

Review

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Review

The Contribution of Sleep Texture in the Characterization of Sleep Apnea

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Abstract: Obstructive sleep apnea (OSA) is multi-faceted world-wide distributed disorder exerting deep effects on the sleeping brain. In the latest years strong efforts have been dedicated to find novel measures assessing the real impact and severity of the pathology, traditionally trivialized by the simplistic apnea/hypopnea index. Due to the unavoidable connection between OSA and sleep we reviewed the key aspects linking the breathing disorder with sleep pathophysiology, focusing on the role of cyclic alternating pattern (CAP). Sleep structure, reflecting the degree of apnea-induced sleep instability, may provide topical informations to stratify OSA severity and foresee some of its dangerous consequences such as excessive daytime sleepiness and cognitive deterioration. Machine learning approaches may reinforce our understanding of this complex multi-level pathology, supporting patients' phenotypization and easing a more tailored approach for sleep apnea.

Keywords: cyclic alternating pattern; sleep texture; sleep apnea; polysomnography

1. Introduction

Sleep-disordered breathing (SDB) defines a heterogeneous group of sleep pathologies encompassing obstructive sleep apnea (OSA), central sleep apnea (CSA) and other rarer sleep-related breathing pathologies.

OSA is a world-wide diffused disorder associated with serious multi-systemic consequences. Conventionally OSA is investigated by means of home-set nocturnal cardio-respiratory recording, and diagnosis is based on the number of respiratory events occurring per hour of sleep, as expressed by the apnea-hypopnea index (AHI). A minimum of 4 recording hours is required to consider the sleep study reliable for diagnosis and, according to the number of respiratory events, the clinical relevance is classified as mild (AHI: 5-14 events/h), moderate (AHI: 15-30 events/h) or severe (AHI > 30 events/h).

As the condition is typically associated with both diurnal and nocturnal consequences, their assessment is also required, according to current diagnostic criteria. In the International Classification of Sleep Disorders (ICSD-3), sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance and observed apneas, associated medical or psychiatric disorders support the diagnosis of OSA.

Notably, the coexistence of other chronic diseases, especially cardiovascular disorders, has been evaluated to assess prognosis, and the novel indicator of C-OSA (comorbid-OSA) has been proposed to ease sleep clinicians in the evaluation of mortality risk in patients with OSA [1]. In a bidirectional perspective, if the concurrence of other disabling pathologies may worsen prognosis, intermittent hypoxia and sleep-fragmentation induced by OSA can increase the severity of comorbid cardiovascular and metabolic pathologies [2]. Moreover, C-OSA with cardiovascular diseases may

