Adv Exp Med Biol - Advances in Internal Medicine
DOI 10.1007/5584_2018_146

Central Sleep Apnea with Cheyne-Stokes Breathing in Heart Failure – From Research to Clinical Practice and Beyond

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Abstract

Characterized by periodic crescendo-decrescendo pattern of breathing alternating with central apneas, Central sleep apnea (CSA) with Cheyne-Stokes Breathing represents a highly prevalent, yet underdiagnosed comorbidity in chronic heart failure (CHF). A diverse body of evidence demonstrates increased morbidity and mortality in the presence of CSB. CSB has been described in both CHF patients with preserved and reduced ejection fraction, regardless of drug treatment. Risk factors for CSB are older age, male gender, high BMI, atrial fibrillation and hypocapnia.

The pathophysiology of CSB has been explained by the loop gain theory, where a controller (the respiratory center) and a plant (the lungs) are operating in a reciprocal relationship (negative feedback) to regulate a key parameter (partial pressure of carbon dioxide (pCO_2)). The temporal interaction between these elements is dependent on the circulatory delay. Increased chemosensitivity/chemoresponsiveness of the respiratory center and/or augmented ascending non- CO_2 stimuli from the C-fibers in the lungs (interstitial pulmonary edema), overly efficient ventilation when breathing at low volumes and prolonged circulation time are involved. An alternative hypothesis of CSB being an adaptive response of the failing heart has its merits as well. The clinical manifestation of CSB is usually poor, lacking striking symptoms and complaints. Witnessed apneas and snoring are infrequently reported by the sleep partner. Sometimes patients may report poor sleep quality with frequent awakenings, paroxysmal nocturnal dyspnea and frequent urination at night. Standard instrumental and laboratory studies, performed in CHF patients, may present clues to the presence of CSB. Concentric remodeling of the left ventricle and dilated left atrium (echocardiography), high BNP and C-reactive protein levels, increased ventilation-carbon dioxide output ($VEVCO_2$) and lower end-tidal CO_2 (cardiopulmonary exercise testing), reduced diffusion capacity (pulmonary function testing) and hypocapnia (blood-gas analysis) may indicate the presence of CSB.

CSB and cardiovascular disease are probably linked through bidirectional causality. Cyclic variations in heart rate, blood pressure, respiratory volume, partial pressure of arterial oxygen (pO_2) and pCO_2 lead to sympathetic-adrenal activation. The latter worsens ventricular energetism and survival of cardiomyocytes and exerts antiarhythmogenic effects. It causes cardiac remodeling,

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potentiating the progression and the lethal outcome in CHF patients. Several treatment modalities have been proposed in CSB. The most commonly used are continuous positive airway pressure (CPAP), adaptive servoventilation (ASV) and nocturnal home oxygen therapy (HOT). Novel therapies like nocturnal supplemental CO_2 and phrenic nerve stimulation are being tested recently. The current treatment recommendations (by the American Academy of Sleep Medicine) are for CPAP and HOT as standard therapies, while ASV is an option only in patients with EF > 45%. BPAP (bilevel device) remains an option only when there is no adequate response to previous modes of treatment. Acetazolamide and theophylline are options only after failing the above modalities and if accompanied by a close follow-up.

Keywords

Heart failure · Cheyne-Stokes breathing · Central sleep apnea · CPAP · Home oxygen therapy · Loop gain · Pathophysiology · Controller gain · Plant gain · Circulatory delay

1 Historical Perspective

In 1818 Dr. John Cheyne (1818) published a paper "A case of Apoplexy", where he described a specific breathing pattern which he monitored in a patient, suffering from heart failure and a neurologic disorder, without linking it to a specific etiology. Thirty-six years later, in 1854, Dr. William Stokes (1854) published a description of a disturbed breathing pattern in a patient with a "fat degeneration of the heart" and aortic valve defect, emphasizing the role of the cardiac disorder. These two papers present the first scientific description of the periodic breathing, which later became well-known as Cheyne-Stokes breathing.

Despite almost 200 years of history, at present the CSB invokes a vivid contrast between its high social-economic and medical value and still insufficient understanding and recognition of the problem. Its importance is defined by the high prevalence (of heart failure and CSB) among the population, as well as by the negative impact it may imply on the prognosis of heart failure.

2 Definition

Central sleep apnea (CSA) with Cheyne-Stokes Breathing (CSB) is the most common of 8 types of central sleep apnea, according to the newest version of the international classification of sleep disorders (ICSD-3) (AASM 2014). It is usually associated with chronic heart failure (CHF).

Shorter cycle length indicates a different type of CSA (AASM 2014). A typical representation of CSB is shown on Fig. 1. Alternatively, CSB may present with central hypopneas, instead of apneas.

> CSB is characterized with periodic crescendo-decrescendo pattern of breathing alternating with central apneas with a cycle length > 40 s (most commonly 45–60 s). (AASM 2014)

3 Diagnostic Criteria (ICSD-3) (AASM 2014)

According to ICSD-3, the diagnosis CSA with CSB should satisfy the following criteria: the presence of symptoms (A) OR atrial fibrillation/flutter, congestive heart failure, or a neurologic disorder (B) AND specific polysomnography (PSG) characteristics (C) AND the disorder is not better explained by another cause (D).

The symptoms criterion (A) includes one or more of the following: sleepiness; difficulty initiating or maintaining sleep, frequent awakenings, or non-restorative sleep; awakening short of breath; snoring; witnessed apneas.

PSG findings (C) should present ALL of the following: >5 central apneas and/or central hypopneas per hour of sleep; central events are >50% of all events; the pattern of ventilation

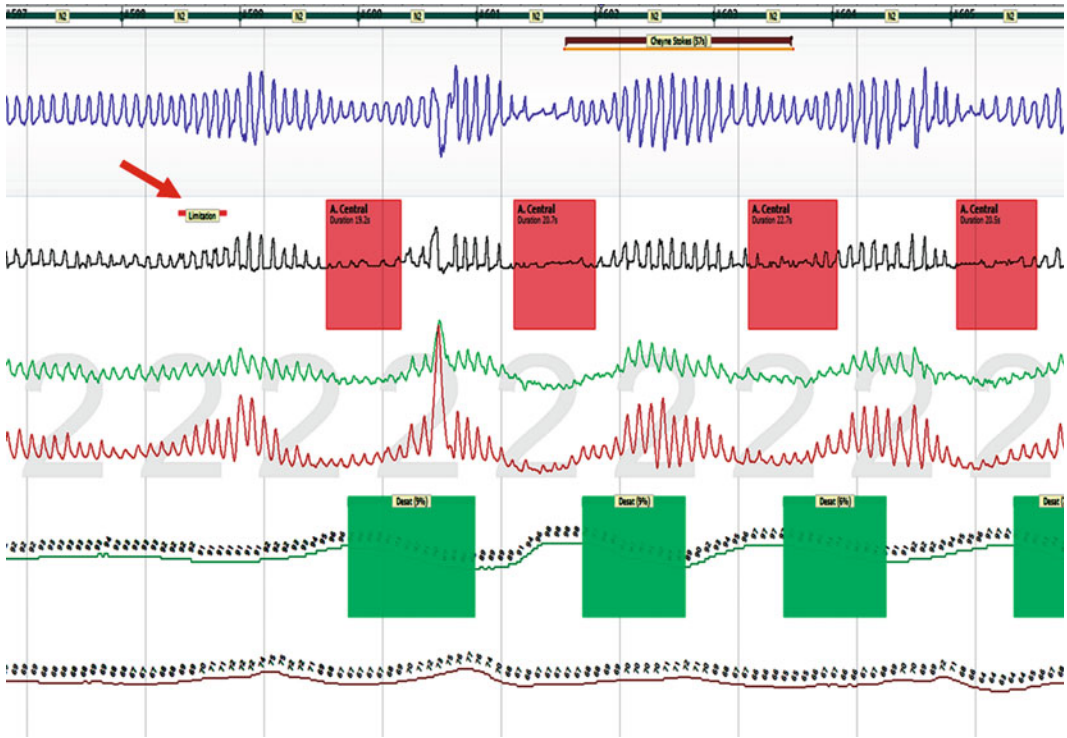

Fig. 1 A typical presentation of CSB. 5-min sample of the "ventilatory part" of a polysomnography (thermistor, nasal cannua, thoracic and abdominal belts, oxygen saturation, heart rate – from top to bottom). Crescendo-decrescendo pattern of ventilation is observed, mirrored by respective fluctuations in effort and followed by desaturations. The length of a single cycle is about 55 s falling within the definition for CSB. Similar variability in heart rate is observed. One may notice the flattening of the nasal flow (red arrow), preceding the start of the CSB sequence
Legend: *CSB* Cheyne-Stokes breathing

meets criteria for CSB. PSG findings are defined according to the newest AASM criteria (Berry et al. 2012; Iber 2007).

