International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Assessment and interpretation of sleep disordered breathing severity in cardiology: Clinical implications and perspectives☆

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ARTICLE INFO

Article history:
Received 9 December 2017
Received in revised form 14 April 2018
Accepted 17 April 2018
Available online xxxx

Keywords:
Sleep disordered breathing
Atrial fibrillation
Arrhythmias
Hypoxia
Sleep apnea
Heart failure

ABSTRACT

Sleep disordered breathing (SDB) is highly prevalent in patients with atrial fibrillation, heart failure and hypertension and is associated with increased risk of mortality, cardiovascular (CV) events and arrhythmias. Current assessment of the severity of SDB is mainly based on the apnea-hypopnea index (AHI) representing the number of hypopneas and apneas per hour of sleep. However, this event-based parameter alone may not sufficiently reflect the complex pathophysiological mechanisms underlying SDB potentially contributing to CV outcome risk. In this review article, we highlight important limitations and pitfalls of current assessment, quantification and interpretation of SDB-severity in patients with CV disease and will discuss pathophysiological considerations from preclinical and clinical mechanistic studies and possible clinical implications.

1. Introduction

Sleep disordered breathing (SDB) is highly prevalent in patients with atrial fibrillation, heart failure and hypertension and is associated with increased risk of mortality, CV events and arrhythmia [1]. Current assessment of the severity of SDB is mainly based on the apnea-hypopnea index (AHI) determined during one or two unattended overnight sleep screenings (polygraphy) or an attended overnight sleep study (polysomnography). The AHI is an event-based measure of severity of SDB based on the number of hypopneas and apneas per hour of sleep. According to guidelines [2–6], treatment of SDB should be initiated when the AHI >30/h, dependent on the symptoms (principally daytime sleepiness) and the concomitant CV disease and risk factors despite the absence of evidence from randomized controlled trials that treatment has any impact on CV events [7]. Being the most established parameter to diagnose SDB, to determine SDB severity and to guide SDB-treatment, the AHI was used as one of the main inclusion criteria in recent clinical trials investigating the effects of SDB-treatment on CV outcome. However, it is generally recognized that the event-based parameter AHI may not sufficiently reflect the complex pathophysiological mechanisms underlying SDB potentially contributing to CV outcome risk, and this may have contributed to unexpected results of recent intervention outcome studies [8–11].

The purpose of this review article is to highlight important limitations and pitfalls of current assessment, quantification and interpretation of SDB-severity in patients with CV disease (Table 1) and to discuss pathophysiological considerations from preclinical and clinical mechanistic studies and possible clinical implications.

2. Established scoring of SDB-severity

2.1. The apnea-hypopnea index (AHI)

Scoring systems for the complex phenomenon of SDB are largely consensus based and have undergone several changes in recent years; towards improving inter-scorer agreement, and responding to an increasing evidence base regarding the association of sleep abnormalities with symptoms, CV outcomes and advances in sensor technologies [12].

The gold standard to diagnose SDB is polysomnography (PSG), which can be either performed in-laboratory, technician-attended (level I) or unattended outside of the laboratory (level II). A portable polygraphy device (PG) recording airflow, respiratory effort

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2018.04.076
0167-5273/

Table 1
Assessment and interpretation of sleep disordered breathing (SDB) severity in cardiology.

Established scoring for SDB-severity	
- Apnea/hypopnea index (AHI)	- Number of apneas & hypopneas per hour
- Subclassification of respiratory events	- e.g. Central vs obstructive respiratory events
Additional signs of SDB-severity (not captured by AHI)	
- Nocturnal temporal distribution of events	- e.g. Events during rapid eye movement (REM) vs non-REM
- Night-to-night variability in SDB severity	- Determined by long-term SDB recording (SDB-burden)
- Nocturnal hypoxemic burden	- e.g. Time below 90% saturation (T90)
- Nocturnal autonomic and hemodynamic changes	- e.g. Heart rate variability, QT interval variability
The bidirectional relationship between SDB and heart failure	
- "SDB begets heart failure"	- Detrimental effects on the heart of SDB (e.g. hemodynamics and cardiac remodeling)
- "Heart failure begets SDB"	- Involvement of hemodynamics in the genesis of SDB (e.g. nocturnal fluid shifts)

and oxygen saturation can be used to screen for SDB. However, as sleep stages are not recorded this is classed as a level III test.

