Variability of breathing during wakefulness while using CPAP predicts adherence

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Summary at a glance

We investigated the variability of breathing, a marker of respiratory control, as a predictor of CPAP adherence. Our findings indicate that breathing regularity while awake during CPAP acclimatization predicts subsequent adherence to CPAP at 1 month.

Abbreviations:

AHI: apnea-hypopnea index

BMI: body mass index

CPAP: continuous positive airway pressure

CV: coefficient of variation

EMG: electromyogram

ESS: Epworth sleepiness scale

HADS: the Hospital Anxiety and Depression Scale

HADS-A: Hospital Anxiety and Depression Scale, anxiety subscale,

HADS-D: Hospital Anxiety and Depression Scale, depression subscale

OSA: obstructive sleep apnea

PSG: polysomnography

RIP: respiratory inductance plethysmography

ROC: receiver-operating characteristics

Ttot: respiratory duration;

V_T: tidal volume

ABSTRACT

Background and objective: The standard therapy for obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP) therapy. However, long-term adherence remains at ~50% despite improvements in behavioral and educational interventions. Based on prior work, we explored whether regularity of breathing during wakefulness might be a physiologic predictor of CPAP adherence.

Methods: Of 117 consecutive patients who were diagnosed with OSA and prescribed CPAP, 79 CPAP naïve patients were enrolled in this prospective study. During CPAP initiation, respiratory signals were collected using respiratory inductance plethysmography while wearing CPAP during wakefulness in a seated position. Breathing regularity was assessed by the coefficient of variation (CV) for breath-by-breath estimated tidal volume (V_T) and total duration of respiratory cycle (Ttot). In a derivation group (n=36), we determined the cut off CV value which predicted poor CPAP adherence at the first month of therapy, and verified the validity of this predetermined cut-off value in the remaining participants (validation group; n=43).

Results: In the derivation group, the CV for estimated V_T was significantly higher in patients with poor adherence than with good adherence [median (interquartile range); 44.2 (33.4-57.4) vs. 26.0 (20.4-33.2), $p<0.001$]. The CV cut-off value for estimated V_T for poor CPAP adherence was 34.0, according to a receiver-operating characteristics curve. In the validation group, the CV value for estimated V_T >34.0 confirmed to be predicting poor CPAP adherence (sensitivity; 0.78, specificity; 0.83).

Conclusion: At the initiation of therapy, breathing regularity during wakefulness while wearing CPAP is an objective predictor of short-term CPAP adherence.

Key words: breathing regularity, CPAP adherence, obstructive sleep apnea syndrome, predictive marker, respiratory physiology

Short title: Breathing variability and CPAP Adherence

INTRODUCTION

Continuous positive airway pressure (CPAP) is a standard therapy for obstructive sleep apnea (OSA) and can have favorable effects on quality of life, medical and neurological comorbidities, as well as mortality [1-3]. However, CPAP adherence in clinical practice is sub-optimal, with 46 to 83% of patients non-adherent at 12 months or more after initiation of therapy [4]. Over the past decade, investigators have examined demographic, behavioral, and/or polysomnographic factors to predict adherence. Studies report sex[5-7], age[8] , severity of disease[9-12], symptoms of sleepiness[4, 12-14], and socioeconomic status[15, 16] are associated modestly with subsequent adherence to CPAP therapy. In contrast physiological factors, specifically the individuality of respiratory control, have not been explored in predicating CPAP usage.

We reported previously that breathing variability might affect CPAP adherence; specifically, breathing irregularity in a 5-minute period before sleep onset during the diagnostic polysomnography (PSG) was associated with lower CPAP adherence and acceptance [17, 18]. However, our previous studies were retrospective and observed at sleep onset, and questions arose about confounding issues of micro-sleep intrusion and fatigue. Thus, we conducted this prospective study to address whether breathing regularity during wakefulness predicts CPAP adherence, and if so to determine a cut-off, which would predict suboptimal CPAP adherence.

METHODS

Study participants

One hundred and seventeen consecutive OSA patients with an apnea-hypopnea index (AHI) ≥20/h who were prescribed CPAP over the period 2010 to 2013 were screened. Those taking medication for chronic lung, cardiac, and kidney diseases were excluded, leaving 79 patients who agreed to participate in this study. Patients were asked about their sleeping habits including sleeping duration, daytime sleepiness, nasal symptoms such as nasal obstruction and nasal mucus, anxiety and depression, and regular medications. Daytime sleepiness was assessed using a validated Japanese version of the Epworth Sleepiness Scale (ESS)[19]. Symptoms of anxiety disorders and depression were evaluated by the respective subscales of the Hospital Anxiety and Depression Scale (HADS-A and HADS-D)[20]. Patients scoring more than 11 were considered as a probable case of anxiety/depression. This study was approved by the Ethical Advisory Committee at Nara Medical University (No. 461), and all patients gave written informed consent.

