Periodic Breathing during Incremental Exercise

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Abstract

Periodic breathing during incremental cardiopulmonary exercise testing is a regularly recurring waxing and waning of tidal volume due to oscillations in central respiratory drive. Periodic breathing is a sign of respiratory control system instability, which may occur at rest or during exercise. The possible mechanisms responsible for exertional periodic breathing might be related to any instability of the ventilatory regulation caused by: (*1*) increased circulatory delay (i.e., circulation time from the lung to the brain and chemoreceptors due to reduced cardiac index leading to delay in information transfer), (*2*) increase in controller gain (i.e., increased central and peripheral chemoreceptor sensitivity to arterial partial pressure of oxygen and of carbon dioxide), or (*3*) reduction in system damping (i.e., baroreflex impairment). Periodic breathing during exercise is observed in several cardiovascular disease populations, but it is a particularly frequent phenomenon in heart failure due to systolic dysfunction. The detection of exertional periodic breathing is linked to outcome and heralds worse prognosis in heart failure, independently of the criteria adopted for its definition. In small heart failure cohorts, exertional periodic breathing has been abolished with several dedicated interventions, but results have not yet been confirmed. Accordingly, further studies are needed to define the role of visceral feedbacks in determining periodic breathing during exercise as well as to look for specific tools for preventing/treating its occurrence in heart failure.

Keywords: periodic breathing; cardiopulmonary exercise testing; heart failure

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Periodic breathing during incremental exercise is a regularly recurring waxing and waning of tidal volume due to oscillations in central respiratory drive (1); it is a sign of respiratory control system instability, which may also occur at rest before the exercise stimulation. Periodic breathing was first described two centuries ago (2, 3), and it is detected during exercise in normal subjects with a broad cardiovascular risk factor profile (4), in cardiovascular disease populations, and in patients who have undergone liver transplant and patients with anemia (1). Nonetheless, periodic breathing during exercise is above all recognized in patients with heart failure with depressed left ventricular ejection fraction (5–11). In these patients, periodic breathing can be observed at rest and during sleep (12), before exercise testing (13), and in awake patients (14), always having a prognostic value.

An Example of Periodic Breathing during Exercise

An example of periodic breathing during exercise in heart failure with depressed left ventricular ejection fraction is shown in Figure 1; it is characterized by cyclic variation of ventilation without interposed apnea. Typically, manual scoring or visual interpretation is used, and ventilation is the reference parameter derived from symptom-limited cardiopulmonary exercise testing (CPET), but other gas exchange variables do work and can be used in the assessment process. A programmed computerized analysis adopting period breathing during exercise criteria can facilitate its detection (15, 16); however, visual and manual scrutiny are performed in clinical routines (1). A diagram with broadened ventilation and time scales might be supportive to improve posttesting assessment, and no additional equipment is needed to detect periodic breathing during exercise.

Exercise-induced periodic breathing definitions were categorized in nine subsets, but only four refer to an original definition (6, 7, 17, 18); primary period breathing

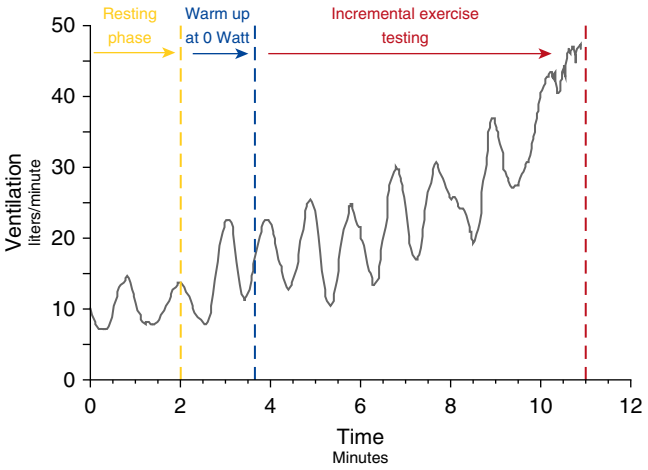

Figure 1. An example of periodic breathing during incremental exercise in chronic heart failure due to reduced left ventricular ejection fraction. *x-Axis* indicates time in minutes divided into three phases: 2-minute resting stage, 2-minute warm-up segment at 0 W, and incremental exercise phase. Resting phase: minute ventilation measured during the resting phase, in sitting position. Warm up at 0 Watt: pedaling phase at 0 W, anticipating the incremental exercise period. Incremental exercise testing: the exercise period on a bicycle. For patients with heart failure, a ramp protocol is used with 10-W increments every 1 minute. *y-Axis*: minute ventilation was measured during three phases.

during exercise delineations are summarized in Table 1. Beyond the original period breathing during exercise definitions, other subdivisions were combinations of the original definitions—quantifications, computational, vaguely defined, or undefined (1). The American Heart Association recommends the modified Kremser periodic breathing definition, with the respiratory phenomenon lasting greater than or equal to 60% of the exercise phase and the amplitude of the single oscillation of greater than or equal to 15% of the resting averaged ventilation value (19).

