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Central Sleep Apnea: a Brief Review

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Abstract

Purpose—The purpose of this review is to discuss the pathogenesis, clinical manifestations, diagnosis and treatment, including areas of controversy and uncertainty.

Recent Findings—Central apnea may be due to hypoventilation or to hypocapnia following hyperventilation. The occurrence of central apnea initiates a cascade of events that perpetuates breathing instability, recurrent central apnea and upper airway narrowing. In fact, breathing instability and upper airway narrowing are key elements of central and obstructive apnea. Clinically, central apnea is noted in association with obstructive sleep apnea, heart failure, atrial fibrillation, cerebrovascular accidents tetraplegia, and chronic opioid use.

Management strategy for central apnea aim to eliminate abnormal respiratory events, stabilize sleep and alleviate the underlying clinical condition. Positive pressure therapy (PAP) remains a standard therapy for central as well as obstructive apnea. Other treatment options include adaptive-servo ventilation (ASV), supplemental oxygen, phrenic nerve stimulation, and pharmacologic therapy. However, ASV is contraindicated in patients with central sleep apnea who had heart failure with reduced ejection fraction, owing to increased mortality in this population.

Summary—There are several therapeutic options for central apnea. Randomized controlled studies are needed to ascertain the long-term effectiveness of individual, or combination, treatment modalities in different types of central apnea.

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Conflict of Interest
Shahrokh Javaheri reports fees from Respicardia as a constulant.
M. Safwan Badr declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Central apnea; sleep; opioid; heart failure; positive-pressure therapy; CPAP; BPAP; adaptive-Servo ventilation

Introduction

Central apnea during sleep is not due to a single etiology. Rather, it is a manifestation of central breathing instability in a variety of clinical conditions.[12] Although our understanding of the specific mechanism(s) of central apnea has grown appreciably in the past decade, the underlying pathophysiology remains incompletely understood. Further, the pathophysiologic overlap between central and obstructive sleep apnea (OSA) defies the separation into two distinct “silos”. Not surprisingly, a number of current treatment options for treatment of central sleep apnea (CSA) are derived from approaches used for the treatment of obstructive sleep apnea. This review will address the pathogenesis, clinical manifestations, diagnosis and treatment of CSA, including areas of controversy and uncertainty.

I. DETERMINANTS OF CENTRAL APNEA DURING NREM SLEEP

I.1. Initiation of Central Apnea

Central apnea is the result of transient inhibition of ventilatory motor output. Sleep state, transient hypocapnia, unstable ventilatory control system, upper airway reflexes, and depression of brain stem rhythm generation may all contribute to “turning off” the ventilatory motor output and the development of central apnea.

The fundamental mechanisms of central apnea could be due to hypoventilation or post-hyperventilation. Withdrawal of the wakefulness drive to breathe leads to decreased ventilatory motor output, which may be inconsequential in healthy individuals but leads to hypoventilation and even apnea in patients with inadequate ventilatory reserve such as those with neuromuscular disease or thoracic cage disorders. Opioid analgesics and other CNS suppressants may also contribute to hypoventilation. It is of note that hypoventilation-related central events may occur before diurnal hypercapnia is noted.

Central apnea occurs most commonly during non-rapid eye movement (NREM) sleep. The removal of the wakefulness “drive to breathe” during NREM sleep renders respiration critically dependent on chemical influences, especially PCO2. Thus, NREM sleep unmasks the apneic threshold, a phenomenon that is sleep state-dependent.[3] Accordingly, central sleep apnea occurs if arterial PCO2 drops below a highly sensitive “apneic threshold”.[2–4]

Transient hypocapnia (PCO2 dropping below the steady state NREM PCO_2) is a powerful mechanism of reduced ventilatory motor output during NREM sleep. However, several factors modulate and may counter the inhibitory effects of hypocapnia on ventilatory motor output.

Duration of hyperpnea: The occurrence of central apnea requires hypocapnia that is sufficient in magnitude and duration to affect medullary central ventilatory control centers.

Accordingly, brief hyperventilation rarely produce central apnea in sleeping humans[5]or dogs[6] Therefore, short periods of hyperventilation (less than a minute) are unlikely to cause central apnea possibly due to insufficient medullary hypocapnia.

