Study objectives: To evaluate the relationship between sleep structure and continuous positive airway pressure (CPAP) delivered by an automatic CPAP (auto-CPAP) machine in patients with obstructive sleep apnea syndrome (OSAS).

Design: Nocturnal polysomnography was performed during CPAP administration by an auto-CPAP machine (Autoset Clinical 1; ResMed; Sydney, Australia).

Setting: Sleep-disorders center in a research institute.


Measurements and results: During the night, in most cases, the lowest CPAP level was recorded during a prolonged nonrapid eye movement (NREM) sleep period uninterrupted by arousals, whereas the highest level during wake-sleep transitions or NREM sleep fragmented by arousals. In four subjects, rapid eye movement sleep was always associated with increasing CPAP. Sleep efficiency was negatively correlated with CPAP variability, evaluated as the SD of the mean nocturnal CPAP level averaged epoch by epoch ($r = 0.63$, $p < 0.02$). Eighty-eight percent of rapid CPAP augmentations (increases by at least 2 cm H$_2$O in ≤ 2 min) were observed during sleep-wake transitions or after arousals/awakenings (Ar/Aw); 63% of such Ar/Aw were not preceded by any detectable respiratory abnormality.

Conclusions: CPAP levels and variations during auto-CPAP application may be mainly related to sleep continuity and efficiency. The recording of a highly variable pressure during auto-CPAP administration in an unattended environment must raise the question whether the patient’s sleep quality was acceptable. A poor sleep quality during an autotitration night could lead to an undesirable overestimation of the CPAP level needed for use with fixed-level CPAP machines.

Abbreviations: AHI = apnea-hypopnea index; Ar/Aw = arousals/awakenings; auto-CPAP = automatic continuous positive airway pressure; CPAP = continuous positive airway pressure; NREM = nonrapid eye movement; OSAS = obstructive sleep apnea syndrome; REM = rapid eye movement; $SaO_2$ = arterial oxygen saturation; TIB = time in bed; TST = total sleep time

Continuous positive airway pressure (CPAP) is the most widely used and effective treatment for obstructive sleep apnea syndrome (OSAS). It is applied before going to sleep during all sleep time until awakening, at a level that is effective in abolishing upper-airway obstruction. Titration of the effective CPAP level is classically performed during a full polysomnographic study with the constant attendance of a technician throughout the night.1

*From the Istituto di Fisiopatologia Respiratoria del Consiglio Nazionale delle Ricerche, Palermo, Italy.

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Correspondence to: Oreste Marrone, MD, Istituto di Fisiopatologia Respiratoria del C. N. R., Via Ugo La Malfa, 153, 90146 Palermo, Italy; e-mail: marrone@ifr.pa.cnr.it
In the last decade, CPAP machines have been developed (so-called automatic CPAP [auto-CPAP]) that deliver variable pressure levels during the night in response to rapid automated detection of different ventilatory abnormalities, according to the software of the machine. In this way, the administered pressure tends to remain near the lowest effective level required by the patient every moment. The variability of the effective pressure level throughout the night is believed to depend mainly on sleep state, body posture changes, or degree of nasal congestion. The effectiveness of several auto-CPAP devices in the treatment of sleep-disordered breathing has been demonstrated in many studies.

Many auto-CPAP machines are used as autotitrating CPAP devices. Pressures automatically delivered throughout the night are taken into consideration to identify a fixed pressure level that may be appropriate for home treatment by means of traditional fixed-level CPAP machines (ie, that is able to make the patient’s ventilatory activity regular enough during the night). For that purpose, there is not yet an universally accepted criterion; one of the most commonly used methods is to consider as an appropriate fixed pressure the pressure level that is exceeded only 5% of the nighttime. Whatever the criterion adopted, the main advantage expected from autotitrating machines is to save costs linked to the traditional CPAP titration procedure. Therefore, they may be exploited at best if used in an unattended environment and without a simultaneous polysomnographic monitoring. However, this procedure does not provide information about sleep structure during auto-CPAP application, while little is known about the importance of the effect of sleep structure, duration, and quality on the identification of a fixed CPAP level from the analysis of an autotitrating machine recording. In fact, sleep structure during auto-CPAP application has been reported in many studies that explored whether these devices are able to ensure a satisfactory sleep quality, but very little is known about how the administered CPAP-level changes in relationship to sleep state. Although two articles reported that pressure delivered is lowest during stages 3 and 4 of nonrapid eye movement (NREM) sleep, no detailed investigation about the relationship between sleep structure and pressure delivered has been published.

