Cheyne-Stokes respiration in patients with congestive heart failure

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Summary

Cheyne-Stokes Respiration (CSR) is a breathing pattern characterised by rhythmic oscillation of tidal volume with regularly recurring periods of hyperpnoea, hypopnoea and apnoea. CSR is no longer solely regarded as a symptom of severe congestive heart failure (CHF), but has been recognised as an independent risk factor for worsening heart failure and reduced survival in patients with CHF. CSR is associated with frequent awakening that fragment sleep and with concomitant sympathetic activation both of which may worsen CHF. Cheyne-Stokes Respiration is very common in patients with severe CHF and its prevalence may have been underestimated in the past due to technical limitations that precluded respiratory monitoring outside sleep laboratories. Since treatment of CSR appears to be beneficial and safe, patients at risk should be promptly diagnosed and treated. Treatment of CSR has been demonstrated to improve left ventricular ejection fraction and potentially prolongs survival in patients with severe CHF. This article briefly summarises the current knowledge of the patho-physiology, prevalence and therapy of Cheyne-Stokes respiration.

Key words: Cheyne-Stokes respiration; periodic breathing; congestive heart failure; circadian monitoring of respiration; non-invasive ventilation

Introduction

In 1854, Stokes poetically described a breathing pattern that was later named after him and after Cheyne who had previously published a similar description in 1818 [1, 2]: *"The decline in the length and force of the respirations is as regular and remarkable as their progressive increase. The inspiration becomes each one less deep than the preceding, until they are all but imperceptible and then the state of apparent apnoea occurs. This is at last broken by the faintest possible inspiration; the next effort is a little stronger, until so to speak, the paroxysm of breathing is at its height, again to subside by a descending scale ... This symptom, as occurring in its highest degree, I have only seen during a few weeks previous to the death of the patient ..."* Ever since, physicians have looked at Cheyne-Stokes Respiration (CSR) not only as a symptom of severe congestive heart failure (CHF) but also as a bad prognostic sign. In fact, several studies proved the association of CSR with a bad prognosis in patients with CHF. Hanly et al reported the cumulative survival after 2 years to be 86% vs. 56% in patients with lone CHF compared to patients with CHF and CSR [3]. Lanfranchi et al. found the apnoea-hypopnoea index – that is, a measure of the severity of CSR – and the left atrial area to be independent predictors of mortality in severe CHF [4]. CSR becomes more common as CHF worsens. CSR may not just be a marker of the severity of CHF but may also aggravate it. The recurrent cycling of apnoea/hypopnoea and hyperpnoea during CSR can cause sympathetic over-stimulation possibly due to microarousals that occur either at the end of the apnoea when the CO_2-level reaches the apnoea-threshold [5–7] or at the peak of hyperpnoea when the respiratory drive reaches its height [8, 9]. During sleep, CSR causes recurrent awakening and thereby reduces slow wave and REM sleep [10, 11]. The observation that patients with CSR have higher levels of endogenous catecholamines than patients with the same degree of CHF, but without CSR, has sparked new interest in the treatment of CSR [12]. Since sympathetic over-stimulation has a well known harmful influence on CHF and the treatment of CSR has been demonstrated to diminish sympathetic nerve activation [13–16], CSR became a therapeutic target for the treatment of CHF. In fact, there are several small studies that demonstrated a positive influence of the treatment of CSR on heart failure [13, 17, 18]. The markers of sympathetic nerve activation and the arrhythmias that are possibly related to sympathetic stimulation decreased if CSR was successfully treated [19, 20]. Accordingly, treatment of CSR with con-

tinuous positive airway pressure (CPAP) increased left ventricular ejection fraction and survival in a small number of patients with severe CHF awaiting heart transplantation [12, 17, 18]. The most likely effect of CPAP supposedly was to reduce cardiac preload and afterload, as such improving CHF and thereby CSR. Although there is a lack of large randomised controlled trials, the treatment of CSR by such means appears to offer a promising and safe therapeutic supplement for patients with severe CHF. The necessity to adequately diagnose and treat CSR is growing.
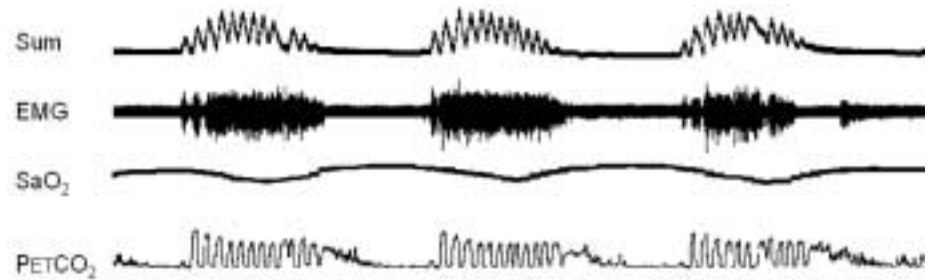
Definition and pathophysiology