Study design

Consecutive patients referred for CPAP therapy were enrolled prospectively. All participants received a sleep education program before CPAP therapy was initiated. This program included education on pathophysiology, consequences, mortality, and treatment of OSA as well as a detailed explanation regarding CPAP usage. The first half of patients who participated in this study were assigned to the derivation group to determine if a cut-off value of breathing irregularity could predict poor CPAP adherence. The next group of participants was assigned to a validation group to confirm whether the cut-off value was valid (Supplementary Figure S1).

Sleep study

The diagnostic overnight full PSG was performed using the Alice 5 Diagnostic Sleep System (Philips Respironics, Murrysville, PA). Apneas were defined as an episode of complete airflow cessation lasting more than 10 sec measured from the thermal sensor. Hypopnea was defined by ≥50% reduction in amplitude of the respiratory inductance plethysmography (RIP) sum signal or nasal pressure signal lasting more than 10 s with ≥ 3% oxygen desaturation and/or arousal.

Analysis of breathing regularity

At the initial visit, just after the sleep education program, participants wore CPAP at a pressure of 5cmH_2O, while in the seated posture in a quiet room. No instructions as to how to breathe or what to expect were given. Resting breathing during wakefulness was monitored for 15 min from the thoracic excursion of a single band RIP (LS-300®, Fukuda Denshi, Tokyo, Japan). Sampling rate of the respiratory signal was 12.5Hz. Data collection was performed in the same environment and time in the afternoon for all subjects. Patients were requested to keep their eyes open. Six-minutes of artifact-free respiratory signal was extracted for the evaluation of breathing regularity. The 6-minute period was randomly selected for analysis by a single investigator blinded to the patient's characteristics and OSA severity. Breathing regularity was assessed by coefficient of variation (CV; SD/mean x 100) for breath-by-breath total duration of respiratory cycle (Ttot) and estimated tidal volume (V_T).

CPAP therapy and assessment of adherence

All participants were prescribed an auto-titrating CPAP (REMstar Auto®, Philips

Respironics, Murrysville, PA) with a nasal mask. No patients were changed to a fixed mode or to a full-face mask during the study. PSG was performed to confirm the efficacy of auto-titrating CPAP during the first night of CPAP initiation. One month following CPAP initiation, CPAP usage data for each patient was downloaded from the memory card, and hours of daily usage and days used per month were obtained. According to the CPAP usage data, patients were divided into good and poor CPAP adherence group using two criteria. First we examined the data using the conventional definition for good adherence proposed by Kribbs and colleagues,≥ 4 hours for 70% nights monitored[21] . We also adopted an enhanced definition for CPAP adherence that included hours of potential use; the criteria for the group of good CPAP adherence included the CPAP usage for more than 70% of nights monitored, for more than 4 hours a night, and for more than 80% of self-reported sleeping duration. Otherwise, patients were assigned to poor CPAP adherence group. This definition took into consideration the overnight duration without CPAP , rather than the duration with CPAP in a night. We considered an added dimension for CPAP usage by asking about how much of total sleep the individual used CPAP, rather than just machine usage per se.

Determination of a threshold or “cut-off” value for adherence

Among the initial 36 patients assigned to a derivation group, parameters for breathing irregularity, i.e. CV values for Ttot and estimated V_T, were compared between good and poor adherence groups. Receiver-operating characteristics (ROC) curve analysis was examined to estimate a cut-off value for CPAP adherence.

Verification of the Validity of a cut-off CV value

The next 43 participants formed the validation group and categorized in accordance with the pre-determined cut-off value of breathing irregularity. At the one month post-CPAP clinic visit, CPAP adherence was assessed as previously described.

Statistical Analysis

Continuous variables are reported as median (interquartile range). The chi-square test for categorical data and the Mann-Whitney U-test for non-parametric continuous variables were conducted for comparison between two groups. Differences with $p<0.05$ were considered significant. Statistical analysis was done with IBM SPSS Statistics 20 for Windows software (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant characteristics

Table 1 shows characteristics of all enrolled patients (n=79). Patient characteristics were similar between derivation and validation groups (Table 1). All patients were Japanese. CPAP adherence in all participants were 5.3 (3.8-6.6) hours for a nightly duration of CPAP usage, 100 (82.2-100) % the number of nights of CPAP usage in the first one month, and 86.4 (57.2-103.6) % for the percentage of actual nightly duration of CPAP usage in the self-reported sleeping duration. A histogram shows the distribution of CPAP usage for all subjects (Supplementary Figure S2).