Therefore, in this study, we evaluated the relationship between sleep structure and CPAP levels administered by an auto-CPAP machine (Autoset Clinical 1; ResMed; Sydney, Australia). Specifically, we looked for a pattern of CPAP changes associated with sleep phases and arousals.

Materials and Methods

Fifteen consecutive subjects (12 male and 3 female; mean ± SD age, 49.2 ± 9.5 years; mean body mass index, 35.0 ± 5.0 kg/m2) who needed home CPAP treatment for a newly diagnosed OSAS (mean apnea-hypopnea index [AHI], 64.8 ± 25.4 events/h; mean of the lowest arterial oxygen saturation [Sao2], 63.9 ± 13.2%) were studied. One subject showed mild airway obstruction at spirometry (FEV1 67% predicted; PaO2, 66 mm Hg; PaCO2, 47 mm Hg), while all the others showed normal lung function and were free from associated diseases. In all subjects, standard polysomnography was performed in our sleep laboratory during CPAP administration by an Autoset Clinical 1 CPAP machine (ResMed; Sydney, Australia). This instrument can work both as a fixed-level CPAP device and as an autotitrating CPAP device. In the latter case, it administers variable CPAP levels, starting from a minimum of 4 cm H2O and increasing pressure at a rate of 0.2 cm H2O per breath after automatic detection of flow limitation, evaluated as an average flow/time ratio below a conventional threshold value of 0.15 U. If snoring or apneas with a closed upper airway > 10 s appear without previous flow limitation, the system reacts to them increasing more rapidly the CPAP level. Detection of apneas with open upper airway (identified by cardiac oscillation on the flow signal) does not lead to CPAP increase. A 20-cm H2O pressure level is never exceeded. As unobstructed breathing is resumed, pressure is decreased towards 4 cm H2O with a time constant of 20 min. Reliability of this auto-CPAP device as an autotitrating machine has been confirmed in various studies. Data relevant to the administered pressure, the detected events, and possible air leaks through the mask are stored on a computer and may be retrieved with a printout; data are considered valid if mask leaks are not > 0.4 L/s. The machine is equipped with an analogic output for nasal airflow, as detected by the built-in pneumotachograph. The polysomnographic studies were done with the ventilator set in the automatic working fashion. In six patients, an adaptation period at a fixed 4-cm H2O level was necessary at the beginning of the study for up to 45 min. Printout elaborated by the Autoset computer were evaluated for excessive (> 0.4 L/s) air leaks. Such periods, together with adaptation times spent at 4 cm H2O and periods during which the mask was taken off, were identified on the polysomnographic recordings and excluded from any analysis. Although a technician was in attendance during the polysomnographic recordings, he did not intervene during the night unless the mask was completely pulled off and had to be repositioned.

The polysomnographic studies were performed by a computerized system (Somnostar; Sensormedics; Yorba Linda, CA). Nasal airflow was obtained from the Autoset machine output. The recording included a calibrated CPAP signal that was detected from the nasal mask by a small hose connected to a pressure transducer (Validyne MP45–26–871; Validyne Engineering; Northridge, CA).

