Clinical Update

Treatment of Cheyne-Stokes Respiration in Patients with Congestive Heart Failure

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Introduction

Cheyne-Stokes respiration is an event observed in patients with cardiopathies and brain/neurological diseases. It affects around 40% of stable cardiopaths with an ejection fraction (EF) < 45%\(^1\). It is a sign of heart failure severity, being associated to an increase in the sympathetic stimulation, which is a known poor prognosis factor in these patients\(^2\). Although it can be observed during the state of wakefulness, its diagnosis is achieved through polysomnography and consists of:

- At least 03 consecutive cycles of an increasing-decreasing alteration in the respiratory range.
- One or both of the following:
  a) Index of central apnea/ hypopnea ≥ 5 per hour.
  b) The increasing-decreasing cyclic alteration of the respiratory range lasts at least 10 consecutive minutes\(^3\) (Figure 1).

The mechanisms that lead to Cheyne-Stokes respiration (CSR) have yet to be completely clarified. It is known that these patients are hypocapnic, which would cause the occurrence of central apnea. Several reasons for this chronic hypocapnia/hyperventilation are speculated: a higher sensibility of the respiratory CO\(_2\) chemoreceptors; low body oxygen stores, leading to respiratory instability and hyperventilation; interstitial pulmonary edema due to high lung capillary pressure. The increase in the circulatory time of patients with congestive heart failure (CHF) is also implicated in the physiopathology of CSR, as the delayed information of the lung

Fig. 1 - Cheyne-Stokes respiration: observe the increasing-decreasing pattern associated to central apnea (absence of abdominal and thoracic effort), leading to a decrease in the oxyhemoglobin saturation and awakening.

Key words

Cheyne-Stokes respiration; heart failure, congestive; hypocapnia.

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PaCO₂ variation to the respiratory chemoreceptors would cause the typical oscillation of this type of respiration⁴.

A research on the subject at MEDLINE showed that Continuous Positive Airway Pressure (CPAP) is the most studied modality (40%). Oxygen therapy comprises 16% of the References. The treatment of CSR aims at fighting hypoxia and the nocturnal awakenings present during the respiration, which increase the sympathetic activity, as well as improving diurnal somnolence and heart function. The therapeutic modalities that will be shown subsequently try to attack one of the probable mechanisms that generate the respiration (Table 1).

**CPAP**

The CPAP has been extensively shown as the therapeutic modality of choice in Sleep Obstructive Apnea/Hypopnea Syndrome, where it has the function of preventing the collapse of the upper airways. However, in CSR, CPAP has other functions. It increases the body oxygen stores² through the increment of the functional residual capacity, in addition to increasing PaCO₂ by decreasing the current volume. By increasing the body oxygen stores of, it reduces the respiratory instability, which is responsible for the respiration variations. The elevation of PaCO₂ impairs the occurrence of central apneas due to the increase in the difference between the patient’s PaCO₂ and the PaCO₂ of the apnea threshold. Krachman demonstrated the effects of the CPAP on body stores of O₂. CPAP diminished the velocity of the oxyhemoglobin saturation decline (dSat/dt) caused by the apneas, a value that correlates negatively with the body oxygen stores³.

The positive pressure in the airways also acts by improving the ventricular function in patients with CHF by decreasing the pre- and post-load.

Naughton demonstrated that CPAP reduces the left ventricle (LV) end-systolic transmural pressure (LVESTMP = systolic pressure of the left ventricle – esophageal pressure) and the product LVESTMP x cardiac frequency (an index of systolic myocardial power generation and O₂ consumption), decreasing the LV load⁵. It has also been demonstrated that cardiopathic patients with CSR have elevated pulmonary venous congestion and interstitial pressure², which causes increased afferent vagal stimulation resulting in hyperventilation. CPAP also fights the interstitial edema.

Due to the fact that many of these patients snore, CPAP can also act by decreasing the airway resistance. In snorers, there is a higher decrease in the pleural pressure and therefore, a higher LV pre-load, which is corrected by making the airways more pervious with CPAP.

Several studies have shown the effects of CPAP on CSR of patients with cardiopathies, by reducing the central apnea/hypopnea index (AHI)²,3,6-12, improving nocturnal oxyhemoglobin saturation (SatO₂)²,6-10,12, decreasing the time of CSR during sleep⁶ and the number of brief awakenings⁶-⁸, increasing the percentage of slow-wave sleep¹⁰,¹¹. Its effects are also maintained during the day as observed in the LV EF improvement²,¹¹,¹², in the NYHA classification of CHF²,5,9,11, in the reduction of diurnal somnolence at the Epworth scale and decreased heart frequency during the state of wakefulness¹¹. It also decreases the sympathetic activity by reducing the concentrations of nocturnal urinary norepinephrine and morning plasma norepinephrine² and decreases the frequency of ventricular arrhythmias¹⁰. It increases the heart transplant free-survival and decreases the mortality/heart transplant rate as shown in a study with more than 2 years of follow-up¹³. As for quality of life, there was improvement in the “Chronic Heart Failure Questionnaire” score regarding the items dyspnea, fatigue, emotional well-bring, and disease domain¹¹.