Breathing irregularity and CPAP adherence in the derivation group

Typical examples of respiratory signal obtained by thoracic excursion using a single band RIP for patients with good and poor CPAP adherence are shown in Figure 1. The

CV values for Ttot and estimated V_T were significantly higher in patients with poor CPAP adherence than those with good CPAP adherence (enhanced definition: CV for Ttot; 18.7 (13.3-25.0) vs. 11.0 (7.1-22.6), $p<0.05$, CV for estimated V_T; 44.2 (33.4-57.4) vs. 26.0 (20.4-33.2), $p<0.01$: Kribbs definition: CV for Ttot; 19.4 (17.2-24.6) vs. 12.6 (7.6-21.8), $p<0.05$, CV for estimated V_T; 43.3 (34.6-46.6) vs. 28.0 (22.2-42.9), $p<0.05$, respectively) (Figure 2). Age, sex, BMI, AHI, ESS, HADS, psychiatric diagnosis and marital status were similar between good and poor adherence groups. Results did not differ between CPAP adherence definitions, except for age (Table 2).

CV value predicting poor CPAP adherence

Based on the strength of statistical significance, we adopted the CV for estimated V_T, rather than CV for Ttot, as the cut-off value to predict poor CPAP adherence in the ROC curve analysis. The area under the curve (AUC) was 0.84 (SE 0.067, $p<0.01$, 95% CI 0.70 to 0.97), indicating moderate accuracy (Figure 3). Cut-off value of CV for estimated V_T for poor CPAP adherence was 34.0 from the ROC curve, with a sensitivity and specificity of 0.78 and 0.83, respectively. When the Kribbs' definition of CPAP adherence was used, statistical significance remained, however AUC was 0.71 (SE 0.086, $p<0.05$, 95% CI 0.55 to 0.88), indicating less accuracy than our enhanced definition of CPAP adherence (Figure 3). Cut-off value of CV for estimated V_T for poor CPAP adherence in the Kribbs' definition was 34.0, which was the same as the value in the enhanced definition, with a sensitivity and specificity of 0.77 and 0.70, respectively.

Validity of the CV value for CPAP adherence

Among the 43 patients in the validation group, 19 patients had CV for estimated V_T ≥ 34.0, (Table 3). The number of patients showing poor CPAP adherence using our enhanced definition were 12 in group with CV for estimated $V_T \geq 34.0$ and 4 in those with CV for estimated $V_T < 34.0$, with a significant difference between groups ($p<0.01$, sensitivity; 0.75, specificity; 0.74). This validation analysis revealed that the cut-off value for CV for estimated V_T was appropriate enough to predict poor CPAP adherence. When the Kribbs definition for CPAP adherence was used, statistical significance remained, but it was weaker than when the enhanced definition was used ($p<0.05$, sensitivity; 0.71, specificity; 0.69).

DISCUSSION

This study demonstrated that breathing regularity as measured by estimated tidal volume during wakefulness while using CPAP during an acclimatization period was a predictive factor for CPAP adherence. Specifically, if the variance (CV) for breath-by-breath tidal volume over a 6-minute period exceeded a value of 34.0, CPAP adherence was more likely to be poor at the one month CPAP review visit.

In this study, we focused on individuality in the pattern of breathing to predict CPAP adherence. Individuality of breathing patterns during wakefulness are maintained during sleep and there are highly significant similarities within identical but not non-identical twin-pairs in the pattern of breathing [22-24]. These observations are consistent with genetic or at least familial factors influencing the pattern of breathing. Breathing patterns represents the output of the respiratory control system, and are the result of a complex combination of anatomic and behavioral factors.

We have previously reported that breathing variability during the diagnostic PSG before sleep onset reflected OSA phenotype and the response to CPAP treatment[17,

[18]. Patients having a greater proportion of central apneas exhibited irregular breathing, implying a higher controller gain. Furthermore CPAP adherence in those patients was poor[18]. In another study[17] of pure OSA patients, CPAP acceptance was also poor in patients whose resting breathing before sleep onset was irregular. We speculated that factors such as anxiety may lead to breathing instability and thus poorer CPAP acceptance[17]. However, in the current study, anxiety and depression assessed by the HADS questionnaire were not associated with poor CPAP adherence. Furthermore, although there is literature linking breathing pattern with anxiety[25, 26], no correlation between CV for estimated V_T and HADS was seen in the present study (data are not shown). Reasons for this might be that slight feelings of anxiety with positive pressure and a nasal mask may not be identified with the questionnaire we used. Although socio-economic status was not evaluated in the present study, age, gender, marital status, and severity of OSA were not associated with CPAP adherence. Taken together, in the present study, we suggest that breathing irregularity while wearing CPAP at the initiation of CPAP therapy is more related to physiological characteristics in terms of respiratory control. In addition, when we performed logistic regression analysis in which the dependent variable was CPAP adherence, and the independent variable was CV for estimated V_T, the coefficient of determination (R^2) was 0.44, implying that 44% of the variability in CPAP adherence was explained by the CV for estimated V_T. We suggest this is clinically a useful and powerful tool for CPAP adherence prediction.