The studies were manually analyzed. Sleep was scored according to standard rules. Time in bed (TIB), total sleep time (TST), and sleep efficiency (TST/TIB × 100) were measured. Arousals were identified according to American Sleep Disorders Association rules; events lasting > 15 s were classified as awakenings, and an arousals/awakenings (Ar/Aw) index was calculated as the number of arousals plus the number of awakenings per hour of sleep time. Apneas were defined as a flat airflow signal for at least 10 s and classified as central, mixed, or obstructive according to usual criteria. Hypopneas were considered as a decrease in the airflow signal by at least 50% for at least 10 s. AHI was calculated as number of apneas plus hypopneas per hour of sleep time. CPAP recorded during polysomnography was analyzed by computer. The relationship between sleep stages and changes in
CPAP was evaluated. Since all subjects spent all or almost all sleep time in the supine posture, the relationship between posture and CPAP level could not be analyzed.

Mean CPAP levels were calculated for each epoch of the sleep studies and averaged for each subject; the SD of mean CPAP levels was considered as an estimate of nocturnal CPAP variability. CPAP variability was correlated to sleep efficiency by linear regression analysis. Lowest (after a decrease) and highest CPAP level administered during the night were measured. Epochs where these levels occurred were classified as NREM, rapid eye movement (REM), or wake. In turn, NREM was classified as “unstable” if preceded within 4 min by at least an arousal or awakening, or “stable” if it was not. Similarly, wake was classified as unstable if it occurred no longer than 2 min after a sleep epoch, or stable if it was not preceded by any sleep epoch for at least 5 consecutive min; in fact, no highest or lowest CPAP occurred during wake epochs preceded by sleep by 3 to 4 min.

Finally, rapid CPAP augmentation events, arbitrarily defined as increases in pressure by at least 2 cm H2O within 2 min, were identified. This definition was not based on the machine algorithm, but was adopted because such events could be easily identified and could be reliably related to EEG and respiratory events preceding and following them. Sleep state where they began and their possible relationship with Ar/Aw were identified. Besides, a detailed analysis of respiratory pattern before their occurrence was performed. In addition to apneas and hypopneas, other abnormalities were looked for: flow limitation, defined as a flat, concave, or notched airflow signal for at least three consecutive breaths; minor abnormalities, defined as isolated big breaths, minor alterations in respiratory rhythm, or decreases in respiratory irregularities, defined as prolonged (≥ 10 s) alterations in breathing pattern, where the airflow signal was highly variable and irregular, often in association with body movements.

### RESULTS

Table 1 reports the characteristics of sleep during auto-CPAP application. Sleep quality differed among subjects. A wide range of Ar/Aw index and sleep efficiency was found; all but one patient reached REM sleep. The machine was able to lower AHI in all subjects to a very low value. SaO2 constantly remained normal in all subjects but one. In fact, a moderate degree of hypoxemia was observed in the subject with airway obstruction whenever he entered REM sleep; however, his lowest SaO2 during sleep was substantially higher during auto-CPAP application than in the baseline sleep study (83% vs 50%, respectively).

Visual inspection of the recordings showed that each vigilance state was not solely associated to an increasing or to a decreasing CPAP trend; however, each state was commonly associated to a peculiar CPAP behavior. In particular, wakefulness was associated to increasing CPAP before sleep stage 1 could be scored; conversely, prolonged wakefulness periods (approximately 30 min) occurring toward the end of the polysomnographic study (observed in only three subjects) were associated with a decrease in the administered CPAP. Alternating wake and stage 1 periods were usually associated to high or increasing CPAP. Conversely, prolonged NREM sleep periods without Ar/Aw, especially stages 3 and 4, were almost always associated to a decrease in the administered pressure. The relationship between CPAP behavior and REM sleep was the most variable among subjects, since in four subjects CPAP increased by up to 3 cm H2O whenever REM sleep occurred, while in the others it rarely increased, rather remaining stable or even decreasing. Some examples of the relationship between sleep structure and CPAP are shown in Figure 1.

The automatically administered CPAP levels are shown in Table 2. In most cases, lowest CPAP levels were recorded during stable NREM sleep, while highest levels were recorded during unstable NREM sleep.