Periodic breathing with regular cycling between hyperpnoea and apnoea or hypopnoea is called Cheyne-Stokes Respiration (CSR) (Figure 1). When CSR occurs during sleep, it constitutes a specific type of Central Sleep Apnoea (CSA) [21]. In contrast to the central sleep apnoeas that are accompanied by hypercapnia in the obesity-hypoventilation syndrome, CSR is accompanied by hypocapnia. Since patients with CSR have a low $paCO_2$ that is close to the apnoeic threshold, the high sensitivity of the chemoreceptors for CO_2 seems to play an important role in the generation of respiratory oscillations [7, 22]. When the wakeful drive to breathe is abolished and the apnoeic threshold increases at sleep onset, the inherent instability of respiratory control associated with increased CO_2 sensitivity is revealed and periodic breathing commences. During the hyperpnoeic phase of CSR, $paCO_2$ falls below the apnoeic threshold and breathing stops until $paCO_2$ exceeds the apnoeic threshold again at the end of the period of apnoea (figure 1). Both, the chemical stimulus and the stimulus of the microarousal that often arises at the end of apnoea, initiate the sub-
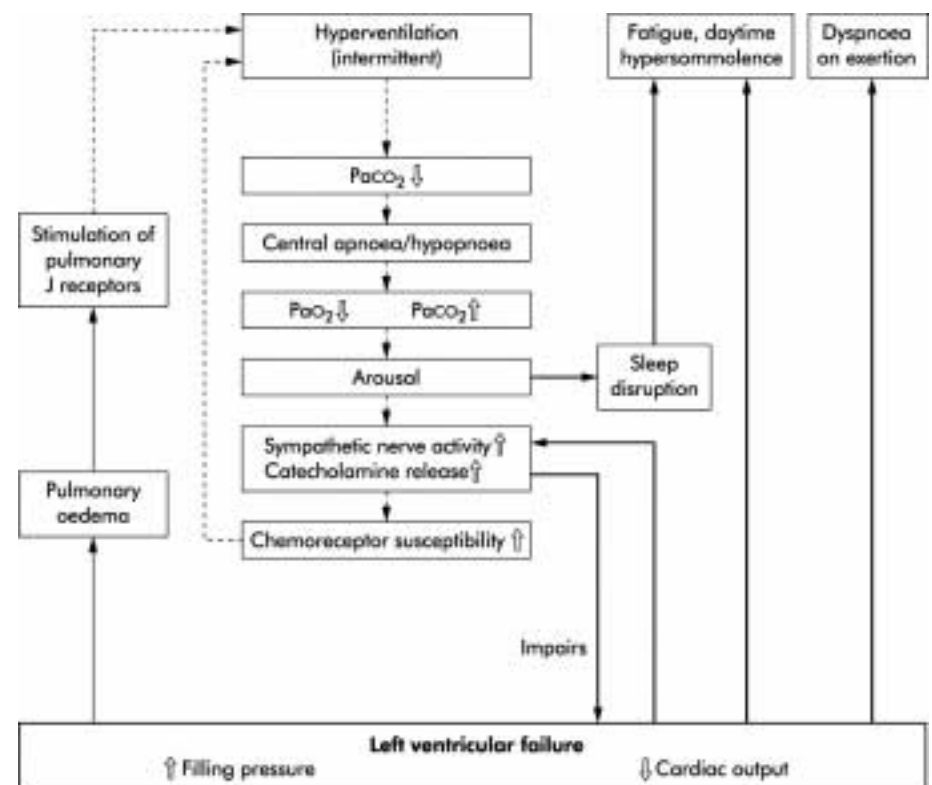
Figure 1

Tracing during 90 sec of Cheyne-Stokes respiration in a patient with congestive heart failure. The top panel shows the instantaneous lung volume (Sum) measured with an inductance plethysmograph. The needle electro-myography (EMG) of the scalene muscle depicts the tonic and phasic activity during the hyperpnoea in opposite to the atony during the apnoea. Oxygen saturation (SaO_2) monitored by pulse oximetry at the ear lobe oscillates between 85% and 95% during apnoea and hyperpnoea, respectively. End-tidal CO_2 ($P_{ET}CO_2$) peaks at 38 mm Hg at the beginning of hyperpnoea and continually decreases to 28 mm Hg before apnoea occurs.

