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# Cyclic alternating pattern and positive airway pressure titration

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**Abstract**

**Objective**: To demonstrate that stability of the upper airway during continuous positive airway pressure (CPAP) titration is influenced by the microstructure of sleep as defined by the cyclic alternating pattern (CAP).

**Methods**: Retrospective review of 12 CPAP titration records. The patterns of flow-limitation during CPAP at subtherapeutic pressures were characterized as 'stable' (persistent and non-progressive inspiratory flow limitation) or 'unstable' (progressive increase in inspiratory flow-limitation terminating in an arousal), and continuous periods of at least 10 min were identified. Sleep stage scoring by both conventional Rechtshaffen and Kales criteria and the CAP were done. The relationship between flow type and CAP was determined. Responses to an increase in applied pressure on flow-limitation were noted.

**Results**: There were a total of 50 periods fulfilling the above criteria, totaling 1113 min of titration time. Thirty periods (757 min, 68% of total) showed a stable flow-limitation pattern. A total of 29/30 periods showing a stable flow pattern during sleep was scored as non-CAP, and only a single 18-min period of stable flow was scored as CAP. A total of 19/20 periods showing an unstable flow pattern was in sleep with CAP characteristics, the exception being a single 14-min period where unstable flow was noted in non-CAP. Flow-limitation was stable and non-progressive or absent during non-CAP, even at less than optimal pressures. This was noted irrespective of the presence or absence of delta sleep as scored by conventional criteria. Pressure increases during non-CAP, when the profile of the inspiratory flow was flattened, never resulted in a discernable change in the flow profile, while at least two-thirds of pressure increments during CAP periods improved flow.

**Conclusions**: The microstructure of sleep as determined by CAP and non-CAP have practical implications for manual pressure titration algorithms and research on upper airway physiology during sleep. The appearance of a period of non-CAP, irrespective of conventionally scored delta sleep, may falsely suggest that the CPAP is optimal or close to it. Large increases in non-CAP that may be seen during a titration night can reduce the window of opportunity for titration. Increases in CPAP should be avoided in non-CAP. © 2002 Elsevier Science B.V. All rights reserved.

*Keywords*: Cyclic; Alternating; Pattern; Positive; Pressure; Titration

## 1. Introduction

Obstructive sleep-disordered breathing (OSDB) is characterized by repetitive episodes of progressive airflow limitation terminating in arousals. When severe, the pattern is that of a complete or near complete cessation of airflow (apnea). The precise definitions of an arousal or a hypopnea, a less than complete obstruction to flow, remain controversial [1]. Though there is evidence that in adults most obstructive respiratory events are terminated in association with discernable EEG changes, arousals may not all fulfill the 3-s 'ASDA rule' [2].

Measurement of nasal pressure fluctuations using a simple nasal cannula system attached to a pressure transducer provides a degree of sensitivity not attained by the thermistor, and more closely correlates with flow as measured by a pneumotachograph [3]. Flow-limitation is a non-invasive assessment of residual upper airway resistance during continuous positive pressure therapy [4,5]. The normal flow profile is sinusoidal (rounded), and various degrees of flattening (plateau) reflect degrees of flow-limitation. A goal of titration is to normalize flow.

Conventionally scored stages 3 and 4 (delta) sleep is characterized by stability of cardiopulmonary and EEG variables. Patients with severe sleep apnea may have minimal abnormalities during delta sleep. It is likely that this is a two-way process: (1) stability of sleep reduces sleep-disordered breathing; during titration, a delta sleep rebound is associated with stable sleep and breathing even at low CPAP pressures; and (2) when respiration of sleep apnea patients is improved, they progress into delta sleep as reduced arousals allow the development of delta sleep. In older subjects, conventional delta sleep may be minimal or

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even absent, but periods of stability and delta-like sleep are seen, often with EEG frequencies in the ≤2 Hz range but short of satisfying the 75-microvolt amplitude requirement.

A key feature of OSDB is the cyclic nature of the abnormality, with a periodicity of 20–40 s. This is similar to an arousal rhythm of normal NREM sleep called the cyclic alternating pattern (CAP), a biphasic pattern consisting of transient arousals (phase A) that periodically interrupt the tonic delta/theta activities of NREM sleep (phase B) [6–8]. Absence of A phases for at least 60 consecutive s is scored as non-CAP (NCAP). Functionally, CAP is a condition of sustained arousal instability oscillating between a greater and lesser arousal level, while NCAP is a prolonged stationary condition of arousal stability. Three subtypes of A phases have been distinguished: A1-predominantly synchronized and weak activation of polygraphic variables of arousal, A2-a mixture of EEG synchronization and desynchronization and moderate degrees of arousal, and A3-a desynchronized EEG and overt arousal. The ASDA-defined arousals fall into A2/A3 categories of CAP [9]; normative data for CAP are now available [10]. The longest duration CAP cycles are found among older subjects, and A2/A3 subtypes are more frequent in the elderly

CAP seems to reflect a propensity to increase arousal and sleep disruption and to trigger specific abnormalities that arise from sleep, such as epileptiform activity. CAP has been linked to an increased probability of arousals in SDB [11,12]. Epileptiform activity during sleep is linked to A phases of CAP, and CAP rate is increased in patients with seizures disorders [13–15]. Other associations include bruxism [16], periodic limb movements during sleep [17,18], NREM parasomnias [19], and asymptomatic HIV encephalopathy [20]. Patients with insomnia have increased CAP rates, which are reduced by sedative-hypnotic medications [21–23]. Acoustic stimulation during sleep can increase CAP [24].

