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Polysomnographic parameters during non-rapid eye movement sleep predict continuous positive airway pressure adherence

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ABSTRACT

The aim of this study was to investigate the potential polysomnographic predictors of CPAP adherence using polysomnographic parameters at the time of obstructive sleep apnea diagnosis that distinguished between REM and NREM sleep. This was a retrospective cross-sectional study of 173 patients. Patients who used CPAP for more than 4 hours per night for at least 70% of nights over a 6-month period were considered to have good adherence. The poor adherence group included those who had used CPAP for 6 months from initiation, but did not fulfill the definition of good adherence or gave up the treatment within 6 months of treatment initiation. Of the 173 participants, 44 patients had good CPAP adherence and 129 patients had poor adherence. Univariate analysis showed that patients with good adherence had significantly higher apnea-hypopnea index during NREM sleep ($p = 0.043$), oxygen desaturation index during NREM sleep ($p = 0.011$), and cumulative percentage of time spent at saturations below 90% (CT90) during NREM sleep ($p < .001$). In multiple logistic regression analysis including all variables, CT90 during NREM sleep was the only factor independently associated with CPAP adherence (odds ratio, 0.693; 95% confidence interval, 0.582–0.824; $p <.0001$). The area under the receiver-operating characteristic curve of CT90 during NREM sleep was 0.823 (95% confidence interval, 0.745–0.901).Evaluating NREM sleep is important in reliably predicting CPAP adherence using polysomnographic parameters. CT90 during NREM sleep was the best predictor of CPAP adherence.

Key Words: adherence, continuous positive airway pressure, obstructive sleep apnea,polysomnography

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by periodic complete or partial collapse of the upper airway during sleep, resulting in snoring, recurrent oxygen desaturations, increased arousals from sleep, and excessive daytime sleepiness. Patients with untreated OSA are at increased risk for hypertension,[1)] cardiovascular disease,[2)] cerebrovascular disease,[3)] metabolic

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disease,[4] and motor vehicle accidents due to daytime sleepiness.[5]

Continuous positive airway pressure (CPAP) treatment is recognized as the most effective treatment for patients with moderate to severe OSA. Adequate use of CPAP reduces respiratory events, and improves clinical symptoms of OSA and daytime sleepiness.[6,7] CPAP treatment is a symptomatic rather than a radical treatment; therefore, maintaining adherence is crucial to obtain the beneficial effects. Kribbs *et al.* defined good adherence as use of the CPAP machine for more than 4 hours per night for at least 70% of the days monitored, and indicated that adherence was only 46% in their study.[8] Another study reported that the rates of poor CPAP adherence, as defined by mean use of CPAP less than 4 hours per day, was 29–83%.[9] Therefore, improvement of adherence is an important issue. Previously, several interventions such as supportive and cognitive behavioral intervention have been shown to improve CPAP adherence.[10,11] Technological advances such as improvement in mask fit and humidified air have also had an impact on CPAP adherence.[12] In some cases, surgical intervention has improved CPAP adherence.[13]

Patterns of CPAP use are established early in the treatment period, with a previous study reporting that it is established during the first week of treatment.[14] Therefore, it is important to predict CPAP adherence prior to treatment initiation and apply intensive intervention for patients who are likely to need it.

Clinical predictors of CPAP adherence have been demonstrated in many studies, and include severity of disease, degree of sleepiness before treatment, age, sex, and CPAP pressure at initiation.[15-17] However, our search of the literature revealed no reports investigating the predictors of CPAP adherence regarding sleep architecture, especially in rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.

Compared with NREM sleep, REM is associated with greater sympathetic activity and cardiovascular instability,[18] and minute ventilation, tidal volume and respiratory frequency in REM fluctuate widely.[19] Moreover, upper airway muscle activation is more severely suppressed during REM sleep than during NREM sleep.[20] In other words, REM sleep is a more unstable time that has many variable factors affecting several parameters recorded via polysomnography (PSG) compared with NREM sleep.