In this study, we adopted an expanded definition of CPAP adherence that focused on sleeping time without CPAP; that is, "good adherence" required not only >4 hours for 70% of nights monitored, but additionally > 80% of self-reported sleeping duration. Most frequently CPAP adherence is defined as usage ≥ 4 hours for 70% nights monitored[21]; however, evidence supporting this conventional definition has not been convincing[27-29]. We propose that considering how many hours a patient sleeps without CPAP may be more appropriate than how many hours they use CPAP. We repeated the analysis using the Kribbs' definition of CPAP adherence, and the results were essentially unchanged (Table 2). However, specificity and sensitivity for poor CPAP adherence were better with our enhanced definition than the Kribbs' definition of CPAP adherence (Figure 3). Our results demonstrate that our alternative definition of CPAP adherence might better capture therapy usage; however further studies will be needed to determine whether CPAP adherence by our definition relates to clinical outcomes and mortality.

There are potential limitations to our study. First, we assessed one month CPAP adherence. It has been reported that CPAP usage in the first few weeks can predict longer term adherence[30, 31]. Thus, responses to CPAP for the very first month are relevant, but later time points may be needed. Second, a causal relationship between breathing irregularity and CPAP adherence was shown only in a temporal sense. Lastly, we measured resting breathing using the single band RIP, which is not recommended to assess sleep disordered breathing during PSG[32]. However, we measured resting breathing during wakefulness in the sitting position, during a period free of apneic events, and calculations were of relative rather than absolute values.

In conclusion, short-term CPAP adherence is predicted by reduced variability of breathing during wakefulness CPAP acclimatization. The next step would be to use this measure in multi-center studies with multi-modality assessments of adherence to identify individual patients who may be likely to use CPAP suboptimally. The assessment of breathing pattern during wakefulness would be a relatively easy, accessible and objective measure to identify those less likely to tolerate CPAP and needing more clinical support.

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Figure legends

Figure 1: Typical examples of respiratory signal obtained by thoracic excursion using a single band RIP for the patients with good (A) and poor CPAP adherence (B).

Figure 2: The comparison of CV values for Ttot and estimated V_T between good and poor CPAP adherence groups in using our enhanced definition (left panel) and the Kribbs definition (right panel). In the Box-and-Whisker plots, center lines represent the median, boxes represent the quartiles, and bars represent the maximum and minimum values of CV for breath-by-breath Ttot (A; our enhanced definition, B; Kribbs definition) and estimated V_T (C; our enhanced definition, D; Kribbs definition) during wakefulness under CPAP. The CV for Ttot and estimated V_T in poor adherence group was significantly higher compared with good adherence group in either definition.
CPAP = continuous positive airway pressure, CV= coefficient of variation; Ttot = respiratory duration; V_T = tidal volume

Figure 3: ROC curve analysis of CV for estimated V_T for poor CPAP adherence in using our enhanced definition (left panel) and the Kribbs definition (right panel).
ROC = Receiver-operating characteristics, CPAP = continuous positive airway pressure, CV=coefficient of variation; AUC = area under the curve; V_T = tidal volume

Table 1 Subject Characteristics

	All patients (n=79)	Derivation group (n=36)	Validation group (n=43)	*P* value
Age, yr	58.0 (48.0-68.0)	57.5 (48.3-64.0)	60.0 (47.0-69.0)	N.S.
Male, n (%)	67 (84.8%)	32 (88.9%)	35 (81.4%)	N.S.
BMI, kg/m^2	28.0 (25.0-32.0)	27.5 (24.0-30.8)	29.0 (25.0-33.0)	N.S.
AHI, /hr	37.0 (30.0-56.0)	37.0 (30.3-53.5)	38.0 (30.0-59.0)	N.S.
AHI with CPAP, /hr	4.5 (1.5-6.1)	4.8 (1.1-5.5)	4.2 (1.8-6.1)	N.S.
ESS	10.0 (7.0-14.0)	8.5 (5.3-13.5)	11.0 (8.0-16.0)	N.S.
HADS-A ≥ 11, n (%)	4/79 (5.1%)	2/36 (5.6%)	2/43 (4.7%)	N.S.
HADS-D ≥ 11, n (%)	7/79 (9.0%)	3/36 (8.3%)	4/43 (9.3%)	N.S.
marital status	66/79 (83.5%)	30/36 (83.3%)	36/43 (83.7%)	N.S.
Comorbidity				
Hypertension	50/79 (63.3%)	23/36 (63.9%)	27/43 (62.8%)	N.S.
Dyslipidemia	43/79 (54.4%)	20/36 (55.6%)	23/43 (53.5%)	N.S.
Diabetes Mellitus	22/79 (27.8%)	13/36 (36.1%)	9/43 (20.9%)	N.S.
Past history of cerebral infraction	8/79 (10.1%)	5/36 (13.9%)	3/43 (7.0%)	N.S.
Nose symptom	44/79 (55.7%)	24/36 (66.7%)	20/43 (46.5%)	N.S.
Psychiatric diagnosis	7/79 (8.9%)	3/36 (8.3%)	4/43(9.3%)	N.S.
Nightly duration of CPAP usage in the first 1 month, hr	5.3 (3.8-6.6)	5.3 (2.9-5.9)	5.3 (4.0-6.6)	N.S.
The number of nights of	100 (82.2-100)	96.2 (77.8-100)	100 (91.1-100)	N.S.

