Long term ventilation into pediatric central apneas: etiologies, profiles and therapeutic approaches over a decade

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Abstract

Central apneas are a prevalent yet complex phenomenon, particularly among children. This retrospective study, conducted over a decade (from 2012 to 2022), analyzed central apneas in a cohort of 612 pediatric patients who underwent ventilation at the Sleep Medicine and Long-Term Ventilation Unit of the Bambino Gesù Children's Hospital in Rome, Italy. Among this group, 67 patients met the inclusion criteria for central apneas. Central apneas often arise within the context of various underlying pathologies, including neurological disorders, genetic syndromes, and brain tumors. We categorized patients into three main groups including patients with "exclusively central apneas", "predominantly central apneas", and "predominantly obstructive apneas". Ventilation modes were diverse, with pressure-controlled ventilation and pressure support being commonly used, reflecting the individualized nature of therapy. The choice of ventilation mode has been influenced by the underlying diagnosis and the severity of central apneas, with pressure support ventilation being the most frequently employed mode. Continuous Positive Airway Pressure was also employed in select cases. A statistically significant reduction ($p<0.05$) in mean cAHI was observed in patients with multimalformation syndromes, hypoxic-ischemic encephalopathy and Prader-Willi Syndrome. The reduction in mean cAHI was not statistically significant in the case of patients with brain tumors. While non-invasive ventilation was commonly used, invasive mechanical ventilation was selectively employed in more severe cases. The study highlights the need for personalized therapeutic strategies when managing central apneas in pediatric patients.

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Abstract

Central apneas are a prevalent yet complex phenomenon, particularly among children. This retrospective study, conducted over a decade (from 2012 to 2022), analyzed central apneas in a cohort of 612 pediatric patients who underwent ventilation at the Sleep Medicine and Long-Term Ventilation Unit of the Bambino Gesù Children's Hospital in Rome, Italy. Among this group, 67 patients met the inclusion criteria for central apneas. Central apneas often arise within the context of various underlying pathologies, including neurological disorders, genetic syndromes, and brain tumors. We categorized patients into three main groups including patients with "exclusively central apneas", "predominantly central apneas", and "predominantly obstructive apneas". Ventilation modes were diverse, with pressure-controlled ventilation and pressure support being commonly used, reflecting the individualized nature of therapy. The choice of ventilation mode has been influenced by the underlying diagnosis and the severity of central apneas, with pressure support ventilation being the most frequently employed mode. Continuous Positive Airway Pressure was also employed in select cases. A statistically significant reduction ($p<0.05$) in mean cAHI was observed in patients with multimalformation syndromes, hypoxic-ischemic encephalopathy and Prader-Willi Syndrome. The reduction in mean cAHI was not statistically significant in the case of patients with brain tumors. While non-invasive ventilation was commonly used, invasive mechanical ventilation was selectively employed in more severe cases. The study highlights the need for personalized therapeutic strategies when managing central apneas in pediatric patients.

Keywords

Central Apneas; Respiratory Disorders; Polysomnography; Non-Invasive Ventilation (NIV); Sleep Medicine

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Introduction

The prevalence of central apneas affect approximately 4-6% of children, although the prevalence might be higher than expected[1–3]. In children, central apnea is defined as a reduction in airflow by at least 90%, accompanied by the absence of respiratory effort lasting more than 20 seconds, or more than 2 respiratory efforts coupled with a reduction in oxygen saturation (SaO_2) of at least 3% and/or arousals and/or bradycardia in infants[4]. The Central Apnea Index (cAHI) reflects the number of central apneas per hour of sleep. cAHI observed during polysomnography (PSG) is considered significant when [?] 1 event/hour; indicating clinical relevance, and indicative of severe pathology when [?] 5[2,4,5]events/hour. Nevertheless, cAHI values between 1 and 5 can be associated with significant desaturations and/or prolonged cycles of periodic breathing (PB)[6–8]. PB entails the occurrence of at least 3 central apneas lasting at least 3 seconds interspersed with period of normal breathing, each lasting less than 20 seconds[4,6,9,10]. Typically, central apneas and PB, if not excessively represented and not associated with significant desaturations, are considered normal during infancy due to the physiological immaturity of the respiratory centers. With the maturation of the respiratory centers beyond the first year of life, central apnea events become infrequent. However, there are various clinical conditions in which patients may present with pathological central apneas and/or PB. Such conditions encompass idiopathic central apnea syndrome, central hypoventilation syndromes, instances involving heart diseases, Prader-Willi syndrome, Down syndrome, achondroplasia, and various neurological conditions such as Arnold-Chiari malformation and encephalopathy and/or epilepsy[11]. Additionally, central apneas can also manifest within the context of obstructive apneas, likely stemming from hyperrventilation[2,12–21]. Therapeutic options for central apneas remain relatively underexplored and sparsely documented in the literature so

