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Summary

Catathrenia is a loud expiratory moan during sleep that is a social embarrassment and is sometimes confused with central apnea on polysomnography. It affects about 4% of adults, but cases are rarely referred to sleep centers. Catathrenia affects males and females, children and adults, who are usually young and thin. A "typical" catathrenia begins with a deep inhalation, followed by a long, noisy exhalation, then a short, more pronounced exhalation, followed by another deep inhalation, often accompanied by arousal. The many harmonics of the sound indicate that it is produced by the vocal cords. It is often repeated in clusters, especially during REM sleep and at the end of the night. It does not disturb the sleepers, but their neighbors, and is associated with excessive daytime sleepiness in one-third of cases. The pathophysiology and treatment of typical catathrenia are still unknown. Later, a more atypical catathrenia was described, consisting of episodes of short (2 s), regular, semi-continuous expiratory moans during NREM sleep (mainly in stages N1 and N2) and REM sleep, often in people with mild upper airway obstruction. This atypical catathrenia is more commonly reduced by positive airway pressure and mandibular advancement devices that promote vertical opening.

Key words: catathrenia; expiratory groaning; central apnea; parasomnia; sleep-disordered breathing

Abbreviations

ICSD: International classification of sleep disorders

MAD: Mandibular advancement device

PAP: Positive airway pressure

NREM: Non rapid eye movement sleep

REM: Rapid eye movement sleep

1. Introduction

Catathrenia is an exhalation sound similar to a whimper that occurs exclusively during sleep, especially REM sleep, and almost every night. The sound is loud and may disturb roommates. It is a little-known and relatively rare sleep disorder that is probably underdiagnosed. Yet it fascinates clinicians who first hear it because of its loud, sudden, human-like, and mysterious nature. It contrasts with the absence of laryngeal abnormalities during wakefulness. Its mechanism and treatment are poorly understood and controversial.

2. History

The first case was reported in 1983 in a congress abstract [1]. The authors described a strange nocturnal moaning that had occurred every night since the age of 10 (shortly after recovery from Stevens-Johnson syndrome) in a 35-year-old engineer. His wife could no longer tolerate the noises at night. Polysomnography ruled out snoring or apnea, helped to localize the noise in REM sleep, while concurrent electroglottography indicated that the noise was produced by the vocal cords. Between 1983 and 2001, this disorder was not reported. Two small case series were published in 2001 [2, 3]. Vetrugno et al. described four young people between the ages of 15 and 23 whose nocturnal noises disturbed those around them, while the patients themselves had no complaints [2]. They proposed that the disorder be called "catathrenia," a neologism derived from the Greek roots *kata* meaning "below," and *threnia*, meaning "to lament". Pevernagie et al. reported on ten patients who underwent polysomnography using an esophageal probe and a tracheal microphone [3]. However, this disorder was not included in the 2001 International Classification of Sleep Disorders (ICSD) [4]. It was classified as a parasomnia in the revised version of ICSD-2 in 2005 [5], and then as an isolated symptom in the Sleep-Disordered Breathing chapter of ICSD-3 in 2014 [6]. This back-and-forth classification illustrates the difficulty of classifying this disorder as a parasomnia or a sleep-disordered breathing when the pathophysiology is unclear. The literature begins with isolated case reports and small, mostly descriptive series. The authors then report on therapeutic trials, usually based on medication if the disorder is thought to be a parasomnia, or on positive airway pressure (PAP) or a mandibular advancement device (MAD), if it is thought to be a respiratory disorder. Finally, while cases were initially described primarily in REM sleep, several authors have subsequently reported expiratory noises in NREM sleep and discussed their similarities and differences with REM catathrenia [7].

3. Systematic review methodology

The search using the words "catathrenia," "nocturnal groaning," "sleep-related groaning," and "expiratory groaning" in the PubMed database from 1980 to December 2023 yielded 67 references. After eliminating 7 reviews, 4 articles written in Chinese, and 2 unrelated articles, this systematic review included 54 articles. Clinical cases published as conference abstracts were not included because their full content was not accessible. A total of 261 cases (single cases or case series, including 253 cases with primary catathrenia) were analyzed after eliminating duplicates. Case information was reported in a table, including country, sex, body mass index, age at diagnosis, age at onset, comorbid conditions, sleep study measures, and treatment trials and their effects.

4. Epidemiology

4.1. Prevalence

Patients with catathrenia have been reported on several continents. First reported in Europe, they have been described in Belgium [1, 3, 8, 9], Italy [2, 10-16], the United Kingdom [17-19], Portugal [20-22], Spain [23-28], the Czech Republic [29], Germany [30, 31], Switzerland [32], Norway [33] and France [34]. In the Americas, cases have been reported in the United States [18, 19, 35-44] and Peru [45], and in Asia, in Turkey [46], South Korea [47, 48], India [49], China [50-52] and Japan [53, 54]. No cases have been reported in Africa or Australia.

The exact prevalence of the disorder is difficult to determine because of confusion with mimics and possible benign cases that do not seek medical attention or are identified incidentally during a sleep study. For example, among 21 children identified with catathrenia over 23 years in a pediatric sleep laboratory, catathrenia was the chief complaint in 24% and was incidentally identified in 76% who were referred for respiratory distress. [38]. In an epidemiological telephone survey focused on the prevalence of parasomnias in a random sample of 1,000 adults in Norway, up to 31.3% reported lifetime sleep-related groaning (snoring - but not stridor - was excluded), 13.5% had current symptoms, and 4.2% had current weekly symptoms [55]. Subjects with apnea symptoms were more likely to report sleep-related groaning than those without apnea symptoms. This high frequency contrasts with the rarity of cases referred to sleep centers. Pevernagie et al. identified 10 cases of catathrenia among 1836 subjects referred to their sleep center in Belgium over 3 years, or 6 cases per 1000 patients and 0.5 new cases per year [3]. Overland et al. identified 4 patients out of 1004 (4 per 1000) who underwent polysomnography over a one-year period at a center in Norway [33]. A recent study conducted through social networks (Yahoo and Facebook) in the United Kingdom gathered 667 people who claimed to suffer from this disorder [19]. Finally, a more detailed questionnaire was used to identify 47 potential cases of catathrenia among these 667 individuals. Of the 29 who underwent polysomnography, only 5 had an expiratory moan, underscoring the difficulty of identifying this disorder in the general population by simple media questioning.

4. 2. Gender

Men and women are equally affected by this disorder **(Table 1)**. In the largest series of 38 patients, there were more males (N = 23, 60%) than females (N = 15) [18]. In contrast, there were more females (15/22; 68.8%) in the series of Hao et al. [50]. Finally, by synthesizing the case series and individual case reports, i.e., a total of 253 people with a primary form of catathrenia, we calculated a ratio of 57% males and 43% females.

4. 3. Age

Catathrenia has been reported as early as birth [38] and as late as 76 years of age [35] **(Table 1)**. In individual case reports, the mean age at diagnosis is 30 years. However, of the 71 patients for whom information is available, 32.4% were diagnosed in childhood, 33.8% in adolescence, and 32.4% in young adulthood. Thus, the majority of cases of catathrenia occur before the age of 30. A recent series from Boston Children's Hospital included 21 children. Parents reported onset between birth and 6 years of age, with a mean age at diagnosis of 8 years [38]. In general, these individuals are not obese. Most cases are sporadic, but two groups reported a family history of catathrenia (unrecorded) in 4 (14.8%) of cases, including siblings, a pair of twins, father-son, and cousins [12, 50].

