Peer reviewed article

Cheyne-Stokes respiration in patients with heart failure: ominous sign or innocent bystander?

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Summary

Cheyne-Stokes respiration (CSR) during the day and at night is common in patients with severe heart failure. CSR harms the failing heart through recurrent sympathetic overstimulation caused by sleep disturbances and intermittent hypoxia brought about by apnoea and hypopnoea. CSR impairs patients' quality of life and wakefulness, and probably also increases cardiac mortality in patients with heart failure. Thus, CSR should be actively sought in patients with a left ventricular ejection fraction <40%. When CSR persists despite optimal drug therapy for heart failure, non-invasive ventilation, particularly as adaptive servoventilation, and cardiac resynchronisation therapy are currently the most promising treatment options

Key words: heart failure; central sleep apnea; periodic breathing; Cheyne-Stokes respiration

Introduction

First Cheyne, in 1818, and later Stokes, in 1834, described a breathing pattern with alternating apnoea and hyperpnoea in terminally ill patients, a periodic breathing pattern which was later named after them (figures 1 and 2) [1, 2]. The oscillating respiration was viewed as an ominous sign of looming death. Although our knowledge of the pathophysiology of Cheyne-Stokes respiration (CSR) has grown in the past two hundred years, it is widely controverted whether CSR is merely a marker of the severity of its underlying disease or an important factor that independently worsens the underlying condition and therefore requires treatment. CSR most often occurs in patients with congestive heart failure, after stroke or with advanced renal failure. This article focuses on the patho-physiology and therapy of CSR in patients with heart failure, in view of recent evidence that treatment of CSR independently improves heart failure.

Prevalence and importance of heart failure and Cheyne-Stokes respiration

Some 0.5% and 16% respectively of the general population and of people over 75 years suffer from heart failure. Severe heart failure accounts for some 20% of all hospital stays in the elderly and carries a mortality of approx. 45% per year, a figure higher than for most cancers [3, 4]. More than half of patients with a left ventricular ejection fraction of less than 35% display CSR during sleep [5–7]. CSR is diagnosed by a sleep study which reveals more than 15 cycles of alternating hyperpnoea and apnoea per hour; viz. an apnoea-hypopnoea index of ≥15/h [8]. CSR not only occurs during the night but also during the day, since patients with severe heart failure were recently found to breathe periodically during some 10% of daytime [6, 7]. We continuously recorded the breathing pattern in 60 patients with severe heart failure during their usual activities over 24 h at home, and found CSR to peak at 1pm, 5 pm and 3 am [7]. Daytime CSR was associated with higher mortality, while nighttime CSR was not an independent predictor of survival during an observation period of more than two years. In the past, CSR was repeatedly found to predict mortality in patients with heart failure. Hanly et al. reported mortality of 86% and 56% respectively in patients with and

No financial support declared.

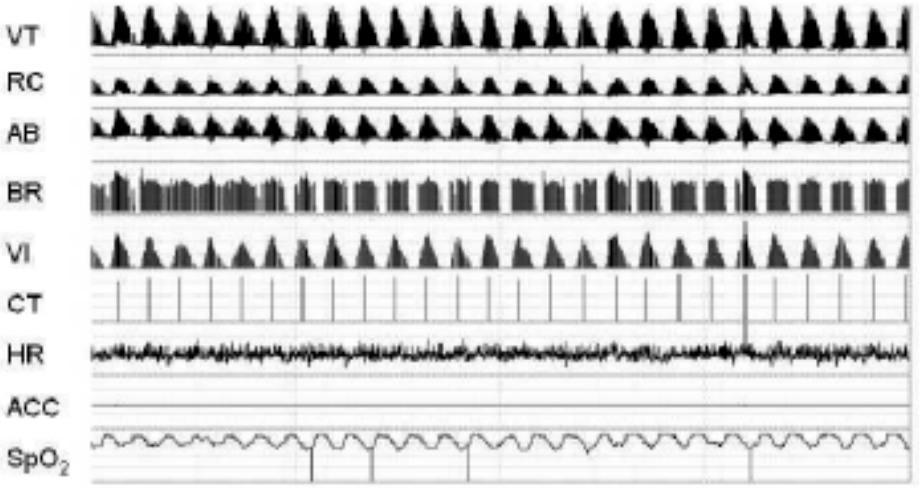

Figure 1

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 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, which is approx. 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 oxygen saturation (SpO_2) during CSR (range 97% to 84% SpO_2).

