (EOV) (Figure 2). EOV has recently been recognized in significant numbers (7%-51%) of symptomatic HF patients, both those with reduced and preserved ejection fraction[8-12]. The presence of PB is an indicator of poor prognosis in HF patients, whether it arises at rest[13,14],during sleep[5,9,15], or during exercise[9,10,16,17]. Despite the frequent occurrence of PB in patients with HF, pathophysiologic mechanisms that induce irregular breathing in HF still remain incompletely understood. In this review, we focus specifically on EOV discerned in the context of measuring expired gas exchange variables during exercise through cardiopulmonary exercise testing.

**CARDIOPULMONARY EXERCISE TESTING**

Cardiopulomnary exercise testing (CPET) provides a unique opportunity to evaluate patient’s aerobic capacity with breath-by-breath expired gas parameters. The gas exchange parameters obtained during routine CPET such as peak oxygen uptake (VO2), carbon dioxide output (VCO2), partial pressure of end tidal CO2 (PETCO2) and ventilation (VE) along with other variables are valuable in differentiating various aspects of HF pathophysiology and prognostication. Peak VO2[18] and ventilatory efficiency (VE/VCO2 slope)[16,19,20] are significant prognostic indicators in HF, especially VE/VCO2 slope indicative of pulmonary vascular abnormalities and often being better predictor of HF outcomes than peak VO2. Respiratory exchange ratio (VCO2/VO2) provides objective assessment of patient's volitional effort during symptom limited CPET, and the ratio exceeding one during exercise indicates that a subject has surpassed the anaerobic threshold. Heart rate (HR) augmentation and recovery also have prognostic implications both in patients with cardiovascular disease and normal healthy individuals and is related to the autonomic function during exercise[21,22].Oxygen uptake efficiency slope (OUES), VO2 uptake kinetics, and VO2 at the anaerobic threshold are the submaximum CPET parameters which are indicative of cardiac reserve capacity during low-level physical activities of advanced HF patients[23]. Pulmonary limitation to exercise, both primary and secondary, is measured by breathing reserve which is the relationship between exercise VE and maximal breathing capacity as estimated by the resting maximal voluntary ventilation (MVV) [VE/(forced expiratory volume in 1 s (FEV1) × 35) > 0.7][18]. Integration of CPET with other forms of testing such as invasive hemodynamic monitoring, echocardiography, or radionuclide ventriculography can provide wealth of additional physiologic information during exercise that helps in comprehensively phenotype HF population. EOV which is easily discernible in HF patients at submaximal exercise should therefore be integrated with other gas exchange variables during CPET.

**EXERCISE OSCILLATORY VENTILATION**

***Definitions***

Previous investigators have defined EOV in multiple ways based on somewhat arbitrary criteria. Presence of EOV is identified by ventilatory oscillations during CPET with a typical cycle length and amplitude but there are a lot of variations on defining those parameters[24]. Cycle length of an oscillation in VE is the time between nadirs of two ventilatory oscillations and the amplitude of oscillation is the difference between the peak VE during an oscillation and the nadirs in VE (Figure 2)[17]. Some of the definitions used for EOV are: (1) Kremser *et al*[8] andCorrà*et al*[9,17]: Oscillations in VE with a cycle length of approximately 1 min, amplitude > 15% of resting VE, and duration > 60% (> 66%[8]) of exercise duration. (2) Ben-Dov *et al*[25]: 3 or more consecutive regular oscillations in VE with oscillation amplitude > 25% of average VE, cycle length 30-60 s. (3) Leite *et al*[26]: 3 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. and (4) Sun *et al*[10]: 3 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.

An AHA consensus statement has defined EOV as an oscillatory pattern that persists for at least 60% of the exercise test at an amplitude 15% or more of the average resting value[27]. Due to the lack of automated measurement methods, presence of EOV during CPET is usually analyzed manually which can lead to variations in definitions and appropriate identification. More recently custom software has been used to identify EOV during exercise[28,29].

***Epidemiology and prognostic significance***

Based on these various definitions, EOV has been described in 19%-51%[8-10,12,26,30,31] of patients with HF and reduced ejection fraction (HFrEF). EOV is similarly common in patients with HF and preserved ejection fraction (HFpEF) with one previous study showing prevalence of 31%[23]. Olson *et al*[31] reported that 41% of HF patients with EOV had left ventricular ejection fraction (LVEF) ≥ 40%, and in the study by Matsuki *et al*[32]the mean LVEF in HF patients with EOV was 41.3 ± 16.3. We found EOV prevalence of 45% in a subset of patients with HFrEF (*n* = 56, mean ±SEM: LVEF = 30% ± 1%, peak VO2 = 12.4 ± 0.5 ml/kg/min)[11]. The prevalence of EOV tracks with the metrics of HF severity such as higher NYHA class, lower peak VO2, higher VE/VCO2 slopes and lower PETCO2[8-11,17,23,26,30-38] (Table 1). However, EOV has been shown to provide strong independent prognostic information even after adjustment for these variables.