Short-term potentiation: Brief active hyperventilation (e.g. hypoxia) elicits an excitatory neural mechanism referred to as short-term potentiation (STP) [[3–5]], which mitigate the post hyperventilation reduction in ventilatory motor output.[7,8]

In summary, the duration and the magnitude of hyperventilation may determine the level of medullary hypocapnia and short-term potentiation determines the occurrence of post-hyperventilation apnea during stable sleep. A practical application of the aforementioned phenomena is the infrequent occurrence of central apnea following acoustically induced arousals from sleep in healthy individuals without hypoxia.

Depression of rhythm generation: Medications such as opioids suppress rhythm generation in the neurons of Pre-Botzinger complex, the presumed site of rhythm generation in mammals, located in the brain stem. Opioids, like beta agonists, act on seven transmembrane G protein receptors, but in contrast to beta agonists suppress downstream signal transduction by decreasing cyclic AMP.[9] Some neurodegenerative disorders may cause central sleep apnea by a similar mechanism. In this case, neurokinin 1–expressing (NK1R) neurons of the pre-Botzinger complex are potentially permanently damaged.[10]

I.2. Recurrent central apnea and perpetuation of breathing instability

The ventilatory control system includes multiple components that operate as a closed feedback with the goal maintaining arterial blood gas tensions within a narrow physiologic range. The overall gain of the system is referred to as “loop gain”,[11,12] which represents the overall response of the multiple components of the ventilatory feedback loop including: 1) the plant (representing the lung and respiratory muscles), 2) the controller (representing the ventilatory control centers and the chemoreceptors), and 3) the circulatory delay, dilution and diffusion required to carry the signal between the plant and the controller. Increased loop gain is the underlying mechanism of ventilatory control instability and development of central sleep apnea in heart failure.[13]

Central apnea occurs in cycles of apnea/hypopnea alternating with hyperpnea and NOT as isolated events. The occurrence of central apnea initiates a cascade of events that perpetuate unstable breathing (Figure 1) including the inertia of the ventilatory control system, upper airway narrowing/occlusion, hypoxia, hypercapnia and transient EEG arousal. The ventilatory control system exhibits marked inertia upon cessation of the ventilatory motor output. Consequently, rhythmic breathing does not resume until arterial $P_aCO_2$14 is 4 to 6 mmHg above eupneic P_aCO_2. In addition, central apnea results in narrowing or occlusion of the pharyngeal airway[15], which additional force to overcome gravitational craniofacial forces or mucosal tissue adhesion.[16,17].Finally, the combination n of gas exchange derangements and transient EEG arousals results in ventilatory overshoot, hypocapnia and recurrent central apnea. This sequence explains why apnea rarely occurs as a single event (i.e., “apnea begets apnea”) Furthermore; central apnea is often accompanied by obstructive and mixed apnea in the same patient.

II. CLASSIFICATION OF CENTRAL SLEEP APNEA

II.1. The International Classification of Sleep Disorders (ICSD-3).[18]

The ICSD-3 provides the following classification of central apnea.

- Central sleep apnea with Cheyne-Stokes breathing (CSB)
- Central sleep apnea due a medical disorder without CSB
- Central sleep apnea due to high altitude periodic breathing
- Central sleep apnea due to a medication or substance
- Primary central sleep apnea

Treatment-emergent central sleep apnea

The aforementioned classification is useful clinically by identifying clinical syndromes associated with central apnea. However, it is not based on pathophysiologic mechanisms and hence may not inform therapeutic decisions.

II.2. Pathophysiologic Classification

Central sleep apnea secondary to alveolar hypoventilation: Individuals with diurnal hypercapnia, and those with marginal respiratory status, may develop sleep-related hypoventilation due to the removal of the wakefulness drive to breathe. The spectrum of disorders causing daytime hypercapnia is wide (1) and includes conditions such as neuromuscular diseases (post-polio syndrome, ALS, brain stem stroke, central alveolar hypoventilation, or severe abnormalities in pulmonary mechanics such as kyphoscoliosis). In the face of hypercapnia, the alveolar ventilation equation dictates that ***small*** alterations in ventilation will result in ***large*** changes in PCO2 (increased plant gain). Therefore, under such circumstances, a transient arousal from sleep, with associated small rise in ventilation could lower the P_aCO_2 below the apneic threshold with subsequent central apnea.

