Two main types of sleep-related breathing disorders occur in patients with congestive heart failure: obstructive sleep apnoea and Cheyne–Stokes respiration with central apnoeas. Obstructive sleep apnoea is characterized by recurring upper airway collapse with ongoing respiratory effort during sleep, causing repetitive surges of negative intrathoracic pressure, arousals, and oxygen desaturations. This gives rise to sympathetic activation and increases systemic blood pressure. Obstructive sleep apnoea is strongly related to increased body weight and is common in the general population. In epidemiological and animal studies, an association between systemic hypertension and obstructive sleep apnoea independent of obesity was found. There is also evidence linking obstructive sleep apnoea with endothelial dysfunction and increased cardiovascular mortality.

In 1818 John Cheyne, and in 1854 William Stokes, were the first to describe a regularly waxing and waning breathing pattern with central apnoeas (i.e. absence of respiratory effort) now known as Cheyne–Stokes respiration. With the propagation of polysomnography in the last decade it appeared that Cheyne–Stokes respiration, with repetitive oxygen desaturations, occurred at night in many patients. The high prevalence of sleep disordered breathing in congestive heart failure is highlighted by the systematic investigation using polysomnography by Tremel et al. in this issue. The authors reported that about 80% of 34 consecutive patients with a left ventricular ejection fraction <45% had an apnoea+hypopnoea index (AHI) >15 h\(^{-1}\). Obstructive sleep apnoea was less common (25%) than Cheyne–Stokes respiration, with repetitive oxygen desaturations, occurred at night in many patients.

The high prevalence of sleep disordered breathing in congestive heart failure is highlighted by the systematic investigation using polysomnography by Tremel et al.[1] in this issue. The authors reported that about 80% of 34 consecutive patients with a left ventricular ejection fraction <45% investigated 1 month after an episode of pulmonary oedema had an apnoea+hypopnoea index (AHI) >15 h\(^{-1}\). Obstructive sleep apnoea was less common (25%) than Cheyne–Stokes respiration (75%) and was chiefly observed in the more overweight patients. Recently Javaheri et al. reported on 81 ambulatory male congestive heart failure patients with a left ventricular ejection fraction <45%[2]. The authors noted that 51% of their patients had an apnoea+hypopnea index >15. Again most of the patients had Cheyne–Stokes respiration, but some more obese patients had obstructive apnoeas. Similar findings were made in a comparable congestive heart failure group[3] and in patients on a waiting list for heart transplantation[4]. The somewhat higher prevalence of Cheyne–Stokes respiration in the study by Tremel et al. might be accounted for by the inclusion of patients shortly after left heart decompensation and the medical therapy instituted (at the time of the first polysomnogram only 68% were on ACE inhibitors). A second polysomnogram was performed about 1 month after the first without a significant improvement in the apnoea+hypopnea index. Although the lower sample size in the second study might have led to bias, the follow-up underscores the alarming prevalence of Cheyne–Stokes respiration in the congestive heart failure population.

As Tremel et al. pointed out, the pathophysiology of Cheyne–Stokes respiration is interpreted as an instability of the feedback loop controlling respiration. According to cybernetic modelling, the following synergistically acting mechanisms favour an oscillation of ventilation:

1. Low cardiac output, increased intracardiac dimensions and pulmonary congestion prolong the transit time between the lungs and chemoreceptors.
2. In congestive heart failure, hyperventilation with concomitant hypocapnia is common. This is due to a non-CO\(_2\)-dependent central neural drive, probably mediated by reduced blood flow to chemoreceptors, altered input from muscle metaboreceptors, as well as humoral factors such as catecholamines. Hypocapnia causes the arterial CO\(_2\) partial pressure to move closer to the apnoea threshold and thus favours Cheyne–Stokes respiration.
3. Oxygen uptake and CO\(_2\) production at rest decrease with the severity of heart failure and with increasing age. This, as well as low oxygen and CO\(_2\) stores (due to restrictive lung function as commonly found in congestive heart failure), increases the plant gain (i.e. responsiveness of blood gases to ventilatory changes) and therefore favours ventilatory instability.
4. An individually relatively high hypercapnic or hypoxic ventilatory response.
(5) Sleep itself promotes Cheyne–Stokes respiration. Lung volumes are reduced in a prone position compared to upright posture. Furthermore, during sleep the stabilizing influence of higher cortical structures on respiration are lacking.

Points 1–4 are related to the severity of congestive heart failure and it is therefore not surprising that in the present and a previous study a negative correlation between apnoea+hypopnea index and maximal oxygen consumption during exercise testing was found.

However, Cheyne–Stokes respiration is not just a marker of congestive heart failure severity. Cheyne–Stokes respiration has distinctly unfavourable effects: the repetitive apnoeas occurring during Cheyne–Stokes respiration are followed by sleep disruption due to arousals. This causes daytime sleepiness in patients with congestive heart failure, as has been shown by the Multiple Sleep Latency Test. During Cheyne–Stokes respiration, simultaneous changes in wakefulness, cerebral blood flow velocity, and respiration with accompanying changes in heart rate and blood pressure (thereby increasing left ventricular afterload) are observed. This is probably caused by a close anatomical and functional link between cardiac and respiratory efferents in the brain stem. Ventricular arrhythmias may occur during hyperventilation. Hypoxia and hypercapnia, as well as arousals, follow apnoeas and act synergistically in activating the sympathetic nervous system. Consistent with these findings, the occurrence of Cheyne–Stokes respiration in congestive heart failure patients is accompanied by an increased concentration of norepinephrine in plasma and urine, regardless of left ventricular function.

Furthermore, sympathetic nerve activity (evaluated by microneurography, thus providing direct measurement of efferent sympathetic-nerve activity related to muscle blood vessels) is higher during Cheyne–Stokes respiration as compared to normal respiration.

Sympathetic activation has negative effects on the diseased myocardium and is associated with reduced exercise tolerance and poor prognosis. Therefore Cheyne–Stokes respiration is expected to have an unfavourable influence on the course of congestive heart failure. Recent studies in accord with historical observations suggested that Cheyne–Stokes respiration is independently associated with increased mortality.

Further evidence of the negative effects of Cheyne–Stokes respiration comes from a number of studies in which Cheyne–Stokes respiration was treated, as discussed in an earlier editorial. Successful treatment of Cheyne–Stokes respiration with nocturnal oxygen reduced apnoea+hypopnea index, enhanced exercise tolerance and reduced urinary norepinephrine excretion. Similarly treatment of obstructive sleep apnoea as well as Cheyne–Stokes respiration with continuous positive airway pressure improved left ventricular function and reduced urinary norepinephrine excretion in patients with congestive heart failure.

Altogether, the high prevalence of sleep-disordered breathing, mainly Cheyne–Stokes respiration, in patients with congestive heart failure is not trivial. There is ample evidence suggesting that Cheyne–Stokes respiration per se has negative effects on left ventricular function and exercise capacity, mediated by sympathetic activation and increased afterload to the failing left ventricle. Large controlled studies will be started in the near future to verify this idea and to test the assumption that successful treatment of Cheyne–Stokes respiration will reduce the high mortality of congestive heart failure. For cardiologists the time has come to have a heart for their patients’ sleep.

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References