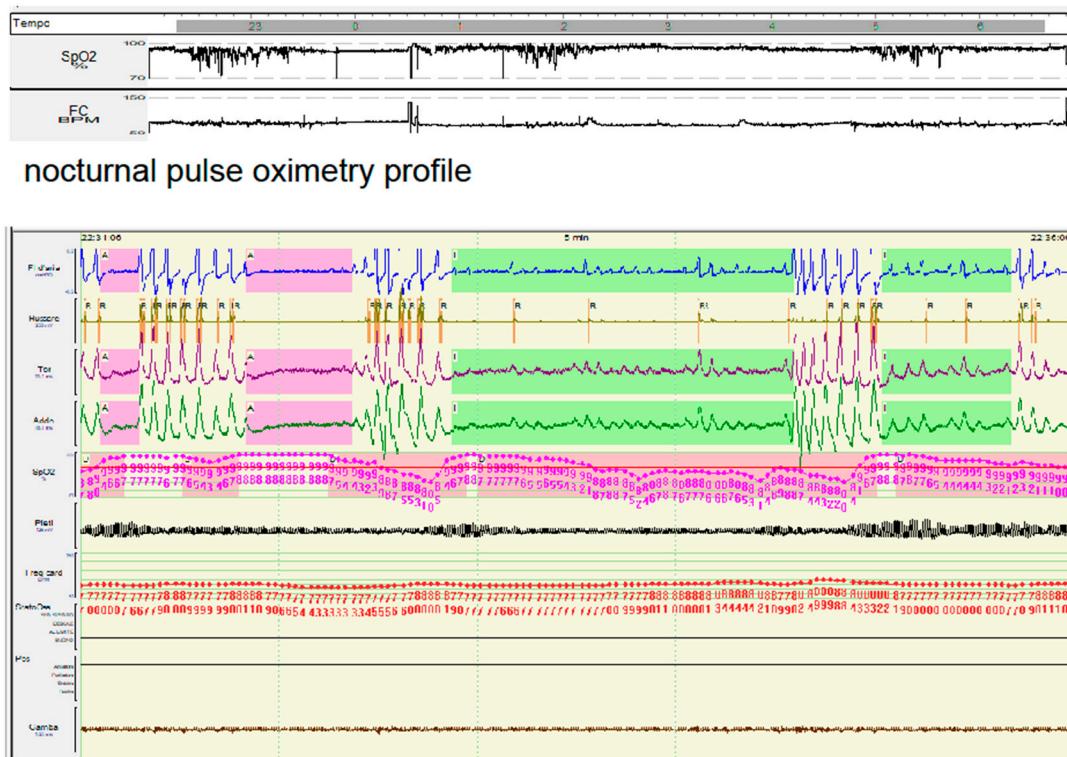


co-exist with central-type respiratory patterns, such as Cheyne-Stokes breathing (CSB). It has been recently proved that the remote monitoring of CPAP devices in OSA patients may reveal early signs of incipient heart failure, such as long cycles of CSB [3]. The tight association between clinical disorders and sleep apnea, suggest to seek for SDB in all patients.

2. The Limits of AHI

Once sleep apnea has been identified, it is important to measure severity with reliable methods. The predictive value of AHI has been evaluated in a real-world setting, demonstrating a low sensitivity (19%) and a high specificity (84,4%) in the identification of patients affected by mild, moderate or severe OSA [4]. AHI also fails in the identification of OSA patients at higher risk for diabetes, while the hypoxic burden appears more reliable to predict the metabolic consequences of the disease [5]. Overall, AHI appears as a poor indicator for disease severity and alternative measures are deemed necessary.

In fig. 1 we summarize the polysomnographic data of a 52 year-old obese Italian woman (body mass index 42), with a personal history of arrhythmia and nocturnal sinus pauses, complaining of snoring and non-refreshing sleep. Her cardio-respiratory recording was consistent with a mild OSA (AHI 12,2 events/h). However looking at the Sat O₂ profile and the morphology of her apneas, we could ascertain that the hypoxic load of the patient was compatible with a much more severe clinical condition and thus, regardless of the number of respiratory events measured by the AHI, nocturnal non-invasive ventilation was applied with clinical benefits.



Detail on nocturnal respiratory events

Figure 1. Example of a nocturnal pulse oximetry profile (upper part of the figure), with a detail on her nocturnal respiratory events (lower part of the figure), in a female patient affected by mild OSA (AHI 12,2 events/h). Despite the lower value of AHI her hypopneas (highlighted in light green) were associated with severe drop of oxygen saturation and respiratory efforts.

In the latest years increasing efforts have been dedicated to the identification of non-AHI-dependent measures for OSA severity, the most significant being the Sleep Revolution Project [6].

Furthermore, current definitions neglect the 'OSA patients' pathophysiologic traits', such as upper airway function, anatomical collapsibility, loop gain, arousal threshold, and sleep structure.