The initial study describing the prognostic significance of periodic breathing predicted poor 2-year survival in HF patients independent of peak VO2[39]. Leite *et al*[26] and Corrà*et al*[17] both demonstrated that HF patients with EOV had nearly 3-fold higher mortality compared to those patients without EOV (Table 1). In HF patients, presence of EOV along with other abnormal breathing patterns such as those during sleep indicates high risk for adverse events (54% in patients with EOV and AHI > 30/h *vs* 17% with EOV alone, OR = 6.65, 95%CI: 2.6-17.1, *P* < 0.01)[9]. Similarly when EOV is present along with elevated VE/VCO2 slope, the odds ratio for 6-mo mortality in HF patients increased by more than 4-fold (9.4 to 38.9)[10]. Guazzi *et al*[12] found EOV to be the independent predictor of overall mortality and sudden cardiac death predominantly due to arrhythmia in 156 HF patients. In another study of 240 patients with HFrEF, EOV was a predictor of mortality independent of peak VO2, VE/VCO2 slope, LVEF, age, and 6-min walking distance[34]. EOV has recently been recognized as a potent prognostic indicator in patients with congenital heart disease as EOV along with the percentage of maximum predicted HR was found to be the independent predictors of the combined outcome of death, transplantation or cardiovascular hospitalization in patients who underwent Fontan procedure[28].

The superior prognostic value of EOV and VE/VCO2 slope compared to peak VO2 has been observed in multiple studies which examined the relative predictive values of various CPET variables, and the feasibility of EOV measurements during submaximal exercise makes it particularly attractive in HF population who are not able to do maximum effort exercise testing[10,12,16,33,40].CPET parameters combined with biomarkers such as NT-pro BNP have also been found to be the powerful predictor of cardiovascular death in stable HF patients[16]. EOV along with other CPET -derived variables (VE/VCO2 slope, OUES and ventilatory equivalent for carbon dioxide nadir) has been shown to outperform the traditional Heart Failure Survival Score in predicting outcomes in patients with mild-to-moderate HF[41]. Guazzi *et al*[42] recently characterized EOV in patients with broader cardiovascular risk factors and found the EOV to be an indicator of worse CV risk factor profile in patients even without clinical manifestations of HF.

***Mechanisms***

There is limited data regarding the mechanistic basis for EOV despite its significant association with poor outcomes in HF patients[43]. The control of the normal ventilation is through the feedback loop between pulmonary gas exchanging capillaries and chemoreceptors in the carotid bodies (peripheral) and the medulla (central) (Figure 3)[39,44-47]. Instability of ventilatory regulation leading to its oscillations can be caused by: (1) delay in information transfer (*i.e.* increased circulation time from the lung to the brain and chemoreceptors due to reduced cardiac index.)[26,46]; (2) increase in controller gain (*i.e.* increased chemosensitivity to PaCO2 and PaO2)[13,45,48], or (3) reduction in system damping (*i.e.* baroreflex impairment, Figure 3). The possible mechanisms responsible for generation of PB during exercise (*i.e.* EOV) have largely been extrapolated from studies of PB at rest and during sleep[26,49,50] even though there has been limited overlap between PB during exercise and during sleep[9].

**Circulatory delay**: Reduced cardiac output in patients with HF increases the circulation time from lungs to chemoreceptors and respiratory centers which causing delayed transfer of information has been postulated to generate delayed feedback signals leading to oscillatory ventilation[45,51]. Reduced resting CI and prolonged lung-to ear circulation time (LECT) has been shown to be the major determinants of PB at rest[51,52]. Koike *et al*[53] also observed that patients with EOV had significantly lower LVEF compared to those without EOV. Delayed generation of respiratory and pulmonary blood flow oscillations during exercise compared to LVEF fluctuations in HF patients also supports delayed circulation causing alterations in respiratory feedback mechanisms[54].

In a study of HFrEF patients, those with EOV demonstrated a greater degree of hemodynamic impairment at both at rest and during exercise and lower CI[11].The amplitude and duration of oscillations were inversely related to exercise CI, and the changes in cycle length and amplitude of EOV after 12 wk of treatment with sildenafil were inversely related to changes in CI[11]. In another small study, patients with advanced HF, as reflected by a lower peak VO2 and higher VE/VCO2 slope, had a longer cycle length of oscillations and a longer phase difference between oscillating VO2 and VE[55]. Attenuation of EOV during high-intensity exercise could be due to reduced circulation time due to increased CI during exercise supporting circulatory delay as an important factor determining factor for generation of EOV[55]. Some investigators have argued against contribution of circulatory delay to EOV but did not directly measure cardiac output or circulation time[56].

**Increased chemosensitivity:** Increased carotid and aortic chemoreceptor sensitivity to small changes in arterial O2 and CO2 may contribute to sympathetic overactivity and excessive and irregular ventilation during exercise. Enhanced hypoxic and central hypercapneic chemosensitivity may cause increased ventilatory response (VE/VCO2) to exercise in HF patients[43,57].Such chronically increased ventilation causes reduction in arterial concentration of both CO2 and bicarbonate[58] which weakens the blood’s ability to buffer against changes in CO2 levels. Pitt, Pembrey and Allen in 1907 observed that a modest increase in partial pressure of CO2 triggers a cycle of hyperventilation-induced reduction in PaCO2 until the apnea threshold is reached leading to Cheyne-Stokes breathing[59]. Similarly modulation of PB with modification of inspired CO2 concentration has also been observed[60].In a quantitative algebraic analysis of the dynamic cardiorespiratory physiology, circulatory delay and increased chemoreflex gain were found to be the primary factors causing EOV[61]. In experimental conditions, an increase in peripheral chemoreceptor discharge induced oscillatory ventilation at rest that was abolished by hyperoxia[62] whereas dihydrocodeine attenuated PB by reducing chemosensitivity[39].