5. Clinical features

5.1. Noise characteristics

Catathrenia is a noise produced by the sleeper during exhalation, that occurs after a deep inspiration and persists during this prolonged exhalation (**Video-clip**). It is most often high-pitched but can also be low-pitched [6]. Depending on the author, it has been described as a whimper, a “gloomy lamentation”[13], a groan, or a grunt. The sound is monotonous and almost identical from night to night. It is produced in a plateau at the beginning of exhalation, and increases in intensity just before the end. It usually occurs in series of 2 to 33 episodes, without rhythmic character, or in isolation. It varies in intensity from 20 to 75 dB: it can be as loud as the noise produced in a classroom [25, 47]. The shape of the sound wave was measured by oscillogram and spectrogram and analyzed with a multidimensional speech program in 5 patients [47]. The shape was regular and sinusoidal in three of them (Yanagihara type 1, according to the International Classification of Sounds) and semi-rhythmic (sawtooth-like) in the other two (Yanagihara type 2). All patients had formants (a concentration of acoustic energy around a particular frequency in the vocal wave, coming from the vocal tract) and harmonics (the faster vibrations that occur simultaneously, coming from the vocal cords) suggesting that the generator of catathrenia may be adjacent to the vocal cord region. In addition to the fact that it occurs during expiration rather than inspiration, it is distinguished from snoring on the spectrogram by the numerous harmonics formed from the fundamental frequency **(Figure 1)**.

5.2. Impact of catathrenia

Patients are usually unaware that they are making a noise during sleep. Diagnosis is made on the basis of complaints from bedfellows or incidentally by polysomnography. Noise may be reported by parents of young children [17, 34, 38], in boarding schools, by roommates, and by spouses. The noise is loud and may exclude the patient from the room when sleeping in pairs or in a group. Some patients complain of a hoarse throat in the morning [24]. The reasons for consultation in one series were complaints of groaning (52.6%), apnea (50%), snoring (18.4%), buzzing (5.2%) and grunting (5.2%) [18]. However, some patients report asthenia, unrefreshing sleep (7.8%), and sometimes a feeling of shame [18].

Catathrenia was associated with excessive daytime sleepiness (Epworth Sleepiness Scale score >10/24) in 44.7% of 38 cases in Drakatos' series [18], in 33% in Oldani's series [12], and in 22% in Abassi’s series [35]. Individual Epworth sleepiness scores were available in 15 of 38 individual case reports, with a mean score of 10.5 ± 4.4 (range 3-17), of which 55% had a score greater than 10/24. Finally, the authors reported the presence or absence of somnolence (with or without Epworth sleepiness score) in 93 cases (excluding the two large series), of which 28 (30%) were somnolent. In contrast, polysomnographic recordings show that sleep times, stage duration, and sleep continuity are not affected by catathrenia, according [3]. Finally, no longitudinal follow-up has shown progression from catathrenia to more severe pathology. This supports the idea that catathrenia is a benign disorder. However, spontaneous remission has not been reported.

5.3. Triggering factors

Almost all cases of catathrenia are primary. However, some patients with narcolepsy have developed catathrenia after starting treatment with sodium oxybate, a treatment for narcolepsy [14, 41]. For example, 9 out of 51 patients with narcolepsy complained of a strange sound after starting evening treatment with sodium oxybate and 7 of them had catathrenia on polysomnography [14]. Episodes predominated at the beginning of the night, at the peak of the drug's effect. The majority occurred during NREM sleep, compared with 20% during REM sleep. No catathrenic episodes were detected on initial polysomnography. They all resolved with discontinuation of sodium oxybate, except in one patient. This is the only drug whose use has been shown to induce catathrenic episodes. In contrast, the use of benzodiazepines, which promote snoring and obstructive apneas, is not associated with catathrenia. Sodium oxybate is gamma-hydroxybutyrate (GHB), a GABA-B and GHB receptor agonist that also transiently blocks dopamine release in the brain. It is a powerful respiratory depressant, and overdose is fatal. [56].

Catathrenia has also been induced by vagal nerve stimulation in a patient with intractable epilepsy [22]. Stimulation of the vagal nerve can produce flow limitation, obstructive and central apneas, and occasionally stridor. Stimulation of the efferent fibers of the vagal nerve via central medullary pathways may result in dynamic contraction of the laryngeal adductors during inspiration, which, as shown here, may be prolonged during expiration, resulting in a sound.

6. Polysomnographic aspects

6.1. Respiratory aspects

Three different types of catathrenia have been reported on polysomnography. In the original, “typical” type, the events occur in the form of bradypnea, itself composed of successive pseudo-central apneas (without normal breathing between them) grouped in clusters **(Figure 2A)** or, more rarely, isolated. These events occur in four phases. They begin with a short, deep inspiration, followed by a rapid expiration, and then an expiratory plateau where the sound is maximal at three-quarters of expiration. This plateau usually stabilizes and often ends with a short further expiration, that looks like a “tail” (also called a “sigh” or a “huff” in some articles) before re-inspiration **(Figure 2B)**. A second (atypical) type of catathrenia consists of regular expiratory groans in NREM sleep that occur with each expiration for long periods of time, up to 30 minutes, without prolongation of the expiration. In this type, the noisy expirations are short and without this "tail" [7, 11]. A third type of catathrenia was recently identified in 9 patients with severe obstructive sleep apnea. The events began with groaning in NREM sleep (N2 stage), but the catathrenic, pseudocentral apnea was followed by an obstructive apnea [9].

Heart rate decreases during the events and increases at time of re-inspiration [12], and pulse wave amplitude in contrast increases during the events and decreases at time of reinspiration **(Figure 2).** The profile of typical catathrenia on a cardiorespiratory polygraphy differs markedly from that of central apneas because: i) central apneas are silent (no accompanying signal on the microphone), whereas catathrenia is noisy [28, 37]; ii) the short marked expiration at the end of the catathrenic sound (a "tail") is absent at the end of a central apnea, as the plateau is immediately followed by an inspiration (**Figure 3**); iii) central apneas are accompanied by oxygen desaturation, whereas catathrenia is not. Sobbing, crying, and talking during sleep (**Figure 3B-D**) also occur during expiration, but are not followed, as in catathrenia, by a short marked expiration ~~to residual volume~~ at the end of the sound (the "tail") as in catathrenia.

Prolonged expiration in typical catathrenia lasts from 2 to 50 seconds. There is no thoracoabdominal movement, and no activation of the diaphragm, the intercostal muscles or the rectus abdominis on EMG recording during the expiratory plateau, but there may be a brief contraction of the expiratory muscles (expiratory intercostalis [11] or rectus abdominis muscles [12]) during the final expiratory phase [2]. When monitoring esophageal pressure, the period of expiratory noise is accompanied by a slight increase in initial intrathoracic pressure, which then gently returns to values around 0 cm [3, 11]. This suggests that the expiratory muscles are little or not active during the plateau, but that expiration is mediated by the non-muscular elastic recoil of the lung, with an expiratory braking mechanism possibly caused by partial laryngeal closure. In contrast, the final expiratory phase appears to be active.