Patients with severe OSDB have an increase in CAP (>80%, at the expense of non-CAP), with apneas typically occurring during B phases [11]. Respiratory events are maximal (96%) during CAP, and A2/A3 patterns dominate. CAP in conjunction with a cyclic abnormality, such as sleep-disordered breathing, could conceivably create a self-perpetuating cycle which feeds upon itself; the respiratory abnormality increases CAP, a state of relative sleep instability, which in turn allows fluctuations in sleep state and respiratory/upper airway control that further worsen the breathing disorder. Sleep and breathing are relatively stable in untreated sleep apnea during non-CAP, irrespective of the conventional stage score. CPAP therapy reduces CAP and increases non-CAP [25].

We hypothesized that during CPAP titration at subtherapeutic pressure settings flow-limitation would be stable and not associated with recurrent arousals during non-CAP, irrespective of conventionally scored delta sleep, thus posing a potential problem for assessing titration adequacy.

## 2. Methods

### 2.1. Polysomnography

The polysomnograms of 12 patients with severe obstructive sleep apnea who underwent CPAP titration were retrospectively reviewed. Eight patients had prior diagnostic polysomnograms, and four were split night studies where severe sleep apnea was noted from the onset of the study. Electroencephalogram (C4-A2, C3-A1, O2-A1, O1-A2), left and right electro-oculograms, submental electromyogram, oral and nasal flow, respiratory effort by piezoelectric effort bands, oxymetry, right and left anterior tibialis electromyogram were recorded. Esophageal pressure monitoring is not performed for routine clinical studies in this laboratory.

All diagnostic studies monitored nasal airflow with a nasal cannula and pressure transducer system, and oral flow by a thermistor. An obstructive apnea was defined as an absence of airflow on the nasal cannula and a reduction in the oral thermistor signal to <10% of baseline, with continued respiratory effort. Central apneas were scored when there was no evidence of effort. An obstructive hypopnea was defined as any clearly evident reduction in amplitude of the nasal pressure signal, or flattening of the inspiratory flow profile, for three or more consecutive breaths abruptly terminated with a return to a rounded/sinusoidal flow profile or a large recovery breath. Hypopneas were scored only if associated with oxygen desaturation of 2–3% or an arousal at event termination. Apneas were scored irrespective of the presence of an arousal or desaturation. Isolated post-arousal central apneas and central apneas during REM sleep, unaccompanied by arousal or desaturation, were not scored.

### 2.2. Scoring of EEG arousals

Modified ASDA rules were applied: an EEG arousal was defined as an abrupt shift in frequency temporally linked to event termination, and included delta, theta, alpha, and/or frequencies greater than 16 Hz, but not spindles. An arousal accompanied by a defined pathophysiological event (apnea, hypopnea, periodic leg movement) required a visible frequency shift (minimum of 1.5–2 s duration or greater). K-complexes or clusters of delta waves that regularly occurred at the termination of a defined respiratory event or periodic leg movement were noted to be arousal equivalents. These modifications were made to accommodate what is evident in clinical practice – that shifts in EEG frequency may be less than 3 s, even in cases of obvious apnea/hypopnea termination, and that delta wave bursts are an accepted arousal marker in the EEG and sleep literature. Many sleep physicians also recognize these modifications in clinical practice.

### 2.3. Nasal flow monitoring for pressure titration

Inspiratory and expiratory flow profiles were monitored

by measuring nasal mask pressure through a differential pressure transducer (Grass PT5 or Braebon dual pressure transducer). Flow was simultaneously recorded from the internal pneumotachograph of the air pressure generator.

### 2.4. Definition of flow-limited profiles

Two types of abnormal flow profiles were identified. Periods of 'unstable' (progressive increase in inspiratory flow-limitation terminating in an arousal) and 'stable' (non-progressive inspiratory flow limitation) airflow with the following characteristics were selected for detailed review: (1) duration of 10 min or longer (2) sub-optimal CPAP (optimal pressure minus minimum 3 cm $H_2O$); (3) no positional change during the period; (4) no REM sleep within 2 min of the beginning or end of the period; and (5) each period of stable flow flanked by a period of unstable flow.

### 2.5. CPAP titration

This was performed by experienced and certified technicians. Pressure increases were expected to be made to eliminate apneas, hypopneas, oxygen desaturations and inspiratory flow-limitation. Pressure decreases were expected to be made if central events appeared, if arousals progressively increased with increases in pressure, or if the patients requested a decrease. Optimal pressure was defined as the pressure in cm $H_2O$ that normalized flow and prevented the occurrence of arousals in NREM and REM sleep and in the lateral as well as supine positions. As this was a retrospective record review, no changes were made for the purpose of the study itself.

### 2.6. Sleep staging and CAP scoring

Sleep was staged during these periods as delta/non-delta (conventional R&K scoring) [26] or as CAP/NCAP [6]. A total of 60-s epochs were scored, rather than the conventional 30, to better accommodate CAP/NCAP scoring. We restricted CAP scoring to NREM sleep.