Despite the proposed increased peripheral chemoreceptor sensitivity, there may be other non-peripheral chemoreceptor mediated mechanisms involved in mediating increased ventilatory response to exercise[63]. In one study, arterial blood gases (PaCO2 and PaO2) at rest and average values across the first 6 min of exercise in HF patients had no relationship with EOV[11].The amplitude and duration of EOV was also not related to mean PaCO2[11,56] which argues against a PaCO2 set point close to the apnea threshold, serving as a major determinant of the presence of EOV in HF patients

**Pulmonary congestion:** Pulmonary congestion and decreased lung compliance[64] causes overstimulation of the ventilatory control center leading to hyperventilation and thus decrease in PCO2 which has been postulated to generate PB[65,66]. Elevated PCWP, a surrogate for pulmonary congestion, stretches J receptors[67] which in turn stimulates the medullary respiratory center *via* vagal afferents, leading to rapid shallow breathing, hypocapnia, and initiation of PB at rest[68]. The damping effects of O2 and CO2 stores which prevent oscillations are also reduced by pulmonary congestion[46]. In 1943, Christie *et al*[69]were able to induce PB by occluding a pulmonary vein leading to pulmonary congestion. Increased resting and exercise cardiac filling pressures and higher NT-proBNP in recent studies of HF patients with EOV compared to those without EOV extends their findings[11,32]. The relationship between pulmonary congestion and EOV has been questioned by some studies which showed disappearance of EOV during later exercise in HF patients despite an increase in PCWP[31,70-72].

**Ergoreflex signaling:** Metabolic abnormalities in skeletal muscle caused by HF may also lead to enhanced ergoreflex signaling during exercise which may be associated with worse NYHA class, decreased exercise tolerance, and hyperventilation during exercise in HF patients[69-71]. Ergoreflex activity contributed to hyperventilation in HF patients with a history of recent decompensation or persistent symptoms as observed by Pardaens *et al*[73] Oscillations in output of neurologic stimuli from the medullary vasomotor center may explain disappearance of respiratory oscillations found at rest or at low levels of exercise during more intense exercise. Decreased activation of both the CO2 chemoreflex and the ergoreflex has been shown to decrease ventilatory drive after cardiac resynchronization therapy[74]. Despite the proposed contribution of ergoreceptors to the autonomic, hemodynamic, and respiratory responses to exercise in HF patients,further investigation is needed to establish its relationship to hyperventilation and EOV in HF patients.

**EOV reversibility:** The potential reversibility of EOV has been examined through serial studies of HF patients undergoing different pharmacological or surgical interventions. In a small randomized double-blind placebo controlled trial of HFrEF patients, serial assessment of EOV before and after 12 wk of sildenafil treatment showed reduction in EOV cycle length and oscillatory amplitude and increase in exercise CI in the sildenafil group compared to placebo[75]. The changes in oscillatory cycle length and amplitude after sildenafil treatment were inversely related to changes in exercise CI[11]. This finding was further supported by another study from Guazzi *et al*[23] who noted resolution of EOV in the majority of patients treated with sildenafil, although EOV was not a pre-specified endpoint in these trials with small number of study subjects (*n* < 40).

Valvular and open heart surgeries[37,76],and cardiac transplantation[77] have also been associated with attenuation of PB. There are few other studies involving small number of patients that showed resolution of EOV with different therapeutic interventions. For example, Ribiero *et al*[78] noticed reduction in EOV with PDE3 inhibitor milrinone in three patients and Castro *et al*[79] reported reversal of EOV and improvement in NYHA class with exercise training in one HF patient despite no change in LVEF. Zurek *et al*[80] also reported reversal of EOV in 71% of 96 stable HFrEF patients after 3 mo of outpatient exercise training program. Recent studies have shown that inhalation of CO2 and acetazolamide treatment significantly reduced PB during exercise in HF patients[81,82].Three months of nocturnal adaptive servoventilation reversed EOV in majority of the HF patients studied by Kazimierczak *et al*[36]. In an experimental study of pacing induced-CHF rabbit models, carotid body chemoreceptor denervation reduced disordered breathing patterns[83].

**CLINICAL IMPLICATIONS**

EOV being a significant prognostic indicator of HF outcomes, it's identification at submaximal levels of exercise during CPET and the possibility of EOV reversal with HF interventions makes it an attractive potential surrogate end point of interest for HF interventions. Further work needs to be done to identify whether HF interventions such as diuretic therapy, physical activity, phosphodiesterase inhibitors, cardiac resynchronization, intensification of neurohormonal blockade, cardiac surgery or other emerging therapies will successfully attenuate EOV, and if that modification of EOV translates into improvement in underlying cardiac dysfunction and clinical outcome of HF patients.

**CONCLUSION**

EOV is an easily recognizable, noninvasive and reproducible submaximal exercise parameter observed during standard cardiopulmonary testing. EOV has been proven to be a strong predictor of reduced survival in HF patients irrespective of the echocardiographic and gas exchange variables. EOV in a HF patient indicates significant impairment in resting and exercise cardiac hemodynamic response, particularly when it occurs during early exercise and when cycle length is longer than one minute. Presence of EOV is an indication to intensify therapy to optimize cardiac hemodynamics, and improve symptoms and functional capacity in HF patients.