without CSR during a follow-up of 2 years [9]. Lanfranchi et al. found that the prevalence of CSR combined with the cross-sectional area of the left atrium could predict mortality in patients with heart failure [10]. The association of CSR with a two- to threefold increase in mortality sparked the hope that treatment of CSR would decrease mortality, although other reports questioned an independent association of CSR and mortality in heart failure [11].

Pathophysiology of Cheyne-Stokes respiration

Left heart failure causing increased pulmonary venous pressure is regarded as the source of CSR. Elevated pulmonary venous pressure leads to pulmonary congestion which stimulates the pulmonary stretch receptors, and they in turn heighten sensitivity to CO_2 through their vagal afferents [12–14]. Since CO_2 sensitivity increases, patients begin to hyperventilate and arterial CO_2 ($PaCO_2$) falls until it crosses the apnoea threshold [15]. If chemical control prevails over cortical influence on the respiratory controller, such as typically occurs during sleep, patients become apnoeic until the $PaCO_2$ rises again above the apnoea threshold and the alternating pattern of apnoea and hyperpnoea continues because of the ongoing oscillations of $PaCO_2$ around the apnoea threshold [16, 17]. This periodic respiratory over- and undershoot causes additional sympathetic stimulation in patients who are already sympathetically stimulated through heart failure, and the already stressed myocardium gets even less rest due to CSR [18]. Nocturnal excretion of noradrenaline as a marker of recurring sympathetic stimulation is increased in patients with CSR and their sympathetic overstimulation may further damage the failing heart, e.g. through arrhythmia and ischaemia [19–22].

The respiratory oscillations also influence other physiological systems, with the result that end-expiratory lung volume, blood pressure, heart rate, cerebral perfusion, pupillary size and electroencephalic activity start to oscillate with the same frequency [23–27]. The change from apnoea to hyperpnoea is accompanied by microarousals which disturb the normal sleep pattern [28]. Despite their distorted sleep architecture, patients with CSR

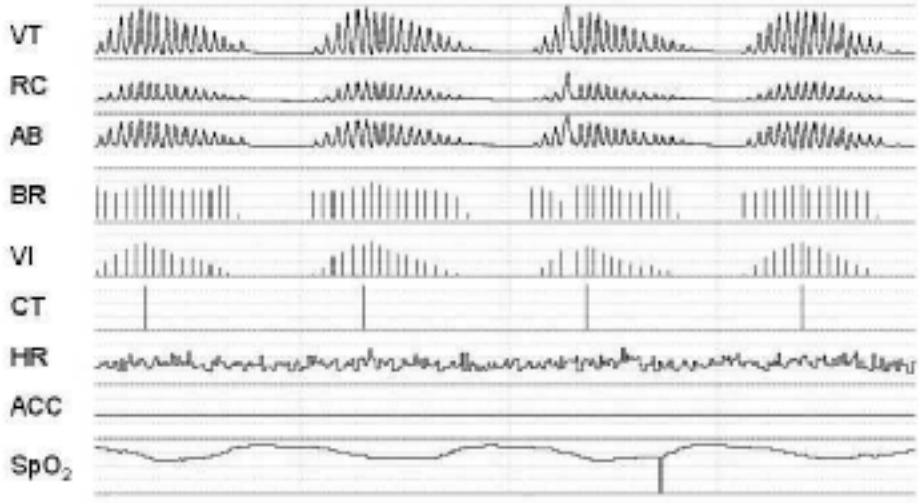

Figure 2

Tracing during 4 min of Cheyne-Stokes respiration from the same patient as in figure 1. Same abbreviations as in figure 1.