The presenting clinical picture of such individuals often includes features of sleep-disordered breathing, ventilatory failure, and features of the underlying disease. The specific etiology responsible for hypercapnic central sleep apnea in a given patient influence(s) the management strategy aimed at restoration of effective alveolar ventilation during sleep, and while awake if applicable. Treatment of choice is assisted ventilation (such as bilevel devices with back up rate); nasal CPAP and supplemental oxygen are unlikely to alleviate the condition. The latter may aggravate the condition, based on the pathophysiology discussed above, such that with suppression of hypoxic drive, PaCO2 increases further, with further increase in plant gain which increases the probability of developing central apnea during sleep.

Central apnea secondary to hyperventilation-—Post-hyperventilation hypocapnia is the most common underlying mechanism of central apnea. This type of apnea is characterized by transient instability of the ventilatory control system AND normal or increased alveolar ventilation. This type of CSA is most common in patients with heart failure who may be hypocapnic during wakefulness. In addition, such patients have a long

circulation time which converts a negative feedback system to a positive one contributing to overshoot and undershoot of ventilation and persistent hyo-and hyperventilation.

III. CENTRAL APNEA RISK FACTORS

Several physiologic or pathologic factories may influence the susceptibility to develop central apnea including sleep state, age, gender, and several medical conditions.

a. Sleep state

The transition from wakefulness to NREM sleep may be associated with recurrent central apnea. The underlying etiology is the oscillation of sleep state oscillates between wakefulness and light sleep [30–33] with a reciprocal oscillation of P_aCO_2 around the "apneic threshold"). Transient arousal leads to brief hyperventilation; the ensuing hypocapnia results in central apnea upon resumption of sleep. Typically, these events resolve with consolidation of sleep and stabilization of P_aCO_2 above the apneic threshold. Sleep onset, manifesting as a transition from alpha to theta, is also associated with prolongation of breath duration[34] which may manifest as central apnea in some individuals. Therefore, transient central apnea at sleep onset may be a normal phenomenon.

Central sleep apnea is uncommon during REM sleep. Decreased propensity to central apnea during REM sleep may be attributed to decreased hypercapnic and hypoxic ventilatory responses, and hence reduced loop gain,[19] possibly due to inhibition of accessory chest wall muscles. Other mechanisms include increased ventilatory motor output during REM sleep relative to NREM sleep.[20] Conversely, decreased accessory muscle activity during REM sleep may exacerbate REM-related hypoventilation in patients with diaphragm dysfunction or paralysis. Consequently, nadir tidal volume may be negligible and appear as central apnea (Pseudo CSA). Thus, central apnea during REM sleep represents transient hypoventilation rather than post-hyperventilation hypocapnia.

b. Age and gender

Central sleep apnea is more prevalent in older adults relative to middle-aged individuals.[21,22] In one large epidemiologic study, the prevalence of central apnea (defined as a central apnea index [CAI] of ≥2.5) was 1.7% in the middle-aged group vs. 12.1% in the older adults group.[23]Physiologically, sleep state oscillations may precipitate central apnea in older adults.[24] Older adults are more susceptible to induced central apnea. Using nasal mechanical ventilation to induce central apnea, Chowdhuri et al demonstrated that the magnitude of hypocapnia required to induce central apnea was smaller in older adults compared to young adults. (-2.6 ± 0.4 vs. -4.1 ± 0.4 mmHg, $P = 0.01$).[25] Increased prevalence of central apnea may also be due to increased prevalence of co-morbid conditions such as hypothyroidism[26], congestive heart failure,[13] and atrial fibrillation[27], in older adults.[47]