Altogether, 59 episodes of rapid CPAP augmentations (range per subject, 1 to 13 episodes) were observed. The distribution of these episodes in relation to sleep state and Ar/Aw is shown in Figure 2. Most episodes followed the occurrence of Ar/Aw. Sixty-three percent of such Ar/Aw were not preceded by any detectable respiratory abnormality and were considered as nonrespiratory Ar/Aw. The remaining Ar/Aw, which followed some respiratory abnormality (mostly flow limitation or hypopnea), were considered respiratory Ar/Aw; however, respiratory patterns, which were more irregular after than before Ar/Aw, and the time of onset of the rapid CPAP augmentations, suggested that only respiratory patterns following the Ar/Aw were responsible for the rapid CPAP increases. Noticeably, Ar/Aw never followed rapid CPAP augmentations in stable sleep. Data on the respiratory pattern before rapid CPAP augmentations are shown in Table 3. Coarse irregularities never preceded Ar/Aw, even in the case of respiratory Ar/Aw, but appeared almost always at the onset of an awakening. An example of rapid

### Table 1—Characteristics of Sleep and Respiration During Auto-CPAP Application in the 15 Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIB, min</td>
<td>346 ± 29</td>
</tr>
<tr>
<td>TST, min</td>
<td>288 ± 51</td>
</tr>
<tr>
<td>Wake, %TIB</td>
<td>16.5 ± 13.1</td>
</tr>
<tr>
<td>Stage 1, %TIB</td>
<td>10.7 ± 5.6</td>
</tr>
<tr>
<td>Stage 2, %TIB</td>
<td>51.6 ± 11.7</td>
</tr>
<tr>
<td>Stage 3–4, %TIB</td>
<td>7.0 ± 8.4</td>
</tr>
<tr>
<td>REM, %TIB</td>
<td>14.2 ± 8.0</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>94.6 ± 13.3</td>
</tr>
<tr>
<td>Ar/Aw index, No./h</td>
<td>11.5 ± 6.5</td>
</tr>
<tr>
<td>AHI, No./h</td>
<td>1.8 ± 1.5</td>
</tr>
<tr>
<td>Lowest SaO2, %</td>
<td>91.6 ± 3.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. %TIB = percentage of TIB.
Figure 1. CPAP levels automatically delivered during the night and contemporary sleep stages as recorded in two subjects. Top: In this subject, please observe initial CPAP increase before established sleep, no consistent trend in CPAP during REM sleep, and nine rapid CPAP augmentations, as defined in the text, among which two were unrelated to wake (W) or Ar/Aw (hatched areas) and the remaining seven (shaded areas) following either an arousal (two cases) or an awakening (five cases). No CPAP level is represented during a short period that followed mask pull-off. Bottom: In this subject, please observe a consistent trend to an increase in CPAP during REM, a trend to a decrease in CPAP during stable NREM sleep, and two rapid CPAP augmentations (shaded areas), one following an arousal and one following an awakening.
CPAP augmentation following a coarse respiratory irregularity is shown in Figure 3. While most rapid CPAP augmentations followed Ar/Aw, only 7.3% of arousals (range per subject, 0 to 26.7%) and 17.7% of awakenings (range per subject, 0 to 77.8%) were followed by rapid CPAP augmentations. As an effect, the Ar/Aw index was not correlated to either the frequency of rapid CPAP augmentations or to CPAP variability. However, sleep efficiency showed a significant (p < 0.02) negative linear correlation with CPAP variability (Fig 4).

DISCUSSION

The results of this study show that sleep structure is strongly related to pressure levels automatically delivered by the Autoset device. Wakefulness was associated with a variable CPAP behavior, and its amount was correlated to nocturnal CPAP variability; NREM sleep was usually coincident to the lowest administered CPAP values when not fragmented by Ar/Aw, and to the highest when fragmented; REM sleep could be associated to increasing CPAP and, sometimes, to highest nocturnal CPAP, but only in some subjects. The Autoset machine was very effective in the abolition of obstructive apneas and hypopneas, as previously shown5; however, some of the most important CPAP augmentations were not related to obstructive sleep-disordered breathing events, but to irregularities in breathing pattern occurring at awakening. Such augmentations are not useful to maintain a regular breathing pattern during

![Figure 2. Distribution of the rapid CPAP augmentations in the whole sample in relation to Ar/Aw and sleep states.](image-url)
sleep and, due to the slow decrease in CPAP after their occurrence, they influence subsequent CPAP levels during the session; therefore, in case of a frequent recurrence, they could lead to an overestimate of the required fixed CPAP value.