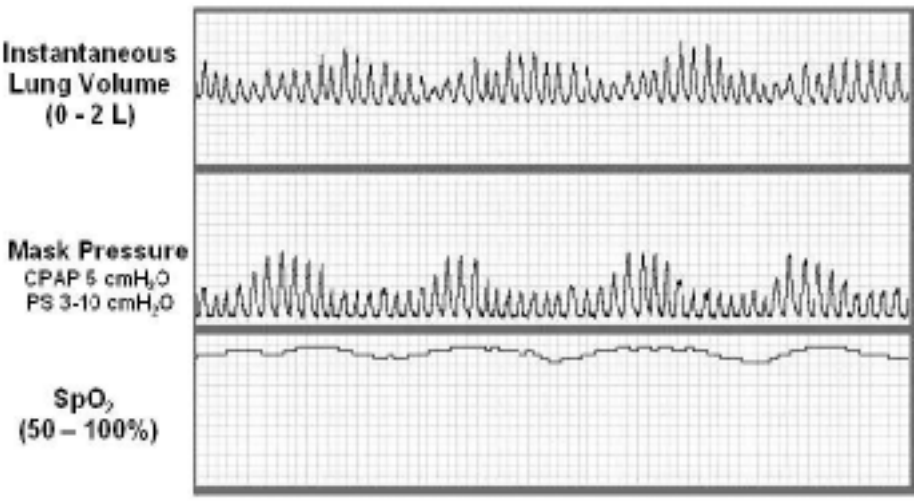

Figure 3

Tracing of 4 min of adaptive servoventilation (ASV) in a patient with Cheyne-Stokes respiration. The top panel depicts the tidal breathing measured by an inductance plethysmograph. The mid-panel shows the mask pressure applied during adaptive servoventilation. Pressure support (PS) is maximal (10 cmH_2O) during hypopnoea and minimal (3 cmH_2O) during hyperpnoea, while end-expiratory pressure (CPAP) remains constant at 5 cmH_2O. Anticyclically supported ventilation smooths the oscillatory breathing pattern and the subsequent oscillations in oxygen saturation (SpO_2).

suffer less from daytime fatigue than patients with obstructive sleep apnoea syndrome (OSAS). In contrast to patients with obstructive sleep apnoea, patients with CSR are very limited in their physical activities due to heart failure, and hence they may experience fewer subjective limitations from fatigue than patients with OSAS. Although their perceived sleepiness as measured by the Epworth sleepiness score was not elevated, a recent report found that patients with CSR remained 1h longer in bed and fell asleep after 17 min during a test of wakefulness (OSLER) compared to heart failure patients without CSR, who stayed awake during the entire 40 min of the test [29].

Recent work confirmed the key role of CO_2 in the pathophysiology of CSR, which appears to be primarily determined by the difference in the prevailing CO_2 and the respective apnoea threshold [30, 31]. Patients with high ventilatory equivalents for CO_2 during exercise testing were particularly prone to CSR since the heightened ventilatory equivalent was an indicator of increased chemosensitivity for CO_2 [32]. The augmented chemosensitivity is probably caused by pulmonary congestion, because the pulmonary capillary occlusion pressure is inversely correlated with $PaCO_2$ during wakefulness [12, 13]. Thus, a high pulmonary wedge pressure causes hyperventilation which predisposes patients for CSR. Other factors predisposing for CSR are age, male sex and atrial fibrillation [33]. Since in about 20% of patients CSR persists in an albeit milder form up to 12 months after heart transplantation, periodic breathing appears to result not only from pulmonary congestion but part of the pattern appears to be learned and engraved in the respiratory controller [34]. It has also become obvious that obstructive and central apnoeas are not strictly different entities but may share a common origin, since the same patient may present with predominantly obstructive apnoeas at the beginning of the night, turning into mainly central apnoeas towards the morning [35]; in addition, the first breath of hyperpnoea often has an obstructive component during CSR [36].