far[5–7]. Usually, non-invasive ventilation (NIV) is the preferred therapeutic approach for clinically relevant central apneas. Despite this, in the literature, very little is known about central apneas and exists limited evidence concerning the optimal ventilatory strategy. Therefore, the objective of our study was to conduct a retrospective evaluation over the past 10 years (2012-2022) of all patients with central apneas who underwent ventilation at the Sleep Medicine and Long-Term Ventilation Unit of the Bambino Gesu Children's Hospital in Rome. Our assessment encompassed identifying the type of pathology, poly(somno)graphic parameters, the chosen ventilatory approach and its effectiveness.

Methods

Patients

We retrospectively considered all patients who underwent poly(somno)graphic evaluation at the Sleep Medicine and Long-Term Ventilation Unit of the Bambino Gesu Children's Hospital in Rome from January 2012 to December 2022.

The following poly(somno)graphic indices were considered:

Mixed and obstructive apnea-hypopnea index (MOAHI): defined as the number of mixed or obstructive apneas and hypopneas per hour of total sleep time (TST);

Central apnea index (cAHI): defined as the number of central apneas per hour of TST.

Patients having a cAHI [?] 1 event/hour have been enrolled for this study. Furthermore, for each patient, the following additional items were assessed:

- whether they received non-invasive ventilation or were ventilated via tracheostomy,
- age at the onset of ventilation,
- ventilation mode with specific technical details,
- and the patient's diagnosis.

Considering the retrospective nature of the analysis, the current study did not require the approval of the competent Ethic Committee, according to current legislation, but a notification was sent. Data were processed and retrospectively analyzed in compliance with the provisions of the GDPR and with the related national legislative and regulatory provisions in force, including any subsequent amendments and/or additions thereto.

Statistical analysis

The patients were categorized based on their diagnosis. The average cAHI was calculated for each diagnostic category, and a Shapiro-Wilk normality test was performed. Subsequently, a paired samples t-test (Student's t-test for parametric tests or Wilcoxon test for non-parametric tests) was employed.

Results

Between January 1, 2012, and December 31, 2022, a total of 612 patients were ventilated at our center. Among these, 67 patients met the inclusion criterion for central apnea (cAHI >1). Patients were categorized based on their diagnosis, and it was observed which diagnoses exhibited the exclusively central apneas, predominantly central apneas, and predominantly obstructive apneas phenotypes (*table 1*). The diagnoses of these patients were as follows: hypoxic - ischemic encephalopathy, 15 (22.39%); Ondine Syndrome, 14 (20.90%); multimalformation syndromes, 10 (14.93%); Prader-Willi Syndrome, 8 (11.94%); brain tumor, 6 (8.96%); Down syndrome, 4 (5.97%); ROHHAD Syndrome, 2 (2.99%); Arnold-Chiari II, 1 (1.49%); primary central apnea, 1 (1.49%); epilepsy, 1 (1.49%); lisosomal diseases, 1 (1.49%); hydrocephalus, 1 (1.49%); myopathy, 1 (1.49%); obesity, 1 (1.49%); Rett Syndrome, 1 (1.49%). It was also determined which diagnoses led to ventilation initiation before the age of one and which diagnoses occurred after (*table 2*). The ventilation mode was analyzed based on the type of diagnosis, as shown in *table 3:*15 patients were managed using pressure-controlled ventilation, 45 with pressure support, and 7 with continuous positive airway pressure (CPAP). To assess the effectiveness of ventilation, the average cAHI at baseline was calculated and compared to that after ventilation (*table 4*) and the p-value reflects the effectiveness. The reduction in average cAHI was statistically significant ($p<0.05$) for the following diagnostic categories: multimalformation syndromes, hypoxic-ischemic encephalopathy, Prader-Willi Syndrome. The reduction in average cAHI was not statistically significant ($p>0.05$) in the case of brain tumors. The rest of the diagnoses exhibited a substantial decrease in the mean cAHI value, but the numbers were not sufficient to apply statistical comparisons. *Table 5* represents the number of patients based on their diagnosis who underwent non-invasive or invasive ventilation. Summary of population averages is represented in*table 6* .

