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PRACA ORYGINALNA

Tomasz J. Kuźniar[1, 2], Kamilla Kasibowska-Kuźniar[3], Thomas Freedom[1, 4]

[1]Sleep Center, and [4]Department of Neurology, NorthShore University Health System, Evanston, IL, USA
[2]Division of Pulmonary and Critical Care Medicine, NorthShore University HealthSystem, Evanston, IL, USA
[3]Department of Pulmonary Medicine and Lung Cancer, Wroclaw Medical University, Wroclaw, Poland

Trials of bilevel positive airway pressure — spontaneous in patients with complex sleep apnoea

Próby leczenia chorych z zespołem złożonego bezdechu śródsennego aparatami wytwarzającymi dwupoziomowe ciśnienie w drogach oddechowych w trybie spontanicznym

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Abstract

Introduction: Patients with complex sleep apnoea (CompSAS) have obstructive sleep apnoea and experience persistent central apnoeas when exposed to positive airway pressure. Elevated loop gain is one of the postulated mechanisms of CompSAS. We speculated that bilevel positive airway pressure — spontaneous (BPAP-S), by producing relative hyperventilation, may more readily produce CompSAS activity than continuous positive airway pressure (CPAP). If found to do so, a trial of BPAP-S might be a simple way of identifying patients with elevated loop gain who are at risk for CompSAS.
Materials and methods: Thirty-nine patients with complex sleep apnoea were included in the study. Segments of NREM sleep on CPAP and BPAP-S matched for body position and expiratory airway pressure ("comparison pressure") were retrospectively analysed. Correlations between clinical and demographic variables and polysomnographic response to CPAP and BPAP-S were sought.
Results: There was no difference in any of the polysomnographic indices on CPAP and BPAP-S. In 19 patients the use of CPAP was associated with lower AHI at the comparison pressure; in 20 patients the opposite was true. No clinical variables correlated to the differential response to CPAP vs. BPAP-S.
Conclusions: BPAP-S was not more effective than CPAP in stimulating complex sleep apnoea activity.

Key words: complex sleep apnoea, central sleep apnoea, obstructive sleep apnoea, continuous positive airway pressure, bilevel positive airway pressure, loop gain

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Streszczenie

Wstęp: Zastosowanie terapii stałym dodatnim ciśnieniem dróg oddechowych (CPAP) u chorych na zespół złożonego bezdechu śródsennego (CompSAS) prowadzi do wystąpienia zaburzeń oddychania typu ośrodkowego. Jednym z podstawowych postulowanych mechanizmów powstawania CompSAS jest zwiększenie *loop gain* — wzmocnienia pętli sprzężenia — definiowanego jako całkowita odpowiedź układu oddechowego na zaburzenie jego stanu równowagi. Teoretycznie, zastosowanie terapii aparatem wytwarzającym dwupoziomowe ciśnienie w drogach oddechowych w trybie spontanicznym (BPAP-S), powinno nasilać hiperwentylację i prowadzić do łatwiejszego powstawania fenotypu CompSAS niż CPAP. Praktyczne potwierdzenie tej teorii pozwoliłoby na łatwiejszą identyfikację osób z wysokim wzmocnieniem pętli sprzężenia, narażonych na CompSAS.
Materiał i metody: Badaniem objęto grupę 39 chorych na CompSAS. Przeprowadzono retrospektywną analizę porównawczą fragmentów snu NREM uzyskanych podczas polisomnografii terapeutycznej (PSG) uzyskanych podczas stosowania

Adres do korespondencji: dr hab. n. med. Tomasz J. Kuźniar, Department of Medicine Clinical Military Hospital, ul. Weigla 5, 50–981 Wroclaw, e-mail: tk@medycyna-snu.pl

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CPAP i BPAP-S, zgodnych co do pozycji ciała pacjenta i ciśnienia wydechowego („ciśnienie porównawcze"). Poszukiwano korelacji pomiędzy parametrami klinicznymi, demograficznymi oraz odpowiedzią chorych na CPAP i BPAP-S.
Wyniki: Nie stwierdzono różnic w żadnym parametrze polisomnograficznym pomiędzy segmentami snu podczas próby stosowania CPAP i BPAP-S. U 19 chorych, wskaźnik bezdechów i spłyceń oddechu (AHI) był niższy podczas leczenia aparatem CPAP na poziomie ciśnienia porównawczego niż podczas leczenia BPAP-S, zaś u 20 pacjentów obserwowano odwrotną zależność. Nie stwierdzono korelacji żadnego z badanych parametrów klinicznych ze skutecznością CPAP lub BPAP-S.
Wnioski: Nie obserwowano zwiększenia częstości wywoływania CompSAS przez BPAP-S w porównaniu z CPAP.