The simultaneous snore detector or the microphone indicates the presence of sound during expiration, which can alert the clinician to the difference from a (silent) central apnea. Listening to the raw sound corresponding to the "snore" confirms the diagnosis **(Video-clip)**. It may vary in timbre and intensity from one patient to another, but is stable in the same patient [3]. The sound can be an "a", an "e" or an "o", and sometimes in between. It may have sexual connotations [7]. Two to 343 episodes of catathrenia may be observed per night and per patient [3, 35]. In patients who underwent two nights of polysomnography, catathrenia persisted from one night to the next [3].

6.2. EEG aspects and sleep stages associated with catathrenia

REM-associated clusters of typical catathrenia episodes often begin with an arousal, associated with the first deep inspiration and followed by a prolonged expiration, whether in REM sleep [18], or in NREM sleep [54]. Most (but not all) catathrenia episodes in REM sleep are followed by an arousal, that occurs at the time of reinspiration [7, 11, 35] (**Figure 4**) or at the end of the “tail” in other cases [34, 57]. In contrast, the atypical type of catathrenia, consisting of short expiratory moans, occurs with a normal underlying respiratory rhythm, lasts for long periods during sleep, and is not associated with arousals [11, 35].

Episodes were first described during or near REM sleep. In REM sleep, they are more likely to occur during tonic (epochs without rapid eye movements) than phasic REM sleep (**Figure 5**). The frequency of events increases throughout the night (with a higher prevalence in the second half of the night than in the first half of the night [38]), and their proportion increases in late versus early REM sleep cycles [3, 29]. Later, cases of catathrenia occurring in both REM sleep and NREM sleep were reported [3, 7, 18, 20]. In

10 patients, 6 had catathrenia episodes only in REM sleep and 4 had episodes in both REM sleep and NREM sleep [3]. In these patients, 1/5° of isolated catathrenia episodes were observed in NREM sleep and 4/5° in REM sleep [3, 18]. Finally, long clusters were more common in REM sleep.

In contrast, in sodium oxybate-induced catathrenia and in women with predominantly NREM catathrenia, 80-90% of the episodes occurred during NREM sleep and 10-20% during REM sleep [7, 14]. Finally, other cases have been reported to occur only during NREM sleep [7, 11, 12, 35, 43, 57]. In the latter cases, catathrenia was observed more frequently in stage N1 (37-100%) and stage N2 (31-46%) and rarely (1.6%) in stage N3 [34, 35]. This repartitioning is in contrast with snoring, which is predominant in stage N3. In the recently described type of catathrenia preceding obstructive apneic events, catathrenia occurred equally in stage N2 and REM sleep [9].

7. Comorbidities

7.1. Neurological comorbidities

Most patients have no other diseases, but sometimes there are comorbidities associated with catathrenia, although it is not known whether there is a relationship between the two. Regarding neurological comorbidities, 3 of 211 cases have associated epilepsy, including idiopathic generalized epilepsy [31], focal epilepsy [29], and somatosensory seizures in polymicrogyria [21]. One case had catathrenia on polysomnography provoked by an epileptic seizure [31], although seizures- associated noises are generally different from catathrenia (see differential diagnosis section). Three cases with catathrenia had mental retardation [29], which may or may not be associated with an identified genetic disorder (Pitt-Hopskin syndrome with 18q deletion [53]). Catathrenia has been incidentally observed in 8 of 11 patients with fatal familial insomnia (a fatal prion encephalopathy) [27], and in two elderly patients with neurodegenerative tau protein disease, including progressive supranuclear palsy (although these patients often have automatic standby vocalizations [58]), and corticobasal degeneration [16].

7.2. Respiratory comorbidities

Only two cases of associated asthma have been reported [48, 57], as well as one case of pulmonary hypertension [46] and one case of exertional dyspnea [32]. In all of these cases, the association appears to be coincidental.

7.3. Comorbid sleep disorders

Regarding parasomnias, confusional arousals, somnambulism, night terrors or a history of tardive enuresis were noted in 15 of 211 patients (7.1% of the sample) [7, 8, 11, 12, 29, 47]. It should be noted that there was never an association with REM sleep behavior disorder (which occurs at the same stage as catathrenia). Among sleep-related abnormal movements, bruxism or teeth grinding during sleep was occasionally found (in 12 adult cases out of 211, i.e. 5.7% of cases) [3, 7, 12, 13, 29, 45, 46, 49, 54]. In contrast, bruxism was reported in 62% of 21 children with catathrenia [38]. When bruxism and catathrenia occur simultaneously, the sequence begins with an arousal, followed by the mandibular rhythmic activity characteristic of sleep bruxism, and then catathrenia begins [54]. One author reports a case in which catathrenia was interrupted by a hiccup (typical of involuntary inspiratory activity) during expiration [36]. Several authors mention the absence of periodic leg movements during sleep [11-13].

In terms of sleep-disordered breathing, only 5 patients with catathrenia had an apnea-hypopnea index greater than 15, or 3.6% of the sample of 139 patients who had polysomnography and reported apnea-hypopnea index. This low frequency is well below the spontaneous frequency of an apnea-hypopnea index greater than 15 in the normal population and therefore appears to be a coincidence. However, cases with exclusively NREM catathrenia more often have mild to severe upper airway obstruction [7, 9, 35], supporting the concept of two types of catathrenia. In this list of respiratory comorbidities, one can now add the newly identified third type of catathrenia, which is a respiratory event that begins with a catathrenic episode (pseuco-central apnea), followed by an obstructive apnea, and ends with a rescue breath [9]. In this case, the patients had severe obstructive sleep apnea in addition to catathrenic apnea.

8. Pathophysiology of catathrenia

Although its acoustic and polysomnographic description is well defined, the pathophysiology of catathrenia is still unknown. Epilepsy is not associated with catathrenia. Research is focused on identifying the source of its production, which is clearly laryngeal, and on the debate between sleep-disordered breathing and parasomnia [7, 8, 10, 59].

8.1. A sound from an apparently normal larynx

Nevertheless, it is safe to say that the sound is produced by the vocal cords [1, 25, 47, 52]. The sound of catathrenia consists of harmonics (frequencies that are multiples of a fundamental frequency) and formants (sound elements produced by the resonance chamber), while snoring consists only of formants (**Figure 1**). Catathrenia is classified as a Type I or Type II sound according to Yanagihara's classification. It has the same acoustic characteristics as sounds produced by the vocal cords. Vocal cord closure (an active, not passive event) during catathrenia has been observed in a single observation of catathrenia occurring even under light sedation [32]. As might be expected from laryngeal differences, females produce a higher pitched sound during catathrenia than males. Unlike stridor, static and dynamic examination of the larynx in the awake patient reveals no abnormalities, except in a single case of reduced mobility of a single vocal cord [32]. The existence of a partial closure dystonia of the laryngeal adductor muscles could be discussed, but due to the complexity, no patient could have electromyographic monitoring of the laryngeal adductor muscles during sleep. Unlike stridor, which is predominant during inspiration and reflects glottic or supraglottic obstruction, catathrenia, which is expiratory, suggests subglottic obstruction.

