Sleep apnoea in patients with heart failure. Part I: Diagnosis, definitions, prevalence, pathophysiology and haemodynamic consequences

Philippe Bordier

Hôpital cardiologique du Haut-Lévêque, avenue de Magellan, 33604 Pessac cedex, France

Summary
Sleep disorder specialists manage 90% of patients suffering from obstructive sleep apnoea, which affects 10% of the general population. From another perspective, cardiovascular disease specialists are particularly challenged by sleep apnoea, since it affects a large proportion of their patients and its complications are largely cardiovascular. At least 50% of patients with chronic heart failure (HF) suffer from sleep apnoea, predominantly central and/or Cheyne-Stokes respiration as opposed to obstructive sleep apnoea. While its effect on survival remains uncertain, sleep apnoea promotes the progression of chronic HF and is a predictor of poor prognosis. After screening by cardiologists, patients presenting with chronic HF and sleep apnoea should be referred to a sleep disorder specialist for diagnostic confirmation and treatment. In Part I of this review, we describe the diagnostic steps recommended when sleep apnoea is suspected in patients with chronic HF. We also review the definitions of abnormal sleep-related respiratory events and the prevalence, pathophysiology and haemodynamic consequences of sleep apnoea in this patient population.

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Abbreviations: AHI, Apnoea-hypopnoea index; CO₂, Carbon dioxide; CompSAS, Complex sleep apnoea syndrome; CSA, Central sleep apnoea; CSR, Cheyne-Stokes respiration; HF, Heart failure; LV, Left ventricular; OSA, Obstructive sleep apnoea; O₂, Oxygen; ODI, Oxygen desaturation index.

* Fax: +33 5 56 04 38 49.
E-mail address: phibordier@aol.com.

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Background

Sleep disorder specialists manage 90% of patients suffering from obstructive sleep apnoea (OSA), which affects 10% of the general population [1]. At least 50% of patients suffering from chronic heart failure (HF) also suffer from sleep apnoea. Studies in these patients suggest a predominance of severe chronic HF or is directly responsible for abbreviating life is unclear [5,7,13,20,21]. These observations have sparked an interest in sleep apnoea among patients suffering from chronic HF, a notorious public health burden associated with a high mortality, making the management of sleep apnoea in patients with chronic HF [18,19]. Whether sleep apnoea is a marker of severe chronic HF or is directly responsible for abbreviating life is unclear [5,7,13,20,21]. These observations have sparked an interest in sleep apnoea among patients suffering from chronic HF, a notorious public health burden associated with a high mortality, making the management of sleep apnoea in patients with chronic HF a medicosocial priority. In Part I of this review, we describe the diagnostic steps recommended when sleep apnoea is suspected in patients with chronic HF. We also review the definitions of abnormal sleep-related respiratory events and the prevalence, pathophysiology and haemodynamic consequences of sleep apnoea in this patient population.

Diagnosis of sleep apnoea

A history of daytime sleepiness suggests a common form of OSA associated with marked sleep fragmentation, which may be screened using the Epworth sleepiness scale score or the Berlin questionnaire. In patients presenting with chronic HF, this screening method reliably identifies OSA in the majority of individuals [18] but not CSA/CSR. Furthermore, the history and physical examination of patients suffering from chronic HF is less likely to suggest the presence of sleep apnoea, since their rate of obesity is lower than among patients presenting with the common form of OSA [2,4,11] and because patients with CSA/CSR are notably less likely to complain from daytime sleepiness [2]. In patients with chronic HF, an arterial carbon dioxide (CO₂) concentration less than 35 mmHg, during the daytime or at night, may be a sign of CSA/CSR, although it is not consistently present [22]. In these patients, a home nocturnal pulse oximetry monitor may be a more reliable first diagnostic step than a questionnaire or blood gases to confirm the presence of suspected sleep apnoea [23]. These monitors can be combined with airflow signals recorded from a nasal cannula. The programming of these instruments, their placement on the patient and the interpretation of the recordings are simple and expeditious and can be implemented by physicians who are not sleep disorder specialists. The recordings can be scored using the automated analysis protocol of the device software. The oxygen (O₂) desaturation index (ODI) is the mean hourly number of less than or equal to 3% or 4% dips in O₂ lasting greater than or equal to 10 s, occurring immediately after the baseline arterial O₂ saturation signal. An ODI greater than or equal to 12 indicates a high probability of sleep apnoea (Fig. 1). The sensitivity of ODI in the detection of sleep apnoea in patients with chronic HF is 100%, although its accuracy in the distinction between OSA and CSA/CSR is less than 20% [23]. Given:

- the paucity of sleep apnoea-related symptoms and the high prevalence of sleep apnoea among patients with chronic HF;
- the high morbidity and mortality associated with sleep apnoea in that population; and
- the availability of simple and expeditious nocturnal oximetry monitoring, their systematic screening seems appropriate, despite the high number of candidates that this represents.