Epidemiologic studies have shown that central apnea is rare in women, with an overall prevalence of central apnea (CI > 0) in women of 0.3%, compared with 7.8% in men.[4,28] This observation has been corroborated by studies demonstrating that men are more susceptible to the development of experimentally induced central apnea during relative to women mechanical ventilation. The magnitude of hypocapnia that is required to induce

central apnea was −3.5 mmHg vs. −4.7 mmHg below room air level in men and women respectively[4]. Interestingly, the phase of the menstrual cycle did not influence the propensity to central apnea in women, indicating that gender difference was not due to progesterone.

c. Medical Conditions

Sleep-disordered breathing is common in patients with heart failure; in one study 51% of male patients with heart failure had sleep disordered breathing. The majority of the patients had central apnea (40%) and the remainder (11%.) had obstructive apnea.[29] Risk factors for central apnea in this group of patients include male gender[30], atrial fibrillation, age > 60 year, very low left ventricular ejection fraction (less than 30%), and hypocapnia Risk factors for OSA differed by gender; the only independent determinant in men was body mass index (BMI), whereas age over 60 was the only independent determinant in women.

Patients with central apnea and congestive heart failure (CHF) demonstrate pulmonary vascular congestion leading to hyperventilation and hypocapnia. Increased ventilation and reduced steady state P_aCO_2 decreases plant gain, which should be stabilizing.[31] In other words, steady-state hypocapnia is potentially stabilizing rather than destabilizing. However, in patients with heart failure the magnitude of hypocapnia required to induce central apnea (referred to as the CO2 reserve) is small owing to controller gain below eupnea[31]

Sleep apnea is common after a cerebrovascular accident (CVA).[32] Forty percent of the patients demonstrate central apnea as the predominant type of sleep disorder after a CVA.[33] Likewise, central apnea occurs in 30% of patients with stable methadone maintenance treatment[34]. Finally, central apnea is common in several medical conditions including hypothyroidism, and renal failure. Nocturnal hemodialysis is associated with improvement in sleep apnea indices.[35] The reported association between acromegaly and central sleep apnea[36] was not corroborated in a cross-sectional study of a clinical cohort.[37]

Individuals living with spinal cord injury are at increased risk of central apnea. [38,39]Specifically, tetraplegia is associated with a high prevalence of central apnea/hypopnea, resembling Hunter-Cheyne-Stokes breathing. Those who do not manifest spontaneous central apnea demonstrate increased propensity to experimentally induced central apnea using noninvasive mechanical ventilation.

Central apnea occurring with no apparent risk factor is described as “idiopathic central apnea”. Increased chemo responsiveness and sleep state instability are commonly noted in these patients.[40] Nevertheless, it is possible that these patients have occult cardio-cerebrovascular or metabolic disease. For example, central sleep apnea is more prevalent in patients with, or asymptomatic carotid atherosclerosis[41]

IV. CLINICAL FEATURES AND DIAGNOSIS

The underlying disease process and the occurrence of apneas during sleep are the two factors that influence the clinical features of hypercapnic central apnea. These include features of the underlying disease such as weakness and dyspnea, as well as features of sleep apnea

syndrome, including daytime sleepiness, snoring, and poor nocturnal sleep as well as morning headache.

Patients with non-hypercapnic central apnea may present with the usual symptoms of sleep apnea syndrome, although generally do not endorse subjective daytime sleepiness.[42] Frequent oscillation between wakefulness and stage 1 NREM sleep may cause sleep fragmentation and poor nocturnal sleep and perception of insomnia as the presenting symptoms.

Central sleep apnea may also be a found as an associated finding in a patient with OSA, either on the initial polysomnography or after restoring upper airway patency with positive pressure therapy. This phenomenon is referred to as “Treatment-Emergent Central Apnea”. The name implies a specific or unique clinical entity. However, it is likely that this phenomenon represents unmasking of the underlying breathing instability in patients with OSA. Spontaneous resolution occurs in the majority of patients with continued use of CPAP.[43]

Nocturnal polysomnography is the standard diagnostic method for the measurement of sleep and breathing. The latter includes detection of flow, measurement of oxyhemoglobin saturation and detection of respiratory effort.[44] Detection of respiratory effort is important to distinguish central from obstructive apnea. This requires measurement of esophageal pressure, as a reflection of pleural pressure changes. However, the complexity and invasiveness of the procedure, and its cost have precluded widespread use. Instead, most clinical sleep laboratories utilize surface recording of effort, to detect displacement of the abdominal and thoracic compartments and dysynchrony during episodes of upper airway obstruction. Invasive esophageal or supra-glottic pressure measurement is reserved for selected cases and for research purposes.