Summary of scoring rules for CAP.

1. Each CAP cycle consists of two components: phase A consisting of EEG transients, and phase B, defined as the interval of delta/theta activity that separates two successive A phases. The duration of each phase ranges from 2 to 60 s.
2. A CAP sequence includes at least two consecutive cycles.
3. Phase A characteristics: (a) intermittent alpha rhythm

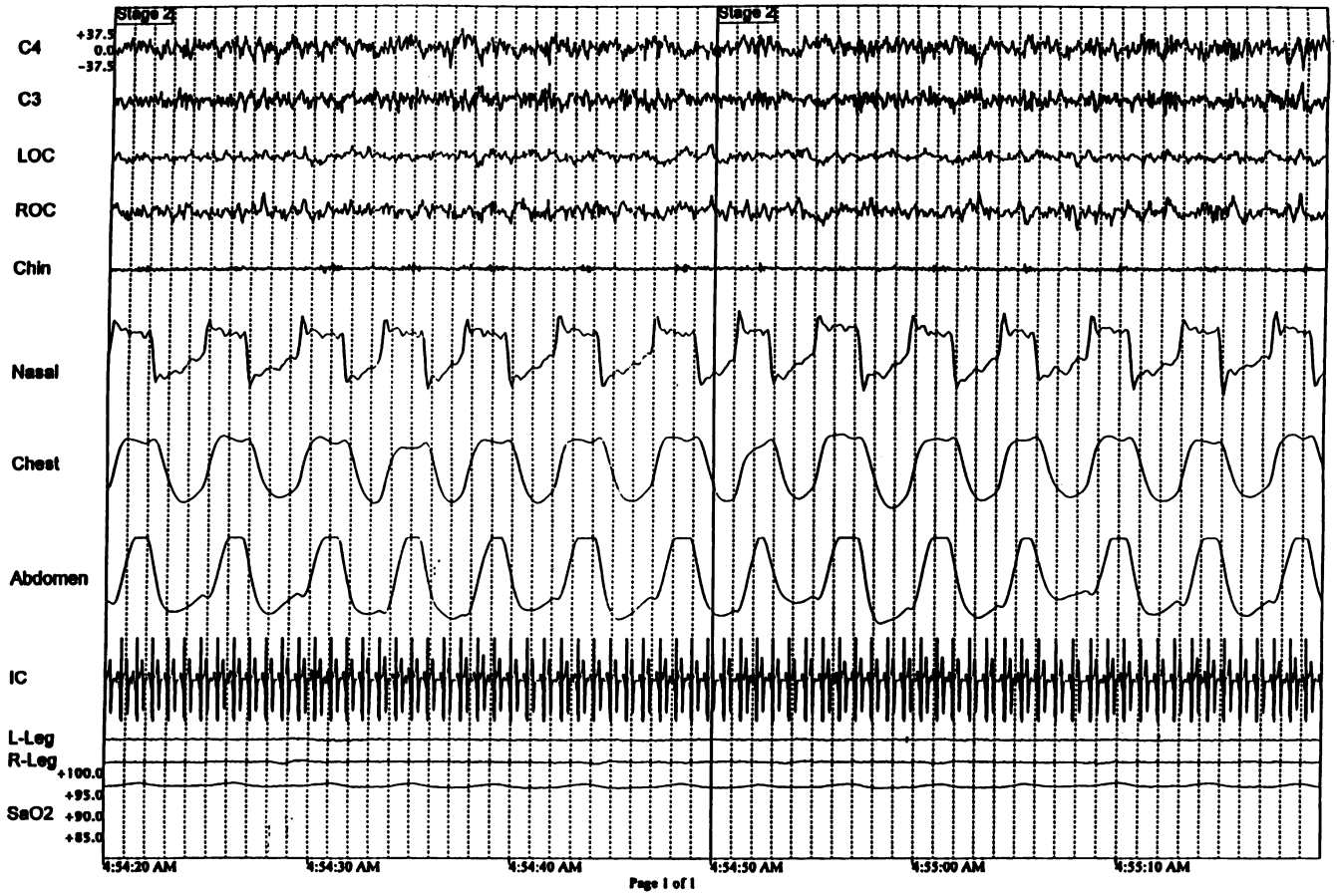


Fig. 1. CPAP is at 8 cm. Persistent severe but stable flow-limitation seen on the nasal flow trace, but sleep and respiration are stable. Sleep is NREM, non-cyclic alternating pattern type, duration of graph is 60 s. Each vertical dotted line represents 1 s.

and sequences of vertex sharp waves in stage I sleep; (b) sequences of two or more K-complexes with or without alpha and beta rhythms; (c) delta bursts showing a difference in amplitude of at least one-third compared with background activity; (d) transient activation phases of microarousals in stages I and II or at the end of stages 3 and 4, characterized by an increase in EEG frequency with decreased amplitude, disappearance of sleep spindles and delta activity when occurring in slow wave sleep, transitory enhancement of muscle tone or appearance of electromyographic activity, body movements, postural changes, and acceleration of heart rate.