CPAP usage in the first 1 month, %				
Actual nightly duration of CPAP usage in the self-reported sleeping duration, %	86.4 (57.2-103.6)	84.6 (47.8-91.6)	92.1 (66.8-105.3)	N.S.

Data are shown as median and interquartile range or No. (%).

AHI= apnea-hypopnea index, BMI= body mass index, CPAP= continuous positive airway pressure, ESS= Epworth Sleepiness Scale, HADS-A= Hospital Anxiety and Depression Scale, anxiety subscale, HADS-D= Hospital Anxiety and Depression Scale, depression subscale, N.S. = not significant.

P values by Mann-Whitney *U*-test or Chi-squared test.

Table 2 Comparison of parameters between good and poor CPAP adherence in the derivation group

	Enhanced definition			Kribbs definition		
	Good adherence (n=18)	Poor adherence (n=18)	*P* value	Good adherence (n=23)	Poor adherence (n=13)	*P* value
Age, yr	61.5 (49.8-67.8)	54.0 (47.8-60.8)	N.S.	53.0 (41.0-57.0)	61.0 (52.5-69.5)	0.015
Male, n (%)	18 (100%)	14 (77.8%)	N.S	22 (95.7%)	10 (76.9%)	N.S
BMI, kg/m2	27.2 (24.2-30.0)	27.6 (24.4-31.5)	N.S	25.6 (23.8-29.4)	28.3 (25.9-33.0)	N.S
AHI, /hr	39.8 (32.4-60.3)	35.8 (30.6-46.2)	N.S	37.3 (33.2-56.6)	35.2 (26.4-46.7)	N.S
ESS	10.5 (5.3-13.5)	7.5 (6.0-11.8)	N.S	9.0 (6.0-13.0)	8.0 (5.0-12.0)	N.S
HADS-A≥11, n (%)	1 (5.6%)	1 (5.6%)	N.S.	2 (8.7%)	0 (0%)	N.S.
HADS-D≥11, n (%)	2 (11.1%)	1 (5.6%)	N.S	3 (13.0%)	0 (0%)	N.S
Psychiatric diagnosis, n (%)	1 (5.6%)	2 (11.1%)	N.S	2 (8.7%)	1 (11.1%)	N.S
Marital status, n	16 (88.9%)	14 (77.8%)	N.S	21 (91.3%)	9 (69.2%)	N.S

(%)

Data are shown as median and interquartile range or No. (%).

Enhanced definition= Defined good adherence is CPAP usage for more than 70% of nights monitored, for more than 4 hours a night, and for more than 80% of self-reported sleeping duration. Otherwise defined as poor adherence.

Kribbs definition= Defined good adherence is CPAP usage for more than 70% of nights monitored, for more than 4 hours a night. Otherwise defined as poor adherence.

AHI= apnea-hypopnea index, BMI= body mass index, ESS= Epworth Sleepiness Scale, HADS-A: Hospital Anxiety and Depression Scale, anxiety subscale, HADS-D: Hospital Anxiety and Depression Scale, depression subscale, CV= coefficient of variation, Ttot= respiratory duration, V_T= tidal volume, N.S.= not significant. *P* values by Mann-Whitney *U*-test or Chi-squared test.

Table 3 Validity of the cut-off value for CPAP adherence

	Enhanced definition			Kribbs definition		
CPAP Usage	CV for estimated $V_T \geq 34.0$ (n=19)	CV for estimated $V_T < 34.0$ (n=24)	*P* value	CV for estimated $V_T \geq 34.0$ (n=19)	CV for estimated $V_T < 34.0$ (n=24)	*P* value
Good adherence (n)	7	20	<0.01	9	20	<0.05
Poor adherence (n)	12	4	<0.01	10	4	<0.05

CPAP= continuous positive airway pressure.