The presence of cardiogenic oscillations (pulse artifacts) on the flow signal has been used as an indirect index of central etiology based on the assumption that pulse artifacts represent transmission of a pulse waveform from the thorax through a patent upper airway. Using fiber optic nasopharyngoscopy, Morrell et al found that cardiogenic oscillations were present even when the airway is completely occluded.44 Therefore, cardiogenic oscillations is not a reliable regarding the patency of the upper airway or the etiology of an apnea.

V. MANAGEMENT

Management strategy for central apnea incorporates clinical features, co-morbid conditions, and the polysomnographic findings in an individualized manner. Available therapeutic options include positive pressure therapy, phrenic nerve stimulation, and pharmacologic therapy including low flow supplemental oxygen administration.[46]

a. Positive pressure therapy (PAP)

Optimal treatment of concomitant clinical conditions is a critical first step, which may result in amelioration of the severity of central apnea. Positive pressure therapy could be delivered as continuous positive airway pressure (CPAP), bi-level pressure (B-PAP) or Adaptive servo

ventilation (ASV). CPAP is the recommended treatment first line therapy for central apnea with about 50% response rate. Reasons for response to CPAP include: 1) a direct effect of CPAP on central apnea by preventing pharyngeal narrowing during central apnea[15] and dampening the ensuing ventilatory overshoot., 2) co-occurrence of central and obstructive apnea, and 3) the difficulty distinguishing central from obstructive SDB on routine polysomnography. Interestingly, nasal CPAP has been shown to ameliorate central sleep apnea, even in the absence of obstructive respiratory events,[47] especially supine-dependent central sleep apnea. Most of the studies on the use of nasal CPAP in central apnea address patients with CHF. Nasal CPAP may have significant salutary effects in patients with congestive heart failure and central sleep apnea. Several lines of evidence, both theoretical and empiric, underpin the use of CPAP in this setting. Specifically, CPAP suppresses CSA in 50% of patients with heart failure, with ensuring decrease in nocturnal ventricular arrhythmias

The premise that nasal CPAP therapy was an effective therapy for central apnea and CHF was not supported by empiric evidence. The Canadian Continuous Positive Airway Pressure trial, or CANPAP ([80]), tested the hypothesis that CPAP would improve the survival rate without heart transplantation in patients with heart failure and central sleep apnea. The study enrolled 258 patients who had heart failure and central sleep apnea; participants were randomly assigned to the nasal CPAP treatment group (n=128) or no CPAP (130 patients). CPAP was associated with improvement in intermediate outcomes, including the apnea-hypopnea index, ejection fraction, mean nocturnal oxyhemoglobin saturation, plasma norepinephrine levels, and the distance walked in 6 min at 3 months. However, there was no difference in the overall event rates (death and heart transplantation) between the two groups. Therefore, current evidence does not support the use of CPAP to extend life in patients who have heart failure and central sleep apnea. Conversely, post hoc analysis of the findings demonstrated a significant improvement in survival of heart failure patients in whom CSA was suppressed.[48]

Non-invasive positive pressure ventilation (NIPPV) using pressure support mode (bi-level nasal positive pressure) is effective in restoring alveolar ventilation during sleep. Clinical indications include nocturnal ventilatory failure and central apnea secondary to hypoventilation. There is evidence that NIPPV exerts a salutary effect on somnolence, fatigue and survival in patients with ventilatory failure secondary to amyotrophic lateral sclerosis.[49] The effect on NIPPV on other neuromuscular conditions associated with nocturnal ventilatory failure remains unclear.

The development of central apnea may be mitigated by altering the mode of delivering positive pressure therapy. Specifically, Adaptive Servo Ventilation (ASV) provides varying amount of ventilatory support, against a background of positive end expiratory pressure (EPAP). In the new generation of ASV devices, EPAP changes automatically similar to auto-PAP used to treat OSA. There are 2 such devices available in US with completely different algorithms,[50] making it difficult to be familiar with both devices.