An important remark is that the diagnosis CSA with CSB does not exclude the diagnosis OSA (AASM 2014).

4 Prevalence

The prevalence of CSB in CHF is strikingly high, but the condition is being seriously underdiagnosed. Though, a big body of data in support of that has been accumulated, the numbers reported by different studies are varying in a wide range due to the lack of coherence in the methodology, population characteristics (severity of HF, medication therapy, atrial fibrillation, body-mass index (BMI), age), diagnostic and severity criteria, scoring criteria, etc. The difficulties in differentiating central from obstructive hypopneas (Krawczyk et al. 2013) and the frequent coexistence of central and obstructive events in a single CHF patient (Javaheri et al. 1998; Sin et al. 1999; Tkacova et al. 2006) may explain the discrepancy in the ratio OSA/CSA in these studies. The most important of them are presented on Fig. 2.

Furthermore, elements of Cheyne-Stokes breathing pattern with a gradual increase and decrease of ventilation may be present during obstructive events (Tkacova et al. 2006). Tkacova et al. hypothesize that both breathing disturbances are a part of a vicious cycle, involving cardiovascular, pulmonary and autonomous mechanisms, contributing to the progressive heart decline. In general, the obstructive events are concentrated during the first half, while the

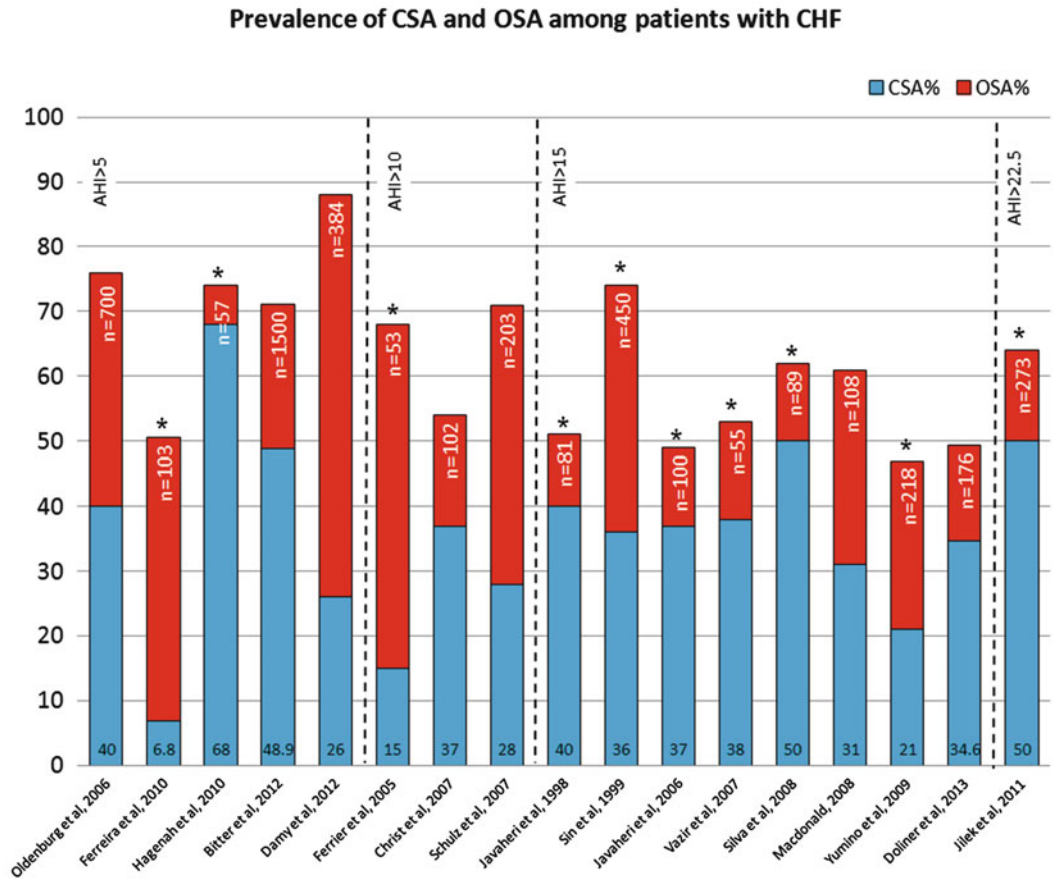

Fig. 2 Prevalence of CSA and OSA among patients with CHF (Javaheri et al. 1998; Sin et al. 1999; Oldenburg et al. 2007; Ferreira et al. 2010; Hagenah et al. 2010; Bitter et al. 2012; Damy et al. 2012; Ferrier et al. 2005; Christ et al. 2007; Schulz et al. 2007; Javaheri 2006a; Vazir et al. 2007; Silva et al. 2008; MacDonald et al. 2008; Yumino et al. 2009; Dolliner et al. 2013; Jilek et al. 2011)
Legend: *CSA* central sleep apnea, *OSA* obstructive sleep apnea, *CHF* chronic heart failure, *AHI* apnea-hypopnea index
Blue bars represent CSA frequency in % (shown as a number at the bottom of the respective bar) of the total number of CHF patients (n = at the top of each bar) in the study (indicated below). Red bars stand for OSA frequency. Combined bar height (blue + red) corresponds to the frequency of sleep disordered breathing in each study. * indicates polysomnography (gold standard study), while its absence – polygraphy (no sleep data). The studies are grouped (vertical dotted line) by the AHI threshold for diagnosing sleep apnea.

central events – during the second half of the night (Tkacova et al. 2001). The shift OSA-CSA is accompanied by a decrease in the arterial partial pressure of CO_2 (pCO_2), increase in the circulation time and duration of periodic breathing cycles. The inversed relation between the latter and the cardiac output (Hall et al. 1996) suggests that the shift from OSA to CSA within a single night is associated with an analogical impairment of the cardiac function, characterized by an increase in the left ventricular filling pressure and a decrease in the cardiac output (Tkacova et al. 2006). The increased venous return due to the rostral fluid shift in supine position is probably a significant contributor to that effect.

5 Etiology

By definition (AASM 2014) CSB has been linked to the presence of CHF.

However, a significant proportion of the CHF patients do not develop CSB. Several risk factors for its occurrence have been identified so far.

1. Age

Patients with CHF and CSB are generally older than CHF patients without the disorder (Bitter et al. 2012; Ancoli-Israel et al. 2003; Javaheri et al. 2017). However, in the study of Bitter et al. CSA regression analysis excluded age as an independent risk factor (Bitter et al. 2012).

2. Gender

Male gender was determined as an independent risk factor for CSA in a large study on 1506 patients with CHF (Bitter et al. 2012). The reasons for gender differences have not yet been fully understood.

