Pathophysiology of Central Sleep Apnea Syndrome

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CENTRAL SLEEP APNEA (CSA) SYNDROME IS AN HETEROGENOUS SYNDROME CHARACTERISED BY CESSATION OF RESPIRATORY EFFORT AND SUBSEQUENT APNEA DURING SLEEP. Pure central sleep apnea syndrome is less frequent than the obstructive type of sleep-breathing disorder. In a detailed study by DeBaker et al,[1] 327 patients were referred to a sleep laboratory for suspected sleep-related breathing disorder due to snoring and/or hyper somnolence. Only 4% had pure central sleep apnea syndrome, defined by central apnea index > 5 per hour of sleep, or central apnea hypopnea index > 10/h without obstructive events (< 5/h). Incidence estimated from specialised sleep clinics may, however, underestimate the real incidence of the problem, particularly in the context of heart failure. In this condition, incidence of central sleep apnea, typically associated with Cheyne-Stockes respiration (CSR-CSA), may be high. In a longitudinal prospective study of stable patients, Jahaveri et al. reported an incidence of CSR-CSA in 45% of patients medically treated for chronic heart failure without recent exacerbation.[2] In our experience, among patients previously admitted for acute left ventricular failure in a cardiology department (n=42), we observed that 82% of patients had sleep-related breathing disorders, among whom 75% had CSR-CSA and 25% had obstructive sleep apnea.[3] This was not only observed within the first month after the acute episode, but also this persisted after two months of additional optimal medical treatment.

In addition to its incidence, the importance of CSA relies on its potential value in the prognosis of heart failure. As part of a large scale study, Ancoli-Israel et al[4] showed that patients suffering from CSA had a poorer prognosis than age-matched subjects without CSA, the more severe Cheyne-Stockes respiration was (% of Total Sleep Time in CSR), the poorer the prognosis. Whether this corresponded to more severe heart failure or, whether CSR is an independent prognosis factor, cannot be inferred from this study. Findley et al[5] further suggested, in a small group of patients, that mortality is increased in patients with CSR-CSA, as opposed to patients without CSR-CSA, for comparable levels of ejection fraction : 6 / 6 patients died within 6 months in the former group as opposed to 3 / 9 in the latter. In another study by Hanly and Zyberi-Khokhar[6] 16 patients were followed for up to almost 5 years. Incréased mortality was observed in those patients with CSR (7 died from cardiac deaths and 2 had transplants) as opposed to 1 patient dying from 'non-cardiac' death in the group without CSR. Both groups had similar Left Ventricular Ejection Fraction (LVEF) at baseline. This area remains controversial, however, since different findings were found in another study by Andreas et al.[7] In this study, the importance of CSR did not have a prognostic impact per se, as opposed to LVEF (≤ or > 20%) and the presence of CSR during daytime which was associated with a high risk of dying within a few months or weeks. Patients, overall, had a wider range of LVEF than in Hanly's study and this may, override the impact of CSR-CSA on the prognosis.

Central sleep apnea: definition

Recognition of central apnea

The widely accepted definition for central apneas is the complete cessation of respiratory effort that leads to the absence of oronasal airflow for more than 10 seconds. An event associating airway obstruction and a reduction (not a complete cessation) of respiratory effort would be considered as an obstructive event in routine practice. The lack of respiratory effort can be determined by esophageal pressure which is still currently the reference method. Recording of diaphragmatic electromyogram by surface electrodes on the skin may be a valuable technique. The proof of the ability of the device to detect respiratory effort at the end of the recording, however, should be used to ensure the validity of the EMG until the end of the recording. Respiratory Inductance Plethysmograph (RIP) or similar devices are often used in practice but misclassifications of central events, particularly hypopneas, are frequent. More recently, Argod et al[8] have proposed a non-invasive alternative method to esophageal pressure by the determination of Pulse Transit Time (PTT). Briefly, this time is the delay between the opening of the aortic valve (in practise the R-wave of the ECG) and the arrival of the pulse wave at the periphery (detected by oxymetry at the finger). This delay (i.e. PTT) has been shown to be inversely correlated with blood pressure. Thus, a close relationship between acute changes in