Słowa kluczowe: zespół złożonego bezdechu śródsennego, ośrodkowy bezdech śródsenny, obturacyjny bezdech śródsenny, stałe dodatnie ciśnienie dróg oddechowych, dwufazowe dodatnie ciśnienie dróg oddechowych, wzmocnienie pętli sprzężenia
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Introduction

Complex sleep apnoea syndrome (CompSAS) is a phenotypic designation of central sleep apnoea appearing in a patient with obstructive sleep apnoea upon correction of airway obstruction, typically with a positive airway pressure (PAP) therapy [1–3]. This infrequent condition affects 1–5% of patients with OSA; patients with CompSAS are usually treated with various forms of PAP therapy, of which adaptive servoventilation seems to have the highest immediate and short-term efficacy [4–10].

The aetiology of CompSAS is unknown, and several mechanisms are likely to contribute to the appearance of this phenotype. The use of opioids is associated with central apnoea, Biot's breathing, and ataxic breathing; additionally, the sedative effects of opioids decrease the respiratory drive — a known protective mechanism against airway collapse [11–13]. The resulting coexistence of obstructive and central phenomena may produce the complex sleep apnoea phenotype. Congestive heart failure frequently results in central apnoea with Cheyne-Stokes pattern, which may give a complex apnoea phenotype and be difficult to treat [14, 15]. Finally, low arousal threshold may result in sleep fragmentation and repeated oscillations around the apnoeic threshold, manifested by frequent central apnoeas. Loop gain, an engineering term reflecting the capacity of a feedback-controlled system, has been used to describe the general propensity of the respiratory system to cycle between hyperpnoea and apnoea [16]. Patients with CompSAS have been postulated to have an elevated loop gain compared to non-CompSAS patients with OSA [17].

Though some patients with OSA cycle between hyperpnoea and central apnoea just with clearance of airway obstruction with CPAP (*positive airway pressure*), this cycling can be enhanced by increasing the respiratory output following the patient's own respiratory effort. This effect is probably due to the lowering of $PaCO_2$ below the apnoeic threshold, and it has been achieved in experimental studies by proportional assist ventilation (PAV), a technique that augments pressure support in proportion to the patient's own respiratory effort [18, 19].

Bilevel PAP devices in spontaneous mode (BPAP-S) with constant pressure support are commonly employed in nocturnal hypoventilation and in patients with OSA who have difficulty tolerating PAP therapy. Since BPAP-S increases tidal volume for any given respiratory drive, and irrespective of this drive, and may thus increase the minute ventilation and lower $PaCO_2$ (potentially exposing the individual to the risk of cycling), we speculated that patients with CompSAS tendency will indeed have more central apnoea activity while on BPAP-S than CPAP. If true, such an exposure to BPAP-S during therapeutic testing could allow for early recognition and shorter evaluation of CompSAS activity, and could prevent repeated in-lab testing with different PAP modalities that are usually necessary in these patients [20].

Materials and methods

The study was approved by the Institutional Review Board of the NorthShore University Health System. All patients were referred to a single sleep centre and were evaluated between 11/1/2006 and 12/31/2010 by one of a team of ten sleep board-certified physicians. Patients underwent a diagnostic and therapeutic polysomnogram. If severe sleep apnoea was observed during the diagnostic study (apnoea-hypopnea index [AHI] > 30/h) over at least two hours of recorded sleep, and sufficient time remained (> 3 hours of expected bed time), the patient had a PAP titration during the same night ("split-night protocol"). All therapeutic polysomnograms started with CPAP; BPAP-S was applied in cases of the appearance of complex sleep apnoea, by the order of the physician, or in cases of poor CPAP tolerance, by technician's discretion.