CV for estimated V_T= coefficient of variation for estimated tidal volume

Enhanced definition= Defined good adherence is CPAP usage for more than 70% of nights monitored, for more than 4 hours a night, and for more than 80% of self-reported sleeping duration. Otherwise defined as poor adherence.

Kribbs definition= Defined good adherence is CPAP usage for more than 70% of nights monitored, for more than 4 hours a night. Otherwise defined as poor adherence.

Figure 1

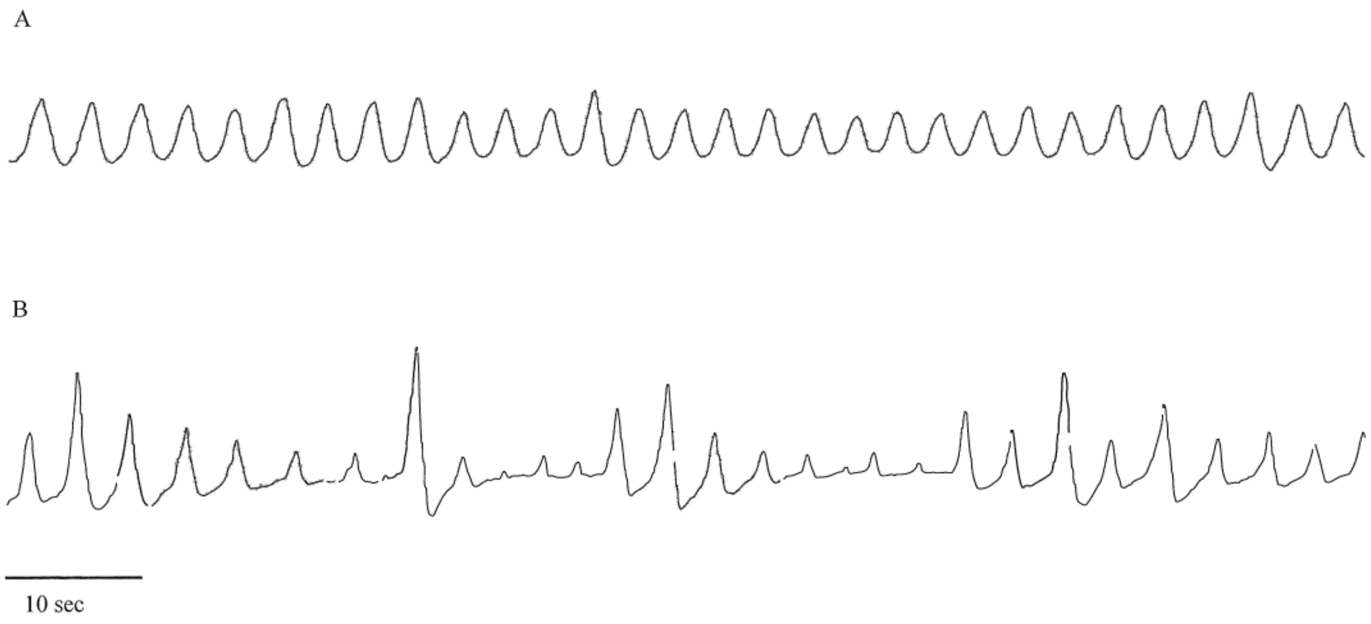
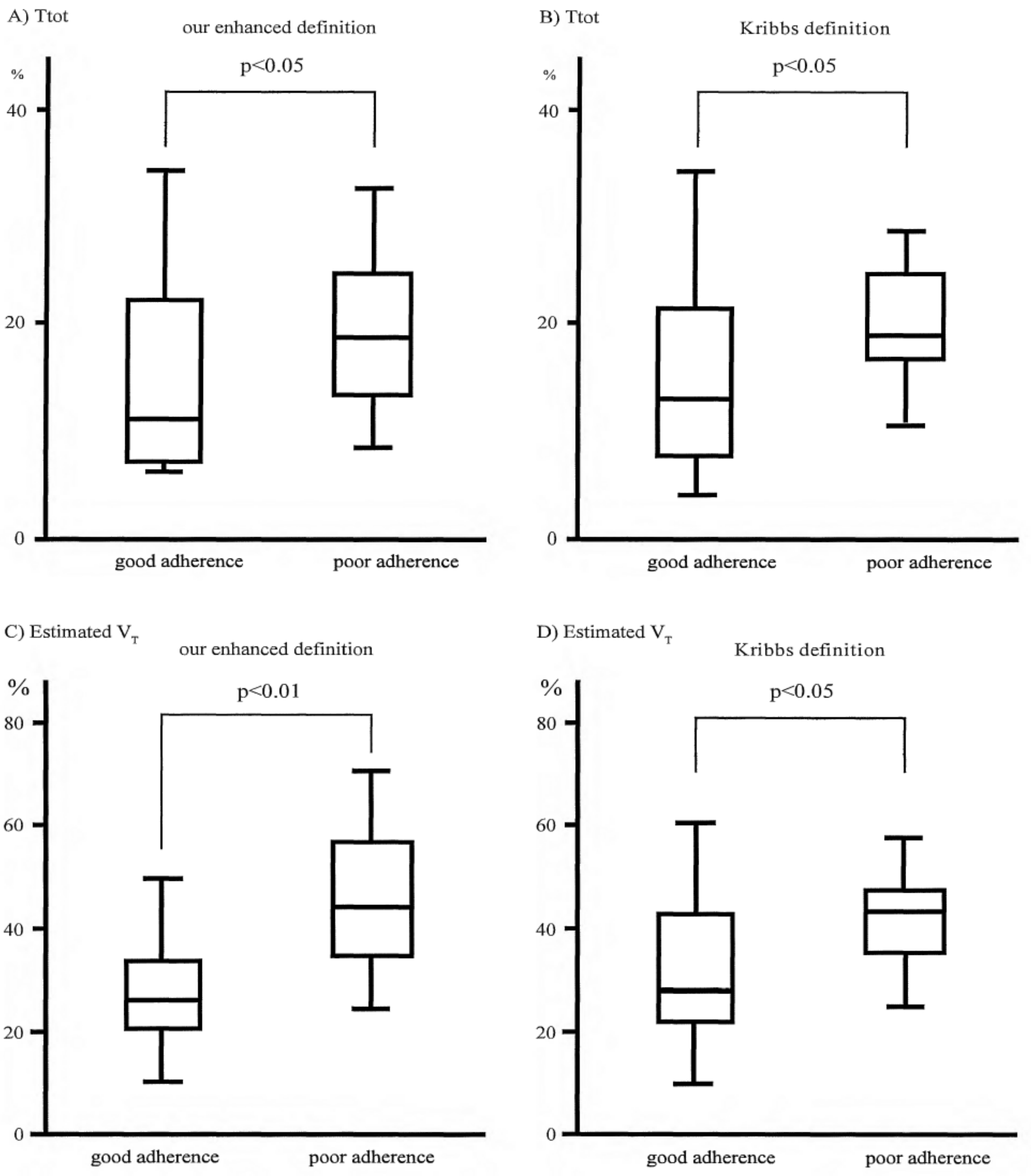