Not all patients respond to CPAP. Javaheri⁰ found a frequency of only 43% of responders (patients whose AHI decreased to less than 15 per hour). The non-responders had a mean AHI of 62 and the responders, a mean AHI of 36, which shows that more severe patients may not respond to CPAP, probably due to the fact that the latter can lead to a tendency to wake up, promoting respiratory instability due to the more elevated pressures used in these patients. Other studies have found a higher frequency of responders, but they had less severe cohorts⁹.

Contrarily, other authors have shown that CPAP failed to improve CSR¹⁴,¹⁵, or even showed that it can be deleterious for these patients¹⁵. A methodological error that might have contributed to the lack of success of CPAP was the protocol used in pressure adjustment, initiated arbitrarily at 7.5 cmH₂O or higher.

Javaheri⁰ and Naughton et al¹¹ created different ways to titrate the correct pressure, but both are in agreement about starting the titration with a pressure of 5 cmH₂O and increasing the pressure gradually until a value that is tolerable by the patient is reached, trying to achieve between 10 to 12 cmH₂O. Another possible explanation for the absence of beneficial effects is the CPAP evaluation after just one night of use¹². It has been demonstrated that the benefits of CPAP are achieved with time (there is an increase in EF within 1 to 3 months of use) and the pressure level can also be optimized during treatment.

### Table 1 - Effects on respiratory parameters and quality of sleep

<table>
<thead>
<tr>
<th>Time in CSR</th>
<th>SatO₂</th>
<th>AHI</th>
<th>Short awakenings</th>
<th>Sleep efficiency</th>
<th>Slow wave sleep</th>
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<tbody>
<tr>
<td>CPAP</td>
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<tr>
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<td>Theophylline</td>
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CPAP - Continuous Positive Airway Pressure; CSR - Cheyne-Stokes respiration; AHI - apnea/hypopnea index.
Recently, an important multicentric study\textsuperscript{16} that involved 258 patients evaluated long-term use (24 months) of CPAP in cardiopathies. The result, however, was not the expected one. Although it reduced the central apnea index, increased the oxyhemoglobin saturation, improved heart function and reduced the levels of plasma norepinephrine, CPAP failed in demonstrating benefits regarding mortality and transplant-free survival.

In the beginning of the study, the transplant-free survival curve favored the control group, but 12 months later it started to favor the CPAP group, with no statistical difference at the end of the study. These results that did not corroborate the expectations generated by previous studies can be a consequence of more frequent beta-blocker use in comparison to the older ones. The comonctance of CPAP use and beta-blocker has limited the potential to improve the ventricular function obtained with CPAP alone.

An undesirable adverse effect of CPAP is the cardiac output decrease and consequent arterial hypotension, which can be prevented with pressure titration from 5 cmH\textsubscript{2}O and its gradual elevation for days or weeks as tolerated by the patient. Another common complaint is the discomfort caused by the nasal mask.

Another method of ventilation with positive pressure (Bi-level Positive Airway Pressure, BiPAP) was compared to CPAP, but did not show any advantage when compared to the latter, in addition to its very high cost\textsuperscript{14}.

**Oxygen**

The main effects of O\textsubscript{2} on CSR are: increase of body oxygen stores, preventing the instability of arterial gases and the removal of the hypoxic stimulus to hyperpnea allowing the increase of PaCO\textsubscript{2}, augmenting the difference between the patient’s PaCO\textsubscript{2} and the PaCO\textsubscript{2} of the apnea threshold\textsuperscript{21}.

Studies have shown the several benefits of O\textsubscript{2} in CSR: AHI reduction\textsuperscript{18-22}, improvement of the nocturnal SatO\textsubscript{2}\textsuperscript{18-22}, decrease in the mean time of CSR\textsuperscript{18,21} and brief awakenings\textsuperscript{19,20,22}, increase of slow wave sleep\textsuperscript{19,22}, reduction in cardiac frequency during the night\textsuperscript{20}. It did not modify symptoms\textsuperscript{20,21}, but improved a cognitive function parameter: the velocity of information processing\textsuperscript{20}. It reduced the sympathetic activation demonstrated by the decrease of nocturnal urinary excretion of noradrenaline\textsuperscript{23}. There was an increase in peak O\textsubscript{2} consumption at the ergometric cycle test\textsuperscript{20}, which is a strong predictor of mortality; this leads to speculations about the improvement of survival com O\textsubscript{2}. Krachman et al\textsuperscript{18} compared O\textsubscript{2} with CPAP in prospective randomized study with 25 patients and concluded that the two modalities of treatment are equally effective, although in this study CPAP as well as O\textsubscript{2} were used for only one night. As seen before, CPAP effect depends on its long-term use.