The next diagnostic step requires the expertise of a sleep disorder specialist, who performs and interprets the polysomnographic or nocturnal ventilation polygraphic recordings, to confirm the diagnosis of sleep apnoea and determine its type and severity. While polygraphy does not include neurophysiological sleep variables, unlike electroencephalography or electromyography, it allows the confirmation of sleep apnoea. A polygraphic recording can include measurements of:
Heart failure and sleep apnoea

Figure 1. Detection of sleep apnoea by nocturnal pulse finger oxymetry. Top tracing: recording of normal nocturnal oxymetry. The other tracings are recordings from three different patients, with automatically calculated ODI ≥ 12, consistent with sleep apnoea. ODI: O₂ desaturation index (number of dips in O₂ per hour of nocturnal recording); SpO₂: arterial O₂ saturation, on the vertical axis. Time in h and min is displayed on the horizontal axis.

- continuous airflow by a nasal cannula pressure transducer;
- nasal and oral airflow via a thermistor;
- rib cage and abdominal motion for breathing efforts, using respiratory inductive plethysmograph or piezoelectric sensor belts;
- arterial O₂ saturation and heart rate by pulse finger oximetry;
- synchronized, single- or multichannel electrocardiograms.

Definitions

''Apnoea'' is the complete cessation of oronasal airflow lasting for more than or equal to 10 s (Fig. 2) [24]. Among several definitions, ''hypopnoea'' is a greater than or equal to 30% decrease in the amplitude of inspiratory oronasal airflow below the surrounding baseline, lasting for more than or equal to 10 s, and accompanied by a greater than or equal to 3 or 4% decrease in O₂ saturation from a previous stable baseline (Fig. 3). A greater than or equal to 90% decrease in the amplitude of oronasal airflow is scored as an apnoea. The patterns of apnoea and hypopnoea are obstructive, central or mixed.

Obstructive respiratory events

An obstructive respiratory event is caused by obstruction of the inspiratory airflow through the upper airways, associated with ongoing respiratory efforts and out-of-phase motion of the rib cage and abdomen (Figs. 2 and 3).

Central respiratory events

Impairment of the central respiratory drive during sleep is the cause of central respiratory events. The respiratory efforts and the thoracic and abdominal movements are absent during central apnoea (Fig. 4) and are weak-
Obstructive apnoea documented by nocturnal ventilation polygraphy. The recordings show typical repetitive apnoeic events, each associated with profound dips in blood $O_2$ saturation and autonomic nervous system instability characterized by marked bradycardia caused by vagal stimulation during apnoea, followed by tachycardia due to sympathetic surge at the end of each apnoeic episode. See text for more detailed explanations.

Obstructive, central and mixed respiratory events may be present on the same overnight recording [3,24]. Sleep apnoea is "central" when greater than or equal to 50% of the abnormal respiratory events are of central origin [2,4,20,24], and "obstructive" when greater than or equal to 50% of the events are obstructive or mixed. The diagnosis of sleep apnoea is based on the value of the apnoea-hypopnoea index (AHI), calculated by dividing all episodes of apnoea and hypopnoea by the number of hours of sleep during polysomnography, or by the duration of recording during polygraphy. Sleep apnoea is absent when AHI is less than 5, mild between 5 and 15, moderate between 15 and 30 and severe when AHI is greater than or equal to 30 [5,8,24]. An AHI greater than or equal to 30 has been associated with an increased mortality in patients with OSA [18,19,25], and in patients with CSA/CSR and chronic HF [5,7,16]. In that latter population, an up to 36% prevalence of severe sleep apnoea has been reported [5,8]. In a same patient and under similar conditions of recording, the measurements of AHI remain stable. In 19 patients with chronic HF who underwent four consecutive nocturnal recordings, AHI ranged from $32.1 \pm 14$ to $34.2 \pm 14$ [26]. In another group of
Heart failure and sleep apnoea

Figure 3. Obstructive hypopnoea documented by nocturnal ventilation polygraphy. In this example, the variations in heart rate due to autonomic nervous system instability associated with the dips in O2 saturation during each hypopnoic event are masked by permanent cardiac pacing. See text for more detailed explanations.

