

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Laboratory and the Exercise Laboratory**  
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*Circulation* 2006, 113:9-10

doi: 10.1161/CIRCULATIONAHA.105.590265

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX  
72514

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ISSN: 1524-4539

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## Periodic Breathing in Heart Failure

### Bridging the Gap Between the Sleep Laboratory and the Exercise Laboratory

Jorge P. Ribeiro, MD, ScD

In the 19th century, Cheyne<sup>1</sup> and Stokes<sup>2</sup> described a pattern of periodic breathing in patients with heart failure, but over the past few decades, particular attention has been given to the occurrence of periodic breathing during sleep.<sup>3,4</sup> Central sleep apnea, also referred to as Cheyne-Stokes respiration, is an abnormal periodic breathing pattern in which central apneas and hypopneas alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume that classically has been associated with severe decompensated heart failure.<sup>4</sup> Up to 37% of patients with heart failure may present obstructive sleep apnea,<sup>5</sup> in which there is complete or partial collapse of a narrowed pharynx; as many as 40% of heart failure patients may present central sleep apnea,<sup>6</sup> in which there is reduction in central inspiratory drive. Despite the fact that obstructive sleep apnea and central sleep apnea have different mechanisms, both are associated with increased sympathetic activity at night and during daytime that results in vasoconstriction, an increased peripheral vascular resistance.<sup>3,4</sup> Moreover, small cohort studies had previously demonstrated that the presence of central sleep apnea is associated with increased mortality in heart failure.<sup>7,8</sup>

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Despite the fact that cardiopulmonary exercise testing had been used in selected centers in the evaluation of heart failure since the 1960s, it was only in the mid-1980s that it became clear that patients with compensated heart failure could also have periodic ventilation at rest and during exercise.<sup>9–11</sup> Weber and Szidon<sup>9</sup> first described an unusual “saw-toothed” ventilatory response to exercise in some patients with heart disease that, in their opinion, did not appear to be a Cheyne-Stokes pattern of breathing. In 1987, Kremser et al<sup>10</sup> and Ribeiro et al<sup>11</sup> described the same phenomenon as oscillatory hyperventilation and periodic breathing, respectively, and associated the pattern with Cheyne-Stokes respiration.

Exercise-induced periodic breathing may be identified in as many as 19% of heart failure patients referred to cardiopulmonary testing and is associated with advanced heart failure.<sup>10–12</sup> Like central sleep apnea, exercise-induced periodic breathing is

associated with increased sympathetic activity,<sup>13</sup> and recent studies have demonstrated that identification of this breathing disorder results in poor prognosis in heart failure.<sup>12,14</sup>

Despite similar epidemiological, pathophysiological, and prognostic characteristics, central sleep apnea and exercise-induced periodic breathing had not previously been evaluated in conjunction in patients with heart failure. The most likely reason is that the former breathing disorder is frequently studied in the sleep laboratory, whereas the latter is studied in the exercise laboratory, which may be physically close but intellectually distant in many institutions. In this issue of *Circulation*, Corrà and coworkers<sup>15</sup> finally bridge this gap. In this well-conducted cohort study, 133 patients with chronic heart failure caused by left ventricular systolic dysfunction were followed up for a mean of 3 years to evaluate the prognostic value and interdependence of sleep and exercise-induced periodic breathing, with cardiovascular death and urgent heart transplantation used as end points. Sleep periodic breathing was evaluated with an ambulatory screening device using standard definitions for sleep-related breathing disorders. The authors were careful to exclude patients with severe obstructive sleep apnea. Likewise, exercise-induced periodic breathing was identified during a graded cardiopulmonary exercise test with classic criteria, and a peak respiratory exchange ratio >1.05 was required to ensure that near-maximal effort was obtained. The ventilatory anaerobic threshold was not identified in 28% of patients, underscoring the fact that the presence of periodic breathing does not allow the detection of this parameter.<sup>13</sup> The incidence of combined end points was adequate for the evaluation of prognosis. Medical treatment used by patients and survival curves were compatible with appropriate clinical practice in a contemporary heart failure cohort, suggesting that the findings of the study can be generalized to other clinical environments.

