

Relationship between Arousal Intensity and Heart Rate Response to Arousal

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Study Objectives: The visual appearance of cortical arousals varies considerably, from barely meeting scoring criteria to very intense arousals. Arousal from sleep is associated with an increase in heart rate (HR). Our objective was to quantify the intensity of arousals in an objective manner using the time and frequency characteristics of the electroencephalogram (EEG) and to determine whether HR response to arousal correlates with arousal intensity so determined.

Design: Post hoc analysis of 20 preexisting polysomnography (PSG) files.

Setting: Research and Development Laboratory (YRT Limited).

Participants: N/A.

Interventions: None.

Measurements and Results: Arousals were scored using the American Academy of Sleep Medicine criteria. The EEG signals' time and frequency characteristics were determined using wavelet analysis. An automatic algorithm was developed to scale arousal intensity based on the change in wavelet features and data from a training set obtained from 271 arousals visually scaled between zero and nine (most intense). There were 2,695 arousals in 20 PSGs that were scaled. HR response (Δ HR) was defined as the difference between the highest HR in the interval [arousal-onset to (arousal-end + 8 sec)] and the highest HR between 2 and 12 sec preceding arousal onset. There was a strong correlation between arousal scale and Δ HR within each subject (average $r: 0.95 \pm 0.04$). The slope of the relationship varied among subjects (0.7 – $2.4 \text{ min}^{-1}/\text{unit scale}$).

Conclusions: Arousal intensity, quantified by wavelet transform, is strongly associated with arousal-related tachycardia, and the gain of the relationship varies among subjects. Quantifying arousal intensity in PSGs provides additional information that may be clinically relevant.

Keywords: Arousal, EEG, heart rate, wavelet

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INTRODUCTION

Electrocortical arousals are very common in patients with sleep disorders. Frequent arousals result in sleep fragmentation, which leads to impaired cognitive function.¹⁻⁴ It is also well documented that arousal from sleep is associated with an autonomic reflex activation that increases blood pressure and heart rate (HR).⁵⁻⁹

The standard definition of arousal is “an abrupt shift in EEG to a higher frequency, including alpha, theta or beta, for at least 3 sec, with at least 10 sec of stable sleep preceding the change.”^{10,11} It is well recognized, however, that electroencephalogram (EEG) changes that meet this definition cover a wide range of visual appearances, ranging from changes that barely meet the scoring criteria to very intense changes associated with high-amplitude beta waves. There is some evidence that the visual intensity of arousals is correlated with the magnitude of physiological changes that accompany arousals. Thus, Younes reported that the visual intensity of EEG arousals (classified into four levels) correlated with the magnitude of the ventilatory overshoot that follows obstructive events in patients with obstructive sleep apnea.¹² Also, Sforza et al. found that HR increased more in arousals associated with movement.⁷ The severity of sleep fragmentation on polysomnography (PSG) is conventionally reported as the frequency of arousals, despite the

fact that this index does not reliably predict which patients will experience clinical consequences of sleep disruption.¹³ Thus, it is possible that scoring the intensity of arousals may provide additional guidance into which patients with sleep disorders will develop cognitive and cardiovascular complications.

Visual scoring of arousal intensity would be time consuming and, because of its subjective nature, prone to much interscorer variability. To efficiently and accurately test the clinical significance of arousal intensity, automation of the process would be optimal. In this study, a large number of arousals that met the American Academy of Sleep Medicine (AASM) criteria¹¹ were further classified into one of 10 levels based on visual assessment by an expert scorer (MY). Wavelet characteristics of arousals having different visually defined intensity scales were used as a training set. Subsequently, arousals in test files were classified into one of 10 levels based on their wavelet features and the data from the training set. To confirm the validity of this automatic scaling algorithm, we determined the relationship between automatically scored intensity and the associated increase in HR. The results show an excellent correlation within each subject but with a slope that is quite variable among subjects.