All studies were performed in compliance with American Academy of Sleep Medicine (AASM) standards, were scored according to the AASM scoring criteria, and read by one of the team of 10 board-certified or board-eligible sleep physicians. Airflow and respiratory effort were monitored using a nasal pressure transducer and respiratory impedance plethysmography during the diagnostic study, and using the flow channel from the CPAP or BPAP plus respiratory impedance plethysmography during the positive pressure titration studies. Hypopnoeas were defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thorocoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation. PAP titration was performed in accordance with a local protocol — in cases of residual obstruction, CPAP pressure was increased by 1 cmH_2O every ten minutes; during BPAP-S titrations, the same procedure was followed for expiratory positive airway pressure (EPAP). During BPAP-S titrations the inspiratory positive airway pressure (IPAP) was initially set 4–5 cm H_2O above EPAP and then increased as the EPAP was increased, in order to keep the (IPAP-EPAP, "delta") difference constant. During the BPAP-S studies, if obstruction was successfully controlled and hypoxemia remained, an attempt to increase delta was undertaken. Following the evaluation, patients were treated with PAP modalities at the discretion of their physician. Objective compliance with the PAP device was assessed at the first visit at 4–6 weeks of its use. Patients who did not come for their follow-up appointment were contacted over the telephone regarding their usage. All patients who could not be contacted or could not supply the compliance card were treated as non-compliers.

Patients with complex sleep apnoea were included in the analysis. "Complex sleep apnoea" was defined as the development of central sleep apnoea or having central apnoea index of more than 5/ /hour or prominent and disruptive Cheyne-Stokes breathing pattern in a patient with obstructive sleep apnoea. Patients were included in the study if their supervised PAP titration study contained two segments, one on CPAP and one on BPAP-S, of non-rapid eye movement (NREM) sleep of at least 10 minutes' duration, matched for pressure (where continuous PAP on CPAP equalled EPAP on BPAP-S, called "comparison pressure") and position of sleep. Polysomnograms of thus identified patients were retrospectively reviewed and polysomnographic variables pertaining to sleep segments spent at comparison pressure (apnoea-hypopnea index [AHI], central apnoea index [CAI], hypopnea index [HI], and arousal index [AI]) were collected. Additionally, individual demographic and clinical variables were collected.

Continuous data were presented as medians and interquartile ranges and analysed using ANOVA. Discrete data were analysed using Fisher's exact test. Correlations were analysed with Pearson's correlation.

Results

Of 72 patients with complex sleep apnoea identified and considered for the study, 33 were excluded (16 did not register NREM in the same body position on both CPAP and BPAP-S, in 7 the original polysomnogram could not be reviewed, in 7 patients CPAP and BPAP-S were tried on different nights, and in 3 patients significant residual obstruction was seen at the comparison pressure), leaving 39 patients included in the analysis. In all cases, the BPAP-S trial followed the CPAP trial in the course of the polysomnographic evaluation. Demographic and polysomnographic data of patients included in the study are presented in Table 1.

Table 1. Demographic, clinical, and polysomnographic characteristics of patients with CompSAS (n = 39) included in the analysis. Data are presented as n (percentage) or medians (interquartile range), as appropriate

Tabela 1. Dane demograficzne, kliniczne i polisomnograficzne chorych z zespołem bezdechu złożonego (n = 39) poddanych analizie. Dane przedstawiono jako n (procent) lub mediany (zakres międzykwartylowy)

Variable	Value
Age (years)	61.0 (50.5–71.5)
Gender (M/F)	27/12
Body mass index [kg/m^2]	31.3 (28.7–35.7)
Epworth Sleepiness Scale score	11 (8.5–16)
Congestive heart failure (yes/no)	10 (25.6%)
Opioid use (yes/no)	12 (30.8%)
Stroke (yes/no)	9 (23.1%)
Prior diagnosis and therapy for sleep apnoea	7 (17.9%)
AHI on diagnostic study [1/h]	48.0 (33.0–69.5)
CAI on diagnostic study [1/h]	5.0 (0–9.5)*
AHI on PAP titration study [1/h]	32.5 (21.2–52.2)
CAI on PAP titration study [1/h]	21.0 (14.0–43.0)

*Twenty patients had CAI equal or greater than 5 on diagnostic study
All abbreviations in the text/Objaśnienia skrótów w tekście

The median (interquartile range) "comparison pressure" in the whole group (CPAP during CPAP titrations and EPAP during BPAP-S titrations) was 8 cm H_2O (7–11.5), while the median final pressure attempted during the titration study was 10 cmH_2O (9–12.5), with median IPAP during BPAP-S studies of 15 cm H_2O (14–17.5). Data at the final CPAP and BPAP comparison pressure are presented in Table 2. Overall, there was no difference in any of the polysomnographic indices on CPAP and BPAP-S. Significant residual sleep-disordered breathing was seen on either modality at the comparison pressure; remaining events were classified as mixed apnoeas. In 19 patients the use of CPAP was associated with lower AHI at the comparison pressure; in 20 patients the opposite was true, and residual AHI on CPAP and BPAP-S correlated to each other with a statistically non-significant trend ($r = 0.30$, $p = 0.065$, Figure 1). There was a statistically significant correlation between the CAIs ($r = 0.33$, $p=0.04$) and AIs ($r = 0.62$, $p < 0.001$) on CPAP and BPAP-S at the comparison pressure.