50 patients suffering from chronic HF, the mean variability of AHl between two consecutive nocturnal recordings was 1.4 ± 5.0 [27].

An AHl greater than or equal to 15 is generally considered an indication for treatment of sleep apnoea [2,8,20,21]. Treatment is considered effective when:
• AHl has decreased by greater than or equal to 50%;
• is lowered to less than or equal to 10 or greater than or equal to 15;
• or both [21].

In studies on sleep apnoea, responders versus non-responders to treatments have been defined on the basis of statistically significant changes in AHl from baseline, or on the basis of a decrease in the severity of sleep apnoea graded according to the AHl value.

Patients with OSA may develop manifestations of CSA during titration of nasal continuous positive airway pressure [28]. The mechanisms behind this phenomenon, known as complex sleep apnoea syndrome (CompSAS), remain unclear. It is observed in 10% of patients suffering from sleep-disordered breathing and is sometimes associated with CSR. CompSAS is observed predominantly in patients without chronic HF. However, patients who suffer from chronic HF often present with a mixed central and obstructive form of sleep apnoea and with both apnoea and hypopnoea. Therefore, the term “complex” should be reserved for a clearly defined underlying pathological substrate. From a therapeutic standpoint, the management of “complex” forms of sleep apnoea in patients with chronic HF is particularly challenging.

Prevalence of sleep apnoea in heart failure

In studies of patients with chronic HF and sleep apnoea, the definition of chronic HF has been based on a depressed left ventricular (LV) ejection fraction, measured by echocardiography or radionuclide angiography, varying between less than or equal to 55% and less than or equal to 35%. Some studies have included episodes of cardiac decompensation, or a stable, high New York Heart Association functional class, or both. The variable prevalence of sleep apnoea among studies is, therefore, explained by:
• the variable severity of chronic HF among enrolment criteria;
• the variable methods of patients enrolment, based on the functional manifestations of sleep apnoea or on the presence of chronic HF only;
• on the variable scoring of the sleep recordings and the use of an AHl greater than or equal to 5, versus greater than or equal to 10 versus greater than or equal to 15 to diagnose sleep apnoea. Table 1 shows the prevalence of OSA and CSA/CSR in patients with a LV ejection fraction less than or equal to 35% and a greater than or equal to 10 or greater than or equal to 15 AHl diagnostic cut-off...
value. Others studies have confirmed a high prevalence of sleep apnoea among patients suffering from chronic HF [5–7,14].

Pathophysiology of sleep apnoea in heart failure

The main part of the respiratory drive is located at the level of the medulla oblongata. Among several ventilation regulatory factors, CO₂ and O₂ predominantly influence this drive. The arterial partial pressure of CO₂ is the baseline and, compared to the partial pressure for O₂, the predominant respiratory stimulus. CO₂ crosses freely the blood-brain barrier and its concentration in the cerebrospinal fluid increases proportionally to that in the blood. In the blood, CO₂ is predominantly buffered to HCO₃⁻ by the action of carbonic anhydrase in erythrocytes (Haldane’s effect: CO₂ + H₂O ⇌ HCO₃⁻ + H⁺). H⁺ ions produced by this reaction are bound to the reduced haemoglobin generated by O₂ released to the tissues, preventing blood acidosis. In contrast, the capacity of CO₂ buffering to HCO₃⁻ in the cerebrospinal fluid is weak. Therefore, the CO₂ concentration remains high, and albeit weak, the production of H⁺ ions cannot be buffered in the absence of haemoglobin. Since pH = −log [H⁺] and since CO₂ and H⁺ ions are considered equivalent with respect to the acid-base balance, an increase in the concentration of CO₂ is an immediate cause of cerebrospinal fluid acidosis [29]. Medullary cells of the central chemoreceptors that are sensitive to CO₂ and H⁺ (H⁺ being most probably the main drive) respond to the decrease in cerebrospinal fluid pH by triggering an increase in respiratory muscles activity. Conversely, hypocapnic alkalosis of the cerebrospinal fluid causes hypoventilation. Peripheral chemoreceptors sensitive to the partial pressures of O₂ and H⁺ are located in glomus cells of the aortic arch and in the carotid body, with afferent neural pathways to the medulla via, respectively, the vagus and the glossopharyngeal nerves [30]. Hypoxaemia causes hyperventilation. The phrenic nerve is one of the main drivers of the respiratory muscles. However, vagal and sympathetic efferents from the brainstem are also involved prominently in inspiratory and expiratory efforts as well as in the activity of the pharyngeal muscles and are under the influence of the medullary response to the partial pressure of O₂ and to the venous, more than arterial, PCO₂ concentration [31]. Any change in the medullary or arterial H⁺ ion concentration causes a rapid ventilatory and slower renal compensatory adaptation.