METHODS

Files

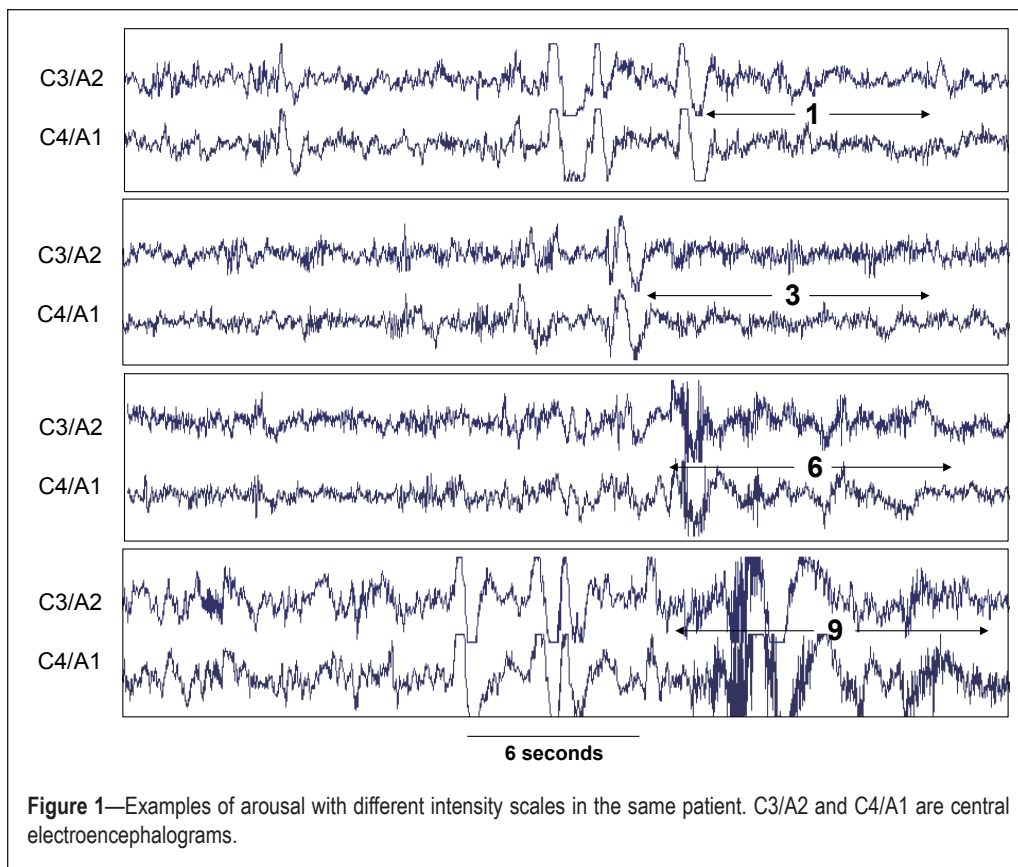
YRT Limited has developed an automatic PSG scoring system that was recently validated in an independent multicenter study.¹⁴ The files used in the current study were obtained during beta testing of the automatic system on 60 PSG files recorded in the Sleep Centre at the University of Calgary in 2011. The files available to YRT were anonymous and contained standard

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PSG data, including three-channel EEG (C3/A2, C4/A1, O1/A2), submental electromyogram (EMG), two-channel electrooculogram, oximetry (Biox 3740, Ohmeda, Boulder, CO, USA), chest and abdomen bands (Respirtrace, Ambulatory monitoring, Ardsley, NY, USA), nasal pressure and thermister signal (Ultima dual pressure sensor 0585, Braebon Medical Corporation, Kanata, Ontario, Canada), snoring sensor, body position, electrocardiogram, and bilateral anterior tibialis EMG to record leg movements. All variables were continuously recorded by a computerized data acquisition system (Sandman, Natus Medical Inc, San Carlos, CA) and stored electronically for later analysis.

The files had already been scored for conventional sleep variables by the automatic system, and the automatic scoring was edited by an experienced PSG technologist (MO). Arousal scoring followed the 2007 AASM guidelines¹¹ both during the automatic scoring and in the editing stage by MO. The onsets and ends of arousals were identified strictly from the EEG without regard to any other signals (e.g., EMG, HR, or breathing).