8.2. Normal morphology of upper airways

Cephalometry and orthopantonogram were performed to compare the craniofacial and upper airway anatomic features of 22 patients with catathrenia with those of Chinese standards and with those of 66 patients with sleep apnea syndrome matched for age, sex, and body mass index [50]. Patients with catathrenia had normal cephalometric features except for more protruding upper incisors, flatter mandibular angles, and wider nasopharynx and oropharynx (small tongue, thinner soft palate). Compared to people with obstructive sleep apnea, their airways were wider at all levels and their jaws, with a wider dental arch, allowed for much better occlusion [50]. This important and robust work responded to an observation by Guilleminault et al. who had found cephalometric abnormalities in 6 out of 7 of their patients with catathrenia (having predominantly NREM catathrenia), but had no healthy or apneic control group [7].

8.3. A sleep-disordered breathing?

Catathrenia is an event produced in a coordinated manner by the respiratory and laryngeal systems, with well-defined temporal and acoustic characteristics. Unlike snoring and obstructive sleep apnea, catathrenia is not associated with obesity and other factors that increase respiratory workload. Its occasional improvement with the use of continuous positive airway pressure or a mandibular advancement device (see below), which alter the geometry of the upper airway, may suggest a sleep-disordered breathing condition. Interestingly, the first case described in the literature occurred at the age of 10 years after recovery from Steven-Johnson syndrome [1]. As a result, the authors hypothesized that the patient (despite normal functional studies) had a morphological impairment of the bronchioles (a known side effect of Steven-Johnson syndrome), which was responsible for excessive constriction during exhalation, to the point that the sleeper was forced to produce a forced exhalation at high positive pressure against partially closed vocal cords, producing this noise. With this hypothesis in mind, these authors treated their patient with theophylline and observed a recovery of the catathrenia [1]. Also, there is no significant increase in intrathoracic pressure during catathrenia, indicating that the sleeper is not performing a Valsava maneuver, such as during defecation or carrying heavy loads. Ortega-Albas et al. suggest that post-inspiratory neurons, which are active during the early phase of expiration, are responsible for this dysfunction [26]. These neurons are located between the ventral and dorsal respiratory groups and exert inhibitory connections to both. Excessive tonic discharge of these post-inspiratory neurons should prolong expiration by blocking the expiratory neurons of the ventral group. In this direction, a social media study found that competitive swimmers were 10 times more likely to experience catathrenia than the general population, suggesting that plasticity in the respiratory pathway may be involved. [19]. The similarity between prolonged expiration during catathrenia and the diving reflex has been emphasized. [57, 60].

The NREM, short expiratory groaning episodes were compared to expiratory vocalizations observed in athletes during exertion, such as tennis players or weightlifters [7]. The authors suggested that it may be an adaptive behavior aimed at facilitating normal breathing. An active positive end-expiratory maneuver can maintain airway patency at the end of expiration, prepare the upper airway for inspiration, and ensure effective inspiratory flow. [7].

8. 4. A parasomnia?

Parasomnias are unwanted physical or experiential events that accompany sleep and the stages of falling asleep or waking up [6]. The most classic examples are sleepwalking (during NREM sleep) and REM sleep behavior disorder. They correspond to hybrid states between wakefulness and sleep. However, the sound produced during catathrenia resembles a wailing or moaning in a loop. It differs from somniloquy (which is a parasomnia) mainly in the long duration of the vocalized episodes, their clustering, and their stereotypy (including the expiratory "tail" at the end of the sound), and shares some (but not all) of the characteristics of a person in pain who moans continuously [3]. The involvement of the vocal cords suggests that the pathophysiology is more complex than that of a respiratory disorder. It has been suggested that it may be the unmasking of an ancestral behavior during sleep, such as an animal call like that of a giraffe, elephant seal, or squirrel monkey [57]. Continuous involuntary moaning and groaning while awake that persists during sleep, except in stage N3, has been described primarily in Parkinson's disease, progressive supranuclear palsy, and dementia. [58, 61]. However, the sounds produced seem to be more vocalized than in catathrenia. The hypothesis raised in these patients is that dopaminergic disinhibition automatically activates a circuit for the production of non-verbal vocalizations (limbic, cingulate, and periaqueductal), such as whimpering, crying, and laughing, different from those for speech or singing (cortex-thalamus-cortical ganglia), leading to behavioral disinhibition with vocal perseveration [57, 62]. In this direction, the periaqueductal gray matter of the midbrain contains neurons that activate stereotyped vocalizations in squirrel monkeys, which are unmasked by local application of GABA-A agonists [63].

Drakatos et al. observed that the sequence of catathrenia episodes in REM sleep always began with an arousal from REM sleep, and based on this observation suggested that catathrenia may be a form of REM sleep arousal disorder [18]. Note, however, that patients remain in REM sleep during the sequence of sounds and do not appear to be in a hybrid state between wakefulness and REM sleep. The presence of arousals and deep inspirations before expiratory bradypneas implies the involvement of a central command that activates vocal cord closure. Finally, the contraction of expiratory muscles at the end of an episode of catathrenia is an active, not a passive action. All these phenomena therefore appear to be active (even more so in REM sleep, when the striated muscles are normally subject to an active paralysis known as muscle atonia).

8.5. Two types of catathrenia

Iriarte and Pevernagie suggested that the cases of catathrenia in NREM sleep reported by Guilleminaut were more likely to be expiratory snoring [8, 24]. Finally, Iriarte et al proposed to reconcile the respiratory and parasomnia hypotheses by suggesting the existence of two types of catathrenia **(Table 2)**:

- the "sirens of the night". Those that occur exclusively during REM sleep, long and loud, are more likely to be parasomnias. The central nature of bradypneas and the reduced benefit of continuous positive airway pressure support this view.
- the "elephants". Those that occur in both NREM sleep and REM sleep, are brief and not very intense, and are close to expiratory snoring, making them more likely to be a breathing disorder. They are more often associated with hypopneas and apneas and would more often benefit from the use of continuous positive airway pressure.

There is a lack of large series to determine whether this conciliatory hypothesis is valid. However, it should be noted that a mandibular advancement device used in 30 patients did not improve NREM catathrenia more than REM catathrenia [51], whereas we would expect a preferential improvement in episodes limited to NREM sleep.

8.6. A new, third type of catathrenia?

Recently, Buyse et al identified a third type of catathrenia, in nine male patients with severe obstructive sleep apnea syndrome [9]. The episodes resembled classic REM sleep-associated catathrenia (including the three sequential phases of deep inspiration, prolonged expiratory plateau at functional residual capacity, and short further expiration ~~to residual volume,~~ and the loud noise), but instead of the classic deep re-inspiration, there was an obstructive apnea followed by a "rescue" inspiration and arousal. In the absence of an accompanying audio recording, the entire event resembles a mixed apnea. Events occurred during N2 and REM sleep. The nine cases resolved with the use of PAP treatment. The authors hypothesized that the enhanced "rescue" breathing induced glottic closure. Whether this new aspect is the combination of a previous typical REM sleep-associated catathrenia and a new obstructive apnea remains to be determined, possibly by following the evolution of patients with REM catathrenia when they develop severe obstructive apnea.

9. Differential diagnoses

Sleepers can make many sounds, often sonorous. However, these sounds are different from catathrenia.

9.1. Somniloquy

Sleep vocalizations consist of clear words, indistinct words, whispers, murmurs, growls, shouts, whistles, and bursts of laughter or tears [64]. Vocalizations are produced on exhalation (as in catathrenia), but are short and varied within the same sleeper and never repeated in a loop as in catathrenia (**Figure 3B-D)**. In particular, an episode of repeated sobbing during REM sleep behavior disorder shares similarities with catathrenia in terms of noisy episodes of exhalation, but is shorter, more irregular and associated with facial expressions of sadness **(Figure 3C)**. Somniloquy is a variation of normal, but the nocturnal talkers may disturb their neighbors with noise or even unwittingly reveal secrets. Somniloquy is more common in populations with parasomnias (arousal disorders, REM sleep behavior disorder) and mental disorders (especially post-traumatic stress disorder) [65].