**REFERENCES**

1 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

2 **Cheyne J**. A case of apoplexy in which the fleshy part of the heart was converted in fat. *Dublin Hosp Rep* 1818; **2**: 216-219

3 **Stokes W**. The Disease of the Heart and Aorta. Dublin: Hodges and Smith; 1854

4 **Douglas CG**, Haldane JS. The causes of periodic or Cheyne-Stokes breathing. *J Physiol* 1909; **38**: 401-419 [PMID: 16992962 DOI: 10.1113/jphysiol.1909.sp001314]

5 **Sin DD**, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999; **160**: 1101-1106 [PMID: 10508793 DOI: 10.1164/ajrccm.160.4.9903020]

6 **Javaheri S**, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998; **97**: 2154-2159 [PMID: 9626176 DOI: 10.1161/01.CIR.97.21.2154]

7 **Weber KT**. Cardiopulmonary exercise testing: physiologic principles and clinical applications. 1986

8 **Kremser CB**, O'Toole MF and Leff AR. Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1987; **59**: 900-905 [DOI: 10.1016/0002-9149(87)91116-7]

9 **Corrà U**, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P, Bosimini E, Gnemmi M, Giannuzzi P. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006; **113**: 44-50 [PMID: 16380551 DOI: 10.1161/CIRCULATIONAHA.105.543173]

10 **Sun XG**, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *J Am Coll Cardiol* 2010; **55**: 1814-1823 [PMID: 20413031 DOI: 10.1016/j.jacc.2009.10.075]

11 **Murphy RM**, Shah RV, Malhotra R, Pappagianopoulos PP, Hough SS, Systrom DM, Semigran MJ, Lewis GD. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. *Circulation* 2011; **124**: 1442-1451 [PMID: 21875912 DOI: 10.1161/CIRCULATIONAHA.111.024141]

12 **Guazzi M**, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S, Pedretti R. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol* 2007; **50**: 299-308 [PMID: 17659196 DOI: 10.1016/j.jacc.2007.03.042]

13 **Ponikowski P**, Chua TP, Anker SD, Francis DP, Doehner W, Banasiak W, Poole-Wilson PA, Piepoli MF, Coats AJ. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation* 2001; **104**: 544-549 [PMID: 11479251 DOI: 10.1161/hc3101.093699]

14 **Poletti R**, Passino C, Giannoni A, Zyw L, Prontera C, Bramanti F, Clerico A, Piepoli M, Emdin M. Risk factors and prognostic value of daytime Cheyne-Stokes respiration in chronic heart failure patients. *Int J Cardiol* 2009; **137**: 47-53 [PMID: 18691782 DOI: 10.1016/j.ijcard.2008.06.028]

15 **Bradley TD**, Floras JS. Sleep apnea and heart failure: Part I: obstructive sleep apnea. *Circulation* 2003; **107**: 1671-1678 [PMID: 12668504 DOI: 10.1161/01.CIR.0000061757.12581.15]

16 **Arena R**, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M. Development of a ventilatory classification system in patients with heart failure. *Circulation* 2007; **115**: 2410-2417 [PMID: 17452607 DOI: 10.1161/CIRCULATIONAHA.107.686576]

17 **Corrà U**, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJ, Giannuzzi P. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest* 2002; **121**: 1572-1580 [PMID: 12006446 DOI: 10.1378/chest.121.5.1572]

18 **Arena R**, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 2011; **123**: 668-680 [PMID: 21321183 DOI: 10.1161/CIRCULATIONAHA.109.914788]

19 **Lewis GD**, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. *Circ Heart Fail* 2008; **1**: 227-233 [PMID: 19808296 DOI: 10.1161/CIRCHEARTFAILURE.108.785501]

20 **Arena R**, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; **147**: 354-360 [PMID: 14760336 DOI: 10.1016/j.ahj.2003.07.014]

21 **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**: 2751-2759 [PMID: 18836201 DOI: 10.1093/eurheartj/ehn437]

22 **Borlaug BA**, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation* 2006; **114**: 2138-2147 [PMID: 17088459 DOI: 10.1161/CIRCULATIONAHA.106.632745]

23 **Kitzman DW**, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail* 2010; **3**: 659-667 [PMID: 20852060 DOI: 10.1161/CIRCHEARTFAILURE.110.958785]

24 **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**: 161-169 [PMID: 25918072 DOI: 10.1016/j.ijcard.2015.04.111]

25 **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**: 776-781 [PMID: 1554201 DOI: 10.1164/ajrccm/145.4\_Pt\_1.776]

26 **Leite JJ**, Mansur AJ, de Freitas HF, Chizola PR, Bocchi EA, Terra-Filho M, Neder JA, Lorenzi-Filho G. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol* 2003; **41**: 2175-2181 [PMID: 12821243 DOI: 10.1016/S0735-1097(03)00460-1]

27 **Balady GJ**, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; **122**: 191-225 [PMID: 20585013 DOI: 10.1161/CIR.0b013e3181e52e69]

28 **Nathan AS**, Loukas B, Moko L, Wu F, Rhodes J, Rathod RH, Systrom DM, Ubeda Tikkanen A, Shafer K, Lewis GD, Landzberg MJ, Opotowsky AR. Exercise oscillatory ventilation in patients with Fontan physiology. *Circ Heart Fail* 2015; **8**: 304-311 [PMID: 25550441 DOI: 10.1161/CIRCHEARTFAILURE.114.001749]

29 **Olson TP**, Johnson BD. Quantifying oscillatory ventilation during exercise in patients with heart failure. *Respir Physiol Neurobiol* 2014; **190**: 25-32 [PMID: 24121091 DOI: 10.1016/j.resp.2013.09.008]

30 **Arena R**, Myers J, Abella J, Peberdy MA, Pinkstaff S, Bensimhon D, Chase P, Guazzi M. Prognostic value of timing and duration characteristics of exercise oscillatory ventilation in patients with heart failure. *J Heart Lung Transplant* 2008; **27**: 341-347 [PMID: 18342759 DOI: 10.1016/j.healun.2007.11.574]

31 **Olson LJ**, Arruda-Olson AM, Somers VK, Scott CG, Johnson BD. Exercise oscillatory ventilation: instability of breathing control associated with advanced heart failure. *Chest* 2008; **133**: 474-481 [PMID: 18071013 DOI: 10.1378/chest.07-2146]