Analyses

The reports generated from the edited automatic scoring were reviewed in random order, and the first 20 files that contained more than 70 arousals and were free of arrhythmias (atrial fibrillation, frequent ectopic beats) were selected. Three files were selected at random from these 20 files. The files belonged to one patient (age 49 y, body mass index [BMI] 59 kg/m², apnea-hypopnea index [AHI] 56 hr⁻¹) with severe obstructive sleep apnea (OSA) and two patients who did not have OSA (ages 35 and 34 y, BMI 26 and 23 kg/m², AHI 1.4 and 2.4 hr⁻¹). Each previously scored arousal in nonrapid eye movement (NREM) sleep in these three files was assigned an intensity

scale between 0 and 9 by MY. Scale 0 was assigned when the arousal was barely perceptible, and MY did not believe it met the minimum AASM criteria. Examples of four other scales (1, 3, 6, and 9) are shown in Figure 1. The visual scaling was entirely subjective, not deliberative, and based entirely on EEG appearance in the two central electrodes (C3/A2 and C4/A1). Arousal intensity was scaled for each of the two electrodes and the higher of the two scales was assigned to the arousal. Visual scaling primarily focused on the most intense region within the arousal duration. Arousal duration was not consciously considered. Full awakenings (arousals > 15 sec) were not analyzed. HR was not available to the scorer at the time of intensity scaling. Only limited analysis of arousals in rapid eye movement (REM) sleep was performed in view of the small

number of such arousals in most files (see Results).

Wavelet analysis of C3/A2 and C4/A1 EEG signals was performed on each of the scaled arousals in the three training files (see the following paragraphs for details of wavelet analysis). A table containing the visually determined arousal intensity scale and various wavelet features for each of the 271 arousals in the three training files was generated. A number of wavelet features that best correlated with arousal intensity in these three files were selected. Thereafter, these features were generated for all NREM arousals in the remaining files, and an intensity scale was automatically assigned to each arousal based on the training set and wavelet characteristics of the new test arousal. No signal other than the EEG was used in this automatic process.

Arousal Scaling

Arousal scaling was performed using wavelet transform (WT).^{15,16} WT is particularly superior for analyzing nonstationary signals such as EEG where other traditional techniques (based on Fourier transform) are not as effective. WT is defined by its unique wavelet and scaling functions.¹⁷ Several WTs have been proposed in the literature. In this study, we used Daubechies wavelets¹⁸ of order 4. Daubechies wavelets are known for their orthogonality and efficient implementation and their order 4 has been found to be the most effective for the analysis of EEG.¹⁹ WT was performed in MATLAB (MathWorks, Natick, MA, USA). Because our signal of interest (EEG) is discrete, we used discrete wavelet transform (DWT), which is obtained by taking the wavelet and scaling functions at discrete values. The DWT of a signal can be efficiently calculated by passing the signal through a series of cascade

filters. Figure 2 shows a two-level wavelet decomposition of a signal using DWT.

As shown in Figure 2, in each level of decomposition, the signal (or the approximation coefficients) is passed through two special filters: a high-pass (or wavelet) filter ($h(n)$) and a low-pass (or scaling) filter ($g(n)$). Figure 3 shows the wavelet and scaling filters for Daubechies wavelet order 4. The high-pass and low-pass filters are related to each other and they are quadrature mirror filters. The frequency ranges corresponding to different levels of decomposition depend on the number of levels and sampling frequency. Table 1 shows the frequency range of detail and approximation coefficients for five levels of decomposition and sampling frequency of 128 Hz.