The first point of information derived from this study is that central sleep apnea and exercise-induced periodic breathing are frequently associated in patients with heart failure: 16% of the patients had both breathing disorders, 29% had isolated central sleep apnea, and only ≈5% had isolated exercise-induced periodic breathing. This demonstrates for the first time that breathing disturbances as a whole are very frequent in heart failure, occurring in 50% of all patients. Even though Corrà et al<sup>15</sup> used standard criteria for diagnosing sleep and exercise-induced periodic breathing and even though cut points were appropriately identified by receiver-operating characteristic curves, these criteria are arbitrary, and one must consider the possibility that these abnormalities in ventilatory control are best represented by a continuum. If, for example, the authors were to use more liberal criteria for the presence of exercise periodic breathing such as those used by Leite et al,<sup>14</sup> the prevalence of the ventilatory disturbances would be different. Moreover, one

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circulation*. 2006;113:9–10.)

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*Circulation* is available at <http://www.circulationaha.org>  
DOI: 10.1161/CIRCULATIONAHA.105.590265

could speculate that if sensitive-enough criteria are used in both conditions, we could find an even stronger association, suggesting that they are basically clinical presentations of the same pathophysiological phenomenon.

The second point of information derived from the study is the prognostic value associated with the presence of breathing disorders in heart failure. On multivariate analysis, Corrà et al<sup>15</sup> confirmed previous observations that sleep disturbance breathing, low peak oxygen uptake, and lack of use of  $\beta$ -blockers were independent predictors of poor prognosis in heart failure. The authors performed a second multivariate model in which the presence of exercise-induced periodic breathing was forced into the above-mentioned variables. Although not orthodox from a statistical point of view, this analysis demonstrated that the association of sleep and exercise-induced breathing disorders predicts a poor prognosis. Because only 6 patients in the cohort had isolated exercise-induced periodic breathing, other studies are required to establish the prognostic value of this finding. Despite these limitations, the results of this study will help clinicians stratify the risk of their patients when the results of sleep and exercise breathing studies are available. Moreover, it would be helpful to include comments on the presence and prognostic implications of periodic breathing in the reports of both sleep studies and cardiopulmonary exercise tests in patients with heart failure.

Both sleep and exercise-induced periodic breathing may respond to therapeutic interventions. Optimization of pharmacological intervention with diuretics,  $\beta$ -blockers, and ACE inhibitors, as well as overdrive pacing, the use of nocturnal oxygen supplementation, and the administration of theophylline, may reduce the severity of central sleep apnea.<sup>4</sup> Likewise, exercise-induced periodic breathing can be improved by heart transplantation or inodilator infusion,<sup>11</sup> and recent data from our laboratory indicate that inspiratory muscle training improves oscillatory ventilation during exercise.<sup>16</sup> Therefore, one is tempted to speculate that when a patient with heart failure is identified with breathing disorders of prognostic relevance, this should stimulate the use of specific interventions to improve periodic breathing with the hope of reducing mortality. Randomized clinical trials have shown that nightly application of continuous positive airway pressure increases left ventricular ejection fraction, reduces mitral regurgitation and muscle sympathetic nerve activity, and improves quality of life in heart failure.<sup>4</sup> Despite the favorable impact of continuous positive airway pressure in these surrogate outcomes, the Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure Patients With Central Sleep Apnea (CANPAP) failed to show a benefit of continuous positive airway pressure on mortality and heart transplantation in heart failure patients with central sleep apnea.<sup>17</sup>

In conclusion, the study by Corrà et al<sup>15</sup> has brought together 2 very similar phenomena that have been recognized in 2 different settings: the sleep laboratory and the cardiopulmonary testing laboratory. Clinicians must be aware that these breathing disorders are frequent in heart failure patients and that they may foretell a poor prognosis, particularly when observed in the same

patient. Unfortunately, there is no conclusive evidence that specific treatment of these breathing disorders will improve the prognosis in heart failure. Finally, the stage is set for future studies in which an integrated cardiopulmonary approach should be used to test the hypothesis that sleep periodic breathing and exercise-induced periodic breathing are clinical presentations of the same disorder.

## Disclosures

None.

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Key Words: Editorials ■ exercise ■ heart failure ■ prognosis ■ respiration