A1: Dominated by synchronized EEG patterns – alpha rhythm in stage I, sequences of K-complexes in stage II, delta bursts in stages 3 and 4.

A2: Synchronization and desynchronization coexist, but the amount of EEG desynchrony does not exceed two thirds of the total A phase duration. K-complexes with alpha and beta activities, K-alpha, microarousals with slow wave synchronization.

A3: Predominant EEG desynchronization (greater than two-thirds duration of phase A), mostly arousals and microarousals coupled with a powerful activation of muscle tone and cardiorespiratory parameters.

Since A3 was rare during titration, we did not differentiate between A1–A3 types of A phases. Pressure changes and the resulting change in flow-limitation were also noted as 'improvement' or 'no improvement'.

### 2.7. Statistical methods

Data are summarized as mean and standard deviation, or percents. Fischer's Exact test (2-sided) was used to assess the association between sleep state (CAP, non-CAP) and airflow pattern (stable or unstable flow limitation).

## 3. Results

### 3.1. Patient characteristics

Mean age: 44 (range: 22–64), mean RDI: 76 (range: 53–96), mean apnea index: 27 (range 4–36), mean minimum oxygen saturation: 78% (range: 90–52%). An oxygen desaturation index was not specifically calculated. Four patients

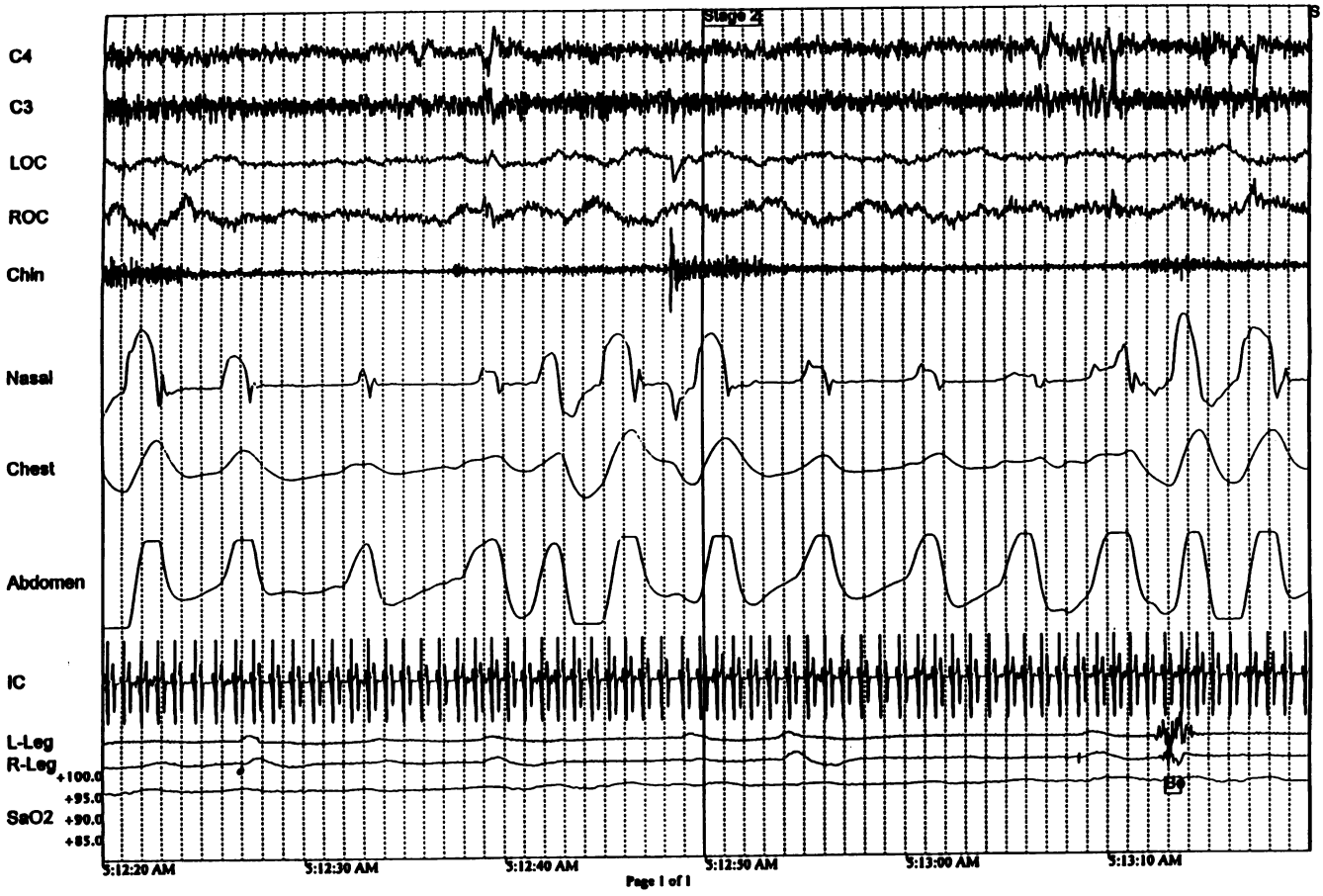


Fig. 2. Same patient as in Fig. 1. CPAP is still 8 cm, but the patient is now in cyclic alternating pattern. Sleep and respiration are markedly unstable. Flow-limitation is unstable and progressive.

had no desaturations below 90%, and would qualify for the term, if preferred, of the upper airway resistance syndrome.