The O\textsubscript{2} flow used in these studies varied from 2 to 4 l/min and the response rate to O\textsubscript{2} (percentage of those who had the AHI reduced to < 15 per hour) was 39%\textsuperscript{14}. As with CPAP, the responders were those with milder CSR (lower AHI, milder oxyhemoglobin desaturation and higher PaCO\textsubscript{2}).

**Theophylline**

The mechanism through which Theophylline acts is uncertain. It is known that it inhibits phosphodiesterase, but at the concentrations used for the treatment of CSR, it does not have the inhibitory effect. At therapeutic concentrations, it competes with adenosine in some of its receptors. At the central nervous system (CNS), adenosine is a respiratory depressor and Theophylline has a respiratory stimulation effect as it competes with the first, preventing central apneas.

It has been demonstrated that Theophylline reduced AH\textsubscript{I}\textsuperscript{21,24}, improved nocturnal SatO\textsubscript{2}\textsuperscript{23,24} and decreased total brief awakenings\textsuperscript{24} and those associated with respiratory alterations\textsuperscript{23}. It did not alter sleep efficiency, sleep stages\textsuperscript{23,24}, or LV EF\textsuperscript{23}. Additionally, it did not alter ventricular arrhythmias, suggesting that it is a safe option for these patients. It is important to know that Javaheri et al\textsuperscript{23} used O\textsubscript{2} in patients due to oxyhemoglobin desaturation during examinations and this fact might have contributed to alterations in the results.

The Theophylline doses used were: 200-300 mg/day (4.3 mg/kg\textsuperscript{24}) and 3.3 mg/kg, twice a day\textsuperscript{23}. Its defenders justify its use by mentioning the limitations of other therapeutic modalities: low adherence to CPAP and the possibility of inadvertently dislodging the O\textsubscript{2} cannula during sleep.

**Other options**

1) CHF drug therapy optimization: In fact, this should be the first-choice treatment, as it is the simplest. Walsh et al\textsuperscript{22} demonstrated that patients with stable CHF with the use of furosemide alone, showed increase of slow wave sleep and REM sleep, reduction of HAI and desaturation events, as well as CO\textsubscript{2} increment at the end of the expiration and ventilation reduction a minute after the addition of captopril 75 mg/day for a month. Dark et al\textsuperscript{23} studied patients who were admitted due to heart failure decompensation, showing respiratory pattern abnormalities (predominantly central apnea with CSR) in all of them. After CHF compensation during hospital stay with diuretics, vasodilators, antihypertensive drugs, antiarrhythmic drugs and positive inotropics, a new polysomnography was performed with decrease in AHI and a tendency of SatO\textsubscript{2} improvement.

2) Pacemaker: Left or biventricular pacemaker implant with atrial trigger mode\textsuperscript{26} showed a reduction in AHI and improvement in SatO\textsubscript{2} as well as in the subjective quality of sleep, possibly due to cardiac function improvement. In this study, no patient had a conventional indication of pacemaker.

3) Benzodiazepine drugs: The reason for not using benzodiazepine drugs is the effect of increasing the awakening threshold, as it is a consequence of CSR and can be a perpetuating factor of the problem, due to hyperventilation and hypcapnia, caused by awakening. Studies have shown reduction of the brief awakenings, but no significant decrease in AHI or nocturnal SatO\textsubscript{2}\textsuperscript{27,28}. Special attention should be given to the patients with obstructive apneas, as the benzodiazepine drugs can aggravate them.

4) CO\textsubscript{2}: The use of CO\textsubscript{2} (0.2-1 l/min) mixed with O\textsubscript{2} (2 l/min)
during sleep has been studied, and showed decrease in the duration of CSR and improvement in \( \text{SatO}_2 \), but decreased the quality of sleep and increased the sympathetic activity\(^{29}\). Additionally, the resulting hypercapnia increases the left and right ventricular post-load. Therefore, it must not be indicated for patients with CHF.

5) Adaptive servo-ventilation (ASV): This new ventilatory modality consists of a variable ventilatory support that adapts depending on the phase of the respiration, being higher in apnea and lower in hyperventilation periods. It corrected CSR, objectively reducing the diurnal somnolence, plasma BNP levels (a marker of heart failure severity) and the excretion of urinary metadrenaline\(^{10}\). It improved the quality of sleep (by increasing total sleep time, sleep efficiency, percentage of REM and slow wave sleep and decreasing the brief awakening index) and reduced AHI and desaturations, when compared to controls. There were significant differences in some of these parameters in comparison to CPAP\(^{11}\).

**Conclusion**

Although it is the most studied treatment modality, the use of CPAP in CSR is still controversial and the experience of this treatment in Brazil is still scarce, as CPAP is not provided by the public Health Services and most patients have difficulty to buy it. \( \text{O}_2 \) is an option for patients who are intolerant to CPAP or who cannot use it for any other reason. However, the long-term survival of this treatment modality has yet to be assessed. The other types of treatment reported here need further studies. CSR is a frequent event in cardiopaths and it is associated with a worse prognosis; thus, the correct diagnosis and treatment are of utmost importance.

**References**