Discussion

Our findings shed light on the diverse clinical landscape of central apneas and highlight different considerations regarding the therapeutic interventions[2,5]. For our study, we considered only those patients with central apneas who required ventilation. During the period spanning from January 1, 2012, to December 31, 2022, our center attended to a total of 612 patients requiring ventilation. Among this cohort, 67 individuals fulfilled the inclusion criteria for central apnea, as indicated by a cAHI exceeding 1. The specific diagnoses attributed to these patients encompassed a spectrum of disorders: notable among these were hypoxic - ischemic encephalopathy (22.39%), Ondine Syndrome 20.90% cases, multimalformation syndromes (14.93%), Prader-Willi Syndrome (11.94%), brain tumors (8.96%), Down syndrome (5.97%). Other diagnoses included ROHHAD Syndrome (2.99%), Arnold-Chiari II (1.49%), Primary central apnea (1.49%), Epilepsy (1.49%), Lisosomal diseases (1.49%), Hydrocephalus (1.49%), Myopathy (1.49%), Obesity (1.49%), Rett Syndrome (1.49%). These findings are consistent with the existing understanding that central apneas can be a manifestation of a wide range of underlying pathologies. It is important to note, that primary central apneas, although highly prevalent in infants, our study demonstrates that rarely require ventilation when occurring

in the absence of underlying causes. In fact, over the course of 10 years, ventilation was only initiated in one case. It is noteworthy that in this particular instance, a pressure support mode, rather than controlled pressure, was employed intentionally to promote the neurological development of respiratory centers. Furthermore, the prevalence of Ondine Syndrome and the variety of genetic, neurological, and developmental disorders identified in our study underscore the intricate interrelationships between respiratory control, neurological function, and genetic factors. Literature suggests that in instances where central apneas are unexpectedly observed during a PSG performed for suspected obstructive apneas, it might be advisable to consider a brain MRI. While this concept remains debatable due to limited strong evidence, confounding factors such as the presence of gastroesophageal reflux can induce central apneas in an otherwise healthy individual. Therefore, a thorough investigation into the possibility of GERD is warranted in cases of unexpected central apnea findings[22,23]. Our results highlight a consistent conditions with an overlapping of both obstructive and central apneas: this association has been largely demonstrated. It's noteworthy that in children with central apneas and concurrent adenotonsillar hypertrophy, adenotonsillectomy has been observed to lead to the resolution of central apneas. While not considered a specific treatment for central apneas, this association has been noted. It's plausible that the resolution of central apneas follows the alleviation of hyperventilation and arousals caused by obstructive apneas[18,24–29]. An intriguing study conducted by Hwang et al. highlighted that pediatric patients with both central and obstructive apneas, in the context of adenoid hypertrophy, exhibited a more adverse polysomnographic profile compared to those with only obstructive events. Notably, children with this overlapping pattern were usually younger. We agree with those in literature speculate that central apneas in these cases might not be independent events but rather triggered by arousals resulting from airway obstruction[30]. Our study does not include patients with adenoid hypertrophy who exhibit central apneas, as the treatment in this case is typically medical or surgical rather than ventilatory.

Within our study, in line with existing literature, we categorized patients into three main groups based on the prevalence of specific types of apneas, regardless of age. As showed in *table 1* , these categories include patients with "exclusively central apneas" (MOAHI <5), "predominantly central apneas" (MOAHI 5-10), and "predominantly obstructive apneas" (MOAHI >10). Notably, patients with exclusively central apneas tend to exhibit a higher cAHI, while those with primarily obstructive apneas show a lower cAHI[11]. Analysis of the data has revealed several interesting observations:

- Brain Tumors, Prader-Willi Syndrome, and Hypoxic-Ischemic Encephalopathy: these diagnoses exhibited a remarkable variability among patients. Many of them presented with a combination of both central and obstructive apnea forms.
- Arnold-Chiari Syndrome, idiopathic central apneas, multimalformation syndromes, Rett syndrome, and Ondine Syndrome: in contrast, these diagnoses showed a phenotype almost exclusively of "exclusively central apneas."
- Down Syndrome and obese patients: these patients tend to have a "predominantly obstructive apneas" phenotype. It is our opinion that in these cases central apneas may likely be triggered by arousals and hyperventilation, as previously explained;
- Hydrocephalus, epilepsy, and ROHHAD syndrome: it appears that these patients exhibit a "predominantly central apneas" phenotype;

As showed in *table 2* , among infants under one year of age, 57.89% of cases were attributed to Ondine Syndrome, while 26.31% were infants with hypoxic-ischemic encephalopathy. Only three infants had different diagnoses, accounting for 5.26% each, including multimalformation syndrome, Prader-Willi syndrome, and brain tumors. This data highlights a crucial distinction, underscoring the importance of early intervention in cases of Ondine Syndrome, as nearly 78.57% of such cases required ventilation within the first year of life. This underscores the critical need for prompt diagnosis and ventilatory support in infants with this condition. A study conducted by Felix et al. aligns with ours in demonstrating that diagnoses of central apneas occurring after the first year of life are rarely Ondine's syndrome but rather neurological disorders such as Arnold-Chiari malformation, encephalopathies, and brain tumors. The study also reports several cases of Prader-Willi syndrome[5].