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pleural pressure (with subsequent effects on blood pressure) and inspiratory-expiratory ocillations of PTT has been demonstrated. Determination of changes in PTT swings as a reflect of acute changes in pleural pressure revealed a high sensitivity (from 91 to 94 %) and specificity (95 to 97 %) in recognising central events (apneas and / or hypopneas).[8]

Central sleep apnea syndromes

Central apneas may occur in a variety of circumstances during sleep. However, central sleep apnea syndrome will be restricted to those syndromes where central apneas occur frequently (> 5/h of sleep) and where the majority (more than 85%) of the events are central in nature. This excludes sleep breathing disorders where a significant number of events are obstructive. In these cases, increased upper airway collapsibility would be considered as a primary pathophysiological event and would require appropriate therapy. This also excludes mixed apneas where an obstructive event coexists with the central component of the apnea. These events are usually treated as OSAS, at least, initially. It is sometimes after removal of obstructive events that a pure central component may be unmasked. Relationships between central and obstructive events are complex for several reasons. We shall consider later in this text how primary central events associated with passive narrowing of the upper airways may lead to subsequent obstructive breaths by resuming the drive to ventilation. On the other hand, inhibitory influence from mechanoreceptors of the upper airways when stimulated by obstructed efforts may favour the occurrence of central events by their action on the central drive to breathe.[9] A recording with the application, CPAP, to remove the obstructive component may be a practical and useful approach.

If the mechanism which leads to apneas is a reduced drive in breathing associated with sleep and if this occurs in individuals with subsequent daytime hypoventilation, it is called hypercapnic central sleep apnea. The central feature, here, is the reduction in ventilation and tidal volume associated with sleep, the complete cessation of airflow being particularly severe phenomenon. An abnormal increase in $PaCO_2$ during sleep is a consequence of hypoventilation. The desaturation episodes may, thus, be prolonged (up to several minutes) and are most severe in degree and duration during REM sleep.

Other forms of central sleep apnea syndromes can be seen associated with normo (or hypo) capnia. These are: 'Idiopathic' central sleep apnea, Cheyne-Stockes respiration and High Altitude Sleep Apnea. The latter can be considered as a normal physiological response to hypoxia, but indeed, may lead to recurrent central apnea during sleep (particularly for those subjects and conditions where a marked response to hypoxia is observed). There is growing evidence, however, that these events - sometimes referred to as 'periodic breathing' during sleep - have detrimental pathophysiological consequences which, in particular would make the subjects more susceptible to High Altitude Pulmonary Edema (HAPE).[10] Cheyne-Stockes breathing, typically associated with chronic heart failure, is characterised by fluctuations in breathing during which, central apneas (or hypopneas), occuring at the nadir of ventilation, alternate with periods of progressive hyperventilation in a characteristic crescendo-diminuedo pattern. Idiopathic central sleep apnea is presumably an uncommon condition where subjects may have increased ventilatory response to CO_2 and, thus, hyperventilate. The resultant PCO_2 is, thus, closer from the sleep-induced apneic threshold.

Pathophysiology of hypercapnic CSA

Hypercapnic CSA is a rare condition during which abnormalities in the control of breathing are characterised either by defective brainstem medullary center, or a defect in peripheral and central chemoreception.

Careful physiological studies have been conducted in children with Central Chronic Congenital Hypoventilation Syndrome (CCHS). Characteristically these children severely hypoventilate during sleep. During wakefulness, higher brain centres allow them to adapt ventilation to near-normal, including during exercise. Minor abnormalities such as changes in breathing associated with attentional tasks[11] and/or a more variable level of ventilation during steady-state exercise[12] are the only abnormalities observed. In contrast, during sleep, there is marked reduction of ventilation due to the suppression of the 'wakefulness drive to breathing' and a defective breathing control, leading to hypoventilation or apneas and life-threatening decreases in oxygen saturation.