Therapy of Cheyne-Stokes respiration

CSR fuels the vicious cycle of heart failure through recurrent sympathetic overstimulation and intermittent hypoxia, so that the transformation of periodic into regular breathing has been a longstanding aim of cardiac therapy [37]. Primarily, the therapy seeks to exert direct influence on the source of CSR, the failing heart, by improving pulmonary congestion through a decrease in afterload (e.g. with ACE inhibitors) and to lessen the consequences of sympathetic overstimulation through blockade of β1-receptors. If cardiotherapy fails to reverse CSR, the goal of therapy is to directly influence the respiratory controller in order to smooth the periodic breathing [3, 4, 38].

Respiratory stimulants

Theophylline increases respiratory drive and improves myocardial contractility, with the result that periodic breathing decreases, but at the same time the drug doubles the serum concentration of renin, causes arrhythmias and possibly increases the risk of sudden death [39]. In a randomised study of 15 patients, treatment with theophylline over 5 days improved CSR but not cardiac pump function; hence theophylline is not currently recommended as first line treatment for CSR [40].

Acetazolamide is a carboanhydrase inhibitor which causes metabolic acidosis, and this stimulates respiration and reduces periodic breathing by widening the difference between the prevailing $PaCO_2$ and the respective apnoea threshold. In a short randomised trial of 12 patients with heart failure, acetazolamide decreased periodic breathing by 38% and improved daytime sleepiness [41],

but since long-term results are still pending the drug cannot yet be generally recommended, though it may be tried in selected patients under careful supervision.

Oxygen and inhalation of carbon dioxide

Supplemental oxygen suppresses periodic breathing since oxygen blunts the hypoxic respiratory drive and consequent hyperventilation. Under nocturnal oxygen administration over 1–4 weeks CSR was cut by half, nocturnal norepinephrine excretion decreased and oxygen uptake during exercise increased due to improved physical performance, while left ventricular ejection fraction and the patients' quality of life did not improve [42–45]. Thus, and in the absence of large-scale trials, oxygen cannot be generally recommended for the treatment of CSR. Additionally, it is suspected that supplemental oxygen causes cardiovascular damage through the accumulation of free radicals [46].

Inhalation of supplemental CO_2 or addition of artificial dead space interrupts CSR by permanent elevation of $PaCO_2$ above the apnoea threshold [47–50]. In a recent trial including 6 patients without heart failure, Thomas et al. found the addition of computer controlled CO_2 at an inspiratory concentration of 0.5 to 1% through a CPAP circuit to be highly effective in treating CSR [51]. Since increased $PaCO_2$ can cause sympathetic stimulation, and because trials on long-term effects of CO_2 augmentation are lacking, this therapy remains experimental.

Pacemakers and cardiac resynchronisation therapy

Atrial overdrive pacing was reported to reduce CSR in patients with heart failure, but several consecutive studies failed to reproduce these results [52–55]. Cardiac resynchronisation with biventricular pacemakers has been repeatedly reported to more than halve CSR in patients with severe heart failure and ventricular asynchrony. Cardiac resynchronisation therapy has also been shown to improve sleep quality, quality of life and cardiac pump function, and thus this albeit very expensive therapy should be evaluated in patients with severe heart failure [56, 57]. Cardiac resynchronisation with a biventricular pacemaker is limited to a subgroup of patients with ventricular asynchrony due to conduction abnormalities.

