EDITORIAL COMMENT

The Ups and Downs of Periodic Breathing

Implications for Mortality in Heart Failure*

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Periodic breathing is a regularly recurring waxing and waning of tidal volume due to oscillations in central respiratory drive. It is a sign of respiratory control system instability. Under normal conditions, the respiratory and circulatory systems work in concert to deliver O2 according to metabolic demands, and to excrete CO2 to maintain acid-base homeostasis. As a result, arterial PO2 (PaO2), PCO2 (PaCO2) and pH are held within narrow limits. To accomplish this precise matching of ventilation with metabolic demands, respiration is regulated by a rapidly responsive negative feedback system consisting of a central controller and a peripheral plant. The central controller is comprised of the peripheral and central chemoreceptors, which detect alterations in PaO2, PaCO2, and pH, and the brainstem respiratory motor neurons, which generate a central respiratory drive proportional to the degree of chemoreceptor stimulation. The plant, consisting of the respiratory muscles, rib cage, and lungs, alters ventilation in response to changes in central respiratory drive. These alterations in ventilation in turn provoke changes in arterial blood gas tensions (1,2).

Several factors stabilize this respiratory control system. First, alterations in arterial blood gas tensions in the lung are fed back rapidly to the chemoreceptors, owing to a short lung to chemoreceptor circulation time (2). This damps fluctuations in ventilation, just as a rapidly responsive thermostat will damp fluctuations in room temperature. Second, normal chemoreceptor gain is just sufficient to rapidly correct deviations in PaCO2 and PaO2 from their set points, but not to overcorrect. Together, these two factors prevent overshooting of ventilation in response to small increases in chemostimulation. Third, normally the set point for a ventilatory response to CO2 is well above the apneic threshold (1,3). Because PaCO2 is normally the primary stimulus to breathe, maintaining PaCO2 well above this threshold facilitates stability of ventilation and arterial blood gas tensions.

In general, periodic breathing is a manifestation of underdamping of the respiratory control system with recurrent over- and undershooting of ventilation. Factors that predispose to respiratory control system instability include prolonged lung to chemoreceptor circulatory delay, increased chemoreceptor gain and arousals from sleep that trigger hyperventilation, and a low PaCO2 close to the apneic threshold. The critical factor causing very low frequency fluctuations in ventilation in most forms of periodic breathing is an increased amplitude of oscillations in PaCO2 (1). The wider the fluctuations in PaCO2, the greater the amplitude of ventilatory oscillations. In extreme cases, ventilatory overshoot causes PaCO2 to fall below the apneic threshold, resulting in central apnea. When PaCO2 falls but remains above this threshold, a minimal level of ventilation (i.e., hypopnea) is maintained. The observation that periodic breathing during wakefulness at high altitude and during sleep in patients with congestive heart failure (CHF) can be reversed by inhalation of a low concentration of CO2 emphasizes the critical role of hypocapnia and fluctuations in PaCO2 in its pathogenesis (4,5).

Patients with CHF are prone to developing instability of their respiratory control systems and, therefore, periodic breathing. Because of low cardiac output, lung to chemoreceptor circulation time is increased, slowing the response time of the negative feedback loop that modulates ventilation. In addition, a substantial proportion of patients with CHF hyperventilate and have chronic hypocapnia. This tendency to hyperventilate is associated with increased peripheral and central chemosensitivity, and with elevated left ventricular filling pressures (6,7). The latter may give rise to pulmonary congestion that can stimulate pulmonary vagal irritant receptors. Stimulation of these receptors augments central respiratory drive and provokes hyperventilation. The resultant hypocapnia combined with a tendency to metabolic alkalosis secondary to diuretics will tend to keep PaCO2 close to the apneic threshold (3,8,9). In this setting, even small increases in ventilation can drive PaCO2 below this threshold level.

Periodic breathing occurs most commonly when respiration is under predominantly metabolic control, such as during non-rapid eye movement sleep (non-REM) (1). Conversely, it occurs less commonly when non-metabolic, behavioral elements exert a significant influence on respiratory control, such as during wakefulness and rapid eye movement (REM) sleep. These non-metabolic influences include phonation, coughing, swallowing, and dreaming. In patients with CHF, periodic breathing occurs most commonly during non-REM sleep, where it is known as Cheyne-Stokes respiration with central sleep apnea (1). The main clinical significance of this condition is that it is associated with increased mortality independent of other risk factors (10). The reason for this is not clear, but it may

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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be attributable to recurrent apneas accompanied by intermittent hypoxia, arousals from sleep, and sympathetic nervous system activation causing surges in blood pressure and heart rate (11,12). Cheyne-Stokes respiration occasionally occurs during wakefulness, at which time it also seems to be associated with increased risk of mortality (13). In this issue of the Journal, Leite et al. (14) extend those findings by demonstrating that exercise-related periodic breathing (EPB) in patients with CHF is also associated with increased risk of death independent of other risk factors. EPB (8). If so, then one of the probable causes of the relative hyperventilation in the EPB group was a further rise in pulmonary venous pressure at the onset of exercise. Third, subjects had a markedly prolonged EPB cycle length, averaging 79 s. This compares with a much shorter cycle length of periodic breathing during central sleep apnea in patients without CHF of approximately 35% in Corra et al. (17). In both these studies, however, the very high death rate reported by Leite et al. (14) over a median follow-up period of 11 months, 31% of subjects died. The cumulative survival rate at two years was only 57%, a rate much lower than that reported in recent randomized trials of CHF therapy. In contrast, Corra et al. (17) reported a much higher two-year survival rate of 86%, which is probably more representative of the general CHF population in the developed world.