3. OSA and Sleep Architecture

Curiously, SDB occur during sleep, but the recording of brain activity during sleep is not required for diagnosis. This contradiction is due to the high costs and demanding effort to carry out a complete video-polysomnography (PSG) recording, a burden which can be easily by-passed to screen a condition that affects nearly a billion of people world-wide [7]. However it is well-known that OSA strongly impacts the structural organization of the sleeping brain. Compared to healthy subjects, patients with sleep apnea show reduced amounts of slow-wave sleep (SWS) and increased amounts of lighter sleep stages. Severe OSA also presents a longer latency to stage N3 compared to the mild and moderate subtypes [8]. Regardless of the OSA severity, the number of respiratory events in stage N3 is significantly lower compared to the other sleep stages [8]. The lack of respiratory events during SWS probably depends on the higher stability of this sleep stage, which physiologically contains minor amounts of microstructural oscillations [9]. Human NREM sleep is characterized by periodic oscillatory patterns that reflect its inner adaptability and readiness [10]. The cyclic alternating pattern (CAP) is the main representative of NREM microstructural dynamics and is deemed as the electroencephalographic (EEG) hallmark of sleep instability [11].

The restorative power of sleep is influenced by the amount of CAP [12], expressed by repetitive cycles composed of a phase A (activation) and its subsequent phase B (de-activation). Each phase of the CAP cycle is 2 to 60 s in duration. At least two CAP cycles are required to identify a CAP sequence. The amount of CAP oscillations during NREM sleep is measured by CAP rate.

According to the EEG features, CAP A phases can be further classified as subtypes A1, A2 and A3. In the A1 subtype the EEG synchrony (high-amplitude slow waves) is the predominant activity and, if present, EEG desynchrony (low-amplitude fast waves) occupies less than 20% of the entire phase A duration. Phase A2 subtype is characterized by a mixture of slow and fast rhythms with 20% to 50% of phase A occupied by EEG desynchrony. Finally CAP phases A3 are dominated by rapid low-voltage rhythms with more than 50% of phase A expressed by EEG desynchrony [13]. The distinction between phase A subtypes is not trivial as they have different roles in sleep organization. Subtypes A1 prevail in the first half of the night and boost the build-up and consolidation of SWS, while subtypes A2 and A3 increase in the second part of the night and prepare the sleeping brain for the appearance of REM sleep or wakefulness. Furthermore, subtypes A3 exert a stronger impact on cardiovascular parameters compared to subtypes A1 and A2 [14]. Overall, CAP metrics quantify the magnitude of stressful perturbation on the sleeping brain [15].

CAP also reflects the specific impact of diseases on sleep organization providing additional information compared to the American Academy of Sleep Medicine (AASM) arousal rules in OSA patients, the physiological behavior of sleep instability (involving both respiratory events and EEG activation) overcomes the limited quantification of conventional 'fast arousals' [16].

Accordingly sleep instability, which represent one of the main responsible for excessive daytime sleepiness in OSA patients, cannot be measured only with the count of AASM conventional arousal, but should also include the (commonly neglected) 'subcortical arousals', which are frequently accompanied by various degree of autonomic stimulation [17]. In this perspective sleep microstructure may be highly informative. In the clinical domain, CAP subtypes A1 prevail in the milder OSA phenotype, whilst subtypes A2 and A3 abound in patients with moderate-to-severe OSA [18]. If the CAP system still promotes sleep continuity in milder cases, the situation becomes unbalanced in moderate-severe OSA, where the CAP system turns into an intrusive phenomenon, perturbing sleep dynamics [18]. The existence of two distinct arousal-related mechanisms in human sleep is similar to what has been described in rodents [19]. According to this model, depending on the stimulated regions of the parabrachial nucleus (PBN), arousal may yield to either fast frequency bursts, strongly similar to A2/A3 CAP subtypes (when the more lateral regions of the PBN are stimulated) or high-amplitude slow-waves, in response to the medial PBN stimulation [20]. In this perspective, CAP can phenotype the 'arousal-gate' in patients with sleep apnea.