The severity of SDB is evaluated using the AHI [2], defined by PSG as the number of apneas and hypopneas per hour of sleep. In the case of PG AHI is defined per hour of recording and arousals cannot be detected for hypopnea classification, which may systematically under-estimate the actual AHI. Respiratory effort is usually assessed by respiratory inductance plethysmography or other sensors responding to chest and abdominal displacement, and airflow is inferred from a nasal pressure cannula and/or oro-nasal thermistor.

According to the American Academy of Sleep Medicine (AASM) [2], apneas are defined as a >90% drop from the peak signal excursion of the pre-event baseline for >10 s on the oro-nasal thermal or nasal pressure trace, without a requirement for oxygen desaturation (using both traces is important in case of mouth breathing since apneas detected on the nasal pressure trace may actually be hypopneas as evidenced on the oro-nasal trace where there is a persistent signal) [2]. Hypopneas typically occur far more frequently than apneas in obstructive sleep apnea (OSA), and are assessed on the basis of a peak signal excursion drop in nasal pressure by ≥30% for at least 10 s. According to hypopnea definitions, the reduction in airflow needs to be accompanied by a ≥4% drop in oxygen desaturation from pre-event baseline (recommended hypopnea rule A). However, an alternative rule (alternative rule B) specifies that hypopneas must be accompanied by a ≥3% drop in oxygen desaturation from pre-event baseline, or by an arousal. Therefore, the current scoring system of SDB is mainly focused on the occurrence of significant respiratory events, combined with their effects on sleep (arousals) and/or oxygen saturation but it does not take into account the absolute level and duration of oxygen desaturation.

SDB severity in adults is usually defined as mild when the AHI is 5–15/h, moderate when AHI is 15–30/h and severe when the AHI is >30/h [2]. However, the revised scoring rules [2] with a lower threshold for desaturation resulted in increased diagnosis and severity of SDB, including in patients with chronic heart failure [13–15]. Given the increased sensitivity of current sensor technology, signal processing algorithms and different scoring criteria, prevalence data require cautious interpretation. However, the prevalence of SDB in CV disease is clearly very high [16], reaching 30% in patients with coronary heart disease [17], 45% in hypertension [18], 60% in chronic heart failure [19], 60% in atrial fibrillation [20], 60% in patients with end stage renal failure [21] and 90% in patients with drug-resistant hypertension [22].

2.2. Sub-classification of respiratory events

Respiratory events can be classified into obstructive, central or mixed apneas and hypopneas according to the presence, absence or emergence of thoraco-abdominal movements (indicative of respiratory effort) over the course of the event, where changing effort reflects complex underlying pathophysiological interplay between upper airway neuromuscular and respiratory control processes.

Importantly, obstructive as well as central respiratory events, including apneas and hypopneas, may both be present in one patient. However, individual patients generally show either predominant OSA or predominant central sleep apnea (CSA). Predominant CSA is a common comorbidity of heart failure, renal failure and stroke population and rarely present in the remaining population [1]. OSA patients sometimes convert to central sleep apnea once established on continuous positive airway pressure (CPAP) treatment. This likely reflects a central component of unstable ventilatory control underpinning their OSA, which is then unmasked by CPAP. This phenomenon is more prevalent in patients with heart failure and pulmonary oedema where chronic hyperventilation and more unstable ventilatory control promote frequent central apneas during sleep [1]. Additionally, heart failure patients with reduced ejection fraction have been shown to shift from OSA to CSA over the course of a single night, possibly as a consequence of progressive hypocapnia and a lengthening of circulation time [23].