Other diseases can be responsible for hyercapnic CSA, all of them being associated with anatomical or functional defect of the brainstem respiratory control.[13] These include Shy Drager syndromes and dysautonomia, where the abnormalities of the control of breathing are associated with more diffuse abnormalities of the autonomic nervous system involved in the control of blood pressure and the cardio-vascular system. Similarly, diabetes mellitus and familial dysautonomia can be associated with CSA. A series of affections affecting the brainstem can be associated with hypercapnic CSA: brainstem stroke, poliomyelitis, encephalitis, multiple sclerosis, and vascular malformations. Occasional reports of CSA have been made after trauma, or cervical posterior cordotomy, or even in Chiari malformation of type I, suggesting that lesion in the motor neurones to the respiratory muscles descending from the medulla can lead to similar functional deficits.

Pathophysiology of hypocapnic (or normocapnic) CSA

As opposed to the above-mentioned hypercapnic CSA,

other forms of CSA are characterized by repetitive central apneas separated by periods of relative hyperventilation. Two major forms of hyperventilation CSA will be described: those associated with congestive heart failure referred to as Cheyne-Stockes respiration (CSR-CSA) and the 'idiopathic' form of CSA (idiopathic CSA).

Idiopathic CSA

In the recent years, a sequence of pathophysiogical events has been proposed which could favor the occurrence of CSA. The pivotal role of hyperventilation and its effect of driving PCO_2 below the apneic threshold[14] during sleep has received important experimental support.

Oscillations in ventilation during sleep (sometimes described as periodic breathing at sleep onset) have been observed in normal subjects, particularly those where sleep state is less well consolidated. Sudden changes in ventilation, thus occur, at least in some individuals, during transitions from wakefulness to stage 1 and 2. Pack et al[15] hypothesised that the mechanisms producing these oscillations are changes in state-dependant input to the respiratory controller. These authors have shown a close correlation between mean ventilation (l/min) and the mean frequency of the EEG (or the % of α Power) so that the slowing of the EEG (less α Power) was associated with a reduction in ventilation. Similar conclusions have been proposed by Trinder et al.[16] Thus there are physiological arguments suggesting that sleep instability may promote periodic breathing.

This phenomenon is further amplified by increased sensitivity to chemical stimuli. This has been initially suggested by E. Philipson in an analysis of the factors promoting periodic breathing at altitude.[17] At sleep onset in a normal subject, alveolar ventilation due to mechanisms which include a combination of incréased upper airway resistance and reduction in the drive to the pump muscles.[18] As a result P_aCO_2 increases and ventilation may slightly increase (according to the corresponding sleep-state ventilatory response to CO2). But, if at this time the subject arouses, this drives ventilation to a greater level corresponding to the ventilatory response at this particular P_aCO_2 associated with wakefulness. In addition, the steeper the slope of the ventilatory response to CO_2 during wakefulness, the bigger the increase in ventilation induced by arousal. This is followed by a decrease in $PaCO_2$ and a progressive return to the pre-arousal level of ventilation and $PaCO_2$. Several clinical studies bring arguments in favour of such an hypothesis. Xie et al, in eight consecutive patients with idiopathic CSA syndromes, studied precise interrelationships between ventilation (measured with a Respitrace) and arousals.[19] Consequences of acute hyperventilation was judged by its effects on the subsequent apnea length. Several arguments would favour the role of hyperventilation in ICSA. Firstly, mean ventilation (V_E) is higher and PCO_2 is lower during periods of the night where periodic breathing (and subsequent apneas) occur compared with periods of stable breathing during stage 2 non-REM sleep. Secondly, when comparing an increase in ventilation (and/or tidal volume) associated with an increasing grades of arousals (from 0 = no arousal, to 1 = EEG arousal, and 2 = movement arousal), the greater the grade of arousal, the greater the increase in ventilation. Furthermore, the length of subsequent apneas increased with the grade of arousal, suggesting that hyperventilation of increasing magnitude had proportionally lowered P_aCO_2 (see above). These authors thus suggested that interaction of arousals and hyperventilation were associated to trigger hypocapnia and central apneas in ICSA.