32 **Matsuki R**, Kisaka T, Ozono R, Kinoshita H, Sada Y, Oda N, Hidaka T, Tashiro N, Takahashi M, Sekikawa K, Ito Y, Kimura H, Hamada H, Kihara Y. Characteristics of patients with severe heart failure exhibiting exercise oscillatory ventilation. *Clin Exp Hypertens* 2013; **35**: 267-272 [PMID: 23537269 DOI: 10.3109/10641963.2013.780071]

33 **Guazzi M**, Arena R, Ascione A, Piepoli M, Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J* 2007; **153**: 859-867 [PMID: 17452165 DOI: 10.1016/j.ahj.2007.02.034]

34 **Ingle L**, Isted A, Witte KK, Cleland JG, Clark 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* 2009; **16**: 451-456 [PMID: 19369874 DOI: 10.1097/HJR.0b013e32832a4f54]

35 **Wang JS**, Fu TC, Wang CH, Chou SL, Liu MH, Cherng WJ. Exertional periodic breathing potentiates erythrocyte rheological dysfunction by elevating pro-inflammatory status in patients with anemic heart failure. *Int J Cardiol* 2013; **167**: 1289-1297 [PMID: 22521383 DOI: 10.1016/j.ijcard.2012.03.170]

36 **Kazimierczak A**, Krzyżanowski K, Wierzbowski R, Ryczek R, Smurzyński P, Michałkiewicz D, Orski Z, Gielerak G. Resolution of exercise oscillatory ventilation with adaptive servoventilation in patients with chronic heart failure and Cheyne-Stokes respiration: preliminary study. *Kardiol Pol* 2011; **69**: 1266-1271 [PMID: 22219104]

37 **Ueshima K**, Kobayashi N, Yamazaki T, Saitoh M, Nakamura M, Nakao K. Clinical significance of awake oscillatory ventilation in patients with heart failure and effects of open-heart surgery. *Clin Cardiol* 2010; **33**: E20-E23 [PMID: 20641105 DOI: 10.1002/clc.20572]

38 **Schmid JP**, Apostolo A, Antonioli L, Cattadori G, Zurek M, Contini M, Agostoni P. Influence of exertional oscillatory ventilation on exercise performance in heart failure. *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 688-692 [PMID: 18797406 DOI: 10.1097/HJR.0b013e32830fdfdb]

39 **Ponikowski P**, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, Coats AJ, Piepoli M. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation* 1999; **100**: 2418-2424 [PMID: 10595954 DOI: 10.1161/01.CIR.100.24.2418]

40 **Scardovi AB**, De Maria R, Ferraironi A, Gatto L, Celestini A, Forte S, Parolini M, Sciarretta S, Ricci R, Guazzi M. A case for assessment of oscillatory breathing during cardiopulmonary exercise test in risk stratification of elderly patients with chronic heart failure. *Int J Cardiol* 2012; **155**: 115-119 [PMID: 21402422 DOI: 10.1016/j.ijcard.2011.02.033]

41 **Ingle L**, Rigby AS, Sloan R, Carroll S, Goode KM, Cleland JG, Clark AL. Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart* 2014; **100**: 781-786 [PMID: 24567314 DOI: 10.1136/heartjnl-2013-304614]

42 **Guazzi M**, Arena R, Pellegrino M, Bandera F, Generati G, Labate V, Alfonzetti E, Villani S, Gaeta MM, Halle M, Haslbauer R, Phillips SA and Cahalin LP. Prevalence and characterization of exercise oscillatory ventilation in apparently healthy individuals at variable risk for cardiovascular disease: A subanalysis of the EURO-EX trial. *Eur J Prev Cardiol* 2015; Epub ahead of print [PMID: 25868603 DOI: 10.1177/2047487315580445]

43 **Dhakal BP**, Murphy RM, Lewis GD. Exercise oscillatory ventilation in heart failure. *Trends Cardiovasc Med* 2012; **22**: 185-191 [PMID: 23062973 DOI: [10.1016/j.tcm.2012.07.018](http://dx.doi.org/10.1016/j.tcm.2012.07.018" \t "_blank)]

44 **Cherniack NS**, Longobardo GS. Cheyne-Stokes breathing. An instability in physiologic control. *N Engl J Med* 1973; **288**: 952-957 [PMID: 4571351 DOI: 10.1056/NEJM197305032881810]

45 **Khoo MC**, Kronauer RE, Strohl KP, Slutsky AS. Factors inducing periodic breathing in humans: a general model. *J Appl Physiol Respir Environ Exerc Physiol* 1982; **53**: 644-659 [PMID: 7129986]

46 **Dowell AR**, Buckley CE, Cohen R, Whalen RE, Sieker HO. Cheyne-Stokes respiration. A review of clinical manifestations and critique of physiological mechanisms. *Arch Intern Med* 1971; **127**: 712-726 [PMID: 4929239 DOI: 10.1001/archinte.1971.00310160190015]

47 **Millar TW**, Hanly PJ, Hunt B, Frais M, Kryger MH. The entrainment of low frequency breathing periodicity. *Chest* 1990; **98**: 1143-1148 [PMID: 2225959 DOI: 10.1378/chest.98.5.1143]

48 **Javaheri S**. A mechanism of central sleep apnea in patients with heart failure. *N Engl J Med* 1999; **341**: 949-954 [PMID: 10498490 DOI: 10.1056/NEJM199909233411304]

49 **Naughton M**, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis* 1993; **148**: 330-338 [PMID: 8342895 DOI: 10.1164/ajrccm/148.2.330]