9.2. Stridor, laryngospasm and snoring

Both stridor and laryngospasm differ from catathrenia in that they occur during inspiration (rather than expiration) and are shorter in duration. However, they have a high-pitched sound like some catathrenias. Stridor can occur during wakefulness or sleep, and laryngospasm can occur during wakefulness. Snoring is a low-pitched inspiratory and expiratory sound (but predominantly inspiratory). Snoring is caused by vibration of the soft structures of the pharynx, whereas catathrenia involves the vocal cords. In 2008, however, an interesting controversy arose between the group of Christian Guilleminault, who defended a new form of short catathrenia during NREM sleep, and the group of Roberto Vetrugno, who suggested that it was not catathrenia but expiratory snoring [10]. Clearly, only an electroglottogram would be able to determine the laryngeal or pharyngeal origin of the catathrenia sounds produced during NREM sleep, but it has only been performed in REM sleep yet.

9.3. Central apneas

Central sleep apneas can be confused with catathrenia on a sleep polygraphy, especially if the initial sleep study does not include an audio monitoring [43]. However, their morphology is different, as the plateau ends with an inspiration rather than an expiration to residual capacity as in catathrenia. There is no associated noise, only silence **(Figure 3A)**. Finally, the sleep stage may help the sleep scorer, as catathrenia often occurs during REM sleep, whereas central sleep apnea or periodic breathing sequences usually stop during REM sleep.

9.4. Hiccups during sleep

Hiccups may occur during sleep in patients with chronic daytime hiccups [66]. It is an inspiratory, short sound, produced by an abrupt inspiration followed by glottal closure.

9.5. Night wheezing

The expiratory sound produced by asthma-related bronchoconstriction is a sibilant, low- or high-pitched, expiratory sound during exhalation with little or no extension [67].

9.6. Epileptic grunting

Epileptic seizures during sleep may be accompanied by various sounds, including palilalia (repetition of a syllable such as "tat ta ta tat"), groans and the stertorous breathing that follows the seizure.

9.7. Throat scraping during N2 sleep

The case of a person with repeated short throat clearing noises in sleep stage N2 was recently reported [68]. The noise is certainly repeated in a cluster, but much shorter than in catathrenia. There is no associated nocturnal epilepsy. The authors proposed to classify this new noise as a rare parasomnia.

10. Treatments

10.1. Generalities

Numerous treatments have been tried to limit the discomfort of roommates and the fatigue of people with catathrenia **(Table 3)**. On a case-by-case basis, physicians have empirically tried treatments commonly used for parasomnias (e.g., clonazepam or melatonin), and insomnia (zolpidem, trazodone, cognitive behavioral therapy for insomnia), or treatments of sleep apnea syndrome and nocturnal stridor (positive airway pressure [PAP], mandibular advancement device, orthodontics, upper airway surgery, and botulinum toxin applied to the vocal cords [16]). However, long-term efficacy has been rare, except for the partial benefit of a mandibular advancement device in 30 patients in China [51] and the modest benefit of PAP [20]. As with snoring, patients, their families and physicians often choose not to treat this nocturnal noise. For example, 9/38 adults with catathrenia [18], and 4/6 [33, 37] chose not to treat catathrenia after being reassured of its apparently benign nature. The same attitude has been reported in parents of children with catathrenia [38, 69]. Simple solutions may include sleeping alone or having roommates wear earplugs.

A summary of the treatments found in the literature is presented in **Table 3** and **Table 4**. Many treatments were ineffective, while others were occasionally effective. Therefore, it is not possible at this time to give advice or recommendations other than to try one or another for a sufficient period of time to know if it helps the patient.

10.1. Pharmacological treatments

Clonazepam is commonly used to reduce parasomnias and sleep-related movement disorders, but (like any other benzodiazepine) can cause snoring, obstructive apnea, and residual daytime sleepiness. The benefit of clonazepam was 3 in 8 patients with REM-associated catathrenia[12, 18] **(Table 3)**. One might expect clonazepam to reduce arousals, which may in their turn trigger catathrenia [18]. Gabapentin, an alternative to clonazepam in the same sleep disorders, has been tried only once and resulted in a disappearance of catathrenia for 6 months, but the noise returned after [12]. Melatonin (a chronobiotic drug with mild sedative effects and benefits in REM sleep behavior disorder) has been beneficial in one case [18]. Pramipexole (a dopaminergic drug indicated for restless legs syndrome) was ineffective in two patients [12, 33]. Medications used to alleviate insomnia were mostly ineffective in reducing catathrenia, whether zolpidem, trazodone or antidepressants were used.

10.2. Continuous positive airway pressure

Positive airway pressure (PAP) is the most commonly suggested treatment. Among 127 patients in the literature, PAP was considered useful to try by physicians and accepted to be tried by patients in 67 (48%) of them, and was rejected by more than half of patients/physicians (**Table 4)**. When PAP was tried, it provided a partial or complete benefit in 41/61 (67%) patients. Some authors manually titrate the PAP to eliminate the noise [7]. Dias et al found that mild pressures (6-9 cm of water) eliminated the catathrenia signal and noise on polysomnography in 7 of 8 patients (whereas a PAP of 12 cm failed to eliminate the events in 1 patient), whether the episodes occurred in REM or NREM sleep, and whether mild concomitant obstructive sleep apnea was present or absent [20]. In a 12-year-old child, the PAP pressure required to eliminate the noise was as high as 18 cm of water, but PAP was not used long term. [57]. However, long-term adherence to PAP in people with catathrenia is poorly documented. In the Drakatos series, only 3 out of 4 patients who were satisfied with PAP continued treatment beyond 12 months. [18]. Of interest, the autopilot mode of PAP may misinterpret catathrenia episodes as obstructive events and increase pressure as shown in **Figure 6**. In contrast, several authors reported a lack of efficacy [12, 13, 21, 30, 33, 37]. Finally, the high number of refusals may reflect the low impact of this disorder or the high cost/benefit ratio of PAP in catathrenia (as PAP is usually not reimbursed for this indication).

The partial benefit of PAP in reducing catathrenia-induced noise can be explained by the reduced active closure of the vocal cords. Therefore, its efficacy is reduced compared to obstructive events, since it counteracts an active phenomenon (and not a passive one, as in obstructive apnea). It can be hypothesized that the acoustic properties of the mask may also contribute to noise reduction.