### 3.2. Inspiratory flow

There were a total of 50 periods fulfilling the above criteria, totaling 1113 min of titration time: 30 periods (757 min, 68% of total) showed a stable flow-limitation pattern; 29/30 periods showing a stable flow pattern during sleep were scored as non-CAP; a single 18-min period of stable flow was scored as CAP; 19/20 periods showing an unstable flow pattern occurred during sleep with CAP characteristics, the exception being a single 14-min period where unstable flow was noted in non-CAP (Figs. 1–4). Conventionally scored delta sleep made up 192 min (17.3%) of total tabulated titration time, and was always co-scored as non-CAP. There was a highly significant association of stable airflow with non-CAP and unstable airflow with CAP ($P < 0.0001$, Fischer's Exact test, 2-sided).

### 3.3. Pressure adjustments

There were 53 upward pressure adjustments during the periods evaluated for study, 34 during CAP periods and 19 during non-CAP periods. Pressure (1–2 cm each) increases during non-CAP never resulted in a discernable change in the inspiratory flow profile, while 23/34 (68%) of pressure increments during CAP periods improved inspiratory flow. On 12/19 occasions the pressure had to be decreased to the previous setting following a change during non-CAP at the end of the stable period. All titrations reached the optimal pressure setting by the end of the night. RDI (apneas, hypopneas, flow-limitation associated with arousals) at optimal pressure was <5/h.

## 4. Discussion

The spectrum of abnormal obstructive respiratory events ranges from apneas to hypopneas, snoring, and flow-limitation. In a single patient, all types are often seen if nasal pressure is recorded during a diagnostic study. Severity of symptoms does not show a continuous distribution; those for whom apneas are predominant may be as symptomatic as those with increased upper airway resistance associated with recurrent arousals.

Flow-limitation is the most sensitive indicator of upper airway obstruction during pressure titration [27]. The goal of titration is to find the least pressure effective in normalizing flow in all positions and all stages of sleep. During