Sleep microstructure can also inform on the neurobehavioral adaptability to sleep fragmentation in OSA patients. In fact it has been suggested that the AHI is inconsistently associated with behavioral performances in patients affected by sleep apnea: while some patients may be highly vulnerable to sleep loss, some other can be impressively resistant to the negative effects of sleep deprivation [21]. This is not trivial as, for instance, individual resilience to sleep loss might influence driving performance and subsequent risk for car crashes [21]. While conventional polysomnographic metrics nor AASM arousal index were predictive of neurobehavioral impairment, it has been documented that higher EEG slowing ratio during REM and lower spindle density at the frontal EEG were significantly associated with slower reaction time on psychomotor vigilance task and driving simulator test [22](Parekh et al., 2019). In parallel it has been demonstrated that, in ventilated OSA patients, the utilization of suboptimal continuous positive airway pressure (CPAP) may favor the recurrence of sustained inspiratory airflow limitation, which in turns is associated with abnormal K-complexes (coupled with bursts of alpha as arousal surrogates). Hence suboptimal CPAP therapy can lead to subtle/'nonvisible' sleep fragmentation [23].

Another interesting measure adopted to indicate sleep continuity is represented by the Odds ratio products (ORP) [24]. The ORP represent an attempt to capture the transitions within sleep/wakefulness states during clinical polysomnography, in order to overcome the rigid subdivisions imposed by the conventional Rechtschaffen and Kales rules for PSG scoring. ORP correlate with sleep depth and quality, this metric is calculated as a ratio of the absolute power of different frequency bands over 3-s segments. ORP ratio ranges from 0 to 2.5, with 0 indicative of very deep sleep and 2.5 related to wide awake state [24]. The utilization of ORP might serve as novel biomarkers for PSG in various sleep conditions. In OSA for instance it has been proved that, compare to healthy sleepers, ORP are usually lower during wake (suggesting increased sleep propensity), but higher NREM (consistent with lighter NREM sleep) [25]. Among the advantages of using ORP there is the possibility to verify the arousal effects' towards sleep depth, which can be inferred by the speed with which sleep deepens following an arousal, to so-called postarousal sleep dynamics [26]. When ORP is high, arousal stimuli can easily trigger arousal, whereas when ORP is low strong stimuli are required to provoke an arousal. In other words, the metric of ORP inform us to what extent patients can recover sleep after arousal intrusions [26].

Although the disorder is typically evaluated using cardio-respiratory recording, some informative features can be inferred on the ongoing brain activity: for instance the pulse wave amplitude has been associated to the amount of EEG response (including CAP features) to respiratory events, suggesting a strong coupling between cortical and autonomic activation [27].

4. Breathing Oscillations, Daytime Sleepiness and Treatment Outcomes

The temporal association between CAP oscillations and respiratory events is predictable: most apneas/hyponeas in fact co-occur with CAP phase B and thus the disease is frequently defined as a prototypical example of a CAP phase-B disorder [28]. As a translation of the lesser arousal branch of arousal swings, phase B represents a highly vulnerable background for upper airway collapse and for attenuation of biochemical and neural mechanisms in the control of the ventilatory drive, while the A phase is mandatory to restore breathing. It has been demonstrated that the vast majority of respiratory events are coupled with CAP (96% in NREM and 80% in REM sleep). In details, the apneas and hypopneas are commonly temporally associated with a CAP phase B, while breathing restoration is typically recovered during phase A [29]. Recently, a large study analyzing over 1.6 million cortical arousals, 350,000 apneas and over 1.9 million hypopneas collected from 11,400 manually scored PSG recordings available online, demonstrated that the duration of 95-99% of all respiratory events falls beneath 60 seconds [30]. This finding is supported by a solid physiological background as the length of CAP phase B (which triggers and supports breathing interruption) spans within the 1 min interval [12].

CAP metrics correlate with subjectively perceived daytime sleepiness in patients with OSA [31]. In male subjects with moderate to severe OSA, CAP rate, CAP duration, the number of CAP cycles, and the duration and percentage of the subtypes A2 are significantly higher in patients with excessive

sleepiness (ES) compared to those non-ES. In contrast, the two groups (ES vs non-ES) showed no differences in conventional sleep parameters. In other words, higher levels of arousal activation induced by respiratory events determine a more aggressive sleep fragmentation which leads to a more somnolent daytime setting.