Figure 2

Patho-physiology of Cheyne-Stokes respiration in patients with congestive heart failure (CHF). CHF causes pulmonary congestion and therefore activates pulmonary J receptors which stimulate ventilation. $PaCO_2$ falls below the apnoea threshold and, during the subsequent apnoea, $paCO_2$ raises and paO_2 falls until the apnoea threshold is exceeded. The restart of ventilation coincides with an arousal which also stimulates sympathetic nerve activity (SNA) and catecholamine release. The intermittently released catecholamines and the periodic increases of SNA cause oscillatory surges of heart rate and blood pressure which additionally strain the failing heart and therefore may worsen CHF (Figure from Thorax 2002;57:547–554 [21] with permission from the BMJ Publishing Group).

sequent hyperpnoea; thus, the periodic respiratory oscillations perpetuate themselves [5, 7, 23]. In CHF, the elevated pulmonary capillary pressure and the concurrent pulmonary oedema possibly heighten the sensitivity of the chemoreceptors to CO_2 through stimulation of vascular and pulmonary stretch receptors which can indirectly modulate chemosensitivity with their vagal afferents to the respiratory controller [7, 22, 23]. Pulmonary capillary wedge pressure has been demonstrated to be correlated with the occurrence of CSR while almost all other indicators of CHF are not different between patients with and without CSR [15, 24, 25]. Since Guyton was able to experimentally induce periodic breathing in dogs by inserting long plastic tubes between the proximal and distal carotid arteries [26], the prolonged circulation time of patients with CHF has been suspected to cause CSR through a delayed information transfer of the $paCO_2$ between the lung and the brain stem where the central chemoreceptors

are located [27]. However, several studies have not been able to confirm a close relationship between the prolonged circulation time and the occurrence of CSR in man [15, 21, 24, 25]. Figure 2 illustrates the interactions between the heart and the control of breathing that are likely to be involved in the patho-physiology of CSR as well as its sequelae for sleep and daytime performance [21]. The periodic oscillations of CSR are not limited to respiration but also involve other regulatory circuits of the body so that not only the heart rate, blood pressure and cardiac output but also the cerebral perfusion, EEG-activity, muscle tone, muscle reflexes and pupil size oscillate during CSR [5, 11, 28, 29]. The simultaneous periodic activity of such different physiological systems may indicate that there is a common central pacemaker responsible for the oscillating output to various subordinate regulatory circuits or that the oscillatory output of one system spills over and induces oscillations in other feedback loops [30, 31].
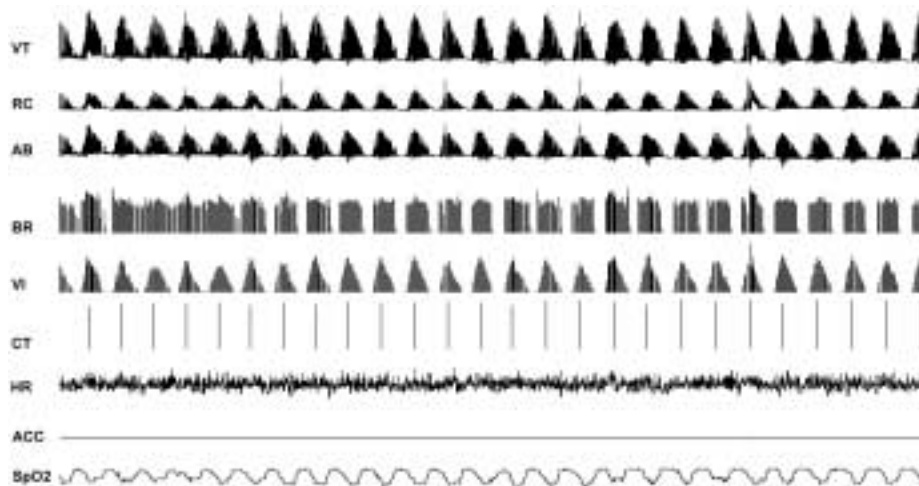
Prevalence and diagnosis