Therefore, we hypothesized that the PSG parameters recorded during NREM might be stable predictive features of CPAP adherence, as there are fewer variable factors during NREM compared with REM. The aim of this study was to identify the potential PSG predictors of CPAP adherence in the initial 6 months of treatment after OSA diagnosis by measuring PSG parameters during REM and NREM sleep.

METHODS

Participants

This was a retrospective and cross-sectional study approved by the Ethics Committee of Aichi Medical University Hospital (AMUH).

Nocturnal PSG was conducted on 1922 patients who first visited the Sleep Disorder Center of AMUH with suspected OSA between January 2008 and May 2011. Of these 1922 patients, 443 patients were diagnosed with OSA and started CPAP treatment. All clinical records and PSG data were available from the medical records databank in a deidentified format.

The criteria for enrollment were: 1) age over 20 years, 2) having started CPAP using the REMstar M series Auto CPAP machine (Philips Respironics GK, Tokyo, Japan), 3) no previous treatment for OSA, 4) never having been diagnosed with any other sleep disorder. In our facility, several kinds of CPAP machines are prescribed to patients. To exclude the influence of the

different algorithms of the machines, all participants used the REMstar M series Auto CPAP machine with nasal mask.

We excluded 34 subjects from the investigation as they transferred to another hospital within 6 months of OSA diagnosis or CPAP initiation because they lived far from our institution and were difficult to follow-up. Of the initial sample, 173 patients were included in this study. There are no missing data in this study.

Procedure

Body mass index (BMI) and neck circumference (NC) were measured at each patient's first visit. The Epworth Sleepiness Scale (ESS) was used to evaluate levels of daytime sleepiness.[21] All patients were diagnosed with OSA by PSG using the Alice4 system (Philips Respironics GK).

Biological variables were continuously recorded using electrocardiography, electroencephalography (F4-M1, C4-M1, O2-M1, F3-M2, C3-M2, O1-M2), submental and anterior tibial electromyography and electrooculography. Air flow was measured by a nasal cannula with a pressure transducer. Chest and abdominal movement was monitored by inductance plethysmography belts. Snoring was recorded using a microphone. Arterial oxygen saturation was measured continuously by pulse oximetry. Body position was assessed by a monitor and a sensor. Sleep stage and arousals were scored based on the American Academy of Sleep Medicine (AASM) 2007 scoring system.[22] The oxygen desaturation index (ODI) was defined as the number of desaturation > 3% per hour of sleep. Obstructive apnea was defined as absence of airflow for longer than 10 seconds; obstructive hypopnea was defined as at least 50% reduction in airflow for longer than 10 seconds, and was associated with an electroencephalographic arousal or desaturation of > 3%. The apnea–hypopnea index (AHI) was calculated as the number of apnea and hypopnea events per hour of sleep.

Respiratory-effort related arousal (RERA) was determined by reduction in airflow for longer than 10 seconds that did not fulfill apnea or hypopnea criteria, with increased respiratory effort and no desaturation, which led to an arousal from sleep. RERA index was calculated as the number of RERA per hour of sleep.

Respiratory events included apnea and hypopnea events. Mean respiratory event duration was calculated as the mean duration per respiratory event. Total respiratory event duration was calculated as the sum of all respiratory event durations. The cumulative percentage of time spent at saturations below 90% (CT90) was calculated as the percentage of time that arterial oxygen saturation as measured by pulse oximetry was below 90% during sleep time. Limb movement index(LMI) refers to the number of limb movement per hour of sleep regardless of periodic movement.

These data were scored manually according to the American Academy of Sleep Medicine (AASM) 2007 scoring system by specialized clinical engineers.[22]

In accordance with the Japanese health insurance system, CPAP treatment was recommended to patients who were found to have an AHI greater than 20 events/hour in PSG. The patients who were recommended CPAP treatment received education about this disease and treatment by a special physician, and mask fitting was performed by specialized clinical engineers. CPAP titration was performed with an auto-titrating device, REMstar Auto M series.