The treatment modality varies depending on the predominant type of SDB. The gold standard therapy for predominant OSA is continuous positive airway pressure (CPAP), which pneumatically splints open the upper airway to maintain upper airway patency, thus alleviating obstructive respiratory events [24]. Minute ventilation adaptive servo ventilation (mvASV) was considered to be the most effective strategy to suppress predominant central sleep apneas/Cheyne-Stokes respiration (CSA/CSR) [25–28]. mvASV ensures upper airway patency by a fixed or varied amount of expiratory positive airway pressure, and the application of a varying amount of inspiratory pressure support sustains inspiration when the device detects decreased breathing amplitude during hypopneas, and ensures inspiration with sustained breathing efforts during central apneas. In the "SERvo VEntilation in patients with Heart Failure and reduced ejection fraction (SERVE-HF)" trial, which recruited patients with symptomatic heart failure (NYHA class II–IV), left ventricular ejection fraction <45%, and predominant CSA/CSR, mvASV increased the secondary endpoint of CV mortality by 34% [10,11]. Therefore, mvASV should not be initiated in patients fulfilling the inclusion criteria for SERVE-HF (symptomatic heart failure (NYHA class II–IV), left ventricular ejection fraction <45%, and predominant CSA/CSR) [5,26]. The Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure trial (ADVENT-HF, clinicaltrials.gov identifier: NCT00733343) [27] is still ongoing and investigates the role of a different, peak flow ASV algorithm applied with lower default pressures on long-term clinical outcomes in patients with heart failure with reduced ejection fraction and includes patients with either predominantly OSA or predominantly CSA/CSR [28]. With over 60% of enrolment complete, the trial's data and safety monitoring board has identified no safety concerns at any of its 6 month reviews and recommended that this trial continue as per protocol.

CV responses to central respiratory events may differ significantly from responses to obstructive respiratory events [1]. While obstructive respiratory events are mainly caused by mechanical obstructions of the upper airway during sleep, central apneas are caused by central dysregulation of respiratory control and are characterized by periodic episodes of hyper- and hypoventilation resulting in intermittent changes in tidal volume and CO_2. Increased sensitivity of peripheral and central chemoreceptors, pulmonary congestion and prolonged circulation time and event lengths [28–31] may contribute to dysregulation of respiratory control. The cycle length of hyperpnea in CSA/CSR is directly related to lung-ear circulation time and hence inversely proportional to cardiac output [30].

Intrathoracic pressure swings during ineffective inspiration against an occluded upper airway in OSA result in myocardial stretch and changes in transmural pressure gradients [1,32], which can contribute to structural remodeling processes and the development of ventricular and atrial cardiomyopathy [33]. Additionally, large swings in intrathoracic pressure can lead to cyclic changes in atrial dimensions and opening of a persistent foramen ovale which can potentially contribute to stroke [1]. Negative intrathoracic pressure has been shown to be associated with a combined sympatho-vagal activation (diving reflex) [34] which leads to transient atrial [35] and ventricular [36] electrophysiological changes which can contribute to atrial and ventricular arrhythmogenesis. In comparison, similar electrophysiological and muscle sympathetic nerve activity changes were not observed during simulated central apneas (holding breath) with comparable drops in oxygen saturation, but without intrathoracic pressure changes [36,37]. In heart failure patients, simulated obstructive apneas (Mueller manoeuvres) elicit greater increases in sympathetic activity measured by muscle sympathetic nerve activity than simulated central apneas (holding breath) [37]. Increased breathing effort frequently triggers brief arousal during obstructive apneas and hypopneas, and in the phase of hyperventilation and hyperpnea of CSR. Post-apneic blood pressure rises and activation of the circulating renin angiotensin system seem to be more pronounced with simulated repetitive obstructive respiratory events than with central apneas in a pig model with simulated sleep apnea [38,39]. Increases in sympathetic nerve activity carry over into wakefulness [40]. This mechanism may contribute to the high prevalence of secondary hypertension in OSA [1]. Daytime sympathetic discharge can be reduced by effective CPAP treatment [41].

Despite its importance and CV relevance, intrathoracic pressure is not routinely measured during sleep studies, as this requires an oesophageal pressure probe associated with some discomfort to the patient.

3. Additional signs of sleep apnea severity

Treatment of SDB is generally guided by SDB severity (mainly quantified by the AHI), symptoms (i.e. daytime sleepiness determined by questionnaires) and the sub-classification of SDB (OSA vs. CSA). Until recently, other characteristics of disturbed breathing during sleep, such as the nocturnal temporal distribution of respiratory events, long-term night-to-night variability in SDB-severity, or the burden of nocturnal hypoxemia have been given less weight when considering whether or not to treat patients with SDB.

Please cite this article as: D. Linz, et al., Assessment and interpretation of sleep disordered breathing severity in cardiology: Clinical implications and perspectives, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.04.076