Additionally, in another series of experiments, the same group[20] confirmed that, compared to control subjects, ICSA patients tend to hyperventilate both during daytime and at night. Mean P_aCO_2 observed was slightly although significantly, lower in ICSA compared with controls, both awake (mean $PaCO_2$ of 35.1±1.3 vs. 38.8±0.9 mm Hg), & during sleep (37.8±1.2 vs. 42.7±10.9 mm Hg). Hyperventilation was associated with an increased ventilatory response to CO_2 in ICSA compared with controls (using both single-breath and rebreathing methods). Thus, this study suggests that idiopathic central sleep apnea is associated with a high gain of chemoreceptors (presumably both a central and peripheral response to CO_2). In another detailed evaluation of 54 patients with acromegaly, Grunstein et al.[21] examined the relationship between sleep-breathing disorders (central sleep apneas: n=11, OSA : n=33, or no SBD : n=10), respiratory control parameters and the hormonal status. Patients with CSA had a significantly higher hypercapnic ventilatory response (HCVR) than OSA or, even, subjects with acromegaly without sleep-disordered breathing. In a multiple regression analysis of the factors explaining the variance of the degree of CSA in acromegaly, the intensity of chemoresponsiveness (HCVR , HHVR) and of hormonal status (level of IGF-1) explained 40% of the observed variance, suggesting that both factors contribute to sleep apnea in these patients. Although the existence of high chemoreceptor gain has long been recognized as a factor for periodic breathing and central apneas at high-altitude CSA[19] or in CSR-CSA associated with heart failure (see below), this also seems to be the case in idiopathic CSA.

CSA associated with chronic heart failure

Increased ciculation time

The close association of sleep disordered breathing with heart disease, particularly in the form of Cheyne Stockes respiration, has long been recognized. Initially, observations have led to the hypothesis that the delays in the transport of the oxygenated blood to the brain (or possibly to the chemoreceptors of the carotid artery) are responsible for

CSR. Indeed, early reports have shown increased circulation time in patients with congestive heart failure who exhibited CSR.[22] However, when inducing CSR by artificially lengthening the lung-to-brain circulation time, Guyton et al.[23] had to lengthen heart-to-brain transport delay up to several minutes. In addition, despite such an extreme increase in the circulation time, induced CSR only occurred in approximately one third of the animals.[23] Increased circulatory delay does not seem to act as the single factor promoting CSR but rather, affects periodicity of the phenomenon. Circulatory delay, as reflected by lung-to-ear circulation time (LECT), has been shown to influence the total time of the breathing cycle and the length of the hyperpneic phase of CSR (the longer the circulation time the longer the total cycle time and the hyperventilatory phase) but not the apnea length per se.[24]

Lesions of the central nervous system

The possibility of brain lesions have been proposed as a causative factor for the existence of CSR. CSR has, indeed, been described in a variety of anatomical lesions of the central nervous system. Almost everywhere, from the cortical regions of the cerebral hemisphere down to the pons, have been reported.[25] However, failure to induce periodic breathing by discrete lesions of the medulla, led to the hypothesis that respiratory fluctuations would reflect an intrinsic oscillation of the brainstem reticular formation which would be unmasked by the loss of a supramedullary inhibitory influence. In a similar hypothesis, Plum & Leigh[26] proposed that patients, who had both some form of neurological damage and cardiovascular disease, would be those who develop CSR, as opposed to infrequent occurrence of CSR in young patients with advanced heart disease of rheumatoid origin with minimal neurological damage. Results from other studies, however, did not confirm association between neurological damage and cardiovascular dysfunction.[25] A common feature, between CSR in chronic neurological lesions and CSA, is the abnormalities in the respiratory control system and its interaction with sleep,[25] emphasising the role of hyperventilation in the genesis of periodic breathing in these conditions.

Role of hyperventilation in the genesis of CSR-CSA in heart failure

Evidence in favor of the role of hyperventilation in the genesis of periodic breathing and central apneas in heart failure has been recently emphasised by Naughton et al.[27] In a series of 24 patients with severe heart failure with (n=12) and without (n=12) CSR-CSA, that awake $PaCO_2$ and mean nocturnal $P_{tc}CO_2$ was significantly lowered in patients with CSR - CSA, suggesting permanent hyperventilation in patients with CSR-CSA (awake $PaCO_2$ = 33.0±1.2 vs 37.5±1.0 mm Hg ; mean nocturnal $P_{tc}CO_2$ = 33.2±1.2 vs 42.5±1.2 mm Hg respectively). Subjects with and without CSR-CSA had, otherwise, similar left ventricular ejection fraction (LVEF), awake P_aO_2, mean nocturnal S_aO_2 or lung-to-ear circulation time (a reflect of circulatory delay between the lung and chemoreceptors of the carotid body).