We calculated all the wavelet coefficients shown in Table 1 for two EEG signals (C3/A2 and C4/A1). The five-level decomposition coefficients (D_1 - D_5 and A_5) were calculated for the period between arousal onset and end, and for an equal period preceding arousal onset (Figure 4). From these coefficients we calculated average power (P_{avg} , six features total), mean of absolute value (MABS, in total six features), ratio of MABS for all combinations of coefficients (e.g.:

$$\frac{MABS(D_1)}{MABS(D_2)}, \frac{MABS(D_1)}{MABS(D_3)}, \frac{MABS(D_1)}{MABS(D_4)}, \frac{MABS(D_1)}{MABS(D_5)}, \frac{MABS(D_1)}{MABS(A_5)},$$

...etc; 15 features total) and total variation²⁰ of coefficients in each level (TV, six features total). TV is the average of all point-to-point absolute amplitude differences in the relevant coefficient over the period of analysis. Thus, 33 features were calculated from every arousal. All features were divided by their prearousal values, resulting in 33 normalized features per arousal.

The 33 features were obtained for each of the 271 training arousals. One-way analysis of variance (ANOVA) was used to determine which of these features discriminated between the different visual scales. Fourteen features were highly significant. These were:

$$P_{avg}(D_1), P_{avg}(D_2), P_{avg}(A_5), MABS(D_1), MABS(D_2), MABS(A_5), \frac{MABS(D_1)}{MABS(D_2)}, \frac{MABS(D_1)}{MABS(D_3)}, \frac{MABS(D_1)}{MABS(D_4)}, \frac{MABS(D_1)}{MABS(D_5)}, \frac{MABS(D_2)}{MABS(D_3)}, \frac{MABS(D_2)}{MABS(D_4)}, \frac{MABS(D_2)}{MABS(D_5)}, \frac{MABS(D_3)}{MABS(D_4)}, \frac{MABS(D_3)}{MABS(D_5)}, \frac{MABS(D_4)}{MABS(D_5)}, \frac{MABS(D_5)}{MABS(A_5)}, \frac{MABS(A_5)}{MABS(D_1)}, \frac{MABS(A_5)}{MABS(D_2)}, \frac{MABS(A_5)}{MABS(D_3)}, \frac{MABS(A_5)}{MABS(D_4)}, \frac{MABS(A_5)}{MABS(D_5)}, TV(D_1), \text{ and } TV(D_2).$$

Next, we built several classifiers to classify (scale) a new arousal based on the training set. We built three k-nearest neighbor classifiers²¹ (classifier 1: $k = 3$, classifier 2: $k = 4$, classifier 3: $k = 5$), three discriminant classifiers²¹ (classifier 4: linear discriminant, classifier 5: quadratic discriminant, classifier 6: Mahalanobis discriminant), and one tree classifier²¹ with pruning at level 6. In total, we built seven classifiers using our training set. This was done to remove the effect of overfitting to the training dataset and to achieve higher predictability over the new testing data. Each classifier generated a scale for an arousal, resulting in seven scales per arousal. The average of all seven scales was calculated and rounded to obtain a single integer scale between 0 and 9. As mentioned, we used two EEG channels for calculating the intensity of arousals. The final scale for a given arousal was the higher of the two EEG channels.

As a control, for each file we randomly selected 10-14 9-sec intervals from periods with stable sleep (i.e., no arousals

Table 1—Frequency ranges corresponding to five levels of decomposition using Daubechies wavelet order 4

	Coefficients					
	D_1	D_2	D_3	D_4	D_5	A_5
Frequency range (Hz)	32-64	16-32	8-16	4-8	2-4	0-2 ^a

^aThe original electroencephalogram signal was passed through a high-pass filter with cutoff frequency of 0.3 Hz.

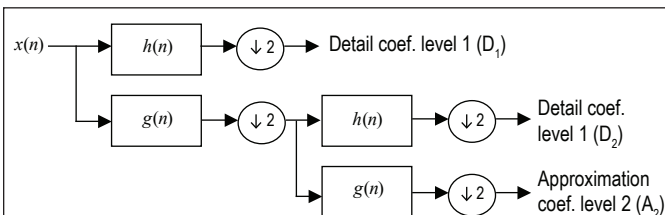


Figure 2—Diagram showing a two-level wavelet decomposition of a signal using discrete wavelet transform. In each level of decomposition, the signal (or the approximation coefficients) is passed through two special filters: a high-pass (or wavelet) filter ($h(n)$) and a low-pass (or scaling) filter ($g(n)$).