10.3. Oral appliances

Mandibular advancement device (MAD) is an alternative to PAP for obstructive sleep apnea that may be more acceptable in young patients. Although the upper airway of people with catathrenia is wider than that of people with obstructive sleep apnea, some authors have tried MAD in people with catathrenia. A partial benefit of MAD was mentioned early in a young woman with mostly NREM catathrenia, in combination with upper airway surgery [7]. Two groups proposed MAD therapy in 6/38 [18] and 30/30 patients respectively [51]. They showed partial benefit in 3/6 (50%) and 11/30 (36%) of patients, respectively. In the largest series in China, 12 males and 18 females with catathrenia aged 16-67 years underwent standard clinical evaluation, craniofacial evaluation, videopolysomnography, and upper airway imaging before and after MAD insertion [51]. At baseline, groaning was present mainly during REM sleep in 37%, mainly during NREM sleep in 50%, and equally during both NREM and REM sleep in 13%. The groaning index decreased significantly from 5.8/h to 2.8/h during the night with MAD, but complete elimination of groaning was never observed. The use of MAD did not change the distribution of the groaning index across sleep stages. However, 70% of patients reported a decrease in catathrenia noises at home, and daytime sleepiness decreased. Good responders were younger and had a greater vertical opening with MAD repositioning than poor responders, while no differences were found in baseline airway size, sleep measures, and apnea-hypopnea index [51].

XI. Conclusion

Catathrenia is a rare, underdiagnosed sleep disorder that clinicians need to be aware of in order to improve patient management and eliminate the many differential diagnoses, especially central apnea. It affects both men and women, and often begins in childhood. On the borderline between a variant of normal sleep, a parasomnia and a sleep-disordered breathing disorder, not all of its characteristics have been studied. To date, no treatment appears to be clearly effective, although MAD is partially effective in 38-70% of patients.

Practice points

1. Typical catathrenia consists of a loud, laryngeal sound during prolonged expiration, usually occurring in intermittent clusters during tonic REM sleep and at the end of the night.
2. Atypical catathrenia consists of regular, brief, low-intensity expiratory groans that occur continuously during NREM sleep.Catathrenia is more disruptive to roommates than to sleepers and is associated with excessive daytime sleepiness in one-third of cases.
3. On polysomnography, the bradypneic aspect of catathrenia differs from central apnea in REM sleep by accompanying sounds, absence of oxyhemoglobin desaturation, and expiration reaching residual volume before deep inspiration.
4. Positive airway pressure is partially effective in the NREM type of catathrenia.
5. Although the size of upper airway is normal in patients with catathrenia, a mandibular advancement device that increases the vertical opening reduces the noise in 38-70% of patients, mostly the youngest.

Research agenda

Future research should address:

1. the pathophysiology of catathrenia;
2. whether it is a parasomnia or a sleep-breathing disorder;
3. whether NREM and REM catathrenia are different;
4. laryngeal examination and sound analysis in the NREM type of catathrenia;
5. the optimal treatment of catathrenia in large series, using randomized controlled designs.

Conflict of interests

The authors have no competing interests in or outside of this topic.

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Figure legends

Figure 1: Acoustic recording of an episode of catathrenia and a snoring episode. The audiographic spectrogram of a catathrenia episode (left) and a snoring episode (right) is plotted as a function of time (horizontal axis) in the hearing range from 300 to 4200 Hz (vertical axis). The catathrenia sound contains many harmonics, including a fundamental frequency and visible lines at multiple frequencies of the fundamental (indicating fast vocal cords vibrations occurring simultaneously). In contrast, snoring produces formants (resonances in the airway) but no harmonics. Figure adapted from Iriate et al, Sleep Breathing 2011, with permission [25].

Figure 2: Polygraphic recording of episodes of typical catathrenia in REM sleep in a male patient from our center. A: Clusters of catathrenic episodes in a 5 minute-long extract; B: Focus on 2 catathrenic episodes in a 1 minute-long extract, starting with maximum inspiration (arrow #1), expiratory plateau (arrow #2), and end-expiratory brief maximum expiration or "tail"(arrow #3). From top to bottom, measurement of transcutaneous oxygen saturation (labeled as SpO2, in %), naso-oral thermistor (thermistance), nasal pressure (flux), thoracic and abdominal plethysmography, heartbeat (pulse, in beats per minute), and pulse wave (Pleth).

Figure 3: Differential diagnoses of catathrenia during REM sleep: aspect on respiratory polygraphy channels. Examples show: (A) episodes of sleep talking (red arrows) in REM sleep in a man with REM sleep behavior); (B) episodes of sobbing episodes (red arrows) in a woman with REM sleep behavior; (C) REM sleep associated stridor in a patient with multisystem atrophy; (D) Central apneas during REM sleep. All examples come from our center.

Figure 4: EEG arousals at the time of re-inspiration (vertical arrows). Extract of polysomnographic 30-sec epoch including 2 episodes of catathrenia in REM sleep in a female patient from our center. From top to bottom, right and left electrooculogram channels (labeled as EOG D and EOG G), Fp1/A1, C3/A1 and O1/A1 bipolar EEG channels, chin muscle EMG channel (Chin), electrocardiogram (ECG), nasal pressure (flux), thoracic and abdominal plethysmography, and transcutaneous oxygen saturation (SpO2, in %).

Figure 5: Catathrenia episodes occur from REM sleep periods without rapid eye movements. Polysomnographic 2 minute-segment of REM sleep. Same channel legend as in Figure 3.

Figure 6: Log recording during 5 min of home continuous positive airway pressure in a patient with catathrenia, showing a pressure increase during a catathrenia episode, which the device misinterprets as an obstructive event. From top to bottom, clock time, detected events (“evenements”, in red: events considered as obstructive), pressure in cm of water (“pression”) and respiratory flow in L/min (“debit”). CPAP is an Autoset®. device from Resmed®., Australia, set as autoPAP between 4 and 14 cm of water. The log software if ReScan®.

Legend of the video-clip

Video-clip: Patient #1 produces in REM sleep several episodes of loud, low pitched expiratory groaning; Patient #2 produces in REM sleep extremely long episodes of loud, low pitched expiratory groaning; Patient #3 produces in REM sleep episodes of loud, high pitched expiratory groaning; Patient #4 has REM sleep behavior disorder (RBD) and sobbing during this RBD episode (note how the sound differs from catathrenia); Patient #5 has RBD; she cries and sobs during this RBD episode (note how the sound differs from catathrenia). All video-clips have been authorized for being shown in a medical journal by the patients.

Table 1 - Characteristics of patients with a primary form of catathrenia

Authors, reference number	N of patients	Male N (%)	Age at diagnosis (y)	Body mass index (kg/m^2)	Epworth sleepiness score (0-24)
Abbasi et al [35]	10	5 (50)	46 ± 23	29 ± 9	10 ± 4
Buyse et al [9]	9	9 (100)	47 ± 12	39 ± 6	Not found
Dias et al [20]	8	2 (25)	33 ± 5	28 ± 9	7 ± 3
Drakatos et al [18]	38	23 (61)	33 ± 8	26 ± 5	10 ± 5
Guilleminault et al [7]	7	0 (0)	27 ± 5	23 ± 1	4 ± 1
Hao et al [50]	22	15 (68)	35 ± 12	22 ± 3	Not found
Katz et al [38]	21	14 (67)	8 ± 4	Not found	Not found
Koo et al [47]	5	0 (0)	31 ± 7	20 ± 1	9 ± 5
Oldani et al [12]	21	13 (62)	31 ± 14	Not found	8 ± 5
Overland et al [33]	4	4 (100)	35 ± 5	25 ± 2	8 ± 2
Petitto et al [44]	3	3 (100)	11 ± 4	NF	3/3 sleepy
Poli et al [14]	9	2 (22)	32 ± 21	22 ± 4	Narcolepsy
Prihodova et al [29]	8	5 (62)	23 ± 8	NF	6/8 sleepy
Vetrugno et al [2]	10	5 (50)	27 ± 7	22 + 2	3 ± 2
Yu et al [52]	30	12 (40)	Median 31	22 ± 3	9 ± 4
Isolated cases	38	24 (63)	31 ± 19	27 ± 5	10 ± 4
Total	253	145 (57)	NC	NC	NC