In accordance with the health insurance system in Japan, patients who were undergoing treatment had to attend the clinic or hospital once every month. At each monthly visit, patients had to bring the built-in monitoring chip from their CPAP device that stored the CPAP usage data to be downloaded for recording. Mean CPAP daily use (hours) and rate of CPAP use were calculated from the collected data. CPAP usage data was analyzed retrospectively for 6 months from CPAP initiation.

Statistical analysis

Patients were dichotomized into good or poor adherence groups. The good adherence group included those with a mean CPAP daily use > 4 hours and a rate of CPAP use > 70% for 6 months from treatment initiation. The poor adherence group included those who had used CPAP for 6 months from initiation, but did not fulfill the definition of good adherence or gave up the treatment within 6 months of treatment initiation.

Univariate analysis was performed using the two-sample *t*-test for normally distributed data, and the Mann–Whitney U test for nonparametric data. The chi-squared test was used for categorical data. Predictive factors of the two groups were evaluated by multiple logistic regression analysis using the backward selection method, including all variables assessed in this study. Predictive ability was assessed by receiver operating characteristic (ROC) analysis using the area under curve (AUC). Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC) and R 3.0.1 (R Foundation for Statistical Computing,Vienna,Austria). A p value of < 0.05 was considered statistically significant.

RESULTS

Participants were mostly male (84.4%). The mean age was 57.3 ± 13.4 years, mean NC was 39.4 ± 3.4 cm, mean BMI was 26.8 ± 4.4 kg/m^2, and the mean ESS score was 9.1 ± 5.0. Of the 173 participants, 44 patients had good CPAP adherence and 129 patients had poor adherence. There was no significant difference between baseline characteristics of patients in the good and poor adherence groups (Table 1).

Concerning the PSG findings, patients in the good adherence group had significantly higher AHI during NREM (36.5 ± 10.9events/h vs. 32.9 ± 13.1 events/h, $p = 0.043$), ODI during NREM (32.8 ± 11.9 events/h vs. 28.3 ± 13.7 events/h, $p < 0.011$), and CT90 during NREM (4.8 ± 7.0% vs. 0.6 ± 1.8%, $p < 0.001$) (Table 2).

Multiple logistic regression analysis with backward selection including all variables found that CT90 during NREM sleep (odds ratio [OR], 0.693; 95% confidence interval [CI], 0.582–0.824; $p < 0.0001$) was the only factor independently associated with CPAP adherence (Table 3).

The ROC curve was plotted to evaluate the predictive ability of CT90 during NREM, the AHI during NREM, and the ODI during NREM. The area under the ROC curve of CT90 during NREM sleep (0.823; 95% CI, 0.745–0.901) was greater than the area under the ROC curve of AHI during NREM sleep (0.603; 95% CI, 0.511–0.694) and ODI during NREM sleep (0.629; 95% CI, 0.535–0.723). The best cutoff value, defined as the maximum of the Youden index,

Table 1 Baseline characteristics of those in the good and poor adherence groups

	Total (n=173)	Good (n=44)	Poor (n=129)	p value
Age (year)	57.3±13.4	59.6±10.6	56.3±14.2	0.201
Sex male (%)	84.4	80.1	85.5	0.168
ESS	9.1±5.0	9.7±5.0	8.8±5.0	0.258
BMI (kg/m^2)	26.8±4.4	26.7±3.3	26.9±4.7	0.792
NC (cm)	39.4±3.4	40.1±2.6	39.1±3.6	0.077

Date are presented as mean ± standard deviation. The two-sample *t*-test or the Mann–Whitney U test was used for continuous variables, and the chi-squared test was used for categorical variables.
ESS: Epworth Sleepiness Scale; BMI: body mass index; NC: neck circumference.

of CT90 during NREM sleep was 0.06; its sensitivity was 90.9% (95% CI, 0.818–0.977) and specificity was 65.1% (95% CI, 0.566–0.729) (Figure 1).