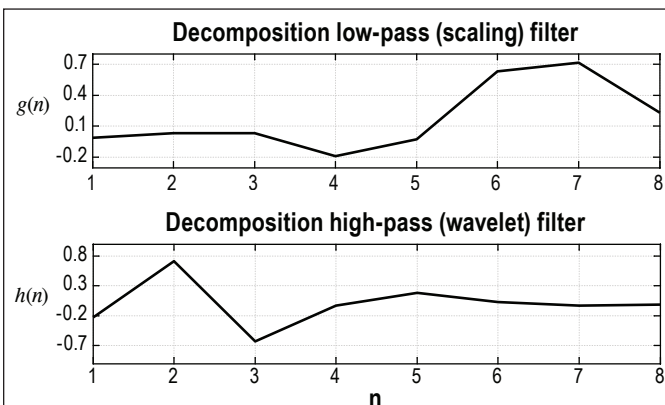


Figure 3—Wavelet and scaling filters for Daubechies wavelet order 4.

scored by the sleep technologist). These intervals are referred to as sham arousals.

HR Measurement

Beat-by-beat HR was measured and the highest value in the interval 2-12 sec preceding the arousal was used as baseline HR. The 2 sec preceding arousal were avoided in baseline determination, because Sforza et al.⁷ reported that arousal-associated tachycardia may begin up to 2 sec before arousal. The highest HR in the interval [arousal onset to (arousal end +8 sec)] was also measured and the difference from baseline HR (ΔHR) represented the change in HR associated with the arousal.

Statistics

Paired t test and ANOVA were used where appropriate (see Results). For each file, we averaged all ΔHR values at each arousal scale. The correlation (Pearson correlation coefficient) between arousal scale and average ΔHR at each scale was determined for each file. Multiple linear regression analysis was