The relationship between sleep state and CPAP needs in patients with OSAS has been more the object of hypotheses than of extensive investigations. A commonly accepted point of view is that a higher CPAP is required to abolish upper-airway obstruction in REM sleep than in NREM sleep. This idea was supported by the greater upper-airway collapsibility in REM sleep. More recently, a study based on the analysis of CPAP levels administered during manual CPAP titration again concluded that REM sleep required a higher pressure; however, the dif-

Table 3—Respiratory Pattern Before Rapid CPAP Augmentations

<table>
<thead>
<tr>
<th>Variables</th>
<th>Episodes of Rapid CPAP Augmentation, No.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During Uninterrupted Sleep</td>
<td>During Alternating Wake-1 NREM</td>
</tr>
<tr>
<td>Regular</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Minor abnormalities</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Flow limitation</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Hypopnea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Apnea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coarse irregularities</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 3. Rapid CPAP augmentation episode following a coarse respiratory irregularity that appears after a respiratory awakening. From top to bottom, EEG (C3A2), EEG (O2A1), right electro-oculogram (ROC), left electro-oculogram (LOC), submental electromyogram (EMG), ECG, pressure at the mask (CPAP), nasal airflow (by the machine pneumotachograph) [V], thoracic movements (Thor), abdominal movements (Abd), and oxyhemoglobin saturation (SaO2). Flow limitation precedes the awakening, which can be classified as respiratory. At awakening, flow stops for a few seconds and, at the same time, thoracic and abdominal movements show gross irregularities. The time of onset of the flow arrest (at awakening rather than before it) and the behavior of thoracoabdominal movements indicate that the respiratory event cannot be an obstructive apnea; it was classified as a “coarse respiratory irregularity.” CPAP starts augmenting rapidly after such event; besides, the amount of increase is disproportionate to the flow limitation preceding the awakening. Therefore, only the flow arrest of the coarse respiratory irregularity can be responsible for the rapid CPAP augmentation. in = inhalation; ex = exhalation.
ferences between NREM sleep and REM sleep were on average small (1 cm H₂O). By contrast, observations performed with auto-CPAP machines led to the impression that highest CPAP levels may be required in stage 1, or to the finding that CPAP levels delivered during REM sleep do not differ on average from the mean levels delivered throughout the whole night. The more extensive analysis performed in this study about the relationship between sleep structure and CPAP supports what was suggested in the previous two articles: REM sleep was constantly associated with an increase in the delivered pressure in four subjects only, and did not represent the most important cause of variable CPAP needs in the sample. The use of fixed or automatic CPAP could explain the different findings about REM sleep. Data obtained by fixed CPAP could appear more reliable, since subjected to human control; however, visual control of respiratory activity during human attempts to vary CPAP cannot be as precise and rapid as the control of the software of automatic machines. Besides, from a theoretical point of view, in REM sleep, the increased CPAP need due to greater upper-airway collapsibility could be overbalanced by weaker respiratory efforts, which could diminish the required level of CPAP.