PSG can also be used to assess treatment benefits on patients with severe OSA. It has been proved that continuous positive airway pressure (CPAP), the first-line treatment for moderate-to-severe OSA, increases the duration of N3 and decreases the lightest NREM sleep stages. With respect to microstructural PSG parameters, the reduction of respiratory events promotes an attenuation of CAP fluctuations, in particular, during stage N3, and a parallel increase of the CAP oscillations that occur independent from apneas/hypopneas [32]. In this perspective we can summarize that CPAP promotes the restoration of a more physiological CAP oscillatory pattern, with oscillations that are disengaged from breathing constraints. Interestingly, the timing of CPAP-dependent PSG variations is not the same for all sleep features: for instance CPAP treatment induces an immediate restoration of sleep continuity, a more consolidated REM sleep, a curtailment of sleep latency and an enhancement of SWS, while the amount of CAP cycles and A1 subtypes remain below normal values even one month after the introduction of ventilatory support [33](Fig.2). An impressive increase in the SWS occurs already during the first night of CPAP, together with a parallel normalization in the overall duration of CAP phases A and B, both significantly longer in patients with severe OSA [34]. Furthermore, in patients with severe OSA treated with CPAP, variations of CAP rate significantly correlate with daytime vigilance [34].

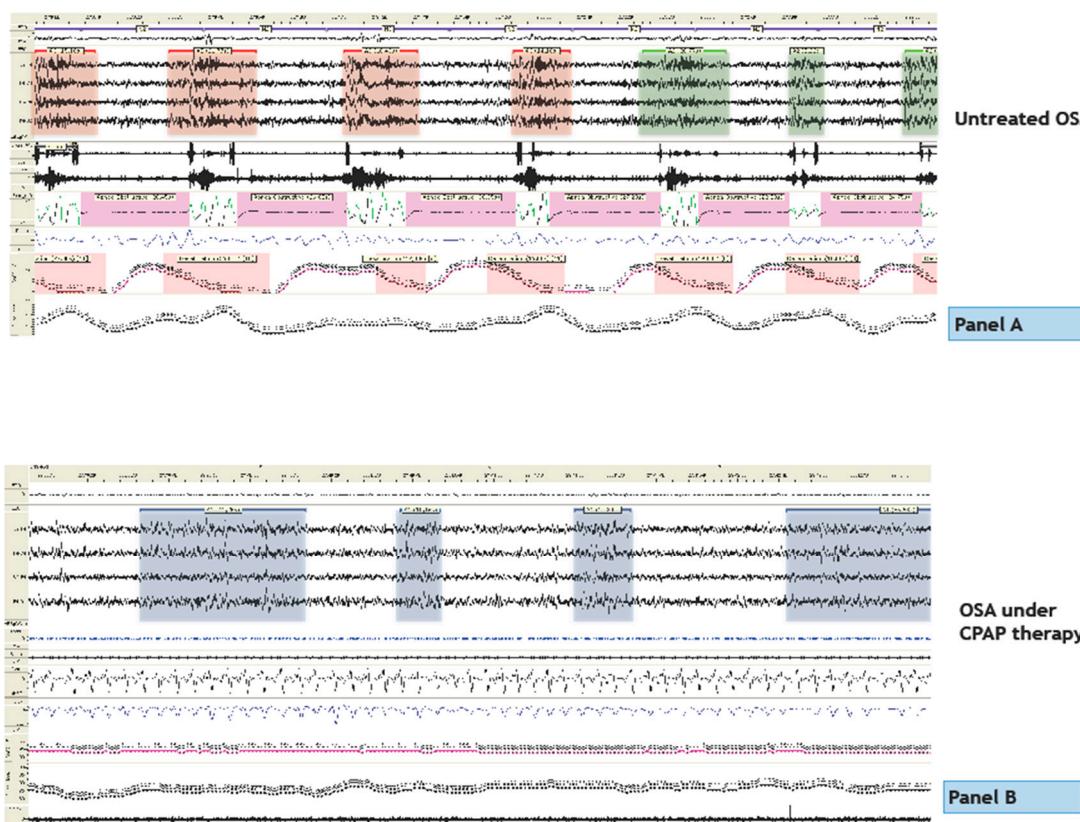


Figure 2. Polysomnographic example of a patient affected by severe OSA before (panel A) and after (panel B) the introduction of CPAP. Panel A: note the tight association between apneas and cyclic alternating pattern (CAP) oscillations, with strong prevalence of subtypes A2 and A3, with high autonomic impact; panel B: observe the restoration of physiologic CAP oscillations, with predominance of subtypes A1.

Sleep recordings may also provide information on the impairment of cognitive processes, a detrimental consequence in patients affected by untreated OSA [35,36]. The extent of cognitive impairment, assessed with Montreal Cognitive Assessment (MoCA), has been found to be related to the severity of sleep fragmentation as expressed by the CAP A3 rate in patients with sleep apnea [37]. A similar association between CAP metrics and cognitive deterioration has been described by Karimzadeh et al. [38], who demonstrated a direct correlation between the quantity of CAP phase A1 fluctuations and cognitive performances, especially in the verbal fluency, memory and visuo-spatial skills, in patients affected by OSA. Patients suffering from sleep apnea presented higher density of CAP phase A oscillations within the fronto-parietal regions, a condition that may interfere with NREM sleep-dependent cognitive processes. Recently, impaired social cognition has also been identified in middle-age patients affected by OSA with no other relevant neurological or psychiatric conditions, potentially associated to the pathology-dependent impairment of REM sleep stage [35].