Periodic breathing can be evanescent or transient. It has been observed in some only at rest, before starting the exercise test, or disappearing during the early stages of exercise (before the ventilator anaerobic threshold achievement), or indeed only disappearing at peak exercise in heart failure due to left ventricular dysfunction. Periodic breathing disappeared during exercise in 42% and remained through the entire exercise in 58% of the patients with heart failure (20), but gas exchange response is almost similar.

Table 1. Original definitions of periodic breathing during exercise in chronic heart failure due to left ventricular systolic dysfunction

Definition by Kremser and colleagues (17): Ventilatory oscillations lasting ⩾66% of the exercise protocol, with an amplitude of each $\dot{V}_E$ oscillation ⩾ 15% of the average value at rest
Definition by Leite and colleagues (6): Three or more regular $\dot{V}_E$ oscillations (i.e., clearly discernible from inherent data noise). Regularity was defined if the SD of three consecutive $\dot{V}_E$ cycle lengths (time between two consecutive nadirs) was within 20% of the average; minimal average amplitude of $\dot{V}_E$ oscillation ⩾ 5 L (peak value minus the average of two in-between consecutive nadirs)
Definition by Ben-Dov and colleagues (18): Marked $\dot{V}_E$ oscillations of 30–60 s duration. Magnitude (Δ)$\dot{V}_E$ (Δ = peak nadir/mean over the time period of the oscillation) ⩾25% in two or more consecutive cycles (nadir to nadir) during exercise
Definition by Sun and colleagues (7): Three or more consecutive cyclic fluctuations of $\dot{V}_E$: amplitude of oscillatory $\dot{V}_E$ ⩾ 30% of concurrent mean $\dot{V}_E$ with a complete oscillatory cycle within 40–140 s. $\dot{V}_E$ oscillations of similar frequency must also be visible in three or more of the following variables: oxygen pulse, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E/\dot{V}CO_2$, RER, $P_{ET_{O_2}}$, or $P_{ET_{CO_2}}$

Definition of abbreviations: $P_{ET_{O_2}}$ = oxygen end-tidal pressure, $P_{ET_{CO_2}}$ = carbon dioxide end-tidal pressure; RER = respiratory gas exchange ratio (i.e., $\dot{V}CO_2/\dot{V}O_2$).

Mechanisms of Period Breathing during Exercise in Heart Failure due to Left Ventricular Dysfunction

The primary purpose of the lung is to maintain the arterial partial pressure of oxygen and carbon dioxide near normal resting levels. During exercise, this is challenged because (*1*) oxygenation of the mixed venous blood delivered to the lungs is reduced greatly; (*2*) a fourfold increase in cardiac output causes a reduction in pulmonary capillary transit time, thus decreased time, for complete equilibration of oxygen between alveoli and pulmonary capillaries; (*3*) the lung receives all of the cardiac output, so it has to adapt to maintain low vascular pressures and protect against exudation of plasma water into the alveoli; and (*4*) there is a 20-fold increase in minute ventilation to meet the increased metabolic demand, which necessitates a need for efficiency in breathing. The control of the normal ventilation is through the feedback loop between pulmonary gas–exchanging capillaries and peripheral chemoreceptors located in the carotid bodies and the central chemoreceptors located in the medulla.

Any instability of ventilatory regulation can lead to generation of periodic breathing. There are data regarding the mechanistic basis of periodic breathing (21–33), but, although the underlying mechanism of periodic breathing at rest and during the night in heart failure is somehow similar to that presumed for exercise-induced periodic breathing (26, 27, 32, 33), the underlying mechanism of exercise-induced periodic breathing is not the same. Instinctively, an exercise-induced stimulus may operate differently on central and peripheral hemodynamics and control respiratory systems. However, and of note, both exercise-induced periodic breathing and nocturnal apneas/hypopneas are significantly reduced by increasing cardiac output in patients with heart failure with left ventricular assist devices (34).