Three recent studies found a prevalence of 55%, 40% and 33% of CSR during sleep based on 47, 81 and 450 patients with severe CHF, respectively [20, 32, 33]. Since unique definitions of CSR and its severity are lacking, data on the prevalence of CSR have to be interpreted with reference to in-

dividually applied definitions. Male sex, waking $paCO_2$ <38 mm Hg, atrial fibrillation, age >60 years and coronary artery disease could be identified as risk factors for the occurrence of CSR [20, 33]. Data on the prevalence of CSR during the daytime and outside sleep laboratories are scant and
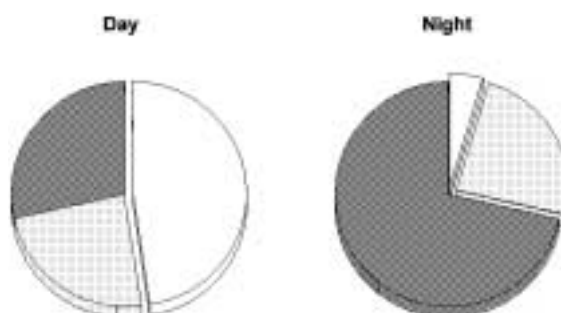
Figure 3

Tracing during 30 min of Cheyne-Stokes respiration in a patient with congestive heart failure. The tracing is part of a 24 h recording obtained in an outpatient with a novel portable monitoring equipment (LifeShirt®, Vivometrics, USA). The tidal volume (VT), ribcage (RC) and abdomen (AB) signals are measured by an inductance plethysmograph. The breath rate (BR) ranges from 0 to 45 breaths/min. Minute ventilation (VI) is extrapolated from VT and BR on a breath-to-breath basis. The cycle time (CT) indicates the length of one CSR cycle that is around 60 sec in this patient. The heart rate (HR) is irregular because the patient has atrial fibrillation. The flat signal of the accelerometer (ACC) shows that the patient is resting. The pulse oximeter at the finger depicts the characteristic oscillations of the oxygen saturation (SpO_2) during CSR (range 97% to 84% SpO_2).

Figure 4

Diurnal and nocturnal prevalence of Cheyne-Stokes respiration in patients with severe CHF (left ventricular ejection fraction <35%). The white area represents patients with less than 5 cycles of CSR/h, the light grey area indicates patients with 5–15 cycles of CSR/h and the dark grey area signifies patients with more than 15 cycles of CSR/h. At a cut-off level of 15 cycles of CSR/h, the diurnal and the nocturnal prevalence of CSR was 28% and 71%, respectively [35].

are based on short term recordings, but CSR was detected in as many as 66% of awake patients who were observed for 30 minutes [30, 34]. In the past, technical limitations precluded long term monitoring of the breathing pattern outside the sleep lab and, hence, the circadian prevalence of CSR is not known. Because of this and because we recognised that CSR has potential prognostic and therapeutic implications, we recorded the breathing pattern of 21 outpatients with a portable light-weight monitoring system (LifeShirt®, Vivometrics, USA) continuously for 24 h (figure 3). This allowed unobtrusive monitoring of the breathing pattern, oxygen saturation and heart rate during the patients' usual activities. We found a diurnal and nocturnal prevalence of CSR of 28% and 71% respectively, in patients with severe congestive heart failure (figure 4) [35].

Therapy

Since the treatment of CHF prolongs survival and CSR is a sequel of CHF, abolishing CSR is primarily a marker of success of the cardiac therapy [36]. None the less, treatment of CSR is beneficial in its own right because of its additional potential for aggravating CHF and because of the sleep disruption that accompanies it. Thus, treatment of CSR aims to enhance the patients' quality of life by improving sleep quality, physical performance and cardiac function. By improving CHF, the therapy of CSR may prolong patients' survival. If CSR persists despite maximal medical therapy aimed at controlling CHF, non-invasive ventilation or delivery of supplemental oxygen, which are the mainstays for the treatment of CSR, should be considered. Theophylline and the inhalation of an air mixture with 3% CO_2 have been demonstrated to diminish CSR in small studies, but both therapies are considered inferior because of their side effects [37, 38]. Theophylline increases arrhythmias through augmented sympathetic activity and CO_2 can cause cerebral vasodilatation and oedema. Recently, atrial overdrive pacing has been demonstrated to eliminate about half the incidence of both obstructive and central apnoea in patients with CHF [39]. This therapeutic approach is under investigation and requires further confirmation in larger trials.

