CPAP-Associated REM Rebound is a Manifestation of Sleep Homeostasis in Patients with Severe OSA

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Abstract

Sleep is homeostatically regulated, as evidenced by experimental sleep-deprivation studies. CPAP-induced REM rebound (CARR) is a phenomenon in which REM% sleep is dramatically increased in a sub-group of OSA patients when CPAP treatment is initiated. Presumably CARR results from a homeostatic process that produces deeper sleep when the hypoxemia stress is reduced by CPAP.

Recurrence analysis (RA) is a method of objectively measuring the extent of regulation on brain electrical manifested in the EEG. RA variables have been shown capable of continuously quantitating sleep depth in a manner that complements traditional sleep staging (1). We hypothesized that the extent of regulation of brain electrical activity manifested in the EEG in patients who exhibit CARR would be greater than that in patients undergoing CPAP titration who did not exhibit CARR (Non-CARR). We planned to interpret such observations as indicating that the extent of regulation of brain electrical activity in the EEG (brain activity governed by law rather than chance) was a regulated variable in sleep homeostasis, at least in patients who exhibited CARR.

Our specific objective was to find statistically reliable effects on EEG regulation in CARR patients.

Methods

Patient Selection

Records of consecutive patients who underwent diagnostic PSG (dPSG) positive for OSA (AHI ≥5) and who subsequently underwent CPAP-titration PSG (cPSG) were reviewed. All studies were required to contain at least 30 minutes of REM sleep. CPAP-association REM rebound (CARR) was defined as >20% increased REM% sleep in the cPSG compared with the dPSG. The first 20 paired studies meeting the inclusion criterion were analyzed. The control group consisted of 20 consecutive patients with
OSA who did not exhibit CARR during the cPSG (Non-CARR). All patients had no significant co-morbidities, were not taking sleep-altering medications, and had not received prior treatment for OSA. All PSGs were staged (AASM rules) by consensus between two sleep-medicine physicians.

**Patient Characteristics**

On the dPSG, CARR patients were sleepier, more likely to be male, and had higher BMI compared with Non-CARR patients (Table 1). Comparing polysomnographic variables, the dPSG in the CARR group revealed a higher mean AHI, a lower REM%, and a shorter longest continuous REM cycle (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>CARR</th>
<th>Non-CARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>47.4 ± 9.4</td>
<td>39.8 ± 7.7</td>
</tr>
<tr>
<td>Age (*years)</td>
<td>46.5 ± 14.0</td>
<td>48.8 ± 10.3</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white</td>
<td>67%</td>
<td>55%</td>
</tr>
<tr>
<td>White</td>
<td>33%</td>
<td>45%</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>Female</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>ESS score</td>
<td>17.3 ± 4.9</td>
<td>12.1 ± 5.7</td>
</tr>
</tbody>
</table>

**Table 1.** Demographic Comparisons Between CARR and non-CARR Groups (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>CARR</th>
<th>Non-CARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (min)</td>
<td>381.9 ± 45.9</td>
<td>367.2 ± 54.5</td>
</tr>
<tr>
<td>SE (%)</td>
<td>83.0 ± 8.8</td>
<td>86.5 ± 8.9</td>
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<tr>
<td>REM (min)</td>
<td>48.3 ± 18.0</td>
<td>152.0 ± 40.5</td>
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<tr>
<td>L-REM</td>
<td>25.0 ± 10.8</td>
<td>79.6 ± 41.7</td>
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<tr>
<td>REM (%)</td>
<td>12.6 ± 3.9</td>
<td>41.1 ± 7.8</td>
</tr>
<tr>
<td>AHI</td>
<td>100.6 ± 27.2</td>
<td>16.1 ± 14.0</td>
</tr>
<tr>
<td>∆ REM (%)</td>
<td>28.5 ± 8.0</td>
<td>0.3 ± 3.5</td>
</tr>
</tbody>
</table>

**Table 2.** Pertinent Sleep Variables (Mean ± SD). Median elapsed time between dPSG and cPSG was 54 days and 57 days for the CARR and non-CARR group, respectively.
Recurrence Analysis

The extent of regulation of brain electrical activity manifested in the EEG was quantified by means of recurrence analysis (RA), employing the variable termed percent recurrence. Details of RA are given elsewhere (1). Percent recurrence (R) is the most useful of a new class of variables capable of capturing important physiological information contained in the EEG that cannot be obtained using conventional methods such as spectral analysis. The physiological meaning of increased R can be expressed as increased regulation, order, determinism, or law-governed activity. Increased R can also be interpreted as decreased chaos, or disorder.