Table 2 Polysomnographic variables of the good and poor adherence groups

	Total (n=173)	Good (n=44)	Poor (n=129)	p value
Sleep latency (min)	9.6±10.2	11.7±13.0	8.9±8.9	0.111
REM sleep latency (min)	138.2±80.4	153.4±83.5	132.8±79.0	0.112
TST (min)	395.6±64.1	386.3±65.7	398.7±63.6	0.103
Sleep efficiency (%)	86.6±11.8	84.5±12.7	87.3±11.4	0.124
Stage REM % of TST (%)	16.4±6.7	16.2±6.3	16.4±6.9	0.822
Stage 1+2 % of TST (%)	81.9±8.0	82.3±6.5	81.8±8.5	0.694
Stage 3+4 % of TST (%)	1.7±3.6	1.5±3.2	1.8±3.8	0.258
REM-AHI (events/h)	39.0±18.7	38.3±16.1	39.3±19.5	0.506
NREM-AHI (events/h)	33.9±12.7	36.5±10.9	32.9±13.1	0.043*
REM- mean respiratory event duration (sec)	32.7±21.4	32.5±10.7	32.8±24.1	0.944
NREM-mean respiratory event duration (sec)	26.8±26.7	33.2±51.8	24.7±6.0	0.392
REM-% of respiratory event duration (%)	33.2±15.2	34.4±16.0	32.7±15.0	0.536
NREM-% of respiratory event duration (%)	23.6±11.3	26.6±12.8	22.6±10.7	0.056
REM-min SpO_2 (%)	79.9±10.8	78.0±12.0	80.6±10.3	0.214
NREM- min SpO_2 (%)	83.6±7.0	82.3±8.0	84.1±6.6	0.089
REM-ODI (events/h)	37.3±19.1	36.9±16.2	37.4±20.0	0.882
NREM-ODI (events/h)	29.4±13.3	32.8±11.9	28.3±13.7	0.011*
REM-CT90 (%)	11.5±14.3	12.4±12.7	11.1±14.9	0.26
NREM-CT90 (%)	1.6±4.2	4.8±7.0	0.6±1.8	<.001*
RERA index (events/h)	38.1±13.2	39.2±9.1	37.7±14.3	0.367
LMI (events/h)	10.5±23.6	10.5±23.4	10.6±23.7	0.554

Date are presented as mean ± standard deviation. The two-sample *t*-test or the Mann–Whitney U test was used for continuous variables.
REM: rapid eye movement sleep; NREM: non-rapid eye movement sleep; AHI: apnea–hypopnea index; ODI: oxygen desaturation index; CT90: cumulative percentage of time spent at saturations below 90%; LMI: leg movement index.
*p < 0.05 comparing the good and poor adherence groups.

Table 3 Results of multiple logistic regression analysis using all variables to predict continuous positive airway pressure adherence

	Coefficients	Std. error	OR	95% CI	p value
NREM-CT90(%)	−0.367	0.089	0.693	0.582–0.824	<.0001*

Dependent variable: 0 = good adherence 1 = poor adherence.
The significant variables were selected using multiple logistic regression analysis via the backward selection method.
NREM: non-rapid eye movement sleep, CT90: cumulative percentage of time spent at saturations below 90%; CI: confidence interval; OR: odds ratio.