The application of CAP scoring can support the phenotyping of various diseases as demonstrated for Down syndrome, Fragile-X syndrome and attention deficit hyperactivity disorder, where the evaluation of sleep microstructure can help in the identification of patients suffering between 'primary disease forms' (lower amounts of CAP oscillations) from those with coexistent sleep-related breathing disorders (higher CAP rate values) [39,40]. In the latest years, the European Sleep Apnea Database (ESADA) has tried to detail OSA heterogeneity using clustering procedures. The OSA clusters identified from the ESADA consortium are based on gender, age, symptoms, comorbidities and respiratory features, but so far no conventional PSG measures have been included. The possibility to identify OSA phenotypes might improve patients' prognostication and ease the identification of targeted therapies. From an operational point of view 'phenotypes' can be described as: "*A category of patients with OSA distinguished from others by a single or combination of disease features, in relation to clinically meaningful attributes (symptoms, response to therapy, health outcomes, quality of life)*". The possibility to reveal through phenotypes individual differences is fundamental to tailor treatment prescription and to increase long-term compliance [41]. For instance, it has been demonstrated that patients with REM-dominant OSA present reduced total sleep time, decreased sleep efficiency and lack of REM sleep representation [42]. REM-dominant OSA patients also present reduced response to mandibular advancement splints [43] and, due to the association between REM-related AHI indices and incident hypertension, they likely deserve non-invasive ventilation, which should be guaranteed in the second half of the night, when REM sleep is largely prevalent [44,45]. Conversely, patients with NREM-dominant OSA present higher ventilator control instability during NREM sleep (which paradoxically improves during REM sleep), a condition that may co-exist with low arousal threshold and which might benefit from pharmacological –sleep-stabilizing– approaches [46–48].

In this perspective, the utilization of polysomnographic features (with combined macro and microstructure analysis) may reinforce the reliability of any attempt of OSA phenotypization, leading to strongly predictive approaches, with potential clinical implications.