Performing a quantitative algebraic analysis of exertional periodic breathing, it was found that the principal physiological factors are circulatory delay and an increased chemoreflex gain (30), and the

inspiration of oxygen evokes a decrease in chemosensitivity and abolishes the periodic breathing pattern (30). Up until now, studies explaining the possible pathophysiology of exercise-induced period breathing suggest that it can be generated by: (*1*) increased circulatory delay, (*2*) increase in controller gain, or (*3*) reduction in system damping (i.e., baroreflex impairment). Potential and promising mechanisms are summarized in Table 2.

As the pathophysiology of exercise-induced period breathing is not fully understood, adequate therapy is challenging.

Prevalence of Periodic Breathing during Exercise in Heart Failure due to Left Ventricular Dysfunction

CPET provides a unique opportunity to evaluate aerobic capacity with breath-by-breath expired gas parameters (19, 35), and several CPET-derived parameters have been shown to be linked to outcome (36) in addition to peak oxygen consumption ($\dot{V}O_2$) and ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ slope). Periodic breathing is discerned during submaximal exercise (35), which makes it an attractive parameter in those patients who are not able to complete maximal effort exercise testing.

In 2015, a systematic review screened 75 studies, accounting for 17,440 patients, of whom 4,638 (26.6%) presented periodic breathing during exercise (1). Due to lack of a uniformly accepted description of periodic breathing during exercise, the appropriate occurrence of this abnormal breathing phenomenon is precluded. Periodic breathing prevalence was 25% using the Corrà method and 31% using the Leite method (37). In limited heart failure cohorts, the prevalence of periodic breathing during exercise ranges from 6 to 58% (5–10, 22, 30, 33, 38), whereas in a study of ~6,000 patients with heart failure on behalf of the Metabolic Exercise, Cardiac, Kidney Index (MECKI) score research group (39, 40), exercise-induced periodic breathing was present in 17.5%, and it is especially observed in those with the most impaired exercise capacity and in women (41), in agreement with what is observed in normal subjects (4).

Characteristics of Patients with Heart Failure with Periodic Breathing during Exercise

Most selection criteria and study prerequisites are chaotic but fairly comparable, and they contribute to misperceptions about the clinical characteristics of patients with heart failure with exercise-induced periodic breathing. Patients with periodic breathing are, on average, older, have an advanced New York Heart Association class, and show a lower percentage of ischemic etiology of heart failure (1) and treatment with β-blockers (9). Mean left ventricular ejection fraction is lower (1), and left atrial dimension, mitral E-wave velocity, and right heart pressures are increased (42). Median exercise duration is shorter, peak $\dot{V}O_2$ is lower, $\dot{V}E/\dot{V}CO_2$ slope is higher (1, 5–9), rest and exercise end-tidal carbon dioxide are reduced, and an increased ventilatory equivalent for carbon dioxide and dead space ventilation is witnessed (42). Peak respiratory gas exchange ratio is similar between patients with or without periodic breathing during exercise (5–7, 10, 37).

Hence, on average, periodic breathing is associated with a more advanced cardiovascular disease condition, reduced left ventricular ejection fraction, advanced New York Heart Association class, impaired hemodynamic response to exercise, and reduced aerobic capacity, together with higher ventilation in heart failure due to reduced left ventricular ejection fraction.

Cost of Breathing of Periodic Breathing during Exercise in Heart Failure

Energy expenditure at rest requires an oxygen uptake in the range between 160 and 290 ml/min or approximately 3.5 ml/kg/min (1 metabolic equivalent; oxygen consumed while seated at rest), depending on such factors as sex, age, body size, and fat-free body mass. Any physical activity performed increases oxygen consumption. Periodic breathing during exercise is likely to increase the respiratory muscles' work, and those with periodic breathing during exercise and at peak exercise show a less efficient ventilatory pattern, which suggests a greater respiratory muscle work and therefore a greater respiration-related $\dot{V}O_2$ (20). The presence of periodic breathing negatively influences exercise performance, and periodic breathing disappearance during exercise allows, in some cases, a more efficient exercise performance.

Prognostic Value of Periodic Breathing during Exercise in Heart Failure with Left Ventricular Dysfunction

Despite a paucity of large-scale studies, there is compelling evidence that periodic breathing during exercise is a strong independent prognosticator in heart failure with left ventricular dysfunction (5–11, 37, 42–46). Periodic breathing during exercise is related to higher risk of events in the whole spectrum of heart failure with left ventricular dysfunction (5, 8), in heart transplantation candidates (6), and in patients chronically treated with β-blockers (9). Moreover, exercise-induced periodic breathing predicts sudden death (10), and it is connected with short-term morbidity and mortality (7).