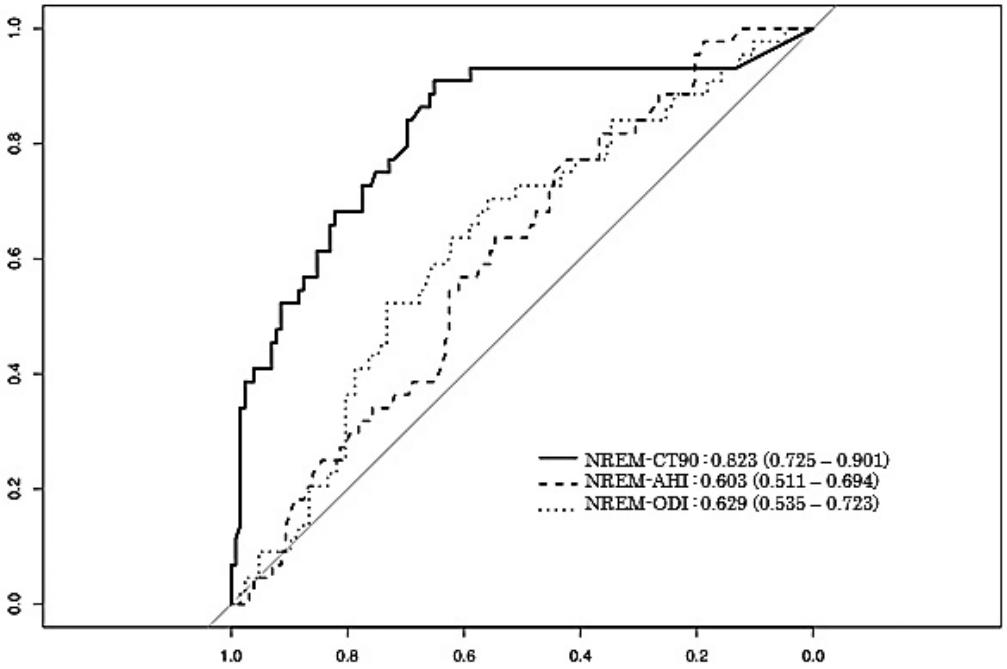

Fig. 1 Receiver-operating characteristic (ROC) curve for comparing predictive ability
The area under the curve for the cumulative percentage of time spent at saturations below 90% during NREM sleep (NREM-CT90) was 0.823, the apnea and hypopnea index during NREM sleep (NREM-AHI) was 0.603, and the oxygen desaturation index during NREM sleep (NREM-ODI) was 0.629.

DISCUSSION

This retrospective and cross-sectional study showed that AHI, ODI and CT90 during NREM sleep were significantly different between patients in the good versus the poor adherence group in univariate analysis. This result also means that all parameters in REM sleep were not significantly different between the good and poor adherence group in univariate analysis.

Compared with NREM sleep, REM sleep is associated with greater sympathetic activity and cardiovascular instability,[18] and minute ventilation, tidal volume and respiratory frequency in REM fluctuate widely.[19] Moreover, upper airway muscle activation is more severely suppressed during REM sleep than NREM sleep.[20] Hence, REM is an unstable time with many variable factors affecting several PSG parameters. Additionally, the percentage of REM sleep is estimated to be about 20% in healthy adults,[23] which means the percentage of NREM sleep is about 80%. To reliably predict CPAP adherence using PSG parameters, it is important to evaluate NREM sleep, as it has fewer variable factors affecting each PSG parameter and occupies a longer proportion of sleep time than REM sleep.

Only CT90 during NREM sleep was independently associated with CPAP adherence. AHI and ODI during NREM sleep were significantly different in the univariate analysis, but were not extracted as significant factors in the multiple regression analysis. CT90 is calculated as the cumulative percentage of time that arterial oxygen saturation was below 90%; hence, CT90 quantifies the severity of hypoxemia and reflects the time of desaturation. ODI is the number of desaturation > 3% per hour of sleep; hence, ODI also quantifies the severity of hypoxemia.