The observation that periodic breathing would occur during exercise is rather counterintuitive, because exercise is performed during wakefulness when non-metabolic behavioral influences should be at play. However, during exercise, the increased metabolic requirements for O\textsubscript{2} consumption and CO\textsubscript{2} production mandate that respiration falls predominantly under the influence of the chemical-metabolic respiratory control system. Although this was not the main focus of the study, the data from the Leite et al. (14) study provide some clues as to the pathophysiology of EPB in their subjects. First, as with Cheyne-Stokes respiration during sleep, subjects with EPB had lower PCO\textsubscript{2} at rest than did subjects without EPB. Second, the higher slope of the relationship between change in minute ventilation (V\text{E}) and change in CO\textsubscript{2} production (VCO\textsubscript{2}) in subjects with EPB suggests that they had greater chemosensitivity to CO\textsubscript{2} than did subjects without EPB. Because it has been demonstrated that PaCO\textsubscript{2} is inversely proportional to left ventricular filling pressure, it is likely that pulmonary venous pressure was higher in subjects with than in those without EPB (8). If so, then one of the probable causes of the relative hyperventilation in the EPB group was a further rise in pulmonary venous pressure at the onset of exercise.

It is interesting to note that the prevalence of EPB in study subjects was 30%, which is very similar to the prevalence of Cheyne-Stokes respiration with central sleep apnea reported in patients with CHF (16). Although the authors did not perform sleep studies in their subjects, it would have been interesting to see whether the presence of EPB is associated with the Cheyne-Stokes respiration during sleep.

The most important finding of Leite et al. was that the presence of EPB was associated with a 2.97 higher relative risk of death than in subjects without EPB, after controlling for the presence of other risk factors. These findings are similar to those reported by Corra et al. (17), but there are important differences that raise questions about the generalizability of the results. Leite et al. (14) found a 30% prevalence of EPB among 84 patients, whereas Corra et al. (17) found a prevalence of only 12% in 323 patients. This difference might be accounted for by the more liberal definition of “EPB” as three consecutive cycles of oscillatory ventilation used by Leite et al. (14). In contrast, Corra et al. (17) defined EPB as oscillatory ventilation occupying at least 60% of the exercise time. The etiology of CHF also differed. Leite et al. (14) included 11 (13%) subjects with Chagas’ disease, a disorder particular to South America, whereas Corra et al. (17) did not include such subjects. In addition, the subjects of Leite et al. (14) were all undergoing heart transplantation evaluation and were young, with a mean age of 45 years. On the other hand, the subjects of Corra et al. (17) were attending a general CHF clinic and were older (mean age of 59 years). The most important difference, however, was the very high death rate reported by Leite et al. (14). Over a median follow-up period of 11 months, 31% of subjects died. The cumulative survival rate at two years was only 57%, a rate much lower than that reported in recent randomized trials of CHF therapy. In contrast, Corra et al. (17) reported a much higher two-year survival rate of 86%, which is probably more representative of the general CHF population in the developed world. Another factor that bears mentioning is the very low proportion of subjects in Leite et al. (14) who are receiving beta-adrenergic blocking agents (6%), which might account for some of their excess mortality. This compares with approximately 35% in Corra et al. (17). In both these studies, subjects with EPB had a tendency to have worse cardiac function, exercise capacity, and functional class than those without EPB. Nevertheless, the similarities between these two studies outweigh their differences: in both cases, multivariate analyses designed to control for confounding variables demonstrated an increased independent risk of death associated with the presence of EPB.

Despite this multivariate analysis, the data of Leite et al. (14) still leave unanswered the question of whether EPB itself contributes to high mortality rates in CHF, rather than simply being a sign of worse underlying cardiovascular function. For example, sedentary patients with CHF will not be exposed to EPB very often. If, on the other hand, EPB is also associated with central sleep apnea, then excess risk may be attributed to periodic breathing in general, rather than specifically to EPB. Furthermore, as in the case of Cheyne-Stokes respiration during sleep (7), it seems very likely that left ventricular filling pressures were higher in subjects with than in those without EPB. Elevated filling
pressures are known to be associated with higher mortality in CHF (18). However, filling pressures were not measured. Notwithstanding such considerations, the data of Leite et al. (14) add to the mounting evidence that instability of the respiratory control system, whether manifest in periodic breathing during sleep (10), resting wakefulness (13), or exercise, heralds a poor prognosis in patients with CHF.

From the practical standpoint, these breathing disorders can be easily and inexpensively identified by non-invasive means and may add prognostic information over and above that obtained from other cardiovascular assessments. Moreover, a small randomized trial suggested that treatment of central sleep apnea by continuous positive airway pressure can improve survival in patients with CHF (19). If these results can be replicated in a larger trial, then periodic breathing may become a therapeutic target in CHF. Approaches to specific therapy of EPB, however, have yet to emerge. Nonetheless, to the credit of Leite et al. (14), their work leads to the conclusion that, in the search for better therapies for CHF, the pathophysiologic, prognostic, and therapeutic implications of periodic breathing warrants more intensive investigation.

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