In order to differentially explore the patient's tolerance of CPAP and BPAP-S, differences of AHI, CAI, and AI on comparison pressure were calculated. If positive, the patient had higher AHI, CAI, and AI on BPAP-S than CPAP, and if negative the opposite was true. Prior diagnosis of sleep apnoea and therapy with CPAP was associated with higher AHI ($p = 0.049$), but not CAI or AI, on BPAP than on CPAP. No other demographic or polysomnographic variable correlated with the AHI difference between the CPAP and BPAP-S (data not shown).

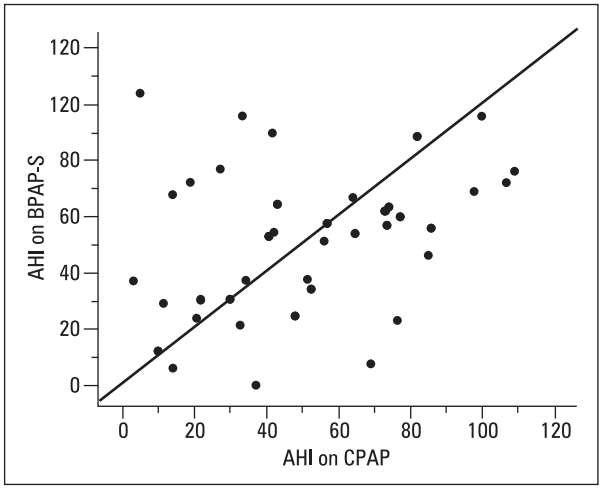

Figure 1. Residual apnoea-hypopnoea index at comparison pressure on CPAP and BPAP-S in 39 patients with complex sleep apnoea. Solid line represents identity line. Spearman's coefficient of correlation between AHI on CPAP and BPAP-S was 0.30, $p = 0.065$

Rycina 1. Wskaźnik bezdechów i spłyceń oddechu (AHI) na poziomie ciśnienia porównawczego u 39 chorych z zespołem złożonego bezdechu śródsennego leczonych aparatami CPAP i BPAP-S. Linia ciągła przedstawia linię identyczności. Współczynnik korelacji Spearmana pomiędzy AHI podczas leczenia CPAP i BPAP-S wyniósł 0,30, $p = 0,065$

Thirty-four patients (87.2%) accepted PAP therapy that was prescribed following the sleep evaluation, and five patients refused any therapy. Of the 34 acceptors, 21 (61.8%) were treated with servo ventilation, 9 (26.5%) received CPAP, 2 (5.9%) were treated with autoadjusting PAP, 1 (2.9%) received BPAP in the spontaneous-timed mode, and 1 (2.9%) was treated with autoadjusting BPAP. A download of the compliance device was available on 30/34 patients; the remaining four patients could not be contacted and were treated as non-compliers. Average nightly use of the device was 4.6 (2.5–6.6) hours, and the device was used for more than 4 hours on 62% (17–94%) of nights; compliance was not associated with individual responses to CPAP and BPAP-S.

Discussion

Complex sleep apnoea (CompSAS) describes an appearance of central apnoea activity in a patient with OSA upon exposure to therapy, typically PAP-based [1–3]. The exact mechanism of this activity is unknown and probably several mechanisms operate together to produce CompSAS phenotype. This multitude of factors contributing to CompSAS is the probable reason for variable behaviour of CompSAS patients during acute testing and longitudinal therapy with PAP in different patient populations [6, 21, 22].

Loop gain is an engineering term describing the general propensity of a negative feedback loop-controlled system to become unstable. Systems with low loop gain have a capacity to stabilize upon the introduction of a destabilizing impulse, while the systems with high loop gain tend to destabilize more and oscillate, or "cycle". In the respiratory system this is reflected by oscillations between apnoeas and hyperpnoeas, typical of periodic breathing [23]. Loop gain can be measured experimentally, but this has requires expensive PAV technology which is not available in a general sleep lab [19]. In our study we attempted to differentiate patients with high and low loop gain by using pressure support delivered by BPAP-S after successful opening of the airway.