NC : not computable

Table 2- A model of two types of catathrenia (adapted from Iriarte et al (2005) [44]

Nickname	**'Sirens of the night'**	**'Elephants'**
Historical type	Typical	Atypical
Sleep stage	REM	NREM and REM
Usual duration	Long (2-49 s)	Brief (1-3 s)
Sound	Loud	Soft (as expiratory snoring)
Active end-expiration phase	Present	Generally absent
Obstructive apnea and hypopnea	None	Frequent (mostly mild)
Suspected sleep disorder	Parasomnia	Sleep-breathing disorder
Benefit from PAP or MAD	Poor	Frequent

MAD: mandibular advancement device; PAP: positive airway pressure

Table 3- Treatment options for catathrenia

Type	Patients (number)	Benefit N (%)	References
Respiratory treatments			
Continuous positive pressure	69	46 (66) partial	See Table 4
Oral appliance	36	14 (38) partial	[18, 51]
Airway surgery***	5	0 (0)	[7]
Nasal dilator (Provent®)	1	1 (100)*	[18]
Theophylline	1	1 (100)	[1]
Botulinum toxin in vocal cords	2	2 (100)	[16]
Treatments used for parasomnias			
Clonazepam (0.5-2 mg)	8	3 (38)**	[3, 12, 18]
Gabapentin (1600mg)	1	1 (100)	[12]
Pramipexole (0.5 mg)	2	0 (0)	[12, 33]
Melatonin	1	1 (100)	[18]
Treatments used for insomnia			
Zopiclone	4	2 (50)	[18]
Trazodone (100 mg)	7	0 (0)	[3, 12, 18, 20]
Antidepressants (paroxetine, fluoxetine, sertraline, dosulepin)	8	2 (25)	[3, 20]
Cognitive behavioral therapy	6	0 (0)	[18]

*combined with mirtazapine 15mg; **combined with continuous positive airway pressure in 1 case; ***Adenotonsillectomy, pharyngoplasty, septoplasty (never efficacious alone)

Table 4 - Positive airway pressure in catathrenia: trials, refusals and efficacy

Author, year	PAP trials/Total number of patients	Primary PAP refusal N (%)	Partial or total efficacy
Pevernagie et al, 2001 [3]	2/10	8 (80)	1/2
Oldani et al, 2005 [12]	8/12	8 (100)	0/8
Iriarte et al, 2006 [23]	1/1	0 (0)	1/1
Grigg-Damberger et al, 2006 [57]	1/1	0 (0)	1/1
Guilleminault et al, 2008 [7]	7/7	0 (0)	7/7
Ramar et al, 2008 [70]	1/1	1 (100)	0/1
Manconi et al, 2008 [13]	1/1	0 (0)	0/1
Songu et al, 2008 [46]	1/1	0 (0)	1/1
Steinig et al, 2008 [30]	1/1	0 (0)	0/1
Ott et al, 2011 [32]	1/1	0 (0)	1/1
Abbasi et al, 2012 [35]	4/4	0 (0)	4/4
Han Kim et al, 2012 [48]	1/1	0 (0)	1/1
Overland et al, 2012 [33]	1/4	3 (75)	0/1
Neutel et al, 2014 [21]	1/1	0 (0)	0/1
Dias et al, 2017 [20]	8/8	0 (0)	7/8
Drakatos et al, 2017 [18]	9/38	29 (74)	3/9
Kasaglis et al, 2018 [37]	1/1	0 (0)	0/1
Petito et al, 2019 (child) [44]	3/3	0 (0)	3/3
Marques Rodrigues et al, 2021 [28]	1/1	0 (0)	1/1

Katz et al, 2023 (child) [38]	1/21	20 (95)	1/1
Buyse et al, 2023 [9]	9/9	0 (0)	9/9
Total numbers	61/127	67/127	41/61
Percentage	48%	53%	67%

Figure 1 :

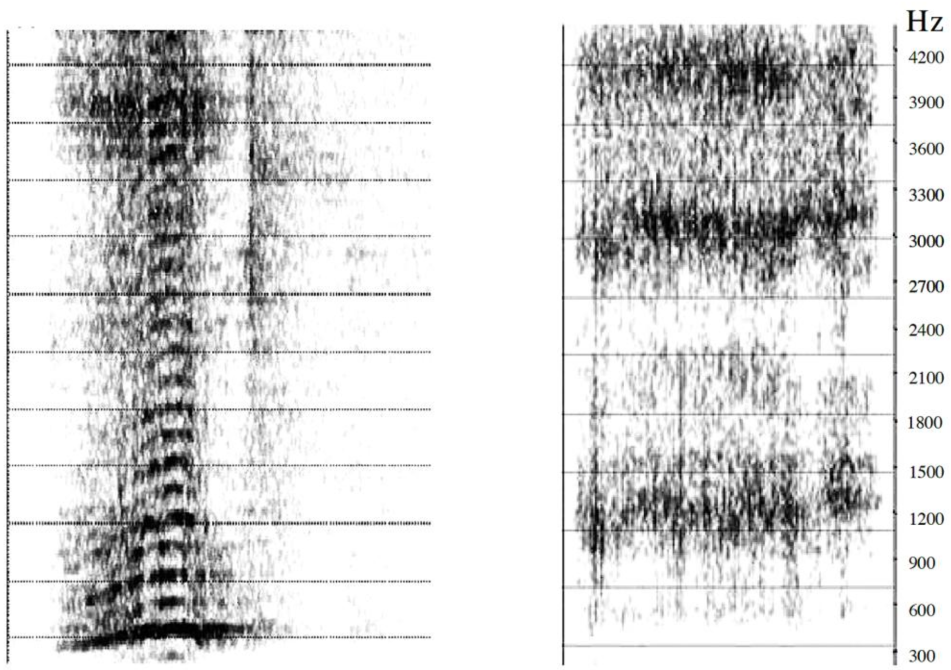


Figure 2 :

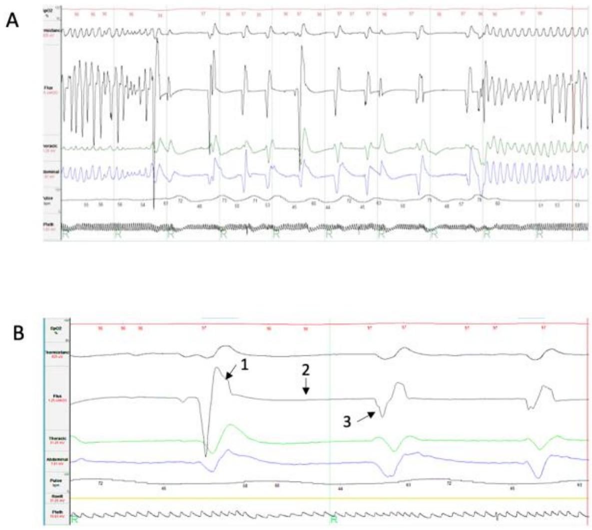


Figure 3 :