Central events usually appear in light sleep, at the wake-sleep transition and especially after an arousal or sleep phase change (Sahlin et al. 2005). Relatedly, males have been found to have a more fragmented and unstable sleep, decreased amount of slow-wave sleep and increased number of wake-sleep transitions, as compared to women (Silva et al. 2008), (Hume et al. 1998). Additionally, central events are usually triggered by a phenomenon, causing hyperventilation hypocapnia, such as an obstructive apnea (Tkacova et al. 2001, 2006; Yumino et al. 2009; Naughton and Lorenzi-Filho 2009). Therefore, the higher prevalence of OSA in men (Young et al. 1993) may contribute significantly to the higher prevalence and severity of CSA in male patients with CHF. The androgens are known to stimulate the deposition of fat in the truncus and the neck region, but also modulate muscle tone of the upper airways during sleep (Phillips and Ancoli-Israel 2001).

Dai Yumino et al. reported approximately 2.5 times higher prevalence of both OSA and CSA in men in a study of 218 stable CHF patients, despite the insignificant differences in BMI, EF and New York Heart Association (NYHA) class (Yumino et al. 2009). Javaheri et al. also reported higher prevalence of CSA with higher obstructive AHI in men (Javaheri et al. 2017).

3. Race and genetic factors

Race has not been found to influence the prevalence of CSB among CHF patients (Javaheri et al. 2017).

Though gene-dependent development of the respiratory center, influencing its functionality and proneness to periodic breathing under provocation (hypoxia, hypocapnia) has been supposed to play a role in CSB generation (Champagnat et al. 2009), studies showing involved genes are scarce and in limited populations (Wang et al. 2016).

4. Anthropometric parameters

Obesity is a classic risk factor for OSA, both in the general population and among CHF patients (Bitter et al. 2012). It could be speculated, that obesity might be among the risk factors for CSA, taking into account the influence of adipokines on respiratory control (Cundrle et al. 2014) and the fact, that obstructive events might trigger CSA in predisposed subjects (Tkacova et al. 2001, 2006; Yumino et al. 2009; Naughton and Lorenzi-Filho 2009).

Neck circumference is a simple anthropometric parameter, used for OSA prediction. As White et al. suggested, it is influenced by the rostral fluid shift during the night, commonly observed in CHF patients. However, the latter affects the lungs as well, increasing pulmonary congestion, which is a part of CSA pathophysiology. Thus, enlarged neck size, although not directly associated with the development of CSA, may be a potentiating factor (White and Bradley 2013).

5. Atrial fibrillation

The relationship between atrial fibrillation (AF) in CHF and presence of CSA has been proven (Sin et al. 1999; Bitter et al. 2012). The association is probably bilateral, since AF may be both a cause and a consequence of CSA, mediated

by circulatory delay and sympathetic-adrenal activation, respectively.

6. Hypocapnia

Hypocapnia is a significant risk factor for CSB in CHF. CO_2 levels in arterial blood were lower in the presence of CSA in the majority of the studies (Bitter et al. 2012; Christ et al. 2007; Szollosi et al. 2008; Bradley et al. 1992). These findings are in consent with the loop gain theory as a mechanism underlying CSB (Lorenzi-Filho et al. 1999; Bradley and Floras 1996; Bradley et al. 2001; Leung and Bradley 2001). Accordingly, nocturnal CO_2 application corrects the disturbance (Lorenzi-Filho et al. 1999; Xie et al. 2002; Andreas et al. 1998; Khayat et al. 2003). It should be noted, however, that the reported data suggest that the majority of the patients with CSA in these studies were nevertheless normocapnic ($pCO_2 > 35$).

7. Others

Low **leptin** concentrations were found in CHF patients with CSA (Cundrle et al. 2014) and subsequently demonstrated as a risk factor for its presence (Cundrle et al. 2017).

Smoking (pack-years) was more prevalent among CHF patients with CSA in 1 study (Javaheri et al. 2017). However, it is not clear if it is a risk factor or an associated factor.

Treatment

Although, as discussed below, the severity of CHF (as measured by NYHA class and ejection fraction (EF)) does not significantly differ between patients with and without CSA (Bitter et al. 2012; Christ et al. 2007; Vazir et al. 2006; Arzt et al. 2003; Meguro et al. 2005), applying contemporary and adequate medication therapy is the important first step towards CSA treatment in these patients. Diuretics and angiotensin-converting enzyme inhibitors reduce the ventricular pre- and afterload and improve the cardiac output (Walsh et al. 1995) and beta-blockers blunt the excessive sympathetic activation effects (Tamura et al. 2007), and therefore could diminish to a certain extent the severity of CSA (Solin et al. 1999). Nevertheless, no differences in the medication profile of the patients with or without CSA were found in the study of Bitter et al. on 1500 CHF patients with optimal treatment (Bitter et al. 2012). The same results were reported in another study on 700 patients (Oldenburg et al. 2007).

6 Pathophysiology of CSB

6.1 Control of Breathing According to the Loop Gain Theory

Control of breathing has been explained by the loop gain theory. Loop gain (LG) is the engineering term describing a system with negative feedback control by quantitative assessment of its (in) stability. LG is a product of the controller gain (CG) and the plant gain (PG) and their temporal interaction (time delay). CG describes the controller response to a certain change ($y = f(x)$) and PG is the resultant effect on the amplitude of the controlled parameter ($x = f(y)$). If LG > 1 the system is unstable due to repeating overshoot/undershoot (the corrective response leads to oversized effects, surpassing the initial changes and creating an abnormal imbalance in the opposite direction). On the other hand, LG < 1 is characteristic to a stable system, reacting with a moderate response to a certain change. It is important to understand that a very small response would not destabilize the system, but rather would need prolonged period of time to restore the equilibrium. The time delay influences the size of the overshoot/undershoot in the first scenario and the time to equilibrium in the second, thus also playing an important role.

Translated to the control of breathing, the controller gain represents the magnitude of the breathing drive produced by the respiratory center with respect to the pCO_2, the plant gain is the efficiency of the lungs to eliminate CO_2 and time delay is the lung-to-chemoreceptor time, a.k.a. circulatory delay (Fig. 3).

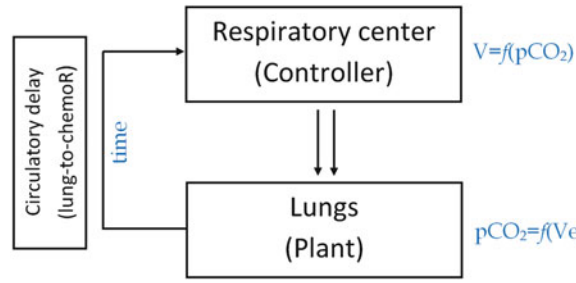

Fig. 3 Components of the loop gain in breathing

The main component of the CG is the chemosensitivity of the respiratory center, i.e. the slope of the function $V = f(pCO_2)$. Significant inter- and intrapersonal variability in the CO_2 sensitivity (Moore et al. 1976; Mountain et al. 1978; Weil 1984; Saunders et al. 1976; Kawakami et al. 1984) has been described with the exact mechanisms behind it still unclear (Orr et al. 2017). An important factor that may influence it is hypoxia (Lloyd et al. 1958). Chemosensitivity represents the "metabolic" control of breathing and may be termed also intrinsic gain. This intrinsic gain is modified by factors such as the upper airway patency to produce the chemoresponsiveness (Orr et al. 2017). One may think of chemosensitivity and chemoresponsiveness as the desired and the actually executed command.

This type of exclusively metabolic breathing control is typical during sleep (Naughton and Lorenzi-Filho 2009), but is not sufficient to respond adequately to various physiologic states and activities during wakefulness (talking, singing, exercising, etc.). Therefore, in addition to the intrinsic gain, other factors, such as the wakefulness/arousal ventilatory drive and conscious cortical overdrive of breathing (descending control) are important for the cumulative CG. Additionally, ascending non-CO_2 stimuli from the C-fibers in the lungs are also an important modulator of the respiratory center, especially under pathologic conditions (Naughton and Lorenzi-Filho 2009; Wellman and White 2011).

