Cheyne-Stokes Respiration

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KEYWORDS

• Cheyne-Stokes respiration • Central sleep apnea • Heart failure

KEY POINTS

- Cheyne-Stokes respiration (CSR) is a disorder of hyperventilation usually in the setting of moderate to severe congestive heart failure. The cycle length (of apnea and hyperpnea) is characteristically greater than 45 seconds in duration and can be used to distinguish CSR caused by cardiac disease from other forms of central sleep apnea such as that seen with narcotics for which the cycle length is less than 45 seconds.
- Measures of hypoxemia, heart rate, and loop gain (eg, ratio of ventilation length/apnea length) during sleep may more reliably indicate CSR severity than simply the apnea-hypopnea index. The apnea-hypopnea index was designed to measure severity of obstructive sleep apnea, not CSR.
- The most effective forms of treatment of CSR are those directed at the cause, namely the heart condition (either the pump, the valves, or the rhythm and rate). This treatment may involve medications, valve replacement, or other mechanical treatments such as pacemakers. One treatment strategy sleep services have to offer is continuous positive airway pressure (CPAP), which helps some types of heart failure. Whether newer forms of CPAP, such as adaptive servo-controlled ventilation, which attempts to provide ventilatory support during the apneas while reducing overall minute ventilation and allowing CO_2 levels to increase, has any long-term additional benefit remains to be proved.

INTRODUCTION

Central sleep apnea (CSA) is a broad descriptive term for apneas during sleep that result from altered respiratory drive. Two categories exist[1]: the first is defined by abnormal nocturnal hypoventilation and hypercapnia ($Paco_2$ evening to morning change >5 mm Hg), which can result from various musculoskeletal, neuromuscular, or neurologic disorders such as kyphoscoliosis, syringomyelia, myotonic dystrophy, or obesity hypoventilation syndrome. This category is not discussed any further in this article.

The second category relates to transient, cyclic, or periodic loss of respiratory drive, interspersed with brief periods of hyperventilation, usually associated with normocapnia or hypocapnia ($Paco_2$<45 mm Hg). This second type of CSA can be caused by conditions such as heart failure (HF) (in which it is known as Cheyne-Stokes respiration [CSR]), narcotic drugs, continuous positive airway pressure (CPAP; also known as complex CSA), premature infancy, and high altitude. This article focuses on the CSA with CSR (CSA-CSR) seen in HF.

EPIDEMIOLOGY

Approximately 70% of the population with HF has a sleep-related breathing disorder (SRBD), as defined by an apnea-hypopnea index (AHI) of more than 5 events per hour.[2–4] This generalized SRBD persists when clinic patients with routine HF have repeated cardiopulmonary studies over a 12-month period.[5] The SRBD group can be further categorized into 2 groups: one with predominantly obstructive sleep apnea (OSA), the second with predominantly CSA-CSR. OSA is considered a cause of HF, whereas CSA-CSR is considered a result of HF.[6]

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HF is a complex disorder caused by a broad range of conditions, an understanding of which is required to understand the pathogenesis and management of CSA-CSR. The diagnostic accuracy of tools commonly used to identify HF needs to be understood. For example, two-dimensional echocardiography is operator dependent and of limited averaging time, and has high variability compared with other markers of left ventricular function such as nuclear medicine techniques, which are three-dimensional and gated over several minutes. The clinician needs to understand the cause(s), duration, age of onset, and stability of HF in order to understand the symptoms and determine management of CSA-CSR. HF is commonly associated with hyponatremia, anemia, renal impairment, skeletal muscle wasting, malnutrition, neurohumoral changes, and psychiatric changes, the symptoms of which can overlap with SRBD symptoms. In addition, some features of HF, such as renal impairment, may interfere with the control of breathing, or anemia may aggravate periodic limb movements (PLMs) and dyspnea. Although stroke is a commonly proposed cause of CSA-CSR, the only study in which patients with stroke with CSA were assessed for cardiac dysfunction identified that hypocapnia and occult cardiac failure were strongly associated with CSA, rather than location or type of stroke.[7]

Although medical therapies directed toward HF severity, which should alleviate CSA-CSR, have advanced in the past 3 decades, the introduction of β-blockers and spironolactone has not altered the prevalence of CSA-CSR.[8,9]

PATHOPHYSIOLOGY

During wakefulness, ventilation is under cortical and metabolic control (ie, CO_2 sensed by the peripheral and central chemoreceptors).[9] During rapid eye movement (REM) sleep, ventilation is under pontomedullary inspiratory neuron control (ie, not metabolic), which is responsible for the characteristic irregular respiratory rate and tidal volume appearance. Ventilation during slow wave sleep is under metabolic control with increased CO_2 and arousal thresholds, which results in the characteristic stable ventilation pattern.

During the transition from wakefulness to stages 1 and 2 non-REM sleep, cortical control is diminished and ventilation becomes dependent on $Paco_2$ (**Fig. 1**).[10] In order to achieve this, minute ventilation transiently decreases (~20%) and accordingly the prevailing $Paco_2$ level increases (~2–3 mm Hg). A new $Paco_2$ and V steady state are reached and a regular respiratory pattern results in this new equilibrium during stable non-REM sleep. During non-REM stages N1 and N2, an unstable respiratory state can be precipitated by an arousal or change in sleep state (of any cause) resulting in the development of CSA-CSR. Ventilation transiently increases with arousal and is followed by a decrease in $Paco_2$, to a level less than the threshold required to stimulate ventilation. This change in $Paco_2$ is called the CO_2 reserve. A central apnea ensues (~30 seconds in HF), during which the $Paco_2$ level increases. A period of hyperventilation follows (~30 seconds), which drives the $Paco_2$ level to less than the threshold again, thereby precipitating a further central apnea. This cycle of hyperventilation followed by central apnea is called CSR. When hyperventilation is followed by cyclic hypopneas, the term periodic breathing is often used, and this pattern can be observed awake and often at the onset of exercise (when undergoing cardiopulmonary exercise testing).

CO_2 Reserve

Patients with CSA-CSR have a low prevailing CO_2 value[11,12] with an increased minute ventilation compared with HF without CSA-CSR. For example, in one study, the $Paco_2$ values were ~33 and ~38 mm Hg and minute volume of ventilation were ~8.3 versus 6.8 L/min in a CSA-CSR group compared with an HF group with normal ventilation.[11] The $Paco_2$ value may decrease by a further 1 to 2 mm Hg during the night, especially if the patient has both OSA and CSA-CSR.[13]

The transient oscillations in $Paco_2$ required to precipitate a central apnea is called the CO_2 reserve. The CO_2 reserve can be measured under experimental and artificial conditions by altering CO_2 with either noninvasive ventilation or addition of CO_2. Patients with HF without CSA-CSR have a CO_2 reserve of ~5 mm Hg for apnea development and ~4 mm Hg for hypopnea development.[14] In comparison, patients with HF with CSA-CSR, have CO_2 reserves of ~3 mm Hg and ~1.5 mm Hg for apnea and hypopnea development respectively.[14] Thus a large CO_2 reserve protects against CSA, whereas a small reserve may predispose to CSA-CSR.

It has been proposed that the CO_2 reserve can be manipulated. For example, metabolic acidosis, almitrine,[15] and clonidine[16] have been shown to increase the CO_2 reserve, whereas metabolic alkalosis and hypoxia have been shown to reduce the CO_2 reserve.[15] Whether this manipulation of CO_2 threshold has a therapeutic role remains to be determined.

Loop Gain

Loop gain is an engineering term that describes the cyclic behavior of an insult (eg, hyperventilation)