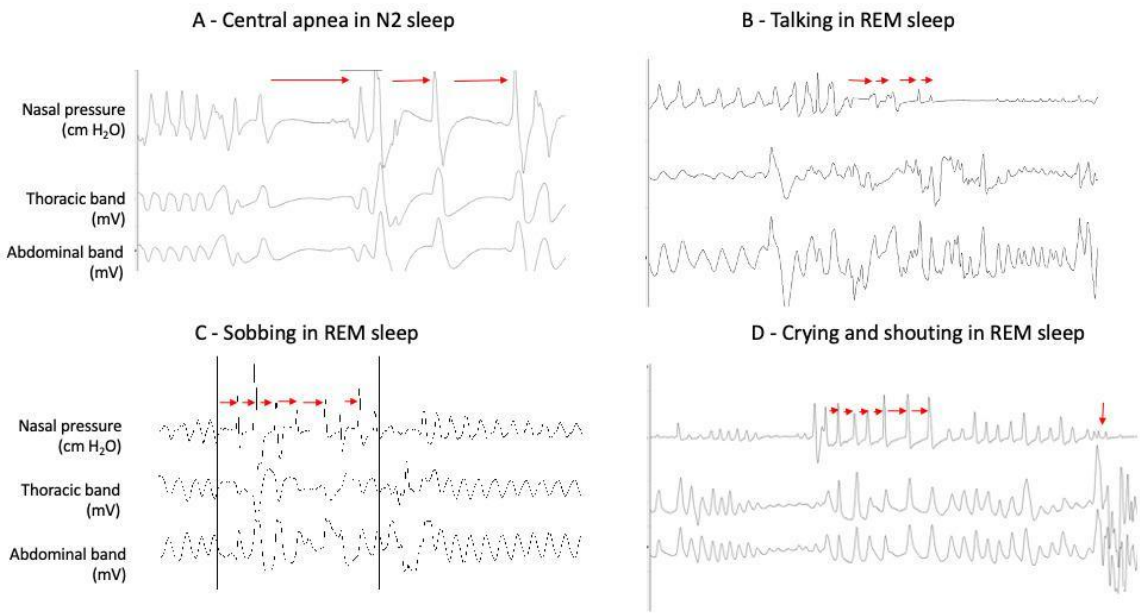


Figure 4 :

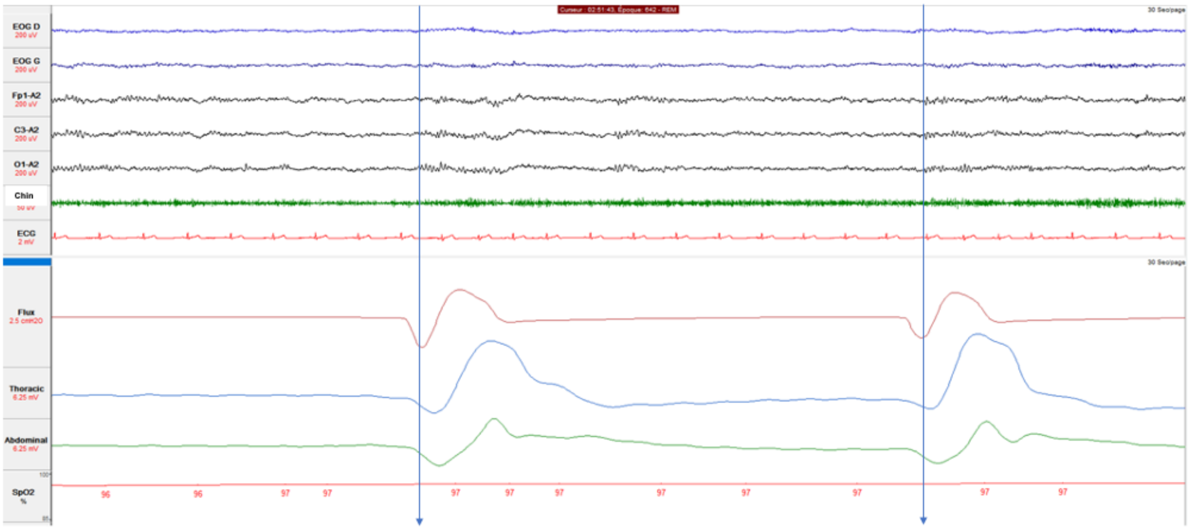


Figure 5 :

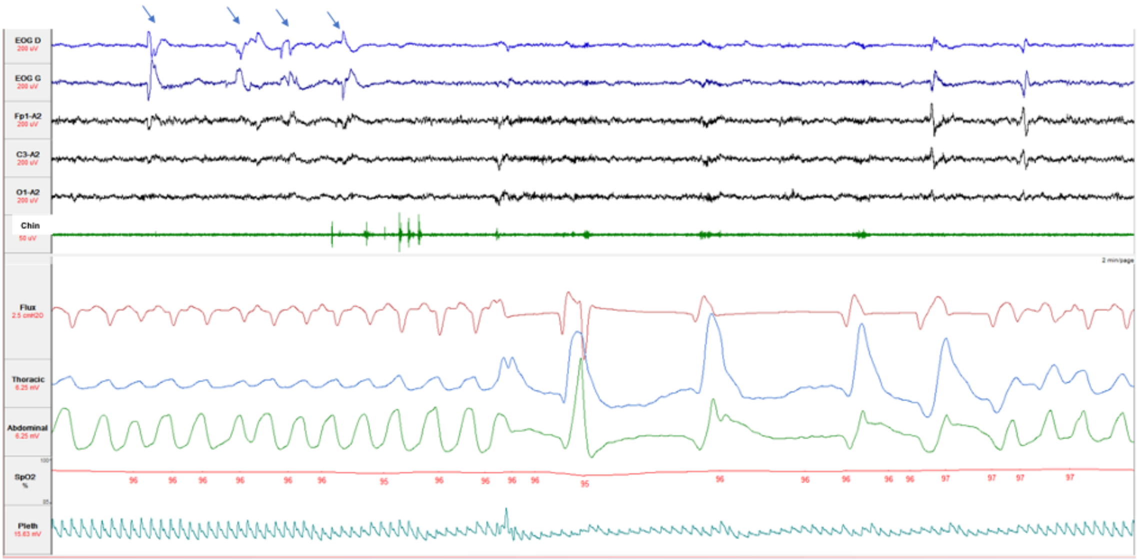
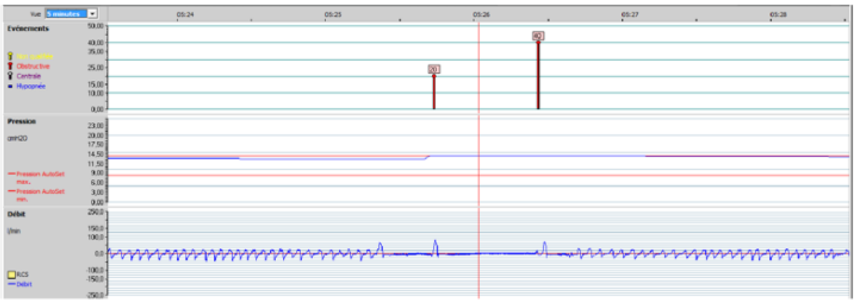


Figure 6 :



Vue
5 minutes
05:24
05:25
05:26
05:27
05:28
Evénements
Non qualifiée
Obstructive
Centrale
Hypopnée
20
40
Pression
cmH2O
Pression AutoSet max.
Pression AutoSet min.
Débit
l/min
RCS
Débit