The plant gain describes the efficiency of the ventilation to eliminate CO_2 and more specifically the change in pCO_2 in response to executing the ventilatory command ($pCO_2 = f(V)$). It has been shown that lower functional residual volume (FRC) is less effective in terms of buffering of CO_2 changes, thus increasing the PG (Szollosi et al. 2008; Khoo et al. 1982).

As it may be seen (Fig. 3), the PG and the intrinsic part of the CG are in reciprocal relationship. To better illustrate the loop gain mechanism, PG and CG may be plotted on a single graph by inverting the axes of the PG, which would produce the metabolic hyperbole (Fig. 4).

The crossing point between the CG and the metabolic hyperbole is the "static" equilibrium point of the ventilation and pCO_2 if breathing was solely under metabolic control. However, due to the wakefulness drive (WD) it is shifted to the left (at lower pCO_2). Other non-CO_2 stimuli may additionally contribute to that effect. The intersection between the CG and the 0X axis corresponds to $V = 0$ and a pCO_2 level known as apneic threshold (AT). Once, the actual pCO_2 falls below the AT, cessation of breathing occurs. The angle between the CG and the 0X axis corresponds to the chemosensitivity. The steeper the slope is, the greater are the changes in the ventilatory drive per unit of pCO_2 (CG) invoking greater changes in pCO2 at the lungs (metabolic hyperbole). The position at the metabolic hyperbole at which the same changes in the ventilation occur would differently impact the pCO_2 levels due to the non-linear function of the metabolic hyperbole (almost linear in the section around normal pCO_2 and much steeper in the hypocapnic region). Finally, the V/pCO_2 equilibrium in the control of breathing is "dynamic", rather than static and at any given moment is gravitating around the intersection (in blue),

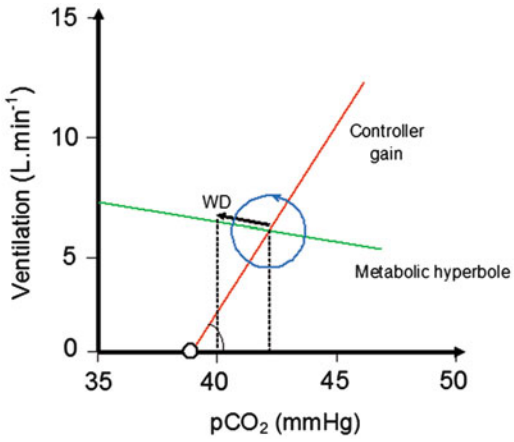

Fig. 4 Control of breathing, according to the theory of loop gain (Modified after Wellman and White 2011)

with the radius of the circle corresponding to the circulatory delay (arbitrary units). Thus, longer circulatory delay would produce greater deviations from the intersection point.

Significant changes in the control of breathing occur during wake-sleep transitions having important implications to periodic breathing. Under normal conditions the eupneic pCO_2 increases by 3–6 mmHg (withdrawn WD), and the AT decreases to prevent breathing pauses (Xie et al. 2002). The cortical descending control during wakefulness supports the breathing even if pCO_2 is below the AT (Khoo et al. 1982; Bradley and Phillipson 1992; Skatrud and Dempsey 1983; Phillipson 1978), while its absence during sleep would result in a central apnea under these circumstances. As a result of the apnea, the pCO_2 gradually increases and after surpassing the AT, the breathing and the equilibrium is restored. If, however, this is accompanied by a (micro)arousal, the momentary level of pCO_2 is relatively hypercapnic for the AT (swiftly changing to levels corresponding to wakefulness). As a result, a fast increase in ventilation, corresponding to the hyperpneic phase of the periodic breathing follows (Xie et al. 1994).

6.2 Causes of CSB in Patients with CHF, According to the Loop Gain Theory

CSB occurs due to increased LG as a result of increased CG, PG and circulatory delay, frequently in combination.

A number of factors may increase the CG in CHF patients. For example, moderate hypoxia affects the chemoresponsiveness increasing the chemosensitivity (the intrinsic gain) (Orr et al. 2017; Lloyd et al. 1958), but also by influencing the upper airway patency (Wellman et al. 2008). The latter may be already disadvantageously altered in patients with obstructive sleep apnea (Wellman et al. 2008). Obstructive events also trigger respiratory associated arousals and hence, an abrupt change in the AT and fluctuations of pCO_2 under and over the AT (Bradley and Floras 1996; Bradley et al. 2001; Leung and Bradley 2001; Lorenzi-Filho and Bradley 2002). Any other cause of sleep fragmentation and increased arousability would elicit the same result. This mechanism may be facilitated further by the inadequate decrease of the AT during sleep, found by Xie et al. in a group of CHF patients (Xie et al. 2002). CHF patients, who are already hypocapnic during wake are especially vulnerable with the withdrawal of the descending effects on the respiratory center (Hanly et al. 1993), (Naughton et al. 1995). On the contrary, application of CO_2 eliminates the central events (Lorenzi-Filho et al. 1999). The chemosensitivity curve may be shifted to the left by non-CO_2 stimuli, other than the WD. The C-fibers reflex is especially important in CHF patients. Pulmonary congestion increases the pulmonary capillary wedge pressure (PCWP) and triggers the reflex resulting in tachypnea and hyperventilation, followed by hypocapnia and central apnea (Paintal 1969; Roberts et al. 1986; Churchill and Cope 1929). PCWP has been correlated with pCO_2 levels and the severity and

number of the central apneas (Solin et al. 1999). Additionally, left ventricle end-diastolic and end-systolic volumes were twice bigger in patients with CHF and concomitant CSB than in CHF only in the study of Tkacova et al. (1997). The presence of CSB has also been associated with left atrium distension (Lloyd 1988) and increased levels of NT-proBNP (Carmona-Bernal et al. 2005; Poletti et al. 2009). In the same regard, optimizing the drug therapy for CHF may result in improving the CSB in some cases (Oldenburg et al. 2009; Olson et al. 2007). The carotid bodies may also play a role in the chemosensitivity, as shown by animal models (Ding et al. 2011; Schultz et al. 2015).

The importance of the interstitial edema is even greater, since it increases the elasticity of the lungs, reducing the FRC (Agostoni et al. 2002) and increasing the plant gain. The importance of PG is underlined by the positive effect of CPAP on CSB, which has been at least partially explained by recruitment of lung volume (Orr et al. 2017).

CHF is also associated with increased arterial circulatory time, causing increased circulatory delay and hence, increasing the LG by mediating "the right changes at the wrong time" (Khoo et al. 1982). Though the importance of circulatory delay is not equivocally accepted, most of the studies support its leading role (Hall et al. 1996; Lorenzi-Filho and Bradley 2002; Naughton et al. 1993; Mortara et al. 1999; Lorenzi-Filho et al. 2008).

An alternative theory for the CSB pathogenesis is the central hypothesis, which describes CSA as an internal oscillation within the CNS and modulating the breathing either indirectly via changes in heart rate and blood pressure or directly through activation of the respiratory center (Yajima et al. 1994).

It is important to note that the importance of the loop gain theory extends beyond being a theoretical canvas of CSB. Recently, it has been successfully used to determine treatment efficacy on central apneas (Stanchina et al. 2015).