Among CSA are distinguished:

• hypercapnic syndromes with hypoventilation, such as congenital central hypoventilation syndrome, respiratory depressant effects of opioid-based medication, obesity
Heart failure and sleep apnoea

Figure 5. Central hypopnoea documented by nocturnal ventilation polygraphy. This recording shows weak respiratory efforts accompanied by an in-phase (as opposed to out-of-phase in obstructive events) decrease in rib cage and abdominal motion, proportional to the decrease in airflow amplitude. The electrocardiogram shows a fixed heart rate due to permanent pacing. Instead of apnoeic events, the tracings show typical Cheyne-Stokes periodicity. See text for more detailed explanations.

Figure 6. Cheyne-Stokes respiration documented by nocturnal ventilation polygraphy. The recording shows an in-phase increasing/decreasing motion of the thorax and abdomen and a proportional increase/decrease in airflow amplitude. The electrocardiogram shows a fixed heart rate due to permanent pacing. See text for more detailed explanations.
Mixed apnoea documented by nocturnal ventilation polygraphy. This example shows marked variations in O₂ saturation with a fixed heart rate, due to permanent cardiac pacing. See text for more detailed explanations.

Several putative mechanisms of CSA/CSR have been proposed as upstream and downstream myocardial consequences of chronic HF. Downstream disorders commonly observed during advanced chronic HF include:

- hyperventilation in the supine position and during sleep [33,34], which promotes hypocapnia;
- a prolonged circulation time [15], which corresponds to the time elapsed between the end of an apnoeic event and the nadir of the associated dip in O₂, and which is considered a surrogate measurement of the cardiac output; prolongation of this time results in deeper hypoxia and, subsequently, compensatory hyperventilation and hypocapnia;
- hypocapnia, the main cause of central apnoea, occurring predominantly at night, though sometimes also observed during the day time [22,32].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Mean left ventricular ejection fraction (%)</th>
<th>AHII ≥ 10</th>
<th>AHII ≥ 15</th>
<th>Sleep apnoea</th>
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<td>–</td>
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**Table 1** Prevalence of obstructive and central sleep apnoea in patients with left ventricular ejection fraction less or equal to 35%, according to a ≥ 10 or ≥ 15 apnoea-hypopnoea index (AHI) cut-off value.

- Values are % of patients.
Hypocapnia, via the central chemoreceptors, causes a decrease in ventilatory amplitude and rate and, below a threshold CO₂ concentration, may cause apnoea [35]. In patients with chronic HF, compared to normal individuals, this apnoeic threshold seems lower during sleep than during waking hours. The slowing or cessation of ventilation causes a rise in CO₂ and ventilation resumes when the CO₂ concentration has returned above the apnoeic threshold. This cyclic phenomenon, or periodic breathing, repeats itself in a sequence of crescendo hyperventilation—decrescendo hypoventilation—respiratory pause. The key role of hypocapnia is highlighted by the elimination of CSA/CSR when patients suffering from chronic HF and hypocapnia during daytime are treated with supplemental inhaled CO₂ during sleep [36]. The high nocturnal pulmonary capillary wedge pressure present in the supine position is one of the upstream complications of advanced chronic HF [34,37]. It increases the pulmonary interstitial pressure that stimulates the alveolar stretch receptors, from which the signals are transmitted to the medulla via the glossopharyngeal and vagus nerves. The medullary response via vagal and sympathetic efferents slows the respiratory muscles activity, decreases the tidal volume and ventilation rate and promotes the development of central apnoea [38,39]. In combination with pulmonary congestion, which inhibits the respiratory reflex, acute hypoxia may prolong the duration of apnoea.