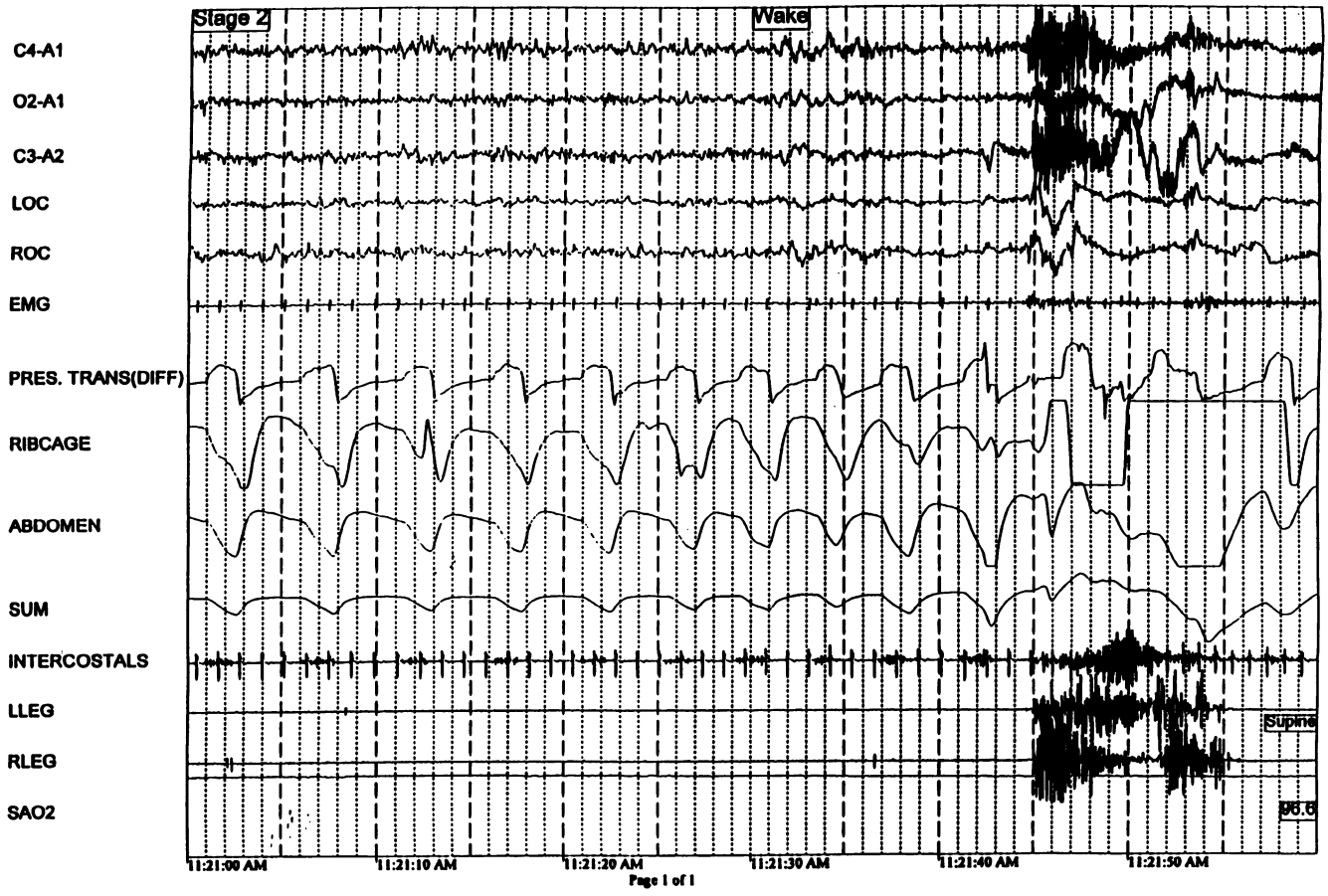


Fig. 3. Daytime CPAP titration in a shift worker with sleep apnea. CPAP is 7 cm, sleep type is NREM, cyclic alternating pattern. Flow is unstable, with changing degrees of flow limitation terminating in an overt arousal.

CPAP titration, before optimal pressure is attained, there is a period characterized by a transition to deeper sleep stages without arousals but with associated unremitting high intrathoracic (esophageal) pressures [5]. These periods invariably have a limited inspiratory flow contour, partially mimicking the upper airway resistance syndrome [28], but differing from this condition in the absence of EEG arousals and deeper sleep stages: the 'stable' pattern of flow-limitation we describe during non-CAP appears to be similar to this phenomenon. The pathological importance of this state, with stable sleep and breathing but persistently high esophageal pressures and normal oxygenation, is not certain.

There are modifiers of respiratory stability during sleep and CPAP titration. (1) Changes in head position can change airflow resistance, resulting in a CAP period if airflow is compromised enough to result in arousals, thus triggering the cycle. There were no changes before or during the periods utilized for this assessment, though it is possible that very subtle changes in head/neck position may have been missed in spite of real time video monitoring. (2) The pattern of instability seen in CAP is different from that seen in REM sleep. This may be seen best in those with periodic breathing, which is associated with marked increases in CAP rate (personal observation). REM sleep often abolishes periodic breathing in the setting of high altitude or congestive heart failure. (3) Sleep rebound effects can be significant. Following a partial resolution of upper airway obstruction, conventional slow wave/delta sleep or REM sleep may appear as a rebound, with very different patterns/degrees of sleep/respiration stability. As non-CAP periods occur all through the night, it is unlikely that the periods of stable and unstable flow we describe are a simple rebound effect.

We found that flow-limitation did not negatively impact sleep quality during non-CAP. The implications for manual titration are direct. Recognition of this stable state of airflow and sleep is important to minimize inappropriate pressure elevations. The flow profile may not change with pressure increases during non-CAP, and there is a definite risk of pressure intolerance at the end of the non-CAP period. Though the patient is generally able to tolerate higher and optimal pressures by the end of the study, the optimal time of titration is during CAP and REM sleep. Technicians are trained not to routinely make pressure adjustments during delta sleep, but true conventional delta sleep may be rare in older patients.

CPAP titration increases non-CAP. In one report, CAP rate (% of NREM sleep showing CAP) reduced from 88 to