6.3 CSB As an Adaptation of the Failing Heart

Naughton et al. proposed the controversial hypothesis of CSB being an adaptive response of the failing heart, rather than a detrimental complication (Naughton 2012). It has been gaining popularity recently with the evidence for increased mortality in CHF-CSB patients when treated with ASV (SERVE-HF) (Cowie et al. 2015). The CANPAP study also failed to produce convincing evidence for a positive outcome in terms of mortality with CPAP treatment in these patients (Bradley et al. 2005), although post-hoc analysis showed otherwise (Arzt et al. 2007). Actually, Naughton et al. structured their hypothesis around several logical arguments related to potential pathophysiological benefits of the hyperpneic phase of CSB, such as: increased FRC; vagal stimulation; improved tissue O_2 extraction (Haldane effect); improved cardiac filling (respiratory pump); increased end-expiratory pressure, etc. (Naughton 2012). It should be noted that the changes in the above-mentioned features are opposite during the apneic phase and the net effect may not be beneficial. For example, it has been proven that CSB is associated with increased sympathetic-adrenal activity (Solin et al. 2003; Carmona-Bernal et al. 2005; Oldenburg et al. 2008a).

Overall, with the lack of experimental studies, directly testing the hypothesis and the proves for higher morbidity, mortality and hospitalization rates in CHF patients with CSB (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005; Mansfield et al. 2003) and treatment benefits (Arzt et al. 2007, 2009), this hypothesis should not be accepted as mainstream.

7 Clinical Manifestation

7.1 Signs and Symptoms

Patients with CHF report a number of somatic complaints, such as generalized fatigue, insomnia, impaired neuro-psychologic functions (Bitter et al. 2012; Braunwald 1988). Although most of the symptoms could be attributed to the cardiac dysfunction, some of them could possibly be granted to the disturbed sleep structure and, to a certain degree, result in the presence of daytime sleepiness. The clinical manifestation of CSA/CSB itself is usually poor, lacking striking symptoms and complaints. Witnessed apneas and snoring are infrequently reported by the sleep partner. Sometimes patients may report poor sleep quality with frequent awakenings, paroxysmal nocturnal dyspnea and frequent urination at night (Javaheri 2006a).

One may pay attention to the fact that the diagnosis CSA with SDB does not need the manifestation of any symptoms (criterion A – sleepiness; difficulty initiating or maintaining sleep, frequent awakenings, or non-restorative sleep; awakening short of breath; snoring; witnessed apneas) in the presence of CHF or AF (criterion B) (ICSD-3 (AASM 2014)), once gain demonstrating the low clinical profile of these patients.

7.2 NYHA Functional Class and Echocardiography

Most of the studies failed to present any significant differences in the NYHA functional class and the ejection fraction between patients with and without sleep-disordered breathing (Christ et al. 2007; Javaheri et al. 2017; Vazir et al. 2006; Arzt et al. 2003; Meguro et al. 2005). Though a correlation between the severity of the CHF and CSA frequency has been reported (Arzt et al. 2003), CSB showed high prevalence among patients with heart failure with preserved ejection fraction (HFpEF) (Berger et al. 2002; Herrscher et al. 2011).

Other EchoCG parameters, however, were found to differ between groups with and without CSA. Javaheri et al. (2017) related concentric remodeling of the ventricle (expressed by elevated left ventricular mass/volume ratio) to be associated with CSA. Left atrial size has also been linked to CSB (Oldenburg et al. 2007; Calvin et al. 2014) through increased chemosensitivity. Calvin et al. speculated that the association between the enlarged left atrium and the enhanced CO_2 chemosensitivity, found in CHF patients, is partially mediated by the J-reflex (Calvin et al. 2014). Right ventricle involvement was also reported (Calvin et al. 2014; Javaheri et al. 2007). Right ventricular systolic pressure is increased in CHF patients in the presence of CSA (Calvin et al. 2014), probably mediated by the hypoxia induced pulmonary hypertension (Javaheri et al. 2007).

7.3 Laboratory Parameters

Increased BNP levels in CHF are associated with poor outcome (Berger et al. 2002; Richards et al. 2001; Omland et al. 2002). The BNP was even further increased in patients with CSB (Carmona-Bernal et al. 2005; Poletti et al. 2009).

C-reactive protein levels are elevated in CHF (Pye et al. 1990; Kaneko et al. 1999; Sato et al. 1999) and influence its prognosis (Anand et al. 2005). In a study on 996 patients with CHF, Schmalemeier et al. reported a significant correlation between the CRP and the severity of CSA (Schmalgemeier et al. 2014). However, the reported effects of the therapy for CSA in CHF on the CRP levels have been controversial (Koyama et al. 2010; Bitter et al. 2012).

7.4 Cardiopulmonary Exercise Testing (CPET)

No clear proof for an association between exercise capacity and the presence of CSA in CHF is present so far. Peak oxygen uptake (VO_{2peak}) was reported to be lower with CSA as an absolute measure (Meguro et al. 2005; Roche et al. 2008)

or percent of predicted (Vazir et al. 2006; Roche et al. 2008) in some studies or without significant differences in others (Arzt et al. 2003). No difference was found in the anaerobic threshold (Roche et al. 2008). The most consistent finding is the increased ventilation-carbon dioxide output ($VEVCO_2$) in CHF with CSB (Arzt et al. 2003; Meguro et al. 2005; Roche et al. 2008; Cundrle et al. 2015). End-tidal CO_2 was lower at peak and at 50% of the exercise intensity in the group with CSB in the study of Cundrle et al. (2015). Periodic pattern of breathing may be observed in the first 4 min of a CPET (Roche et al. 2008).

7.5 Arterial Blood Gases

As already mentioned hypocapnia is a typical finding in CSB patients (Bitter et al. 2012; Christ et al. 2007; Szollosi et al. 2008; Bradley and Phillipson 1992). On the other hand, lower pO_2 is not present (Bitter et al. 2012) or not an independent risk factor (Bitter et al. 2012) in CHF with CSA.

7.6 Pulmonary Function Testing (PFT)

Reduced diffusion capacity of the lungs has been found to be an independent risk factor for CSA and correlated moderately with the AHI in the study of Szollosi et al. (2008). Despite the fact that low lung volumes have been implicated in the pathogenesis of CSB (see above), no difference in PFT parameters in patients with CSA has been reported.

7.7 Periodic Breathing During Wakefulness

CSB may be observed during wakefulness as well (Poletti et al. 2009; Mortara et al. 1999; Brack et al. 2007; Leite et al. 2003) and is associated with increased mortality and poor transplant-free survival (Brack et al. 2007). It has been attributed to low cardiac index and increased circulatory time (Mortara et al. 1999) and linked to increased sympathetic-adrenal activity and BNP levels (Poletti et al. 2009) and lower EF, exercise capacity and hypocapnia (Leite et al. 2003).

8 Consequences of CSB

Breathing disturbances, present in patients with stable CHF, are not just an acute pathological condition, but provoke chronic effects, which could promote a number of diseases, as well as further deterioration of cardiac function. In fact, Somers et al. (Somers 1999) hypothesize that CSA and cardio-vascular disease are linked through bidirectional causality as a part of a vicious cycle.

CSB is accompanied by cyclic variations in heart rate (tachycardia-bradycardia), blood pressure (hypertension-hypotension), respiratory volume (hyperpnoea-hypo/apnea), partial pressure of arterial oxygen (pO_2) (hypoxia-hyperoxia) and carbon dioxide (pCO_2) (hypercapnia-hypocapnia). The pathophysiological mechanisms, responsible for the adverse prognosis in CSA patients include hypoxia with/without hypoxemia, (micro)arousals from sleep, increased negative intrathoracic pressure. Each of them, and especially their combination, leads to sympathetic-adrenal activation.

Hypoxia, followed by an apnea or hypopnea, could provoke bradycardia or even several-seconds asystole (Guilleminault et al. 1983), whereas severe hypoxia could provoke acute ventricular arrhythmia (Leung et al. 2004). It should be noted that mild hypoxia was not related to ventricular arrhythmia in the same study (Leung et al. 2004). The combination between hypoxia and tachycardia impairs myocardial contractility, as it leads to a decreased myocardial oxygen delivery and an increase in the left ventricular afterload (Serizawa et al. 1981). The frequent desaturations and multiple arousals elicit structural changes to the heart as well as left and right ventricular hypertrophy (Ancoli-Israel et al. 2003) and contribute to the development of systemic oxidative stress in OSA (Lavie and Lavie 2009), and may invoke similar effects in CSB.