Figure 2



A) Ttot
our enhanced definition
p<0.05
%
40
20
0
good adherence
poor adherence
B) Ttot
Kribbs definition
p<0.05
%
40
20
0
good adherence
poor adherence
C) Estimated V_T
our enhanced definition
p<0.01
%
80
60
40
20
0
good adherence
poor adherence
D) Estimated V_T
Kribbs definition
p<0.05
%
80
60
40
20
0
good adherence
poor adherence

Figure 3

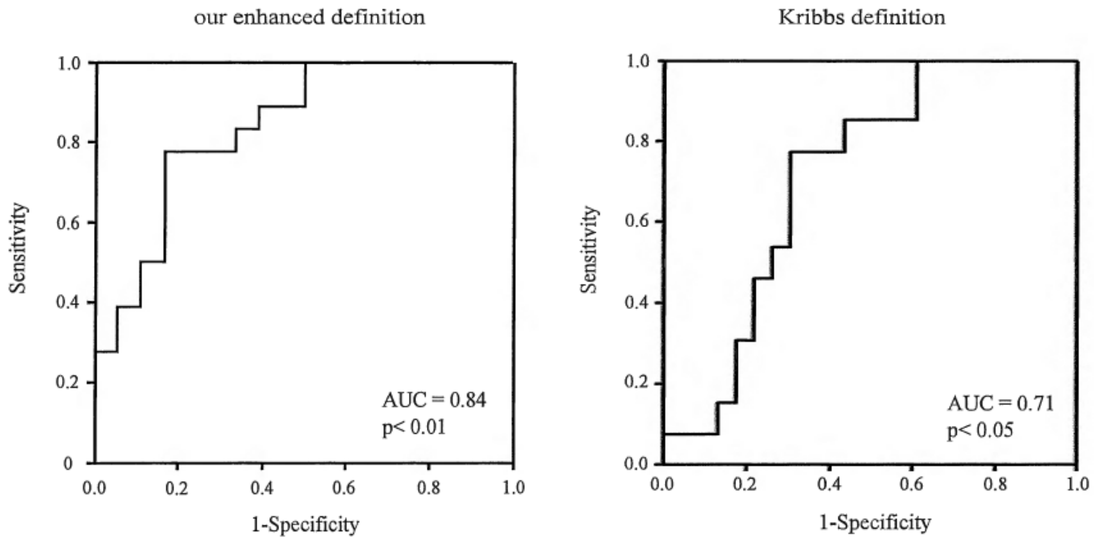

our enhanced definition
Sensitivity
1-Specificity
AUC = 0.84
p< 0.01
Kribbs definition
Sensitivity
1-Specificity
AUC = 0.71
p< 0.05