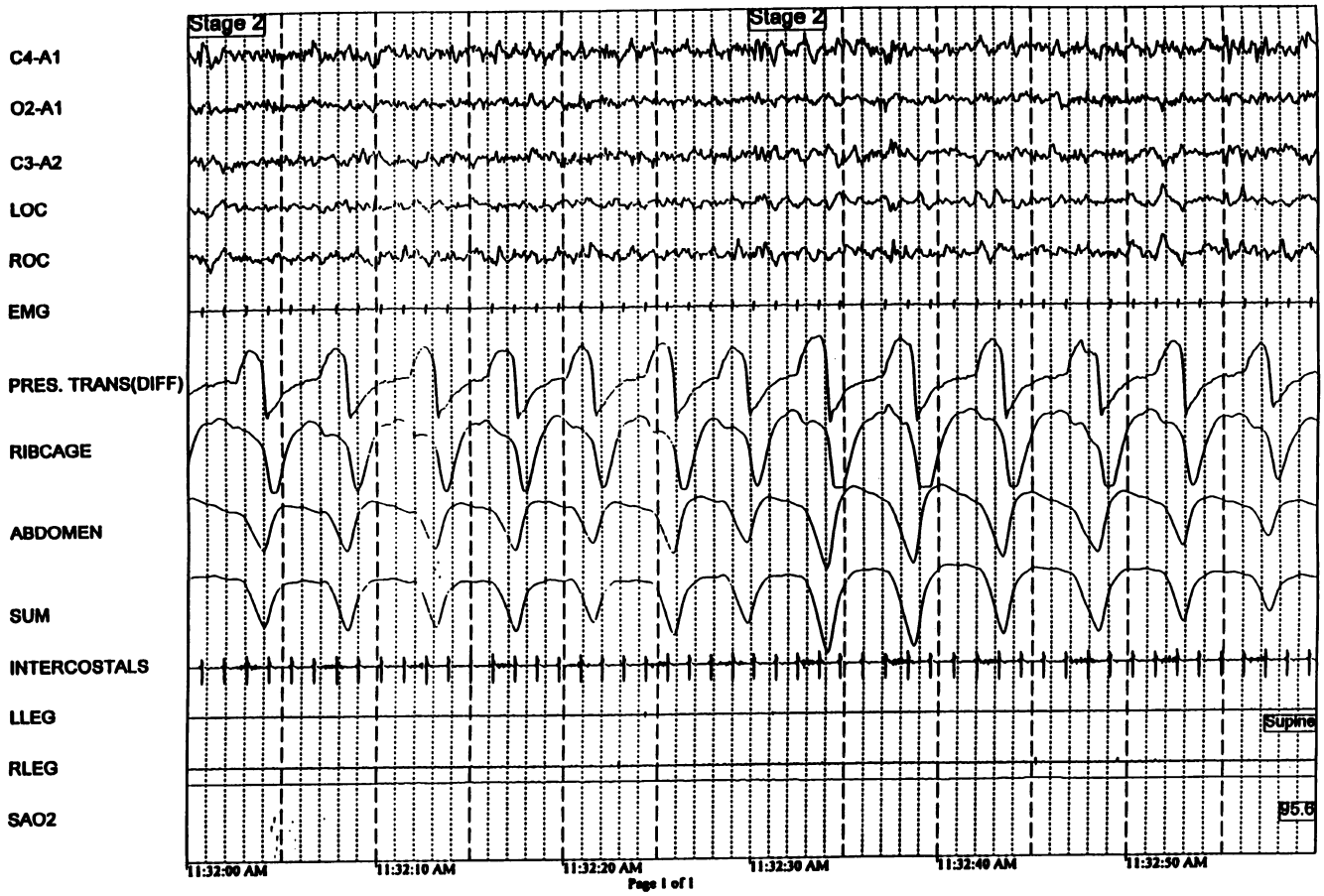


Fig. 4. Same patient as in Fig. 3, CPAP is still 7 cm. However, sleep is now NREM, non-cyclic alternating pattern, and flow is normal. Optimal final CPAP was 11 cm $H_2O$.

25% during the first night of titration [26]. Non-CAP periods occur multiple times across the night, and in six of our subjects was the final sleep period on the titration night. It is impossible to obtain a perfect pressure setting unless previously obtained during a CAP period. In our study, 1–2 cm pressure changes during non-CAP produced no change in flow, and in 12/19 instances had to be decreased to the previous setting when the non-CAP period was complete. The appearance of a non-CAP period can provide a false sense of security regarding the adequacy of titration, and this is true irrespective of classic stage scoring.

Determined by apnea length and peak negative esophageal pressure at arousal, the severity of OSDB is worse in the second half of the night and during REM sleep [29]. During NREM sleep this has been linked to arousal threshold fluctuations in association with cyclic increases of delta power during the night [30], and possibly circadian influences on arousal threshold [31]. Though non-CAP has greater delta activity by visual inspection, this is not a simple relationship as CAP may be seen during periods otherwise scored as delta sleep. For example, the latter could occur when the EEG patterns at respiratory event termination are bursts of K-complexes or delta waves; the R&K system does not allow a differentiation in this instance. Research studies of airway physiology and arousal in normal and patients with sleep-disordered breathing have differentiated REM and NREM sleep, but not CAP and non-CAP. In our study, conventionally scored delta sleep made up 17.3% of total tabulated titration time, and was always co-scored as non-CAP. Our inclusion criteria were restrictive, and do not reflect the total percentages of CAP or non-CAP during the study nights. The transition from CAP to non-CAP during titration was not abrupt, evolved typically over a period of a few minutes, and showed a similar evolution in the stability pattern of airflow. It is possible that the non-CAP nature of deep NREM sleep may be an explanation for its protective influences against overt obstructive episodes.

In conclusion, the conceptualization of NREM sleep as CAP or non-CAP and flow limitation as ‘stable’ or ‘unstable’ has practical implications during positive airway pressure titration. Non-CAP periods may create a false sense of titration success, especially when occurring late in the study, and non-CAP rebounds on the first night of titration may not allow the determination of optimal pressure. These findings have implications for manual titration and research on upper airway physiology.

## References


[1] Thomas RJ. Definitions of respiratory events in sleep-disordered breathing. Sleep Med 2002;3(2):89–91.

[2] American Sleep Disorders Association – The Atlas Task Force. EEG arousals: scoring rules and examples. Sleep 1992;15:174–184.

[3] Hosselet J-J, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med 1998;157:1461–1467.

[4] Condos R, Norman RG, Krishnasamy I, Peduzzi N, et al. Flow limitation as a non-invasive assessment of residual upper-airway resistance during continuous positive airway pressure therapy of obstructive sleep apnea. Am J Respir Crit Care Med 1994;150:475–480.

[5] Montserrat JM, Ballester E, Olivi H, Reolid O, et al. Time-course of stepwise CPAP titration. Am J Respir Crit Care Med 1995;152:1854–1859.

[6] Terzano MG, Parrino L, Spaggiari MC. The cyclic alternating pattern sequences in the dynamic organization of sleep. Electroencephalogr Clin Neurophysiol 1988;69:437–447.