Contrary to bi-level, pressure support devices, changes in respiratory effort results in reciprocal anticyclical changes in the magnitude of ventilatory support. There is evidence

that ASV is more efficacious than CPAP, bi-level pressure support ventilation, or increased dead space in alleviating central sleep apnea.[51]However, a recent clinical multi-center (SERVE-HF) randomized clinical trial in patients with predominantly-central sleep apnea and hear-failure with reduced ejection fraction (HF-rEF) demonstrated increased mortality in patients randomized to ASV.[52] Therefore, ASV is contraindicated in patients with HF-rEF and central apnea.[53] Nevertheless, a concern about the specific algorithm used in the aforementioned trial[52] raised the possibility that fixed - not automatic end-expiratory pressure, and aggressive inspiratory pressure may have contributed to excess mortality.[54] An ongoing study, ADVENT-HF [Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure]; NCT01128816) trial, is examining the role of ASV using a refined algorithm.

2. Pharmacological Therapy

The role of pharmacological therapy for central apnea is very modest, and there are no long-term controlled clinical trials demarcating the boundaries of effectiveness. There is evidence derived from small studies, but no large clinical trials, to support the use of acetazolamide and theophylline in the treatment of central apnea [89]. Acetazolamide, a weak diuretic that causes mild metabolic acidosis has been shown in several studies to decrease the severity of central apnea. when administered as a single dose of 250 mg before bedtime [90]. Improvement in central apnea and Cheyne-Stokes respiration was also demonstrated with the use of theophylline in patients with CHF [91], without adverse effect on sleep architecture. Nevertheless, pharmacologic therapy remains as a potential future opportunity awaiting definitive clinical trials.

3. Supplemental Oxygen (O2) and CO2

Several studies have demonstrated a salutary effect of supplemental O2 in patients with central apnea associated with heart failure.[55]Physiologically, supplemental oxygen may alleviate central apnea by mitigating the magnitude of hypoxemia and hence dampening the magnitude of post-apneic ventilatory overshoot. In addition, isocapnic hyperoxia has been shown to stimulate ventilation in a dose-dependent manner.[56] The most likely explanation is increased cerebral PCO_2 by the displacement of carbon dioxide from hemoglobin by the increased oxygen level (Haldane effect). The American Academy of Sleep Medicine (AASM) recommends nocturnal oxygen as a standard treatment for central apnea related to heart failure.[46]

Supplemental CO2 abolishes central apnea in patients with central sleep apnea. The mechanism of action is by raising PCO2 above the apneic threshold. However, this therapy is not practical given the need for a closed circuit to deliver supplemental CO2.

4. Phrenic Nerve Stimulation

Stimulation of the phrenic nerve is a physiologically appealing intervention that may be an option for patients with central apnea. A new commercially available implantable phrenic nerve stimulator that provides unilateral stimulation of the phrenic nerve. (remedé system, Respicardia Inc, Minnetonka, MN, USA) has been recently approved by the FDA for the treatment of moderate to severe central sleep apnea (CSA) in adult patients. Approval was

based on a randomized clinical trial demonstrating improvement in central apnea indices, oxygenation, sleep metrics and quality of life.[57] Phrenic nerve stimulation appears to be a promising therapeutic approach for central sleep apnea. The precise role of this therapy awaits studies of long term outcome, safety as well as comparative effectiveness.

VI. APPROACH IN SELECTED CLINICAL SYNDROMES

The heterogeneity of central sleep apnea mandates an individualized treatment approach. Several factors have to be considered for proper management of each patient:

1. It is imperative to optimize treatment of the underlying condition such as CHF; Follow up polysomnography is needed to confirm improvement in the severity of apnea.
2. A trial of nasal CPAP is warranted as a starting point. There is good evidence that many patients may respond to positive pressure therapy. The optimal pressure settings have to be determined by a lab observed titration polysomnography.
3. The use of Bi-level-PAP in a pressure support mode is likely to aggravate the severity of central apnea. Adding a backup rate may be beneficial but should not be used for the treatment of CSA in HFrEF, given the potential for potential for adverse cardiac consequences from the constant inspiratory pressure in patients in whom right ventricle is preload-dependent.[58]
4. Supplemental O2 may be beneficial in patients with CSA, particularly in patients with CHF-CSB.
5. The use of pharmacologic agents, remain very modest. Confirmation with efficacy with polysomnography is essential. Likewise, administration of this drug requires meticulous attention to serum levels.