The arousals, following each respiratory disturbance contribute to the increased instability of respiratory control (Phillipson 1978; Naughton et al. 1993; Xie et al. 1994), increased release of catecholamines (Naughton et al. 1995; Horner et al. 1995), and overactivation of the sympathetic nervous system (Solin et al. 2003; Carmona-Bernal et al. 2005; Oldenburg et al. 2008a). Naughton et al. found increased nocturnal urinary norepinephrine levels and increased daytime norepinephrine plasma levels in patients with CHF and CSB, as compared to those without CSB and an association between the norepinephrine levels with increased frequency of arousals (Naughton et al. 1995). Sympathetic overactivation leads to a decreased survival of cardiomyocytes, exerts antiarrythmogenic effects and worsens ventricular energetism. It relates to myocyte hypertrophy, apoptosis and focal myocardial necrosis, which are factors for cardiac remodeling (Costanzo et al. 2015). All of these potentiate the progression and the lethal outcome in CHF patients (Mansfield et al. 2003).

Although the increased negative intrathoracic pressure is a typical consequence of OSA, it could also be present in CSA as well, even though to a lesser extent, as a result of pulmonary congestion and decreased compliance of lungs.

The Inflammatory Pathway According to the cytokine hypothesis, the activation of the immune system plays an important role in the pathogenesis of CHF, pointing out the participation of some pro-inflammatory cytokines for the development of the ventricular dysfunction (Seta et al. 1996; Vasan et al. 2003). Besides, the increased levels of some inflammatory markers show an independent correlation with adverse events and mortality (Anand et al. 2005) and those patients exhibit more severe CHF. Several studies suggest that the presence of obstructive sleep apnea leads to increased levels of some markers of systemic inflammation (Ciftci et al. 2004; Dyugovskaya et al. 2002; Schulz et al. 2000), which could be associated with a further progression of the cardiac dysfunction, forming a vicious cycle. Some markers of systemic inflammation are elevated in CSB (Schmalgemeier et al. 2014), so the aforementioned mechanism may play a role in CSB, as well.

The pathogenesis of the negative consequences of CSB on CHF is summarized in Fig. 5.

8.1 Quality of Life

Patients with CHF have a considerably decreased quality of life as compared with individuals, matched by age and gender (Lesman-Leegte et al. 2009). Undoubtedly, heart failure affects quality of life (QoL) to a greater extend, compared with other chronic conditions (Jaarsma et al. 2010). The influence of the CSB on QoL in patients with CHF is still debated with some studies reporting no effect (Ferrier et al. 2005), while others finding considerable worsening in the group with CSB (Carmona-Bernal et al. 2008), but the correlation with objective indices of its severity was poor (ODI) to moderate (AHI).

8.2 Morbidity and Mortality

The negative impact of the combination CHF/CSB is supported by a diverse body of evidence for increased morbidity and mortality in the presence of CSB (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005; Mansfield et al. 2003; Lanfranchi et al. 1999; Hanly and Zuberi-Khokhar 1996). These findings were confirmed when corrected for the CHF severity (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005; Mansfield et al. 2003; Hanly and Zuberi-Khokhar 1996). The severity of SDB probably plays an important role, as demonstrated in the study of Lanfranchi et al where only severe CSA (AHI $\geq$ 30) was associated with adverse prognosis (Lanfranchi et al. 1999).

Obstructive sleep apnea is a risk factor for arterial hypertension (Nieto et al. 2000). However, the impact of CSA on blood pressure, though expected (Fig. 5) has not been proven yet. In two studies (Bitter et al. 2012; Yumino et al. 2009) arterial hypertension was more

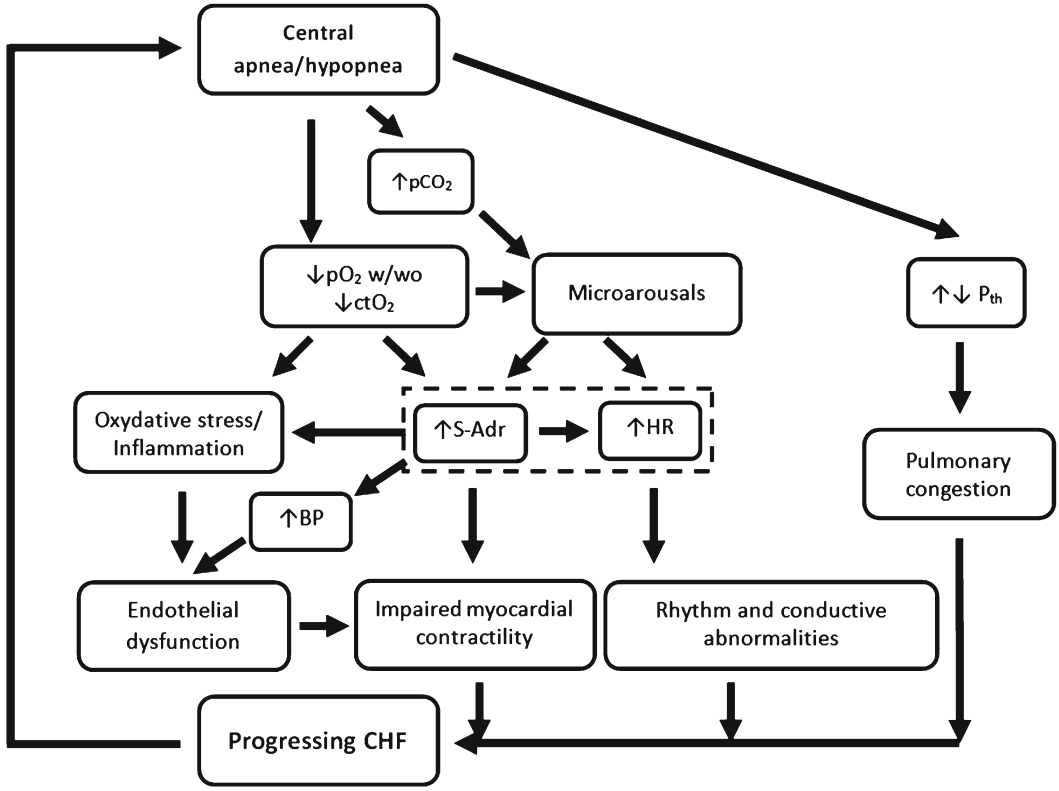

Fig. 5 Pathophysiology of the detrimental effects of CSB on chronic heart failure
Legend: pCO_2 – partial pressure of carbon dioxide, pO_2 – partial pressure of oxygen, ctO_2 – oxygen concentration (in arterial blood); P_{th} – intrathoracic pressure; S-Adr – sympathetic-adrenal activity; HR – heart rate; BP – blood pressure

prevalent in CSA compared to CHF patients without sleep disordered breathing, but the difference was not significant. No difference was found in the prevalence of diabetes mellitus as well (Bitter et al. 2012).

9 Diagnosis and Polysomnographic Pattern

The diagnostic process of patients with CHF, suspected to have CSA, follows the standard steps and includes a profound clinical interview, assessment of the HF condition and a sleep study, each of them having its importance for an adequate diagnostic outcome. A detailed description of the day-time and night-time symptoms is collected, preferably with the participation of the bed-partner, although a negative history of the latter does not exclude a clinically significant disorder. The recommended type of diagnostic study is the standard in-laboratory polysomnography (type 1 device), as it provides detailed information on sleep structure, respiratory and electro-physiological parameters. The polysomnographic characteristics of CSA include:

From the respiratory part: crescendo-decrescendo ventilatory pattern, accompanied by a partial (hypopnea) or complete cessation of breathing without thoracic and abdominal effort, followed by a decrease in the oxygen saturation. Respiratory effort is best measured by esophageal pressure, but currently this method is rarely used in clinical practice.