50 **Andreas S**, Hagenah G, Moller C, Werner GS, Kreuzer H. Cheyne-Stokes respiration and prognosis in congestive heart failure. *Am J Cardiol* 1996; **78**: 1260-1264 [PMID: 8960586 DOI: 10.1016/S0002-9149(96)00608-X]

51 **Mortara A**, Sleight P, Pinna GD, Maestri R, Capomolla S, Febo O, La Rovere MT, Cobelli F. 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* 1999; **84**: 900-904 [PMID: 10532507 DOI: 10.1016/S0002-9149(99)00462-2]

52 **Agostoni P**, Apostolo A, Albert RK. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. *Chest* 2008; **133**: 197-203 [PMID: 18187746 DOI: 10.1378/chest.07-1439]

53 **Hall MJ**, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med* 1996; **154**: 376-381 [PMID: 8756809 DOI: 10.1164/ajrccm.154.2.8756809]

54 **Koike A**, Shimizu N, Tajima A, Aizawa T, Fu LT, Watanabe H, Itoh H. Relation between oscillatory ventilation at rest before cardiopulmonary exercise testing and prognosis in patients with left ventricular dysfunction. *Chest* 2003; **123**: 372-379 [PMID: 12576354 DOI: 10.1378/chest.123.2.372]

55 **Yajima T**, Koike A, Sugimoto K, Miyahara Y, Marumo F, Hiroe M. Mechanism of periodic breathing in patients with cardiovascular disease. *Chest* 1994; **106**: 142-146 [PMID: 8020261 DOI: 10.1378/chest.106.1.142]

56 **Kato J**, Koike A, Hoshimoto-Iwamoto M, Nagayama O, Sakurada K, Sato A, Yamashita T, Wasserman K, Aonuma K. Relation between oscillatory breathing and cardiopulmonary function during exercise in cardiac patients. *Circ J* 2013; **77**: 661-666 [PMID: 23229462 DOI: 10.1253/circj.CJ-12-0925]

57 **Chua TP**, Clark AL, Amadi AA, Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1996; **27**: 650-657 [PMID: 8606277 DOI: 10.1016/0735-1097(95)00523-4]

58 **Hanly P**, Zuberi N, Gray R. Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure. Relationship to arterial PCO2. *Chest* 1993; **104**: 1079-1084 [PMID: 8404170 DOI: 10.1378/chest.104.4.1079]

59 **Pitt GN**, Pembrey MS, Allen RW. Observations upon Cheyne-Stokes' Respiration. *Med Chir Trans* 1907; **90**: 49-82.15 [PMID: 20897081]

60 **Steens RD**, Millar TW, Su X, Biberdorf D, Buckle P, Ahmed M, Kryger MH. Effect of inhaled 3% CO2 on Cheyne-Stokes respiration in congestive heart failure. *Sleep* 1994; **17**: 61-68 [PMID: 8191204]

61 **Francis DP**, Willson K, Davies LC, Coats AJ, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. *Circulation* 2000; **102**: 2214-2221 [PMID: 11056095 DOI: 10.1161/01.CIR.102.18.2214]

62 **Lahiri S**, Hsiao C, Zhang R, Mokashi A, Nishino T. Peripheral chemoreceptors in respiratory oscillations. *J Appl Physiol (1985)* 1985; **58**: 1901-1908 [PMID: 4008410]

63 **Chua TP**, Ponikowski PP, Harrington D, Chambers J, Coats AJ. Contribution of peripheral chemoreceptors to ventilation and the effects of their suppression on exercise tolerance in chronic heart failure. *Heart* 1996; **76**: 483-489 [PMID: 9014795 DOI: 10.1136/hrt.76.6.483]

64 **Agostoni P**, Pellegrino R, Conca C, Rodarte JR, Brusasco V. Exercise hyperpnea in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. *J Appl Physiol (1985)* 2002; **92**: 1409-1416 [PMID: 11896004 DOI: 10.1152/japplphysiol.00724.2001]

65 **Solin P**, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. *Circulation* 1999; **99**: 1574-1579 [PMID: 10096933 DOI: 10.1161/01.CIR.99.12.1574]

66 **Lorenzi-Filho G**, Azevedo ER, Parker JD, Bradley TD. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. *Eur Respir J* 2002; **19**: 37-40 [PMID: 11843325 DOI: 10.1183/09031936.02.00214502]

67 **Paintal AS**. Mechanism of stimulation of type J pulmonary receptors. *J Physiol* 1969; **203**: 511-532 [PMID: 5387024 DOI: 10.1113/jphysiol.1969.sp008877]

68 **Roberts AM**, Bhattacharya J, Schultz HD, Coleridge HM, Coleridge JC. Stimulation of pulmonary vagal afferent C-fibers by lung edema in dogs. *Circ Res* 1986; **58**: 512-522 [PMID: 3698217 DOI: 10.1161/01.RES.58.4.512]

69 **Christie RV**, Hayward GW. Periodic changes in respiratory depth, produced by changes in the lung. *J Physiol* 1943; **102**: 88-94 [PMID: 16991594 DOI: 10.1113/jphysiol.1943.sp004018]

70 **Olson TP**, Joyner MJ, Johnson BD. Influence of locomotor muscle metaboreceptor stimulation on the ventilatory response to exercise in heart failure. *Circ Heart Fail* 2010; **3**: 212-219 [PMID: 20061520 DOI: 10.1161/CIRCHEARTFAILURE.109.879684]

71 **Scott AC**, Davies LC, Coats AJ, Piepoli M. Relationship of skeletal muscle metaboreceptors in the upper and lower limbs with the respiratory control in patients with heart failure. *Clin Sci (Lond)* 2002; **102**: 23-30 [PMID: 11749657 DOI: 10.1042/CS20010077]