Table 2. Plausible mechanisms of periodic breathing during exercise in chronic heart failure due to left ventricular systolic dysfunction

Circulatory delay: prolonged circulation time from the lung to the brain and chemoreceptors leading to delay in information transfer
Reduced cardiac output
Hemodynamic impairment both at rest and during exercise.
Increased chemosensitivity: increased central and peripheral chemoreceptor sensitivity to arterial partial pressure of oxygen and carbon dioxide, leading to:
Increased sympathetic overactivity
Enhanced hypoxic and central hypercapnic chemosensitivity
Nonperipheral chemoreceptor-mediated mechanisms
Pulmonary congestion
Ergoreflex signaling

The definition of periodic breathing during exercise affects the number of patients with heart failure diagnosed and their outcome; although patients with heart failure with exercise-induced periodic breathing observed with Corrá and Leite methods showed higher risk than for peak $\dot{V}O_2$ or $\dot{V}E/\dot{V}CO_2$ slope, Kaplan-Meier curves show a larger separation between patient groups using the Corrà method (37). Table 3 summarizes available prognostic periodic breathing during exercise studies in heart failure; those habitually treated with β-blockers are also listed, as periodic breathing during exercise is less frequent in this setting.

The 2008 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure (47) acknowledged exercise-induced periodic breathing as a powerful risk parameter derived from symptom-limited cardiopulmonary exercise testing, together with peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope. The 2008 European Society of Cardiology predictive model (including periodic breathing during exercise, peak $\dot{V}O_2$, and $\dot{V}E/\dot{V}CO_2$ slope) was validated in heart failure due to left ventricular dysfunction. The 2008 European Society of Cardiology predictive model prognostic performance was not altered by the addition of other supplementary risk CPET parameters except for peak systolic blood pressure (48).

Table 3. Studies that have shown a prognostic impact of periodic breathing during exercise in chronic heart failure due to left ventricular systolic dysfunction

Study	No. of Patients	Mean NYHA and LVEF	Patients with β-Block (%)	Patients with PB (%)	PB Definition	Events during Follow-up	Statistical Relationship between PB Occurrence and Prognosis
Corrà and colleagues, 2002 (5)	323	NYHA 2.2 ± 0.9, LVEF 24 ± 8%	37	11.8	Kremser	CV mortality, urgent HXT	PB present in 28% of nonsurvivors. HR of PB is 10.5 ($P < 0.0001$) at MTV
Leite and colleagues, 2003 (6)	84	NYHA 2–4, LVEF 35 ± 7%	NA	29.4	Leite	All-cause mortality	PB increased the risk of death by 2.97-fold ($P = 0.007$) with 95% CI, 1.34–6.54
Corrà and colleagues, 2006 (60)	133	NYHA 2.3 ± 0.7, LVEF 23 ± 7%	46	21.1	Kremser	CV mortality, urgent HXT	CV mortality 46 and 17% ($P < 0.01$) in those with and without PB. PB is not selected at MTV including CSA alone and combined CSA
Guazzi and colleagues, 2007 (8)	288	NYHA 2.1 ± 0.8, LVEF 33 ± 13%	57	35	Leite	CV mortality	HR of PB 5.5 ($P < 0.0001$) with a 95% CI, 3.2–9.5 at MTV
Guazzi and colleagues, 2007 (10)	153	NYHA 1–4, LVEF 35 ± 11%	52	35.1	Leite	Sudden death	HR of PB is 7.9 (with 95% CI, 3.7–17) for all cardiac mortality and 45.4 (6–34.3) for SD (both $P < 0.0001$) at UTV
Arena and colleagues, 2008 (45)	154	NYHA 2.2, LVEF 30 ± 14%	60	35.7	Kremser	HXT, LVAD, CV mortality	Event-free survival 55% in PB. χ^2 of PB was 10.2 ($P < 0.0001$) at MTV
Ingle and colleagues, 2009 (37)	240	LVEF 34 ± 6%	61	31 Leite 25 Corrà	Leite/Corrà	All-cause mortality	HR of PB is 5.2 (95% CI, 2.8–9.6) for Corrà and 4.8 (95% CI, 2.6–8.8) for Leite method (both $P < 0.0001$) at UTV; at MTV, only Corrà method is selected, with an HR of 6.3 (95% CI, 1.6–25.2)
Corrà and colleagues, 2009 (9)	631	NYHA 1.9 ± 0.6, LVEF 29 ± 8%	100	7	Kremser	CV mortality, urgent HXT	HR of PB is 4.3 with 95% CI, 2.5–7.4 ($P < 0.0001$) at MTV
Guazzi and colleagues, 2010 (PROBE study) (44)	695	NYHA 2.4 ± 0.7, LVEF 25.6 ± 8%	73	36	Leite	CV mortality	HR of PB is 2.2 ($P < 0.0001$) with 95% CI, 1.6–3.2 at MTV
Sun and colleagues, 2010 (7)	580	NYHA 2–4, LVEF 26 ± 7%	NA	51	Sun	6-mo mortality and morbidity	Mean OR increase for mortality (range, 12.7–39.8) and morbidity (2.5–3.9) if PB was added to CPET risk parameters
Scardovi and colleagues, 2012 (46)	370 (⩾65 yr)	NYHA 1–3, LVEF 41%	61	58	Leite	All-cause mortality, Combined end points	HR of PB is 8.9 ($P < 0.0001$ with 95% CI, 1.4–4.9) at MTV