In conclusion, the pathogenesis of central sleep apnea varies depending on the clinical condition. Sleep-related withdrawal of the ventilatory drive to breathe is the common denominator among all cases of central apnea, whereas hypocapnia is the common pathway leading to apnea in non-hypercapnic central apnea. Conversely, in certain conditions, breathing rhythm is suppressed with development of central apnea while asleep, as it occurs with opioids. The pathophysiologic and etiologic heterogeneity may explain the protean clinical manifestations and the necessity of individualized therapy.

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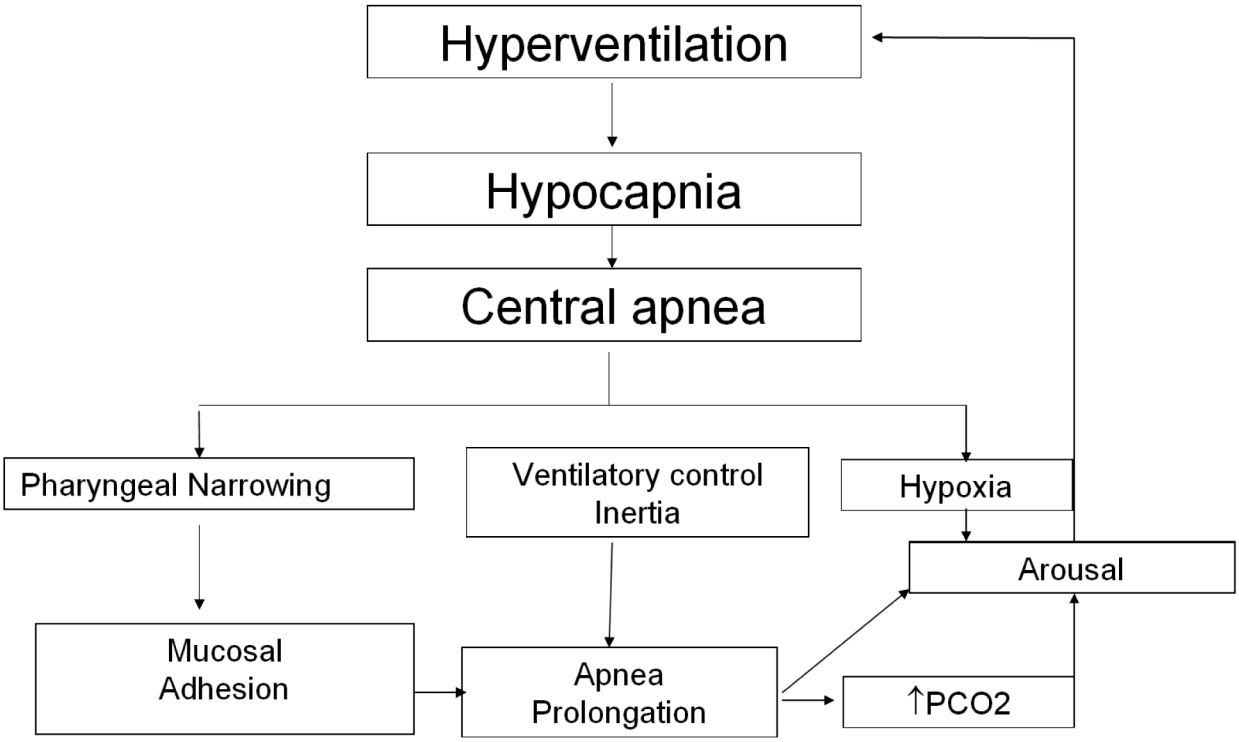

Figure 1. Schematic representation of central apnea

Mechanisms that perpetuates breathing instability and recurrent central apnea