From the EEG part: CSB usually occurs during the transition from wakefulness to NREM 1 and 2 sleep stages. It is alleviated in a non-supine body position (Szollosi et al. 2006), while during slow wave sleep and REM sleep the ventilation tends to normalize. Usually a CSB sequence is preceded by an obstructive event or an arousal. Unlike obstructive events, ending with arousals, EEG arousals in CSB appear at the peak of the hyperventilation phase of the CSB cycle.

The severity of CSA is usually expressed by measuring the apnea-hypopnea index (AHI), which is calculated as the number of apneas and hypopneas, divided by the hours of sleep. Another metrics, although quite less commonly used, is the percentage of sleep time in which CSA/CSB occurs (Naughton and Andreas 2010).

10 Predictors

There is enough body of evidence that the presence of CSA/CSB in CHF patients worsens the overall prognosis (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005) and needs targeted treatment (Arzt et al. 2007, 2009), therefore, a reliable screening system for its timely detection is required. Presently, the golden standard for diagnosing CSA/CSB is laboratory polysomnography, an expensive, laborious and highly specialized procedure, which can differentiate the various types of SDB (AASM 2014), (Ferrier et al. 2005) and determine the need of treatment. In order to optimize polysomnography use, a predictive system could be created, aiming at selecting the appropriate patients.

We have proposed a pathophysiological approach to the selection of some predictors, based on parameters, reflecting the etiology, the pathogenesis and the consequences of CSA/CSB in CHF (Draganova et al. 2016) – Table 1.

11 Therapy of CSB

Treatment of CSB aims at improving the cardiac function, quality of life and life expectancy in these patients. Despite the variety of treatment modalities proposed, it is important to note that, so far, guidelines do not offer a uniform treatment strategy for CSA in patients with CHF.

11.1 Optimization of CHF Therapy

Although according to some authors severity of CHF (as measured by NYHA class and ejection fraction) does not significantly differ among patients with and without CSA (Bitter et al. 2012; Christ et al. 2007; Vazir et al. 2006; Arzt et al. 2003; Meguro et al. 2005), applying

Table 1 Pathophysiological approach to prediction of CSB in CHF (With permission from Draganova et al. 2016)

PREDICTORS				
Etiologic	**Pathogenetic**			**Symptomatic**
✓ Anthropometry ✓ Medical history ✓ EchoCG ✓ NYHA class ✓ Laboratory parameters	Controller	Plant gain	Mixing gain	Symptoms
	✓ Respiratory control	✓ PFT ✓ EchoCG	✓ EchoCG	✓ ESS ✓ MLHFQ
	Loop gain in general			Complications
	✓ Cardiopulmonary exercise testing (CPET) ✓ Hypoxic provocation			✓ ECG/ HRV ✓ CPET

Legend: *EchoCG* echocardiography, *NYHA* New York Heart Association, *ESS* Epworth sleepiness scale, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *ECG* electrocardiography, *HRV* heart rate variability

contemporary and adequate medication therapy, is the important first step towards CSA treatment in these patients. The diuretics, aiming at reducing the cardiac filling pressures, together with angiotensin-converting enzyme inhibitors to reduce ventricular afterload and improve cardiac output (Walsh et al. 1995) and beta-blockers to blunt the sympathetic nervous activation effects (Tamura et al. 2007), could to a certain extent diminish CSA severity (Solin et al. 1999).

Other therapeutic approaches, applied in advanced CHF like resynchronizing therapy (RT), may also have a beneficial effect on CSA. RT improves cardiac pumping function, which is a prerequisite for improved quality of life and sleep, as well as decreased mortality rate (Abraham et al. 2015). A meta-analysis, comprising 170 patients with CHF after RT, shows a considerable decrease of AHI in CSA patients, but not in patients with OSA (Lamba et al. 2011). Atrial overdrive pacing on top of RT in some of the patients in the same study, has led to a minor additional improvement of CSA (Lüthje et al. 2009).

However, despite the optimal CHF therapy, the presence of CSA requires specific treatment. The golden standard is application of positive airway pressure during sleep, although other treatment modalities have been tried.

11.2 Non-positive Airway Pressure Modalities

11.2.1 Nocturnal Oxygen Supplementation

Noxturnal home O_2 therapy (HOT) has been successfully used to treat CSA in CHF patients (Shigemitsu et al. 2007; Seino et al. 2007; Toyama et al. 2009; Sasayama et al. 2006; Nakao et al. 2016). The possible mechanisms involved are improvement in oxygen delivery to cardiomyocytes and influencing the controller gain by decreasing hypoxemia and increasing the cerebral CO_2 (Badr 2009). The effect of O_2 therapy on AHI in CHF with CSA is comparable to CPAP (Teschler et al. 2001). Additional benefits of the therapy are decrease in the nocturnal norepinephrine and the BNP levels (Shigemitsu et al. 2007), improved physical capacity (Toyama et al. 2009; Hanly et al. 1989; Andreas et al. 1996; Staniforth et al. 1998; Krachman et al. 1999) and quality of life (Seta et al. 1996) and lower hospitalization rate and duration (Seta et al. 1996). Unlike reported previously (Hanly et al. 1989; Staniforth et al. 1998; Krachman et al. 1999), EF increased after 3 months of HOT in the study of Toyama et al. (2009).

It should be noted, however, that noxturnal oxygen supplementation may not eliminate upper airway obstruction (frequently co-existing with central event), unless it is caused by an increased loop gain (Wellman et al. 2008).

11.2.2 Nocturnal Supplemental CO_2

Nocturnal inhalation of small amounts of CO_2 or the artificial increase of dead space (and, thus pCO_2) leads to suppression of CSB by shifting pCO_2 above the apneic threshold (Lorenzi-Filho et al. 1999; Xie et al. 2002; Andreas et al. 1998; Khayat et al. 2003). However, sleep quality and quality of life are not improved (Szollosi et al. 2004).

To avoid undesirable side effects of the CO_2 implementation, such as increased sympathetic activity, Mebrate et al. proposed a system with dynamic delivery of CO_2 (Mebrate et al. 2009). Yet, CO_2 therapy is not recommended for clinical use.

11.2.3 Theophylline

Theophylline is a respiratory stimulant (Eldridge et al. 1985; Javaheri et al. 1989) and has been able to decrease the periodic breathing and the AHI and improve oxygen saturation during sleep in the study of Javaheri et al. (1996). No improvement in cardiac function or sleep architecture was found (Javaheri et al. 1996).

11.2.4 Acetazoleamide

The positive effect of Acetazoleamide on high-altitude central sleep apnea and idiopathic CSA (White et al. 1982; DeBacker et al. 1995; Sutton et al. 1979; Hackett et al. 1987) is probably mediated by reduction in the pulmonary

congestion and lowering the apneic threshold through neural plasticity. Analogously, its use in CSA with CHF has been tested in a single small randomized trial on 12 CHF patients. Acetazoleamide for 6 nights has led to a decrease in periodic breathing by 38%, improved the quality of sleep and reduced of daytime sleepiness (Javaheri 2006b).

11.2.5 Phrenic Nerve Stimulation

A novel approach to eliminate CSB is the unilateral transvenous stimulation of the phrenic nerve. A pulse generator is implanted to stimulate the diaphragm during sleep, aiming at maintaining normal respiratory excursions (Ponikowski et al. 2012). Abraham et al. reported a 55% decrease in AHI (on behalf of the central events) at 3 months and a considerable improvement of sleep efficiency, oxygen saturation and quality of life (Abraham et al. 2002).