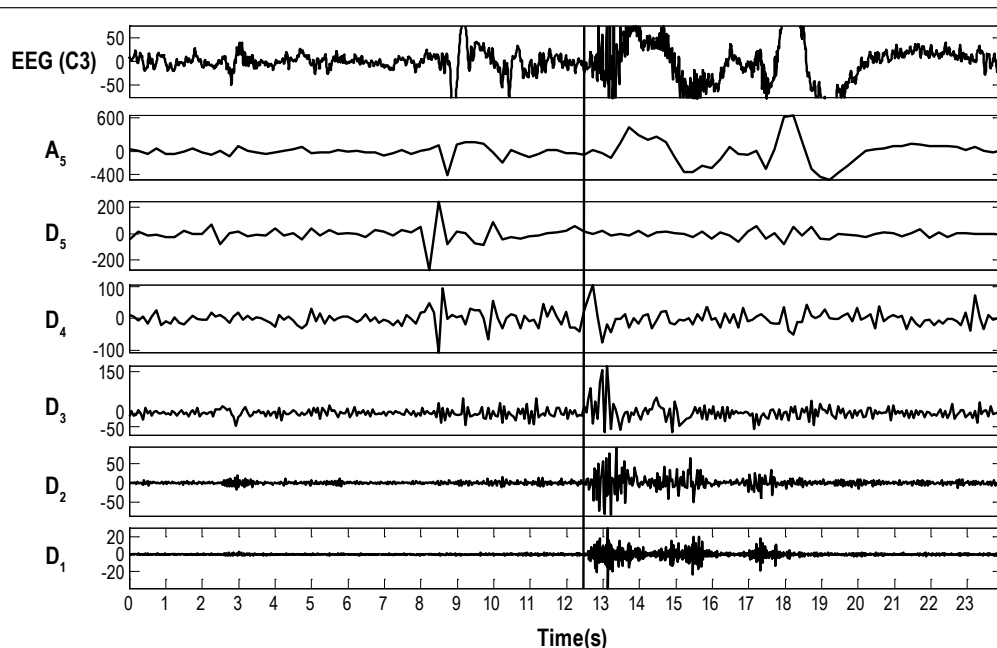


Figure 4—Example of electroencephalogram (EEG) signal (channel C3) before and during arousal with its wavelet decomposition coefficients in all five levels. The top panel shows the raw EEG signal, which is the input to the wavelet filter banks. D_1 – D_5 shows the detail coefficients from level 1 to level 5, respectively. D_1 reveals the high frequency brain activities as well as the time of occurrence of these activities. A_5 and D_5 show the slow brain activities. Note that the powers of wavelet detail coefficients at levels 1 and 2 (and 3, to some extent) are larger during the arousal than in the prearousal period.

The visual intensity of the 271 arousals used in the training set ranged from 0 to 9. There was no difference in average visual scale between the two electrodes (3.7 ± 2.6 and 3.8 ± 2.6). However, the visual scales assigned to the two electrodes differed in 101 of the 271 arousals (37%). Of these, the difference between the two scales was one or two points in 81 arousals and > 3 in only eight arousals. There was a weak but highly significant correlation between the visual scale and duration of arousal ($r = 0.37$; $P < 0.0001$).

Of 244 sham arousals, 168 (74%) received a scale of 0, 35 (15%) a scale of 1, and 24 (11%) a scale of 2, for an average scale of 0.4 ± 0.2 .

Characteristics of Arousals in Different Files

Table 2 shows characteristics of arousals in individual files. The average number of arousals examined per file was 134.8 ± 61.2 , for a total of 2,695 arousals. Figure 5 shows the frequency of different scales. Scale 3 arousals were the most frequent, accounting for 34.3% of all arousals examined. The frequency decreased progressively in either direction, reaching 2.1% for scale 1 and 3.4% for scale 9. Only one of 2,695 visually scored arousals received a scale of 0. Scales 2 through 7 were represented in all files. There were no scale 1 arousals in nine files and there were no scale 8 or 9 arousals in two and six files, respectively.

The arousal scale varied greatly within each file. In most files, almost the entire spectrum of intensities was observed (Table 2). Arousals associated with arousal-related movement (i.e., not including periodic limb movement) were on average more intense than those not associated with movement (5.4 ± 1.0 versus 3.8 ± 0.6 ; $P < 0.0001$, Table 2) but both types covered the entire spectrum of arousal intensities, as judged from the EEG (Table 2).

As in the case of visual scaling, there was a highly significant correlation between arousal intensity and arousal duration in all files ($r = 0.47 \pm 0.09$; $P < 0.001$ or better).

The average arousal scale ranged from 3.4 to 5.9 in different files (4.1 ± 0.7 ; Table 2). The differences between files (subjects) were highly significant by analysis of variance ($P < 0.0001$). There was a significant correlation between intensity of arousals with and without movements ($r = 0.59$; $n = 20$, $P < 0.01$), thereby suggesting that some patients tend to develop generally more intense arousals than others.

Arousal Intensity and HR Response

Consistent with previous studies,^{7,22} peak HR occurred on average 7.1 ± 0.9 sec after arousal onset. Figure 6 shows the

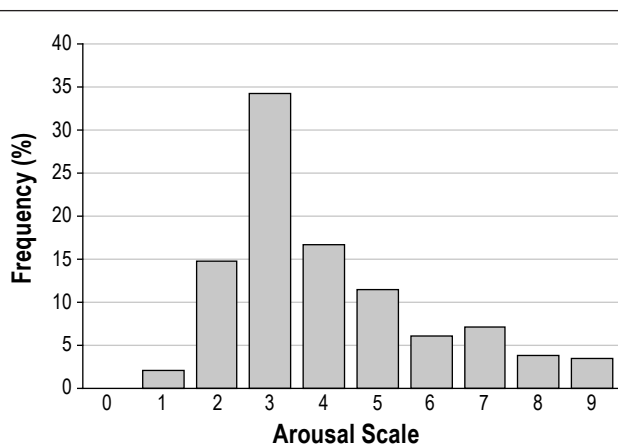


Figure 5—Frequency distribution of arousal intensity.

used to evaluate the effect of other arousal characteristics on HR response to arousal.