However, it does not reflect time of desaturation. AHI is the number of respiratory events per hour of sleep. AHI is usually used to assess the severity of OSA; however, it does not reflect the severity of hypoxemia. Therefore, the results imply that the severity of hypoxemia and time of desaturation are associated with CPAP adherence. Weaver *et al.* also reported that nocturnal hypoxemia was related with CPAP adherence.[15)]

There are various kinds of hypoxemia indices in use. Our results support the hypothesis of Chaudhary *et al.* that CT90 recorded during PSG may be the best clinical method for expressing the severity of nocturnal hypoxemia in sleep apnea.[24)] Our search of the literature revealed no other report directly associating CT90 with CPAP adherence. However, we speculate that assessing the cumulative percentage of time under hypoxemia as measured by CT90 may be the most important method for predicting CPAP adherence, because this is the only parameter that reflects the time of desaturation.[25)]

Zhang J *et al.* reported that CPAP improve hypoxemia measured by CT90 associated with respiratory events during sleep.[26)] There are no previous reports, however we also speculate that improvement of CT90 is associate with good adherence.

We used ROC analysis to compare the predictive ability of three parameters that were significantly different between the good and poor adherence group in univariate analysis. This ROC analysis indicated that CT90 during NREM sleep had a better ability to predict CPAP adherence than other parameters. CT90 was also strongly associated with good CPAP adherence. A previous report indicated that severity of disease had some predictive ability for CPAP adherence.[27)] Our study showed that those with greater CT90, indicating severe hypoxemia and severe OSA, had better adherence; this finding does not contradict any previous reports. Using the CT90, we will able to identify prior to CPAP initiation those patients who are not predicted to have good adherence and are likely to need some intervention or need another treatment option besides CPAP, such as an oral appliance and Auto Bi-level Pressure Relief-Positive Airway Pressure (ABPR-PAP).[28,29)] Because patterns of CPAP use are established early in the treatment period[14)], this information could have important implications.

In many studies indicated that CPAP adherence was closely related to disease severity as measured by AHI[16,30,31)], yet our result show that AHI during NREM sleep which were significantly different in the univariate analysis were not extracted as significant factors in the multiple regression analysis. It was probable that our sample size was small, compared to previous studies. Moreover, in many study, ESS and age are associate with CPAP use[8,32,33)]. On the other hand, there are also studies show that ESS and age are not associate with CPAP use[34,35,36)]. Our result show that age and daytime sleepiness as measured by ESS were not not extracted as significant factors. We consider that age and the self-reported symptomatic severity of OSA are unreliable in identifying those who will use CPAP appropriately.

Our sleep center prescribes several kinds of CPAP machines; however, all participants in this study used the REMstar M series Auto CPAP. Auto-CPAP devices can detect respiratory events, and automatically increase or decrease the positive airway pressure.[28)] However, the algorithm differs depending on the CPAP machine.[37)] To exclude the influence of different algorithms, the CPAP device participants used was limited to the REMstar M series Auto CPAP. This caused a reduction of the sample to 173 subjects from the 443 potentially eligible participants.

We acknowledge that this study has some limitations. There is a potential selection bias as this study was conducted in a single facility. Only a single type of CPAP device was used by all participants in this study (the REMstar M series Auto CPAP), which might have produced selection bias. Moreover, because this is a retrospective study, it is not possible to exclude the influence of unknown confounding factors.

In conclusion, this is the first study to examine PSG predictors of CPAP use focusing on

basic sleep architecture, REM and NREM sleep. This study indicated that evaluating NREM sleep using PSG parameters is important to reliably predict CPAP adherence from treatment initiation. This study also indicated that the percentage of time under hypoxemia during NREM sleep as measured by the cumulative percentage of time spent at saturations below 90% is a significant predictor of good CPAP adherence from treatment initiation. Additionally, we consider that to improve adherence of CPAP use, we also need to explore the predictors of poor CPAP adherence. Further multicenter studies using other CPAP machines are needed to confirm the external validity and generalizability of the results of this study, and to explore the predictors of poor adherence of CPAP use.

COMPLIANCE WITH ETHICAL STANDARDS

Funding: No funding was received for this research.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Formal consent is not required for this type of retrospective study.

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