72 **Ponikowski PP**, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. *Circulation* 2001; **104**: 2324-2330 [PMID: 11696473 DOI: 10.1161/hc4401.098491]

73 **Pardaens S**, Vanderheyden M, Calders P, Willems AM, Bartunek J, de Sutter J. Activation of the ergoreceptors in cardiac patients with and without heart failure. *J Card Fail* 2014; **20**: 747-754 [PMID: 25079301 DOI: 10.1016/j.cardfail.2014.07.006]

74 **Cundrle I**, Johnson BD, Rea RF, Scott CG, Somers VK, Olson LJ. Modulation of ventilatory reflex control by cardiac resynchronization therapy. *J Card Fail* 2015; **21**: 367-373 [PMID: 25576681 DOI: 10.1016/j.cardfail.2014.12.013]

75 **Lewis GD**, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation* 2007; **116**: 1555-1562 [PMID: 17785618 DOI: 10.1161/CIRCULATIONAHA.107.716373.]

76 **Tomcsányi J**, Karlócai K, Papp L. Disappearance of periodic breathing after heart operations. *J Thorac Cardiovasc Surg* 1994; **107**: 317-318 [PMID: 8283910]

77 **Murdock DK**, Lawless CE, Loeb HS, Scanlon PJ, Pifarré R. The effect of heart transplantation on Cheyne-Stokes respiration associated with congestive heart failure. *J Heart Transplant* 1986; **5**: 336-337 [PMID: 3305828]

78 **Ribeiro JP**, Knutzen A, Rocco MB, Hartley LH, Colucci WS. Periodic breathing during exercise in severe heart failure. Reversal with milrinone or cardiac transplantation. *Chest* 1987; **92**: 555-556 [PMID: 3304852 DOI: 10.1378/chest.92.3.555]

79 **Castro RR**, Antunes-Correa LM, Ueno LM, Rondon MU, Negrão CE, Nóbrega AC. Reversal of periodic breathing after aerobic training in heart failure. *Eur Respir J* 2010; **35**: 1409-1411 [PMID: 20513913 DOI: 10.1183/09031936.00177209]

80 **Zurek M**, Corrà U, Piepoli MF, Binder RK, Saner H, Schmid JP. Exercise training reverses exertional oscillatory ventilation in heart failure patients. *Eur Respir J* 2012; **40**: 1238-1244 [PMID: 22408198 DOI: 10.1183/09031936.00167011]

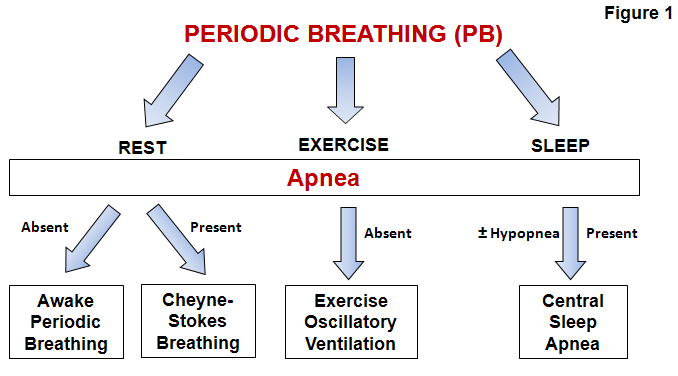
81 **Apostolo A**, Agostoni P, Contini M, Antonioli L, Swenson ER. Acetazolamide and inhaled carbon dioxide reduce periodic breathing during exercise in patients with chronic heart failure. *J Card Fail* 2014; **20**: 278-288 [PMID: 24418726 DOI: 10.1016/j.cardfail.2014.01.007]

82 **Fontana M**, Emdin M, Giannoni A, Iudice G, Baruah R, Passino C. Effect of acetazolamide on chemosensitivity, Cheyne-Stokes respiration, and response to effort in patients with heart failure. *Am J Cardiol* 2011; **107**: 1675-1680 [PMID: 21420051 DOI: 10.1016/j.amjcard.2011.01.060]

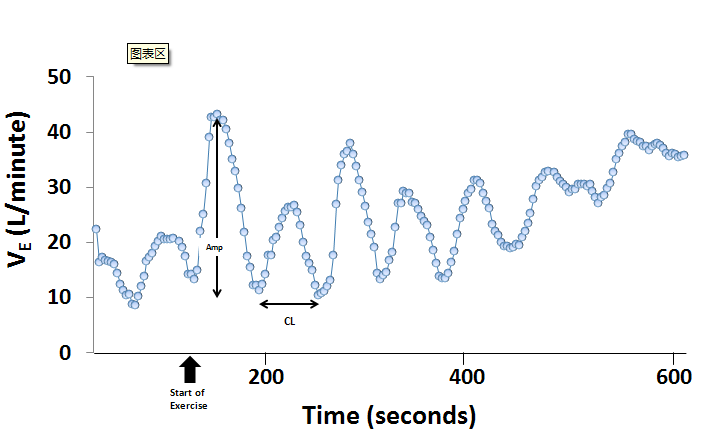
83 **Marcus NJ**, Del Rio R, Schultz EP, Xia XH, Schultz HD. Carotid body denervation improves autonomic and cardiac function and attenuates disordered breathing in congestive heart failure. *J Physiol* 2014; **592**: 391-408 [PMID: 24247985 DOI: 10.1113/jphysiol.2013.266221]

