Central Sleep Apnea due to Other Medical Disorders

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KEYWORDS

• Sleep-disordered breathing • Lung • Respiratory physiology • Control of breathing
• Respiratory muscles • Neurodegenerative • Neuromuscular

KEY POINTS

- Numerous medical disorders can cause central sleep apnea/hypoventilation.
- This review covers the potential link between brain tumors, Chiari type I malformation, stroke, pain/opioids, endocrine and hormonal disturbances, neurodegenerative disease, neuromuscular disease, and sleep-disordered breathing.
- Control of breathing and potential underlying pathophysiology are highlighted.
- In several medical conditions a bidirectional relationship likely exists whereby the primary medical disorder may cause or worsen central apnea and vice versa.

INTRODUCTION

Central sleep apnea (CSA) is a sleep-related breathing condition characterized by cessation or an evident reduction in airflow lasting at least 10 seconds. Unlike obstructive apnea whereby breathing effort continues but airflow is limited because of upper airway narrowing or collapse, central apneas are associated with absent or insufficient respiratory drive and respiratory muscle output. Similar to obstructive apnea, CSA results in disrupted sleep, frequent arousals, hypercapnia, and hypoxemia.[1,2] CSA is associated with numerous adverse health outcomes including daytime somnolence and cardiovascular disease.[3,4]

There are many manifestations of CSA including the classic crescendo/decrescendo Cheyne-Stokes breathing pattern,[5] common in patients with heart failure. Its presence is associated with poor prognosis. However, certain forms of CSA can also be driven by other pathologic factors. For example, CSA can be caused by damage to the respiratory control centers within the brainstem.[2,6–8]

The most common condition associated with CSA, heart failure,[9] is reviewed elsewhere in this issue in the articles by Caples and Naughton.[10,11] This brief review covers several other medical conditions that may lead to CSA or sleep hypoventilation. The key physiologic components involved in the control of breathing and the reliance on CO_2 to drive ventilation during sleep are highlighted. There follows a brief discussion on a range of medical conditions in which CSA/sleep hypoventilation has been shown to occur, including brain tumors, Chiari type I malformation, stroke, pain/opioids, endocrine and hormonal disturbances (acromegaly, hypothyroidism, pregnancy, metabolic syndrome, diabetes), neurodegenerative disease (multiple sclerosis, multiple-system atrophy, Parkinson disease), and neuromuscular disease

Disclosure Statement: D.J. Eckert is supported by a National Health and Medical Research Council of Australia R.D. Wright Fellowship (1049814). The authors do not have any conflicts of interest to declare in relation to the topic of this article.

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Sleep Med Clin 9 (2014) 57–67
http://dx.doi.org/10.1016/j.jsmc.2013.10.002
1556-407X/14/$ – see front matter

(congenital muscular dystrophies, myasthenia gravis, amyotrophic lateral sclerosis). In each case the available evidence linking these various conditions with CSA or sleep hypoventilation are highlighted, and the potential pathophysiologic mechanisms involved are discussed. In many instances a bidirectional relationship likely exists, such that the primary medical condition causes or worsens the CSA while the severity and associated symptoms of the primary medical condition are worsened by the CSA.

PHYSIOLOGY OF CONTROL OF BREATHING AND PATHOPHYSIOLOGY OF CENTRAL SLEEP APNEA

Central Control of Breathing

Neuroanatomically, our understanding of the complex interactions and specific neurons responsible for generating and regulating breathing remains incompletely understood. Primarily based on animal studies, key sites that have been implicated in the central control of breathing within the upper pons include the pontine respiratory group (featuring the nucleus parabrachialis medialis and lateralis, and the Kolliker-Fuse) (**Fig. 1**). These areas have been shown to mediate inspiratory-off phenomena. Lesions above the lower pontine reticular formation cause prolonged inspiratory gasps, and thus are believed to elicit a tonic excitation of inspiratory premotor neurons.[6,7]

Key sites of central respiratory control and rhythmicity, however, lie within the medulla. The dorsal respiratory group, associated with the nucleus tractus solitarius, processes afferent information from phrenic, vagus, and peripheral chemoreceptors to the cortex. This region contains many inspiratory-related neurons, some of which likely mediate inspiratory-off phenomena. It is unclear whether there is direct phrenic output, but nearby projections to the retrotrapezoid nucleus and the ventral respiratory group exist. The ventral respiratory group contains the pre-Bötzinger complex, which has multiple projections to other key brainstem regions involved in the control of breathing.[12] The pre-Bötzinger complex is postulated to be a key pacemaker site, based on the presence of a respiratory rhythm in minimal slice preparations.[13] Conversely, the nearby Bötzinger complex is believed to contribute to expiratory active/inspiratory inhibitory phenomena. The rostral ventral respiratory group contains inspiratory premotor neurons and includes the nucleus ambiguus, which provides motor output to the larynx and pharynx via the vagi.[6,7] **Fig. 1** displays a schematic representation of some of these key sites.

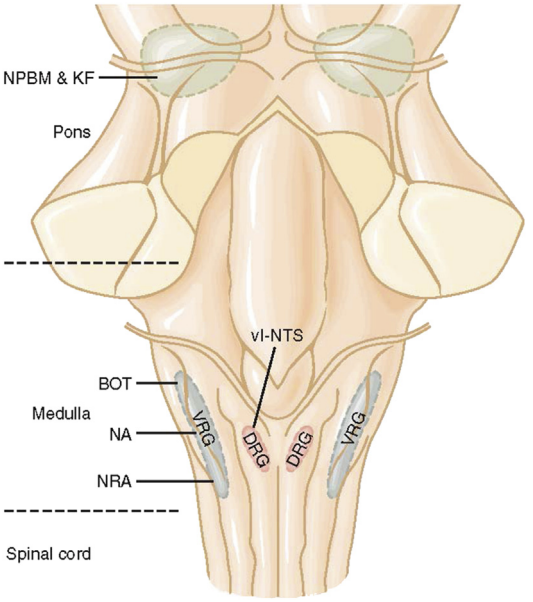

Fig. 1. Central respiratory control centers within the pons and medulla. Refer to the text for further details. BOT, pre-Bötzinger complex; DRG, dorsal respiratory group; KF, Kölliker-Fuse nucleus; NA, nucleus ambiguus; NPBM, nucleus parabrachialis medialis; NRA, nucleus retroambigualis; vl-NTS, ventrolateral nucleus of the tractus solitarius; VRG, ventral respiratory group. (*From* Eckert DJ, Roca D, Yim-Yeh S, et al. Control of breathing. In: Kryger M, editor. Atlas of clinical sleep medicine (2nd edition). Philadelphia: Elsevier Saunders; 2014; with permission.)

Changes in the Inputs to Breathing from Wakefulness to Sleep

During wakefulness, there are multiple inputs that can contribute to the rate and depth at which we breathe, including: cortical voluntary control; emotional input via the limbic system; receptors in muscles and joints; stretch receptors in the lungs; receptors that respond to temperature, pain, and touch; an independent wakefulness drive to breathe; and peripheral chemoreceptors located at the bifurcation of the common carotid arteries.[14] However, the most powerful stimulus to breathe during quiet wakefulness is via the central chemoreceptors.

In reality, virtually all human cells will respond to extreme changes in the surrounding chemical environment. However, certain neurons are exquisitely sensitive to relatively minor changes in the local chemical environment. These areas can either directly regulate the control of breathing or have projections to key central control of breathing sites, and are thus referred to as chemoreceptors. The retrotrapezoid nucleus located on the ventral