The strongest relationship between sleep structure and CPAP level regarded indexes of sleep quality and fragmentation. Highest CPAP levels were in most cases recorded during NREM sleep fragmented by Ar/Aw or during periods of drowsiness. This finding is similar to what suggested by Teschler and Berthon-Jones, who reported the impression of highest CPAP needs during stage 1 NREM sleep. Several mechanisms may explain the relationship between Ar/Aw and CPAP augmentations. The most obvious is that a progressive CPAP decrease may be followed by the appearance of flow limitation or other respiratory alterations, which evoke at the same time an arousal and an increase in the delivered CPAP level. However, we were not able to identify respiratory abnormalities before many Ar/Aw, suggesting that they were spontaneous, nonrespiratory events. These Ar/Aw were sometimes associated to a short hyperventilation or to sighs and were often followed by flow limitation as sleep EEG activity was resumed. In fact, transition between wakefulness and sleep in normal subjects is characterized by an instability of respiratory activity, with immediate reduction in ventilation and upper-airway muscle activity, and is followed by a stabilization of respiratory pattern and an increase in genioglossus phasic activity when a stable sleep state is reached. Similar changes are likely to occur in patients with OSAS receiving CPAP. Eventually, many awakenings were associated with the sudden appearance of coarse respiratory irregularities that could mimic obstructive apneas or other sleep respiratory abnormalities, so that the response of the machine was a rapid, often large, increase in the CPAP level. Conversely, we never found that rapid CPAP augmentations disturbed sleep continuity; this finding is in agreement with previous data. Rather, it could be an excessive CPAP decrease that caused the appearance of respiratory irregularities and subsequent arousals. Despite most rapid CPAP augmentations followed Ar/Aw, the percentage of Ar/Aw followed by rapid CPAP augmentations was very variable among subjects, so that the Ar/Aw index was not significantly correlated to CPAP variability. The only significant correlate of CPAP variability we found was sleep efficiency. In fact, wakefulness could be characterized by either restlessness and irregular breathing causing frequent CPAP augmentations or, more rarely, by complete relaxation with regular breathing for prolonged periods after sleep, causing progressive CPAP lowering.

Uninterrupted stages 3 and 4 NREM sleep were usually associated with a low CPAP level. This finding is in agreement with what was reported in two previous studies, and with the notion that airway collapsibility is least in these sleep stages.

In the analysis of the data, it was deliberately chosen not to base the conclusions on mean values recorded in each sleep stage. In fact, since the rate of
pressure decrease after resumption of regular breathing is much slower than the rate of rise after respiratory irregularities, the CPAP level during each sleep stage may be influenced by respiratory abnormalities occurring in the preceding stage. More meaningful information could be obtained looking at augmentations and at highest nocturnal levels, which depend on events shortly preceding them, or at CPAP variations.

The results of the present study could not be applied to other auto-CPAP devices that are based on different software. Studies are needed with each auto-CPAP machine to improve the knowledge on their utilization. Besides, it was not possible to analyze the influence of changes in body posture, due to the very small amount of time spent in the lateral position by the patients. Although no major difference between CPAP delivered in each posture was observed, the data collected are insufficient to draw conclusions. Studies are needed also to better explore this aspect, for which few and conflicting results have been reported in the literature.

The results of this study indicate that recordings obtained during auto-CPAP application without simultaneous EEG monitoring must be interpreted with caution before using them to prescribe a fixed CPAP level. Since the most important influence on CPAP level (either in the direction of increasing or of reducing it) is exerted by wake and arousals, more reliable conclusions may be reached in patients who are already adapted to CPAP. In any case, a highly variable CPAP level during the night must raise the question whether the patient’s sleep quality was acceptable, and if a poor sleep quality could lead to an undesirable overestimation of the necessary CPAP level. In particular, the conclusion must not be drawn that patients with the highest CPAP variability during the night are the best candidates for home treatment with auto-CPAP. In fact, with clear indications to home treatment with auto-CPAP still lacking, it is hypothesized that such patients could be the ones who may have more benefit of such treatment. Although a high CPAP variability delivered by auto-CPAP machines could theoretically depend on highly variable CPAP needs during normal sleep, this has not been demonstrated yet. Rather, the data of this study suggest that auto-CPAP is more appropriate in subjects who show a low variability in the CPAP level during its application. A possible useful method to use autotitrating CPAP is to apply it during a polysomnographic unattended recording (so-called level II). By using this procedure, the cost of a technician constantly supervising the patient during the polysomnography would be saved, and an erroneous evaluation of the fixed CPAP need due to an unsatisfactory sleep quality would be avoided.

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