The EEGs in each PSG (C3–M2, C4–M1) were analyzed second-by-second. In an 8-hr PSG, 8 hours × 60 minutes × 60 sec = 28,800 values of R were computed and averaged epoch-by-epoch, resulting in 960 values of average percent recurrence (R̄) for each EEG. When applied to normal sleep, RA produces a picture in which R̄(N3) > R̄(N2) > R̄(N1) > aR̄(W), and R̄(REM) ≈ R̄(N1) (Fig. 1).

Patient Characteristics

On the dPSG, CARR patients were sleepier, more likely to be male, and had higher BMI compared with Non-CARR patients (Table 1). Comparing polysomnographic variables, the dPSG in the CARR group revealed a higher mean AHI, a lower REM%, and a shorter longest continuous REM cycle (Table 2).

Figure 1. Example of use of recurrence analysis for characterizing the sleep-staged EEG. Percent recurrence (R) was computed using successive one-sec intervals of the overnight sleep EEG from a clinically normal subject. R was averaged epoch-by-epoch (resulting in avgR) and color coded by sleep stage. Each point represents avgR for one 30-sec EEG epoch. The bar graph shows the grand mean ± SD of avgR and stage-specific number of sleep epochs. Red line depicts avgR for wake.
Statistical Design

The changes in $\bar{R}$ that occurred between the dPSG and cPSG in the CARR group were evaluated using the t test. As a control, the comparable changes in the Non-CARR group were evaluated similarly. Additionally, the cPSGs in the CARR and Non-CARR groups were directly compared using the unpaired t test (Fig. 2).

![Diagram](image)

**Figure 2.** Statistical design.

Results

Results typical of those seen in the CARR group are shown in Fig. 3. The macro-architecture of $\bar{R}$ in the dPSG (left panel) did not evince the 4–5 peak structure of normal sleep (Fig. 1), but CPAP partially normalized the patient’s sleep structure (middle panel). The bar graph gives the stage-specific recurrence increases in $\bar{R}$ (relative to the values in wake) that occurred in the PSGs. Brain electrical activity was more deterministic (more highly regulated) during cPSG, particularly in N2 and N3 sleep.
Figure 3. Typical results for the change in $\bar{R}$ in a CARR patient. Each point in each PSG depicts $\bar{R}$, color-coded to indicate the sleep stage (assessed by blinded experts). The bar graph shows the stage-specific increases in $\bar{R}$ above the wake level.

When the results were averaged across all 20 patients, the effects in N2 and N3 sleep were statistically significant (Fig. 4), indicating that in the CARR group the extent of regulation of brain electrical activity manifested in the EEG during cPSG was greater than that in the same patients during dPSG. No change in regulation occurred during REM or N1. In contrast, CPAP had no average effect on recurrence in any sleep stage in the 20 Non-CARR patients (Fig. 5).
When sleep-stage-specific recurrence in the cPSG was directly compared between the CARR and Non-CARR groups, significant (P < 0.05) increases were again seen during N2 and N3, but not during REM or N1 (Fig. 6).
Discussion

Homeostasis is a law-governed process that drives deviations in regulated physiological variables towards steady-state levels. We found that patients who exhibited a sleep-specific homeostatic response (CPAP-triggered increase in REM%) also exhibited a transient increase in the amount of law-governed brain activity during N2 and N3 sleep, as evidenced by the amount of recurrence (R̅) in the EEG (Figs. 4–6). These results indicated that recurrence was a regulated variable in sleep homeostasis in the patient population studied.

Unexpectedly, the increased homeostatic pressure manifested in N2 and N3 sleep was not seen in REM sleep, the temporal length of which was the essential criterion for formation of the study groups. Comparing CARR and Non-CARR patients, we found no significant difference in brain activity during REM, either in the dPSG (Fig. 4) or the cPSG (Fig. 5). One possible interpretation of the results is that brain activity during REM sleep (hence REM sleep itself) is not directly under homeostatic control.

The observation that CARR occurred in patients with more severe OSA suggests that CARR is a marker for the physiological impact of the stress imposed by obstructive airway pathology and the stress relief provided by CPAP. The changes in R̅ may provide another way to quantify the stress impact of OSA and the relief afforded by CPAP therapy.
References


Abbreviations

AHI  apnea/hypopnea index
BMI  body mass index
CARR  CPAP-association REM rebound
cPSG  CPAP-titration polysomnography or polysomnogram
dPSG  diagnostic polysomnography or polysomnogram
EEG  electroencephalogram
ESS  Epworth sleepiness scale
L-REM  longest REM interval (min)
RA  recurrence analysis
\( \bar{R} \)  percent recurrence; RA variable computed per second from the EEG
avgR  R averaged over a 30-sec epoch
REM%  REM sleep as a percent of TST
SE  sleep efficiency
TST  total sleep time