In patients with chronic HF, obstructive respiratory events may be due to OSA present before the development of chronic HF, in which case the events are associated with typical local flaccidity and collapsibility of the pharyngeal soft tissues. Alternatively, the obstructive events are caused by chronic HF and are due to abnormal central respiratory drive and central respiratory events. Normally, the respiratory drive sends simultaneous signals to the motor neurons of the upper airway musculature leading to stiffening and duct patency and to the diaphragm via the phrenic nerves, triggering an inspiratory effort [40] and activating both muscle territories synchronously. During central apnoea, the absence of central respiratory drive decreases the tone of the pharyngeal muscles, because of a decrease in the afferent, phasic neural drive to these muscles. A cyclic decrease in the activity of the diaphragms and pharyngeal muscles has been observed in CSA/CSR and OSA [41,42]. The consequences of a weak or immobile diaphragm are:

- a weak or absent intrathoracic depression;
- a weak or absent depression-obstruction at the pharyngeal level, resulting in a pattern of central respiratory event.

If the diaphragm is only moderately weak, the intrathoracic depression may be sufficient to cause obstruction of the upper airways, resulting in an obstructive pattern induced by chronic HF. Another putative explanation is that moment, the upper airways remain unobstructed, the breathing efforts resume with an in-phase motion of the rib cage and abdomen, consistent with a state of upper airway obstruction. This is probably due to the gradual return of respiratory muscle activity and stiffening of the pharyngeal muscles, however insufficient, to keep the upper airways properly open. If, at that moment, the upper airways remain unobstructed, the breathing efforts resume with an in-phase motion of thorax and abdomen, appearing as momentary central hypopnoea between the apnoeic phase and the return of normal breathing activity or hyperventilation.

Haemodynamic consequences of sleep apnoea

Obstructive apnoea

Obstruction to the upper inspiratory airflow generates a marked, negative intrathoracic pressure, as high as −50 cm H₂O, compared to −10 cm H₂O during normal inspiration. This causes increases in the pressure differential inside the LV, the LV diastolic pressure and, ultimately, the LV filling pressure [44,45]. In addition, the rise in hypercapnia and hypoxia that occur during apnoea trigger bursts of central sympathetic nervous activity at the end of the apnoeic phases, causing arousals that contribute to ending the apnoea and explaining the sleep fragmentation. These bursts may have peripheral manifestations, such as sinus tachycardia, blood pressure surges and increase in LV afterload [46,47]. Left atrial volume and LV systolic performance were both decreased in normal individuals, by reproducing the marked negative intrathoracic pressure present during obstructive respiratory events [48]. The apnoea-related negative intrathoracic pressure increases the venous return, sharply increasing the right ventricular and LV preloads [45]. The higher venous return also acutely distends the right ventricle, causing paradoxical interventricular septal motion which accentuates the abnormal LV filling. Therefore, the effects of obstructive apnoea on the left and right heart cavities may decrease the LV stroke volume. In a background of chronic HF and elevated baseline LV diastolic pressure [49], a repetition of these obstructive apnoeic events is likely to decrease the cardiac output.

Obstructive and central apnoea

Apnoea-related dips in O₂ deprive the myocardium from its O₂ supply and may exacerbate LV failure [50], particularly since myocardial O₂ demand increases simultaneously, and because of the sympathetic surge that occurs at the end of apnoea [15,33]. The increase in sympathetic activity causes further peripheral vasoconstriction, and increases the blood pressure, heart rate [44] and LV afterload [46,47,51], decreasing the stroke volume. In addition, as observed in vascular endothelium, one might hypothesize that the repetition of hypoxic alternating with normoxic periods causes...
myocardial reperfusion injury from oxidative stress, with increased production of free radicals and lipid peroxidation [52]. Finally, the repetitive nocturnal deprivation of myocardial O₂ is likely to promote the progression of chronic HF [15,33,53].

Conclusions

The prevalence of sleep apnoea in patients with chronic HF is high. Sleep apnoea promotes the progression of chronic HF and is a predictor of poor prognosis in patients with chronic HF. Its effect on survival, however, remains uncertain. The management of sleep apnoea in patients with chronic HF is an important endeavour. Cardiologists should participate in the detection of sleep apnoea before referring their patients for management by sleep disorder specialists.

References