Arguments in favor of the role of hyperventilation (and subsequent hypocapnia in the genesis of CSA) are additionally provided by the effects of the removal of hypocapnia on the occurrence of apneas, presumably above the apneic 'threshold'. Increase in $PaCO_2$ during sleep obtained with low levels of inspired CO_2 (2-3%) and/or the addition of an external dead-space during sleep have been shown to efficiently stabilize ventilation and remove apneas, both in CSR-CSA[28,29] and idiopathic CSA.[30,31] Although efficient, these procedures remain pathogenic in essence and have been shown to be associated with potentially adverse effects on sleep architecture[28] or catecholamine secretion.[29]

Precise mechanisms responsible for chronic hyperventilation during heart failure have long been debated. Stimulation of vagal pulmonary C-fibres by venous congestion and interstitial edema has been suggested on the basis of experimental data in animals.[32] Clinical arguments in favor of this hypothesis include the fact that patients with CSR-CSA has a significantly higher pulmonary capillary wedge pressure (PCWP of 25 mm Hg) compared to those without CSR-CSA (PCWP of 14 mm Hg) and a significant negative correlation between PCPW and awake $PaCO_2$.[33] However, this does not imply a causal relationship, and a recent clinical observation has challenged the possibility that increased vagal afferent traffic is the unique cause of hyperventilation. Solin et al.,[34] thus, reported the case of a patient developing heart failure and CSR following vagal denervation due to previous bi-pulmonary transplantation.

Other factors may be implicated in the genesis of hyperventilation in these patients. Increased chemoresponsiveness, and in particular increased ventilatory response to CO_2 , has been reported to occur in CSR-CSA,[35] although this as not been confirmed in all studies.[36] Although interpreted as negative (the group mean slope of the ventilatory response to CO_2 was within their normals), the latter study showed a positive correlation between ventilatory response to CO_2 and time spent in periodic breathing in the 9 / 21 patients where central apneas occurred (as opposed to hypopnœas). More recently, Wilcox et al.[37] reported that patients with heart failure and CSA's had a greater ventilatory response to CO_2 and lower end-tidal PCO_2 than subjects with heart failure and obstructive sleep apnea. This suggests that augmented chemosensitivity to hypercapnia may be an important factor in the pathophysiology of CSA in patients with heart failure. This is in agreement with the theoretical model of Khoo et al.,[38] which emphasizes the role of increased central gain in promoting respiratory

instability.

Other factors have been implicated in the pathogenesis of CSR-CSA, particularly in patients who display a low or normal chemical CO_2 drive.

Hypoxemia has long been proposed as a possible factor promoting instability through its stimulating effect on carotid chemoreceptors. Hypoxic stimulation (for example in altitude) is able to induce periodic breathing in man. It should be emphasized, however, that arterial hypoxemia is mandatory to the development of CSR-CSA in heart failure and that O_2 administration usually attenuates, but does not suppress CSR-CSA.[39]

Rapid transition between wakefulness and sleep - i.e. the possibility of arousal response as a factor promoting ventilatory instability in CSR - CSA - may be an additional factor. Classically, the arousal response in CSR occurs at the maximum of the hyperpneic phase.[40] Detailed studies of their implication in the ventilatory response after apnea or the interaction of ventilation and arousal in CSR-CSA is lacking. Finally, catecholamine hypersesecretion is an important feature in the pathogenesis of heart failure and has been implicated in detrimental effects on the function of the failing myocardium.[41] The effects of catecholamines on the control of breathing raise the possibility that catecholamine hypersecretion may additionally participate in the hyperventilation observed. Noradrenaline infusion has been shown to increase ventilation after a few minutes of perfusion, an effect which is blocked by propranolol.[42] This may have a self-perpetuating effect on the CSR-CSA observed. Reduction in catecholamine hypersecretion could, thus, be an important target in the therapeutic approach or evaluation.