5. The Contribution of Machine Learning

In order to curtail a timely OSA diagnosis, a number of portable/wearable hardware devices, based on machine learning approaches, have been proposed to screen for this condition. Their lower costs and the ease of use compared to conventional polysomnography stand out among the major advantages. However the absence of a medical supervision may expose patients to the risk of less accurate diagnosis. Most of these devices work on photoplethysmographic (PPG) sensors to detect oxygen desaturations. In this case the information regarding breathing events is indirectly collected from blood flow patterns in the microvascular tissue bed [52]. Although still insufficient to ascertain diagnosis, the utilization of wearable devices has gained increasing importance in the screening of subjects with a high-risk for OSA [53]. Artificial intelligence can be adopted to evaluate polysomnographic findings in order to screen for sleep apnea. The automated classification of polysomnographic features (including macro and microstructure data) has already been tested for various sleep pathologies including narcolepsy, rapid eye movement behaviour disorder, periodic

leg movement disorder, sleep-related epilepsy and insomnia [54,55]. Considering the strong impact of OSA on the sleep organization, the availability of automated methods to score sleep recordings might ease the identification of clusters of electrophysiological data, potentially related to distinct clinical phenotypes. In this perspective machine learning could represent a relevant step forward in the intricate scenario of sleep apnea diagnosis and phenotypization. So far the most important applications of artificial intelligence in obstructive sleep apnea have been: 1) predicting treatment outcomes of various treatment options, 2) improving treatment options, and 3) personalizing treatment thanks to the enhanced understanding of underlying mechanisms of the disease [56]. This new 'personalized' approach to sleep apnea may increase patients' compliance and increase the efficacy of proposed approaches. The utility of machine learning has been suggested to select patients addressed to CPAP therapy, surgical treatment and/or oral appliances. The possibility to predict therapeutic success with non-invasive techniques represents an ambitious goal for sleep specialists. Due to unavoidable links between autonomic system and electroencephalographic findings, few authors explored the bidirectional association between cardiopulmonary functioning and EEG signal. Simplifying all the NREM sleep stages into two opposite dimensions, i.e., stable versus unstable NREM sleep, it has been proved that stable breathing periods result in high frequency coupling of respiration and HRV, with simultaneous presence of higher EEG delta power. In parallel, the so-called unstable NREM sleep may be recognized by a sleep fragmentation phenotype [57]. Sleep apneas are strongly associated to cardiovascular consequences and autonomic imbalance. The periodic alterations in sympathetic nervous activity and parasympathetic nerve activity during each respiratory event define a peculiar heart rate pattern, which seems like a signature of the condition. Typically we can notice a drop in heart rate, which is a physiological reaction to the apnea (known as the "diving reflex"), immediately followed by a phasic acceleration in heart rate (the relative tachycardia), restoring blood gas exchange in the lung. This alternation can also be schematized in terms of periodic shifts between parasympathetic and sympathetic tone dominance. Given the periodic reproducibility of these cardiological variations, mathematical approaches and machine learning techniques have been adopted to assess their dynamics in sleep apnea. However, due to inter and intra-individual variability of cardiovascular activity related to physical training conditions, age, weight, and concomitant diseases, the utilization of the sole cardiac signal is still largely insufficient to represent OSA severity [57,58].

6. Conclusion

Although international guidelines promote the 'one-size-fits-all' strategy for OSA management, it is important to remember that the disease may present important inter-individual differences, reasonably warranting a more tailored approach. In this framework, video-PSG and sleep microstructure could provide additional information in the clinical management of patients with SDB. In addition, CAP-related arousal instability seems to be one of the key mechanisms explaining cognitive decline and vigilance impairment in sleep apnea [17]. The cost and complexity of CAP scoring can be overcome by the availability of reliable automatic scoring systems [59], which will help both researchers and clinicians to better define the impact of SDB on the sleep texture as well as neurological and extra-neurological consequences. The vertical integration of combined approaches might ease our understanding of this complex sleep pathology.

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