Definition of abbreviations: β-Block = β-blockers; CI = confidence interval; combined CSA = CSA with PB or elevated $\dot{V}E/\dot{V}CO_2$ slope (>33); CPET = cardiopulmonary exercise testing; CSA = central sleep apnea; CV = cardiovascular; HR = hazard ratio; HXT = heart transplantation; LVAD = left ventricular assistance device implantation; LVEF = left ventricular ejection fraction; MTV = multivariable Cox regression analysis; NA = not available; NYHA = New York Heart Association class; OR = odds ratio; PB = periodic breathing; UTV = univariate Cox regression analysis.
Data are presented as average, mean, or range.

The Occurrence and Prognostic Consequence of Exercise-induced Periodic Breathing in Heart Failure with Preserved Ejection Fraction

The diagnosis of heart failure with preserved left ventricular ejection fraction is challenging (49), as its pathophysiology is heterogeneous and it is associated with different concomitant cardiovascular diseases (e.g., atrial fibrillation, arterial hypertension, coronary artery disease, pulmonary hypertension) and noncardiovascular diseases (diabetes, chronic kidney disease, anemia, iron deficiency, chronic obstructive pulmonary disease, and obesity). Functional intolerance is the primary symptom in heart failure with preserved left ventricular ejection fraction (50).

Periodic breathing during exercise is detected either in 31% (51) or in 7% (52) of patients with heart failure with preserved left ventricular ejection fraction, and the difference lies either in patients' enrollment criteria or in periodic breathing delineations. In some experiences, peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, and exercise-induced periodic breathing preserve their predictive power (51, 53), whereas, according to the Henry Ford Hospital Cardiopulmonary Exercise Testing (FIT-CPX) project, peak $\dot{V}O_2$ and percentage of predicted peak $\dot{V}O_2$ are linked to outcome but not periodic breathing during exercise (52).

Reversibility of Periodic Breathing during Exercise

Periodic breathing during exercise is reproducible (7). Various pharmacological or surgical interventions have been performed in chronic heart failure due to left ventricular dysfunction to identify the reversibility of this respiratory exercise-induced phenomenon (53–59): heart transplantation, inotropic drugs, continuous positive airway pressure, adaptive servo ventilation, and exercise training might all impact occurrence of periodic breathing during exercise.

Although large-scale clinical trials with periodic breathing vanishing as the primary endpoint are not available yet, these data are fascinating, as revocation of a risk factor such as exercise-induced periodic breathing in heart failure is provocative and motivating. Up to now, it is not clear if a positive response to intervention is abolishing of exercise-induced periodic breathing or reduction of the duration of the respiratory phenomenon/amplitude of single ventilation oscillations.

Conclusions

Periodic breathing during exercise is a frequent phenomenon in patients with heart failure, heralding a poor outcome independently of an optimized medical treatment. Its pathophysiology probably shares some mechanisms of Cheyne-Stoke respiration and central sleep apnea, but periodic breathing during exercise and central sleep apnea have independent prognostic value in heart failure due to left ventricular dysfunction (60), pointing out that exercise, *per se*, is able to trigger periodic breathing in patients prone to abnormal breathing patterns. Further studies are needed to define the role of visceral feedback in determining periodic breathing either at rest or during exercise as well as to look for specific tools for preventing its occurrence, which may be seen as a marker of clinical severity and of prognosis in patients with heart failure. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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