The choice of ventilation strategy for patients with central apneas remains a clinical challenge, compounded by the scarcity of established guidelines. *Table 3* summarizes the ventilation modes among our patients. Pressure-controlled ventilation (PCV) and pressure-supported ventilation (PSV) are well-established techniques that provide varying degrees of respiratory assistance[31]. When it comes to selecting the most appropriate ventilation mode for patients with central apneas, several factors have to be evaluated: these include the severity of the patient's central apneas, the underlying medical conditions, and the patient's response to different ventilation strategies. PSV assists patients in initiating their own breaths while providing additional support in the form of positive pressure during inspiration. This support is synchronized with the patient's own respiratory efforts, making it an excellent choice for those who can still breathe spontaneously but may require assistance to maintain adequate ventilation. PSV mode can be complemented with a timed spontaneous mode in which the patient is given a window of time to initiate inspiration on their own. If the patient delays in initiating inspiration, the ventilator provides support to facilitate inhalation[32]. We used the PSV ventilation mode in the majority of cases (45/67 patients), which reflects its effectiveness and safety in managing central apneas. It was applied across a wide range of diagnoses, underscoring its versatility as a ventilation mode. In our opinion, PSV is reasonably considered for patients with mild to moderate central apneas without important desaturations or severe periodic breathing and it is an excellent ventilation mode in cases of residual functionality of the bulbar respiratory centers. On the other hand, in PCV, the ventilator takes full control of the inspiratory pressure, determining both the maximum and minimum lung pressures[33]. In the context of our ventilated patients, those who have used the PCV mode (15/67) were the ones presenting a more challenging underlying medical condition to manage, along with more severe central apneas. Consistent with what has been explained, it is important to note that the majority of patients who underwent PCV were suffering from Ondine's syndrome, hypoxic-ischemic encephalopathy and brain tumors. On our opinion, this level of control can be beneficial in cases of severe central apneas when the patient is unable to initiate breaths independently or when there is a complete loss of respiratory drive. Thus, we used CPAP among a minimal subset of patients (7/67). This approach indicates a focus on maintaining an open airway during both inspiration and expiration and it is particularly beneficial in cases where obstructive events might coexist with central apneas or where upper airway patency needs to be preserved. In fact, the CPAP mode is primarily known for treating obstructive sleep apnea (OSA) and it can also help in cases where central apneas are related to hypercapnia or arousals. In fact, we reserved CPAP in the case of patients with multimalformation syndromes or patients with Down syndrome. However, it's essential to remember that CPAP may not be suitable for all individuals with central apneas, particularly those with underlying neurological issues or complex factors. Similar optimal results are reported in the literature[5,34–37]. Another approach for managing central apneas, which has been underexplored in the literature, is the use of low-flow oxygen. Interestingly, very few reports document the effectiveness of low-flow oxygen in managing central apneas and PB. Specifically, an older study from 1982 reported that in a 58-year-old man with primary alveolar hypoventilation and central sleep apnea, after initiating treatment with low-flow nocturnal oxygen, there was a significant reduction in the number and duration of sleep apneas and an increase in ventilation levels during sleep[38]. Another study from 2018 by Das et al. demonstrated that low-flow oxygen supplementation significantly reduced cAHI in children during both REM and non-REM sleep[39]. The underlying mechanism remains unclear. However, our study did not include patients treated with low-flow oxygen, as we enrolled individuals who required mechanical ventilation.

A very important concept is the effectiveness of ventilation in central apneas: as showed in *table 4* , our study reflects that all diagnostic categories showed a significant improvement in cAHI. Specifically, a statistically significant reduction ($p<0.05$) in mean cAHI was observed in patients with multimalformation syndromes, hypoxic-ischemic encephalopathy and Prader-Willi Syndrome. The reduction in mean cAHI was not statistically significant in the case of patients with brain tumors. Indeed, brain tumors affecting the respiratory centers are very challenging pathological conditions to treat, often requiring high pressures and controlled modes of ventilation. However, as demonstrated by our study, in these cases significant improvement in central apneas is often not achieved. The rest of the diagnoses exhibited a substantial decrease in the mean cAHI value, but the sample sizes were not sufficient to conduct statistical comparisons. Our findings align with those reported by Ghirardo et al. who showed that the more challenging forms of central apnea are as-

sociated with encephalopathies and brain tumors. These categories pose significant diagnostic complexities. They reported that these diagnostic categories exhibit the highest cAHI[11].