**P-Reviewer:** den Uil CA, Falconi M **S-Editor:** Gong ZM

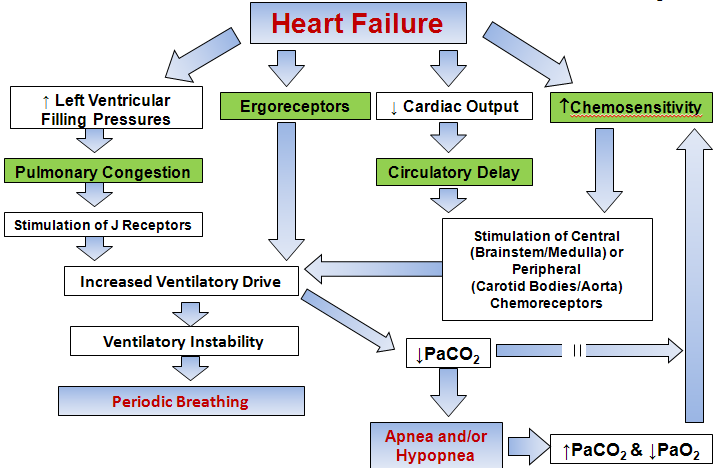
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**Figure 1 Types of periodic breathing in heart failure patients.**



**Figure 2 Oscillatory ventilation during exercise.** CL indicates cycle length; Amp indicates amplitude of oscillation.



**Figure 3 Mechanisms of generation of periodic breathing in heart failure patients.**

**Table 1 Prevalence and clinical significance of exercise oscillatory ventilation in heart failure patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **NYHA class**  **LVEF** | **No. of patients** | **Prevalence of PB** | **Clinical and Prognostic significance of EOV** | **Other predictors of mortality** |
| Kremser *et al*[8], 1987 | NA | 31 | NA | Predicted NYHA class and peak VO2 |  |
| **Corrà** *et al*[17], 2002 | 2.2 ± 0.9  LVEF 24 ± 8 | 323 | 12% | EOV present in 29% of nonsurvivors *vs* 9% survivors | ↑VE/VCO2 slope, AHI and NYHA class, ↓LVEF, peak VO2, peak SBP, resting and peak HR |
| **Corrà** *et al*[9], 2006 | 2.3 ± 0.7  LVEF 23 ± 7 | 133 | 21% | Mortality was 46% in EOV patients *vs* 17% in non EOV  EOV independently predicted mortality in multivariate models |
| Leite *et al*[26], 2003 | 2-4  LVEF 34 | 84 | 30% | EOV alone associated with 2.97 fold increase in risk of death | Peak VO2, NYHA class, ↑ VE/VCO2 slope, ↓LVEF |
| Arena *et al*[30], 2008 | 2.2  LVEF 30 ± 14 | 154 | 36% | Event free survival 55% in EOV *vs* 82% in non EOV patients | VE/VCO2 slope, LVEF |
| Guazzi *et al*[33], 2007 | 1-4  LVEF 35 ± 11 | 156 | 33% | EOV present in 100% arrhythmic and 47% nonarrhythmic deaths | VE/VCO2 slope, peak VO2 |
| Guazzi *et al*[21], 2008 | 2.4 ± 0.8 in HFrEF, 2.0 ± 0.9 in HFpEF | 556 | 35% in HFrEF, 31% in HFpEF | EOV was strongest predictor of mortality in HFpEF and remained as predictor in HFrEF in multivariate models | Peak VO2, VE/VCO2 ratio |
| Bard (2008) | LVEF 19 ± 7 | 44 | 13% | 68% patients with PB died *vs* 52% without PB | Resting ventilatory variation was best predictor of mortality |
| Olson *et al*[31], 2008 | 2.6 ± 0.8  LVEF 37 ± 17 | 47 | 7% | EOV associated with higher VE/VCO2, VD/VT, higher NYHA class |  |
| Ingle *et al*[34], 2009 | LVEF 34 ± 6 | 240 | 31% | 50% of patients diagnosed with EOV by Corrá criteria and 58% diagnosed by Leite criteria died within 1 year |  |
| Sun *et al*[10], 2010 | 2-4  LVEF 26 ± 7 | 580 | 51% | Combination of elevated VE/VCO2 and EOV resulted in an OR of 3.9 for 6 mo mortality | ↑NYHA class, ↓LVEF, ↓peak VO2, ↓AT, ↓peak oxygen pulse |
| Ueshima *et al*[37], 2010 | 2-4 | 50 | 28% | EOV associated with lower peak VO2 and higher VD/VT |  |
| Murphy *et al*[11], 2011 | 2-4  LVEF 30 ± 1 | 56 | 45% | EOV related to ↓exercise cardiac output and ↑cardiac filling pressures |  |
| Scardovi *et al*[40], 2012 | 1-3  LVEF 41% | 370 | 58% | EOV and VE/VCO2 predicted all-cause mortality (23%) independent of LVEF |  |
| Matsuki *et al*[32], 2013 | 3  LVEF 41 ± 16 | 46 | 43.5% | EOV patients had ↑ cardiac filling pressures, ↑ VE/VCO2 , low PETCO2 and greater dyspnea score |  |
| Nathan *et al*[28], 2015 | 1-3 | 253 | 37.5% | 5 yr rate of death or transplant 14.1% with EOV *vs* 4.1% those without EOV | NYHA Class and peak HR |

NYHA: New York Heart Association; VO2: Oxygen uptake; VE/VCO2:ventilator efficiency; NA: not applicable; AHI: apnea-hyponea index; AT: anaerobic threshold; HR: heart rate; LVEF: left ventricular ejection fraction; OR: odds ratio; SBP: systolic blood pressure; PETCO2: End tidal pressure of carbon dioxide; VD/VT: ratio of physiologic dead space over tidal volume.