Non-invasive ventilation

Over the past ten years, continuous positive airway pressure (CPAP) ventilation has repeatedly been shown to reduce CSR, to improve left ventricular function and to decrease nocturnal norepinephrine excretion in patients with heart failure [19, 58]. CPAP increases intrathoracic pressure, which decreases both afterload by lowering transmural cardiac pressure and preload by lowering venous return, with the result that cardiac function improves in patients with high ventricular filling pressure [59]. In a randomised trial involving 66 patients over 5 years, CPAP improved left-ventricular ejection fraction by 7% and decreased the combined rate of mortality and transplantation in the group of 29 patients with CSR, while the 37 patients without CSR did not benefit from CPAP [60]. On the basis of these results, a large randomised multicenter trial comprising 258 patients with heart failure and CSR was performed in Canada (CANPAP) [61] in which 128 patients were treated with CPAP and compared with 130 matched patients without CPAP therapy. CPAP reduced CSR, improved nocturnal oxygen saturation, enhanced left-ventricular ejection fraction by 2%, reduced nocturnal norepinephrine excretion and also prolonged 6 min walking distance. Despite all these advantages of CPAP therapy, the treated patients had shorter transplant-free survival than untreated patients during the initial 18 months of the trial; after 18 months, survival was similar for both groups. The trial was prematurely terminated because of higher mortality among the treated patients, while mortality of the untreated patients and patient recruitment were unexpectedly low. The converse effect of CPAP on mortality compared to the promising pilot study was explained by the improvement in drug treatment of heart failure in recent years. The addition of betablockers, which had become a mainstay of heart failure therapy in the period between the pilot study [60] and the CANPAP trial [61], may have lessened the harmful influence of CSR and its consequent sympathetic overstimulation of the failing heart. Other reasons for the divergent results of the CANPAP trial compared to the preceding study may be the lower compliance of patients with CPAP (4.3 vs 5.6 h/d), the lower CPAP pressure (8 vs 10 cmH_2O) and the lack of statistical power of the CANPAP trial because of the unforeseen low mortality of the control group [38]. As a result of the CANPAP trial, CPAP can no longer be viewed as standard therapy of CSR, though CPAP may still be beneficial in a subgroup of patients with high (>12 cmH_2O) left-ventricular filling pressure and without atrial fibrillation [62, 63]. Henceforth CPAP therapy for CSR due to heart failure should only be tried in judiciously selected patients and under close monitoring.

The disputed benefit of CPAP for the treatment of CSR and the patients' problems with CPAP compliance have spawned interest in alternative modes of non-invasive ventilation. While CPAP operates on the same pressure level during expiration and inspiration, pressure support ventilation (PSV) operates on lower pressure during expiration and higher pressure which actively supports inspiration. Contrary to CPAP, pressure support ventilation offers the option of ventilating the patient during apnoea and supporting respiration during hypopnoea. Two modes of pressure support ventilation are applied for the treatment of CSR: bilevel positive airway pressure (BiPAP) operates with constant pressure support during inspiration

while adaptive servoventilation (ASV) supports inspiration minimally during hyperpnoea and maximally during apnoea, with the result that, on the basis of sophisticated algorithms, pressure support acts anticyclically to the cycles of CSR (figure 3). In some small studies [64, 65], BiPAP ventilation was somewhat better in suppressing CSR than CPAP, but only ASV improved sleep quality more than CPAP and one small trial even demonstrated an increase in left-ventricular ejection fraction during ASV compared with CPAP [66–68]. Since patients with CSR often do not suffer greatly from their daytime sleepiness, compliance with non-invasive ventilation is often low and therefore the recent finding that compliance with ASV was 2 h/d higher than with CPAP is very important [68]. Although large-scale trials are lacking, ASV currently appears to be the most promising mode of ventilation for the treatment of CSR.

Conclusion

More than half of patients with severe heart failure breathe periodically during sleep. Since the treatment of Cheyne-Stokes respiration has been shown to improve cardiac function and quality of life, physicians should actively pursue diagnosis and treatment of periodic breathing in patients with heart failure. CSR clearly harms the failing heart, but the independent impact of CSR on mortality is disputed. Proof that treatment of CSR lowers mortality is also awaited, but CSR should nevertheless be treated in order to combat the debilitating symptoms of severe heart failure. Large randomised controlled trials are needed to define the long-term effects on morbidity and mortality of adaptive servoventilation and cardiac resynchronisation therapy in patients with severe heart failure and Cheyne-Stokes respiration.

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