Prior research on patients with CompSAS tendency showed that use of bilevel PAP led to a significant worsening of central apnoea tendency [24]. However, Johnson et al. combined in their study segments of sleep at different CPAP and

Table 2. Polysomnographic variables of patients with complex sleep apnoea (n = 39), who were treated with both CPAP and BPAP-S. Data are presented as medians (interquartile range). Differences between groups are statistically insignificant

Tabela 2. Zmienne polisomnograficzne chorych z zespołem bezdechu złożonego (n = 39), którzy byli poddani leczeniu CPAP i BPAP-S. Dane przedstawiono jako mediany (zakres międzykwartylowy). Różnice pomiędzy grupami są nieznamienne statystycznie

Variable	CPAP	BPAP-S
Time at comparison pressure [min]	19.5 (12.5–31)	17.0 (11.5–29.0)
Apnoea-hypopnea index (AHI) [1/h]	48.0 (28.5–73.5)	54.2 (30.8–68.9)
Central apnoea index (CAI) [1/h]	21.0 (11.0–52.0)	24.3 (10.7–43.6)
Hypopnoea index (HI) [1/h]	2.9 (0–6.9)	7.2 (0–18.0)
Arousal index (AI) [1/h]	41.8 (22.0–65.7)	34.3 (18.3–73.5)

All abbreviations in the text/Objaśnienia skrótów w tekście

BPAP pressures, exposing their patients to either incomplete therapy or overtreatment [3, 17, 25]. Additionally, in some patients, a third PAP modality, BPAP in the spontaneous-timed mode was used, which may have skewed the data.

In our research, we only used one comparison pressure, and, contrary to our hypothesis, residual AHI, CAI, HI, or AI were not statistically different on CPAP and BPAP-S therapy. Additionally, factors that might predispose to the development of CompSAS (low left ventricular ejection fraction, hypocarbia) did not correlate with the differential effect of CPAP and BPAP-S. Also, in a subgroup analysis, none of the known risk groups for CompSAS (opioid users, CHF patients) had consistent, differential responses to CPAP and BPAP. This apparent lack of the expected effect of BPAP-S may have resulted from insufficient effects of this modality in revealing high loop gain states. Though theoretically plausible and seen in some patients in an experimental setting (Dr Andrew Wellman, Brigham and Women's Hospital, Harvard University, USA, personal communication), constant pressure support generated by BPAP-S (unlike variable and proportionate to effort, in PAV) may not destabilize the respiration enough to produce clinically detectable oscillations of respiration. The high mixed apnoea indices in our patients may indicate that, at least in some cases, some obstruction persisted at the end of central events; although patients with gross obstruction were excluded from analysis, small amounts of airway obstruction may be seen at the end of central apnoeas [26] and it may significantly alter the phenotype of sleep-disordered breathing, irrespective of loop gain [27]. Alternatively, other cofactors such as low arousal threshold may have played a larger role in determining the frequency of sleep-disordered breathing. Based on our results, and based on relatively low correlation between the residual AHI on CPAP and BPAP-S, it seems worthwhile to attempt BPAP-S during testing for CompSAS in patients with very high residual AHI on CPAP, especially when adaptive servo technology is not available.

The major limitation of the study is its retrospective character. Patients did not follow a formal protocol; rather, BPAP-S was applied by doctor's orders or, in cases of poor tolerance of PAP, as perceived by the polysomnographic technician. We were not testing the two PAP modalities immediately after each other; in some cases, CPAP pressure was further increased to eliminate any possibility of obstructive changes prior to the switch to BPAP-S. Additionally, PAP modalities were not tested in random order, and CPAP always preceded BPAP-S. Since there may be some change in the obstructive and central apnoea tendency during the night, with obstructive changes predominating in the earlier part of the night (spent on CPAP in our case), and central events appearing later at night (BPAP-S in our case), any predominance of central or complex apnoea on BPAP-S might have been due to the systematic error [28]. Finally, low patient number may have prevented us from seeing a statistically significant clustering of cases with different physiologies.

In summary, in this clinical and retrospective study, we did not see any differential effects of CPAP and BPAP-S on complex sleep apnoea activity. Further systematic studies on the use of BPAP-S as an inexpensive and easily available way of assessing a patient's loop gain, and thus a patient's risk of complex sleep apnoea, are warranted.

Konflikt interesów

Autorzy nie zgłaszają konfliktu interesów.

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