[7] Terzano MG, Mancia D, Salati MR, Costani G, et al. The cyclic alternating pattern as a physiologic component of normal NREM sleep. Sleep 1985;8:137–145.

[8] Halasz P. Hierarchy of micro-arousals and the microstructure of sleep. Neurophysiol Clin 1998;28:461–475.

[9] Terzano MG, Boselli M, Smerieri A, Spaggiari MC, et al. Cyclic alternating pattern (CAP) and ASDA’s EEG arousals in NREM sleep: what information can be supplied by these microstructural approaches. Sleep Res 1997;26:50.

[10] Parrino L, Boselli M, Spaggiari MC, Smerieri A, et al. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. Electroencephalogr Clin Neurophysiol 1998;107:439–450.

[11] Terzano MG, Parrino L, Boselli M, Spaggiari MC, et al. Polysomnographic analysis of arousal responses in obstructive sleep apnea syndrome by means of the cyclic alternating pattern. J Clin Neurophysiol 1996;13:145–155.

[12] Scharf MB, McDannold MD, Zaretsky NT, Hux GT, et al. Cyclic alternating pattern sequences in non-apneic snorers with and without nasal dilation. Ear Nose Throat J 1996;75:617–619.

[13] Terzano MG, Monge-Strauss MF, Mikol F, Spaggiari MC, et al. Cyclic alternating pattern as a provocative factor in nocturnal paroxysmal dystonia. Epilepsia 1997;38:1015–1025.

[14] Gigli GL, Calia E, Marciani MG, Mazza S, et al. Sleep microstructure and EEG epileptiform activity in patients with juvenile myoclonic epilepsy. Epilepsia 1992;33:799–804.

[15] Terzano MG, Parrino L, Anelli S, Boselli M, et al. Effects of generalized interictal EEG dischargees on sleep stability: assessment by means of cyclic alternating pattern. Epilepsia 1992;33:317–326.

[16] Macaluso GM, Guerra P, Di Giovanni G, Boselli M, et al. Sleep bruxism is a disorder related to periodic arousals during sleep. J Dent Res 1998;77:565–573.

[17] Droste DW, Krauss JK, Hagedorn G, Kaps M. Periodic leg movements are part of the B-wave rhythm and the cyclic alternating pattern. Acta Neurol Scand 1996;94:347–352.

[18] Parrino L, Boselli M, Buccino GP, Spaggiari MC, et al. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep. J Clin Neurophysiol 1996;13:314–323.

[19] Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. J Clin Neurophysiol 1995;12:147–154.

[20] Ferini-Strambi L, Oldani A, Tirloni G, Zucconi M, et al. Slow wave sleep and cyclic alternating pattern (CAP) in HIV-infected asymptomatic men. Sleep 1995;18:446–450.

[21] Terzano MG, Parrino L, Boselli M, Spaggiari MC, et al. Sensitivity of cyclic alternating pattern to prolonged pharmacotherapy: a 5-week study evaluating zolpidem in insomniac patients. Clin Neuropharmacol 1997;20:447–454.

[22] Parrino L, Boselli M, Spaggiari MC, Smerieri A, et al. Multidrug comparison (lorazepam, triazolam, zolpidem, and zopiclone) in situational insomnia: polysomnographic analysis by means of the cyclic alternating pattern. Clin Neuropharmacol 1997;20:253–263.

[23] Parrino L, Spaggiari MC, Boselli M, Di Giovanni G, et al. Clinical and polysomnographic effects of trazodone CR in chronic insomnia asso-

ciated with dysthymia. Psychopharmacology (Berlin) 1994;116:389–395.
[24] Terzano MG, Parrino L, Fioriti G, Orofiamma B, et al. Modifications of sleep structure induced by increasing levels of acoustic perturbation in normal subjects. Eur Neurol 1990;30:235–240.
[25] Parrino L, Boselli M, Smerieri A, Spaggiari MC, et al. Cyclic alternating pattern (CAP) modifications in OSAS patients recorded under basal conditions and during the first night with N-CPAP. Sleep Res 1997;26:461.
[26] Rechtschaffen A, Kales A, editors. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects Los Angeles, CA: UCLA Brain Information Service/Brain Research Institute, 1968.
[27] Ayappa I, Norman RG, Hosselet J-J, Gruenke RA, et al. Relative occurrence of flow limitation and snoring during continuous positive airway pressure titration. Chest 1998;114:685–690.
[28] Guilleminault C, Stoohs R, Clerk A, Simmons J, et al. From obstructive sleep apnea syndrome to upper airway resistance syndrome: consistency of daytime sleepiness. Sleep 1992;15:S12–S16.
[29] Montserrat JM, Kosmas EN, Cosio MG, Kimoff JR. Mechanism of apnea lengthening across the night in obstructive sleep apnea. Am J Respir Crit Care Med 1996;154:988–993.
[30] Berry RB, Asyali MA, McNellis MI, Khoo MCK. Within-night variation in respiratory effort preceding apnea termination and EEG delta power in sleep apnea. J Appl Physiol 1998;85:1434–1441.
[31] Sforza E, Krieger J, Petiau C. Arousal threshold to respiratory stimuli in OSA patients: evidence for a sleep-dependent temporal rhythm. Sleep 1999;22:69–75.