Other factors are susceptible to enhance the oscillatory behaviour of respiration during sleep.[25] Among them, reduced FRC acting as a reduced reserve of O_2 leading to a greater desaturation at the end of an apnea, reduction in whole-body CO_2 stores, and reduced CO_2 production associated with sleep, all enhance the effects of a ventilatory action on blood gases and, thus, would promote periodic breathing. Their restoration (nocturnal CO_2 loading or additional O_2) may have a damping action on the system. The loss of short-term potentiation, a characteristic of the control of breathing system, by which a decrease in ventilation following hyperventilation is progressive and ventilation remains elevated for a few breaths before quiet breathing re-occurs, could be an additional factor favoring post-hyperventilation apneas. Short-term potentiation (STP) has been shown to be reduced during hypocapnia or hypoxia and sleep; all these factors may act to reduce STP, thereby favoring the occurrence of apneas.[25] Lightening of sleep and/or arousals during hyperventilatory phase add to instability of the breathing controller.

Consequences of central apneas

Although central apneas are less studied than consequences of obstructive apneas they both share common features. This concerns changes in blood gases and, also, catecholamine hypersecretion, which may accompany arterial oxygen destruction and sleep fragmentation associated with central apneas.[43] Hemodynamic consequences of central apneas are less well established than their obstructive counterparts. However, in a recent experiments in dogs,[44] where both central and obstructive apneas were experimentally induced, the effects of central apneas on heart rate and cardiac output were proportionally greater (33% decrease in cardiac output) than obstructive ones (27%) for similar apnea duration and change in blood gases. This suggests that the cardiac response to central apneas may be important to consider, particularly in the context of heart failure.

The effects of CSR-CSA on cerebral circulation have been initially studied in an attempt to clarify the influence of the circulatory delay between lungs and brain. From recent experiments using Laser Doppler flowmetry conducted in man, Franklin et al.[45] demonstrated that cerebral blood flow oscillates, during CSR-CSA, in phase with ventilation and out of phase with $PaCO_2$ and the decrease in arterial O_2 saturation. This suggests that central changes in activity may, by themselves, be closely associated with changes in blood flow. A vasodilatory action of increased P_aCO_2 and/or changes in blood pressure are unlikely on the basis of these experiments.[45]

Reduced central drive to breathing may have effects on upper airway patency and stability. Initial reports of upper airway collapse during central apneas have been observed using fluoroscopy.[46] More systematic studies of upper airway calibre during central apneas were performed by Badr et al.[47] In spontaneously occurring central apneas in CSA patients and central apneas induced by hyperventilation in normal subjects using nasopharyngoscopy. These authors confirmed that significant reduction in upper airway calibre was observed during central apneas both in normal subjects and patients. Complete collapse was frequently observed in CSA patients ($n = 4$) and resumption of breathing was associated with persistent narrowing unless arousal occurs. C. Guilleminaut et al.,[48] using fiberoptic techniques, also noted an important decrease in the size of the upper airways (mean decrease in cross sectional area of 71 ± 7 %) during central apneas in the absence of an active contraction of the constrictors of the pharynx. This may predispose susceptible individuals to obstructive events when ventilation restarts with consequences on sleep fragmentation and catecholamine hypersecretion.

CONCLUSIONS

Thus, a possibility exists that recurrent central apneas,

hypoxemia, and arousals from sleep, each of which may be present in CSA and potentially increase sympathoadrenal activity, may actually contribute to create functional morbidity of CSA. This has particular implications in heart failure patients. Recent insights on the pathophysiology of CSA, in addition to our understanding of the mechanisms leading the occurrence of central apneas during sleep, emphasize the role of hyperventilation in the genesis of apneas. Rationalized therapeutic strategies, thus, would aim at reducing hyperventilation or minimizing its consequences on CO_2 depletion. Pharmocological treatment, particularely interacting with catecholamine hypersecretion, would deserve further research in the near future.

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