11.2.6 Heart Transplantation and Supportive Devices

Data showing the effect of heart transplantation and supportive devices are still limited to case reports and no reliable conclusions are possible. Heart transplantation was demonstrated to eliminate CSB in several studies (Fox et al. 2014; Vermes et al. 2009), in the first case the resolution was delayed over time (Fox et al. 2014). Ventricular assistant device eliminated successfully CSB in several cases (Vermes et al. 2009; Vazir et al. 2010).

11.3 Positive Airway Pressure Modalities

11.3.1 CPAP

At present, CPAP therapy is considered the gold standard in the treatment of CSA in CHF. It reduces AHI and improves the saturation profile (Naughton and Lorenzi-Filho 2009; Bradley et al. 2005; Arzt et al. 2007, 2009; Mansfield et al. 2003; Kaneko et al. 2003). According to its effect on AHI, the patients are divided into "responders" and "non-responders" (Javaheri 2000). With adequate titration CPAP increases transplant-free survival among these patients (Arzt et al. 2007; Sin et al. 2000). However, this effect is observed only in responders to the therapy (AHI on CPAP <15) (Arzt et al. 2007). It should be noted, that CPAP response is time-dependent (Arzt et al. 2009) and typically AHI decreases with less than 50% at the first night of treatment (Arzt et al. 2009; Teschler et al. 2001). In the study of Arzt et al., an additional reduction of 42% in the AHI (to the initial 47%) were observed after 12 weeks in the absence of any changes to the therapeutic pressure or medications (Arzt et al. 2009). Therefore, response assessment after at least 2 weeks of CPAP treatment is recommend (Arzt et al. 2009).

Additional benefits of the CPAP are improvement in EF (Bradley et al. 2005; Mansfield et al. 2003; Sin et al. 2000) physical capacity (Bradley et al. 2005), quality of life (Bradley et al. 2005) and sympathetic activity (Bradley et al. 2005; Mansfield et al. 2003; Kaye et al. 2001). CPAP does not affect sleep macroarchitecture, while data on arousals are controversial (Yumino et al. 2009; Kaneko et al. 2003).

CPAP treatment effects are consistent with the loop gain theory. It decreases plant gain by increasing the FRC which serves as a buffer for pCO_2, preventing large swings in it (Sands et al. 2011; Krachman et al. 2003). Controller gain is decreased as well, due to improved oxygenation of the blood affecting chemosensitivity (Lloyd et al. 1958; Arzt et al. 2009). It alleviates cardiogenic pulmonary edema and thus, decreases the non-CO_2 stimuli to the respiratory center (Lenique et al. 1997). The stability of the upper airway may also be improved in some patients (Jobin et al. 2012). Additionally, CPAP serves as a "cardiac assist device", decreasing the preload and the afterload to the heart (Naughton and Bradley 1998; Mehta et al. 2000; Steiner et al. 2008; Philip-Joët et al. 1999). Increasing blood oxygen levels also bears the benefits of reduced sympathetic-adrenal activity (Naughton et al. 1995; Kaye et al. 2001) and improved myocardial oxygen.

Table 2 Treatment recommendations for CSB (AASM)

Treatment modality	Statement	Recommendation
CPAP	CPAP therapy is indicated for the initial treatment of CSAS related to CHF.	STANDARD
O_2	O_2 therapy is indicated for the treatment of CSAS related to CHF.	STANDARD
ASV	ASV is indicated for the treatment of CSAS related to CHF with EF > 45%.	OPTION
BPAP	BPAP therapy in ST mode may be considered only if there is no response to adequate trials of CPAP, ASV, and O_2 therapies.	OPTION
Acetazolamide/ theophylline	Acetazolamide and theophylline have limited supporting evidence but may be considered after optimization of standard medical therapy, if PAP therapy is not tolerated, and if accompanied by close clinical follow-up.	OPTION

11.3.2 BPAP

Bilevel positive airway pressure (BPAP) supports a lower pressure during exhalation, thus facilitating the expiration and increasing tidal volume. In theory, the latter may cause hypocapnia and hence, provoke periodic or worsen breathing in CHF patients with CSA. Additionally, a large difference between the inspiratory and the expiratory pressures (>7 cmH_2O) causes periodic breathing in most healthy individuals (Badr 2009).

Consistent with the abovementioned, worsening of central breathing disturbances with BPAP was shown in the study of Johnson et al. (Johnson and Johnson 2005). On the contrary, several small studies demonstrated positive effect of the therapy (Köhnlein et al. 2002; Willson et al. 2001; Dohi et al. 2008; Kasai et al. 2005), with even superior results compared to CPAP (Köhnlein et al. 2002; Willson et al. 2001).

However, the scarcity of data and the contradictory results pose questions to BPAP therapy in CHF patients with CSA.

11.3.3 Adaptive Servoventilation

Adaptive servo-ventilation (ASV) is a relatively new approach in the CSA therapy in CHF. Its key characteristic is the variable pressure support to prevent hyperventilation, adding to the cardiocirculatory benefits of the CPAP (Teschler et al. 2001). Low expiratory pressures improve the cardiac output and also the compliance to the therapy (Hastings et al. 2010). Meanwhile, the servo-controlled inspiratory support stabilizes the ventilation at about 80% of minute ventilation during rest, avoiding the risk of hyperventilation and improving the efficacy in eliminating central events (Naughton and Lorenzi-Filho 2009). Indeed, studies have shown superiority of ASV over CPAP in eliminating CSB and better compliance (Teschler et al. 2001; Philippe et al. 2006).

ASV therapy has been shown to improve physical capacity, EF, N-pro-BNP levels in CHF patients (Oldenburg et al. 2008b). A positive effect of ASV on echocardiographic parameters has been reported even in patients with heart failure with preserved ejection fraction (Bitter et al. 2010). Additionally, ASV decrease sympathetic-adrenal activation, reduces nicturia and improves sleep architecture and quality of life (Philippe et al. 2006; Pepperell et al. 2003). In that regard ASV also proved superior to CPAP (Teschler et al. 2001; Philippe et al. 2006).

Despite these promising initial data, the results of the biggest multi-center randomized trial on ASV so far – SERVE-HF (Cowie et al. 2015) were disappointing. ASV therapy does not result in a significant improvement in quality of life or symptoms of CHF. More importantly, a considerable increase in cardiovascular and all-cause mortality with ASV treatment were found (Cowie et al. 2015). The results of another large-scale study (SAVIOR-C) show no effect of ASV therapy on EF and plasma BNP levels (Momomura et al. 2015).

The results of the SERVE-HF study provoked an update in the AASM recommendations for treatment of CSA in CHF (Aurora et al. 2012, 2016) which are summarized in Table. 2.

12 Future Perspectives

Though, CSB in CHF has been an extensively studied area lately, a lot of uncertainties remain. Naughton et al. have questioned the necessity of treatment of CSB, proposing an adaptive nature of the disorder (Naughton 2012). This hypothesis was reinforced the SERVE-HF study results (Cowie et al. 2015). It may be even the case of magnitude determining the adaptive or pathological nature of SDB. In that regard, the lack of uniform threshold for its presence and lack of severity metrics may be strongly impeding progress on the topic. Even the use of AHI as a key parameter by analogy to OSA has to be questioned (Naughton 2016). The recent changes in hypopnea definition (Berry et al. 2012) lead to scoring more events (Duce et al. 2015; Ward et al. 2013), though that does not seem to impact the proportion of central and obstructive events in CHF (Ward et al. 2013). Novel therapeutic approaches taking into account the pathophysiology of CSB were attempted (Mebrate et al. 2009; Ponikowski et al. 2012) and need further investigation. Phenotyping patients based on the loop gain seems especially promising in improving therapeutical efficacy (Stanchina et al. 2015). Early diagnosis is of no less importance and reliable laboratory markers for prediction of CSB are still needed.

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