Cheyne-Stokes Respiration and Congestive Heart Failure

Are Oxygen Stores the Critical Factor?

Cheyne-Stokes respiration (CSR) is a pattern of increasing, followed by decreasing, ventilation leading to a period of apnea. CSR is associated with several conditions, including CNS dysfunction, ascent to high-altitude and, as investigated in this issue of CHEST (see page 59) congestive heart failure. Typically, CSR is most obvious during non-rapid eye movement sleep when metabolic control of breathing predominates. The initiation of CSR may depend on a narrow difference between the resting end-tidal CO$_2$ (PETCO$_2$) and the apneic threshold for CO$_2$. This enhances the likelihood that apnea will occur under conditions that favor a decrease in CO$_2$ and an increase in the apneic threshold such as a transient arousal followed by the onset of sleep. As reviewed, once initiated, CSR is maintained, in part, by the interactive effect of fluctuations in CO$_2$ and O$_2$ on central and peripheral chemoreceptors. The increasing ventilation results from progressive elevation of CO$_2$ levels above the apneic threshold plus a progressive decrease in O$_2$. The decreasing ventilation results from a progressive decline of CO$_2$ and increase in O$_2$ due to hyperpnea from chemoreceptor stimulation. As discussed, apnea is then the result of a CO$_2$ level below the apneic threshold possibly combined with little or no hypoxic stimulation. Several factors may make CSR more likely to be present. These include a delayed circulation time from the heart to the respiratory chemoreceptors (eg, from congestive heart failure), chemoreceptors that are overly sensitive to CO$_2$, frequent arousals, various reflexes, upper airway instability, and the interactive effect of an increase in CO$_2$ with a decrease in O$_2$ that is known to produce greater than additive respiratory chemostimulation.

CSR is common in patients with heart failure and appears to occur in approximately 40% of patients with an ejection fraction $< 45%$. For reasons that are not fully defined, patients with CSR associated with congestive heart failure appear to have a higher mortality than those without CSR. In addition, CSR disrupts sleep and can lead to symptoms such as insomnia and daytime sleepiness. Although the pattern of CSR is well established, it is unclear if there are at least two subsets of CSR, one which involves the CNS without any upper airway instability (ie, without potential partial or complete obstruction) and one which is combined with at least the potential for partial or complete upper airway obstruction. This confusion stems, in
part, from several observations including the positive response to continuous positive airway pressure (CPAP), the presence of obstructive apneas and hypopneas in most patients with otherwise classic CSR,2,7 and the observation that many patients with CSR also snore.8 To distinguish between these two subsets is difficult since even intrathoracic pressure measurements to determine respiratory effort may not be able to determine coexistent upper airway instability if there is no respiratory effort during the apnea.

The authors have examined the hypothesis that CSR is improved by increasing body stores of O₂. The hypothesis depends, in part, on the concept that by reducing the degree of hypoxia, the interactive effect of CO₂ and hypoxia will be diminished, leading to reduced stimulation of the respiratory chemoreceptors. The authors and others have previously demonstrated that addition of supplemental oxygen in CSR associated with congestive heart failure reduces the number of CSR episodes.9,10 The current study pursues this hypothesis by attempting to increase O₂ stores in the lung with CPAP by presumably increasing functional residual capacity. The hypothesis is supported by the finding that CPAP of an average of 9 cm H₂O of pressure reduces not only the number of episodes of CSR but also the slope of decline in arterial oxygen saturation during each episode. The authors have made attempts to exclude occult obstructive sleep apnea as a contributor to the reduction in number of CSR events, but the evidence is indirect since no direct measure was made of respiratory effort. Of note, several previous studies have measured respiratory effort by measuring intrathoracic pressure. These studies have documented that there is no obvious respiratory effort during CSR, indicating that the CSR cannot be explained readily by obstructive events. In addition, CSR typically is lessened or ablated during rapid eye movement sleep, a time when obstructive sleep apnea is typically worsened.2

Although the authors’ data support the hypothesis, alternative explanations are possible. As acknowledged by the authors, these include an improvement in cardiac function from CPAP with a decrease in circulation time and/or an increase in CO₂ from CPAP3 so that the CO₂ remains above the apneic threshold. In addition, reversal of occult obstructive sleep apnea may contribute. It is also possible that the pressure of CPAP on the upper airway activates or inhibits a reflex that interacts with the CNS to reduce CSR.