In our study, an intriguing aspect that emerged was the diversity in the choice of ventilation methods dependent on their underlying diagnoses. The *table 5* provides an insightful breakdown of the number of patients who received NIV as opposed to IMV for various diagnostic categories. For patients diagnosed with brain tumors, all six cases were managed with NIV. Interestingly, none of these patients required IMV. While NIV was the chosen approach, it is essential to note that patients with brain tumors exhibited the least significant improvement in central apnea, presenting a non-statistically significant reduction ($p>0.05$) in the cAHI. This observation raises the possibility that for this specific diagnostic category, NIV may not yield substantial benefits in terms of central apnea reduction. Despite the limited therapeutic response, it is plausible that IMV was not pursued in these cases, potentially due to ethical considerations surrounding the avoidance of overtreatment and the anesthetic risks associated with invasive ventilation. Four patients with Down syndrome received NIV, and none required IMV. The choice of NIV aligns with the clinical consideration that central apneas in patients with Down syndrome often result from physiological immaturity and upper airway anomalies, which can be effectively managed with NIV. For Arnold-Chiari II and Primary Central Apnea NIV was the selected mode of ventilation, with no patients needing IMV. Among patients with multimalformation syndromes and hypoxic-ischemic encephalopathy, a significant portion received NIV, and less necessitated IMV. This mixed response demonstrates the complexity within this category, as central apneas could stem from a variety of anatomical and neurological factors. Interestingly, the only one patient with epilepsy required IMV. The results for Ondine Syndrome are particularly noteworthy. A substantial number of patients (nine out of fourteen) received NIV, while five necessitated IMV. It's important to emphasize that patients with Ondine syndrome often require tracheostomy ventilation during the early years of life and, subsequently, NIV during the puberty and young adulthood years. This emphasizes the severity and complexity of central apneas in this syndrome, which often demand invasive ventilation methods. Eight patients with Prader-Willi Syndrome were successfully managed with NIV, with no requirement for IMV. This aligns with the idea that NIV is an effective approach for central apneas associated with this syndrome, which frequently presents with obesity-related breathing issues. These results underscore the importance of tailoring ventilation strategies to the specific diagnostic category and characteristics of each patient. The findings also emphasize the diverse nature of central apneas, ranging from milder cases that can be addressed with NIV to more severe instances necessitating IMV. It's essential to consider the individual patient's condition and needs when determining the most suitable ventilation method.

While our retrospective study provides valuable insights into the diverse clinical manifestations and ventilatory strategies for central apneas in pediatric patients, some limitations must be acknowledged. Firstly, the study's retrospective nature inherently carries the risk of incomplete or inconsistent data collection. Additionally, the relatively modest sample size within specific diagnostic categories may limit the generalizability of our findings. The study exclusively focuses on patients who required mechanical ventilation, potentially overlooking cases of central apneas managed through non-ventilatory means. Furthermore, the absence of a control group and the lack of a standardized protocol for ventilatory management across different diagnoses introduce potential biases in the assessment of treatment effectiveness. Lastly, the study's reliance on a single-center dataset may restrict the generalizability of our findings to a broader population. Despite these limitations, our study offers a comprehensive retrospective analysis, providing a foundation for future research endeavors in understanding and addressing central apneas in pediatric populations. In conclusions, central apneas, while often considered benign in infancy, can emerge as significant clinical challenges when they occur in the context of various underlying pathologies. Our findings underscore the multifaceted nature of central apneas, reflecting the interplay of genetics, neurological function, and respiratory control. Patients with central apneas can be broadly categorized into those with predominantly central apneas, predominantly obstructive apneas, or a combination of both. The choice of ventilation mode often depends on the underlying diagnosis and the severity of central apneas. PSV was the most commonly employed mode, proving effective in various diagnostic conditions and severity levels. PCV was utilized in cases of more severe central apneas when patients were unable to initiate breaths independently. CPAP was also

employed in select cases. While NIV was frequently used, IMV was selectively employed in severe cases. A statistically significant reduction ($p<0.05$) in mean cAHI was observed in patients with multimalformation syndromes, hypoxic-ischemic encephalopathy and Prader-Willi Syndrome. The reduction in mean cAHI was not statistically significant in the case of patients with brain tumors. The rest of the diagnoses exhibited a substantial decrease in the mean cAHI value, but the sample sizes were not sufficient to conduct statistical comparisons.

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