Figure S1

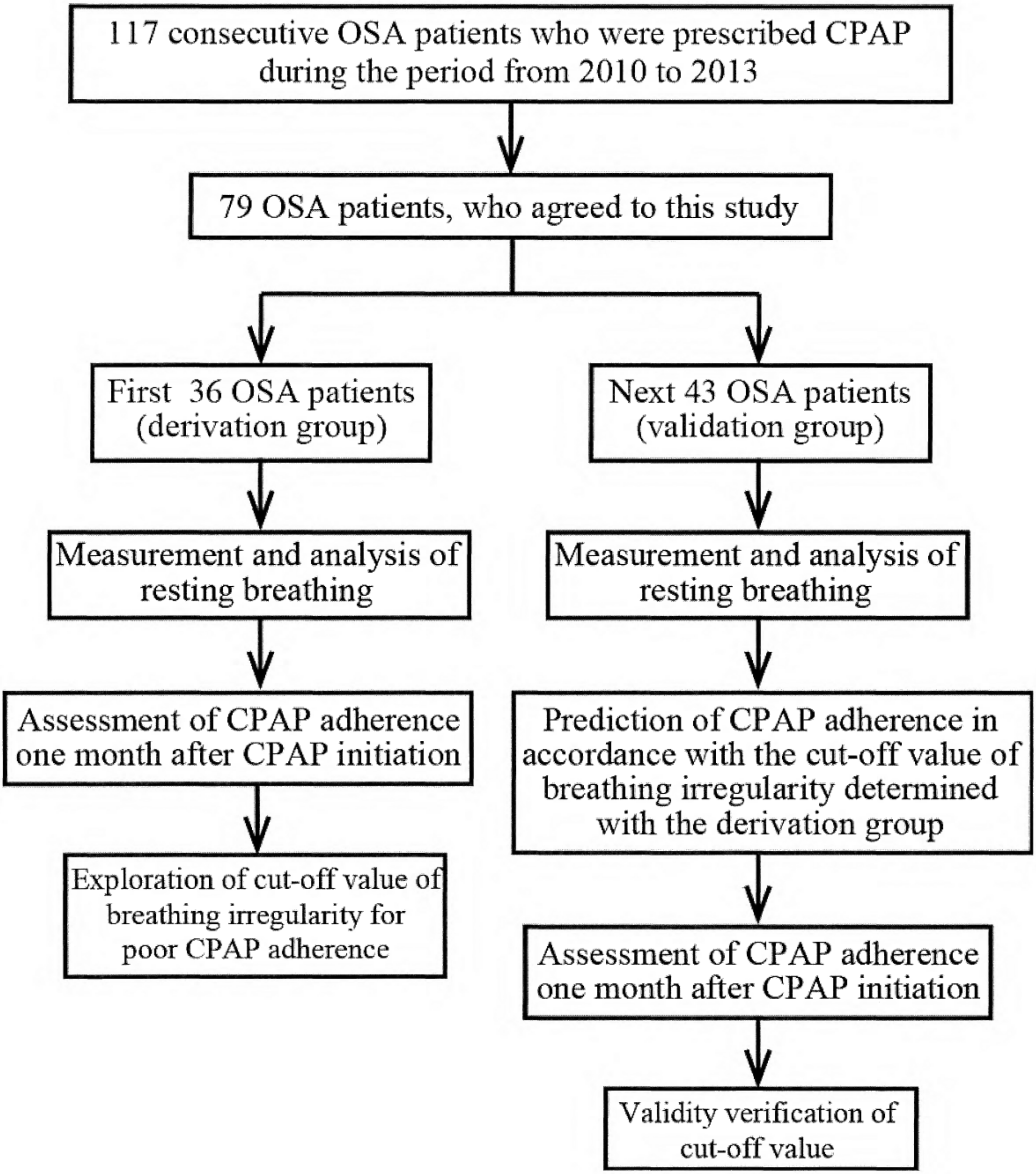

117 consecutive OSA patients who were prescribed CPAP during the period from 2010 to 2013
79 OSA patients, who agreed to this study
First 36 OSA patients (derivation group)
Next 43 OSA patients (validation group)
Measurement and analysis of resting breathing
Measurement and analysis of resting breathing
Assessment of CPAP adherence one month after CPAP initiation
Prediction of CPAP adherence in accordance with the cut-off value of breathing irregularity determined with the derivation group
Exploration of cut-off value of breathing irregularity for poor CPAP adherence
Assessment of CPAP adherence one month after CPAP initiation
Validity verification of cut-off value

Figure S2