Although improvement in CSR with CPAP has been reported in a number of studies,2,9 this response is not universal.6,11,12 The explanation for this discrepancy is unclear. Explanations may include insufficient time of treatment, insufficient CPAP pressure, and selection of cardiac nonresponders to CPAP,13 such as perhaps those with a low left ventricular end-diastolic pressure2,14 or those without any upper airway instability.

As mentioned, CSR is associated with an increase in mortality in patients with congestive heart failure.5 One hypothesis is that there is a contribution to reduced cardiac function from the repetitive hypoxic episodes.2 If correct, it is possible that prevention of hypoxia will decrease mortality. An expansion of this hypothesis is that treatment of congestive heart failure with CPAP will decrease mortality from a sequence of events that includes afterload reduction on the left ventricle as well as from the favorable effects of reducing hypoxemia. If reduction in CSR alone is the goal, then improving O₂ stores with supplemental oxygen may be sufficient. There is a note of caution in that it appears that the reduction in CSR events may be less compared to CPAP or other forms of positive pressure treatment.15–17 If CPAP improvement in heart function is part of the goal, then CPAP will be necessary. It should be pointed out that the effects of O₂ and CPAP are not mutually exclusive. Both may work to increase CO₂, which may increase the difference between PetCO₂ and the apneic threshold. In addition, oxygen may potentially improve cardiac function by improving oxygen delivery to the heart.

The CPAP hypothesis of treatment is currently being tested in a multicenter trial in Canada.18 The hypothesis being tested includes improvement of cardiac function from CPAP independent of the effect on CSR, and there are two limbs to the trial, CPAP and no CPAP.

The current study supports but does not answer the question posed in the title of this editorial. To explore the question further, it would be necessary to determine if reversal of hypoxia by increasing oxygen stores would improve outcome including mortality and health status in CSR associated with congestive heart failure. To date, this hypothesis has not been tested. In order to better understand the role of O₂ stores in the production of CSR and possible mortality in congestive heart failure, a proper prospective randomized trial of supplemental oxygen vs no oxygen vs CPAP should be undertaken. It is also possible that a combination of CPAP and supplemental O₂ may be needed to realize the full benefits of therapy.

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ENTROPY ISN’T WHAT IT USED TO BE
Applying Thermodynamics to Respiration in Sleep

More years than I would care to admit, a class in thermodynamics was required as part of my undergraduate course of study in electrical engineering. All of us who were both engineering and premedicine students that year chose a particular class given by the chemistry department, since we could satisfy both an engineering requirement and a prerequisite for medical school at the same time, a form of “double-dipping” that was hard to resist. In short order, we realized that learning chemical thermodynamics was not a trivial undertaking, and many of us were fortunate to survive that class with our grade point averages more or less intact. Fast-forward 30-something years, and chaos theory has become the darling of applied mathematics, and a characteristic of chaos called entropy, which is dangerously close to a property taught in that dreaded thermodynamics class, is being used to describe all sorts of physical systems including biological systems. A case in point is the article appearing in this issue of CHEST (see page 80) by Burioka and colleagues reporting on measurements of the approximate entropy (ApEn) of respiration during wakefulness and sleep.

To the layman, chaos means undesired randomness or disorder. In mathematics, chaos theory (also known as dynamical instability) began as the study of the evolution in time of systems that are extremely sensitive to initial conditions. The usual example is how the flapping of a butterfly’s wings in South America can change the weather in Kansas. Chaos theory has evolved into the study of the behavior of physical systems that at first seem entirely random but in fact are not entirely so. Physical systems in general are said to inhabit “phase space,” a multidimensional universe where each point corresponds to a fixed value for every variable describing the system, and the evolution in time of such a system can be described as a path (or trajectory) from one point to another. The physical systems described by chaos theory are deterministic, meaning that if it were possible to exactly quantitate the variables describing one point, the trajectory leading to the next point in a time sequence could be entirely predicted. The basis of dynamical instability lies in the precept that