CSR has been treated with several modes of non-invasive ventilation, the most common and best studied being continuous positive airway pressure (CPAP) applied by a nasal mask. CPAP has been found to reduce central apnoea/hypopnoea, circulating catecholamines, sympathetic nerve activation, arrhythmias and atrial natriuretic peptide while it improves left ventricular ejection fraction, mitral regurgitation, sleep quality and quality of life in patients with CHF [13, 17–19]. In a small study of 27 patients with CSR and severe CHF awaiting heart transplantation, CPAP has been shown to decrease the need for transplantation and to prolong survival prior to transplantation by approximately 60% during a median follow-up period of two years; interestingly, CPAP only improved LVEF and mortality in patients with periodic breathing while patients with equally severe CHF without CSR did not benefit from CPAP [18]. A possible explanation for this discrepancy may be that CPAP improves CHF not by decreasing preload and afterload but through its beneficial effects on CSR with consequent reduction in sympathetic nerve activity which is consistently increased in patients with CSR. A large multi-centre study to investigate CPAP as a therapy for CSR in patients with CHF is underway [40]. The mechanism by which CPAP abolishes CSR is not well understood, but the mechanical effect of CPAP on cardiac function is known. CPAP increases intrathoracic pressure that impedes venous return to the right atrium, reduces the end-diastolic volume of both ventricles and hence decreases both preload and afterload [23, 41]. Despite these promising results, CPAP suppresses periodic breathing only in 40% to 60% of patients with CHF and is often not well tolerated [19, 42]. In patients with severe CHF and atrial fibrillation, CPAP has been found to reduce cardiac output so that CPAP should be applied cautiously in this group of patients [43, 44]. Thus, other modes of ventilation such as bi-level positive airway pressure (BiPAP) and adaptive pressure support ventilation have recently been applied for the treatment of CSR. Köhnlein et al. could not find any advantage of BiPAP ventilation over CPAP [45] while Teschler et al found adaptive pressure support to better suppress central apnoea and to improve sleep quality more than CPAP [46].

Supplemental oxygen is also able to suppress CSR, possibly by lowering the respiratory drive through abolition of the hypoxic stimulus to breathe; if the hypoxic stimulus that occurs towards the end of the apnoea is reduced, the subsequent ventilatory response is blunted and the $paCO_2$ may be prevented from falling below the apnoea threshold so that no apnoea will follow [5]. At a rate of 2–4 l/min, oxygen has been reported to diminish CSR in most patients. Krachman et al found oxygen and CPAP to be equally effective for the suppression of CSR in patients with CHF [47]. After 1 week of nocturnal oxygen therapy, Andreas et al found improved exercise capacity, sleep quality and cognitive function while daytime symptoms did not improve in a randomised controlled trial of 22 patients with CHF [48]. After 4 weeks of oxygen therapy, Staniforth et al found a reduction of CSR and of the urinary noradrenaline excretion whilst quality of life and sleep did not improve [49].

Conclusion

Patients with severe congestive heart failure (CHF) frequently suffer from Cheyne-Stokes Respiration (CSR) which disturbs quality of sleep because of the recurrent awakening that accompanies the periodic cycling from apnoea to hyperpnoea; in addition, CSR potentially aggravates CHF through continuing sympathetic nerve activation. Continuous positive airway pressure ventilation (CPAP) and oxygen therapy can abolish CSR with varying success. Both CPAP and oxygen can improve quality of life in patients with severe CHF; in addition, CPAP has been demonstrated to improve cardiac function and possibly even survival of these terminally ill patients. Since abolition of Cheyne-Stokes respiration is a valuable therapeutic aim in itself and is likely to improve congestive heart failure, clinicians should carefully monitor the breathing pattern of patients with severe heart failure and direct therapy to eliminate Cheyne-Stokes respiration.

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