RESULTS

The patients were eight female and 12 male adults with a BMI of 31.1 ± 8.8 kg/m² (range, 22–59). Twelve studies were diagnostic (i.e., did not receive continuous positive airway pressure [CPAP]). Nine of these had no OSA (AHI < 5 h⁻¹) and, other than excessive arousals, were normal, whereas the other three had mild to severe OSA (AHI 10–65 h⁻¹). Seven studies involved patients with OSA who underwent a split night study (the first part was diagnostic and the second part was a CPAP titration). In one study, a patient with OSA was on CPAP therapy throughout (treatment study).

relationship between arousal scale and Δ HR in a representative patient. Each dot represents one or more observations. There was considerable scatter at all intensity scales. With sham arousals (scale 0) the standard deviation (SD) of Δ HR was $2.6 \pm 0.9 \text{ min}^{-1}$ with a range of 1.5 to 4.5 min^{-1} among different files. There was no consistent change in the average SD as arousal intensity increased; average SD ranged between 3.4 and 4.7 min^{-1} for scales 2 through 8 in different files with no significant correlation between the two variables ($r = -0.4$; $P = 0.37$). Rather, average SD was related to the number of observations at each scale (Figure 6). Because the background noise appeared to be independent of arousal intensity, the independent effect of arousal intensity was obtained by averaging Δ HR values at each arousal scale (heavy line, Figure 6).

Figure 7 shows the relationship between arousal intensity (scale) and average Δ HR in individual files. Average HR at an arousal scale of 0 (i.e. mostly sham arousals) was very small, but significantly different from 0 ($0.4 \pm 0.3 \text{ min}^{-1}$ ($P < 0.001$)). There was a highly significant linear correlation between the two variables in each file (Table 3). Furthermore, the gain of the relationship varied greatly among subjects, with Δ HR ranging from 3.1 – 11.7 min^{-1} at an arousal scale of 5 (Table 3) and 8 – 22 min^{-1} at the highest scale of 9 (Figure 7). The overall average slope tended to increase as intensity increased (heavy average line, Figure 7), accounting for the slightly negative intercepts of the linear fit in individual files (Table 3). The average relationship was best fitted with a power function: $y = 0.4(x + 1)^{1.56}$; $r = 1.0$).

Other Determinants of HR Response

Table 4 shows the results of correlation analysis between Δ HR and different arousal characteristics in individual files. With straight correlation (left columns), significant correlations were found between Δ HR and arousal intensity in all files, between Δ HR and arousal duration in 16 files, and between Δ HR and the presence of arousal-related leg movement in 17 files. When the relationship between Δ HR and the three variables was examined by multiple regression analysis (right columns), the correlation with arousal intensity remained significant in all files, whereas a significant independent effect of arousal duration remained in only one file and a significant independent effect of an associated leg movement remained in eight files.

Arousal in REM Sleep

Only nine files contained 10 or more REM arousals (eight files contained more than five arousals). The average arousal scale in these nine files was 4.4 ± 1.2 , which was not significantly different ($P = 0.15$) from the average scale of NREM arousals in the same files (3.9 ± 0.4). There was no correlation between the average scales of REM and NREM arousals

Table 2—Characteristics of arousals in different polysomnograph files

File	n	Average scale	Average duration	With movement			No movement		
				n	Scale	Range	n	Scale	Range
1	140	3.8	7.4	24	5.1	1-8	116	3.6	1-9
2	111	5.1	10.0	21	7.2	2-9	90	4.5	0-9
3	85	3.9	7.6	15	6.5	5-9	70	3.4	0-8
4	320	4.0	8.7	81	5.2	2-9	239	3.5	1-9
5	157	4.2	9.3	14	6.2	5-9	143	4.0	0-9
6	80	3.7	7.6	14	4.6	2-8	66	3.5	0-9
7	182	3.4	8.0	52	4.8	1-9	130	2.9	0-8
8	80	3.9	9.2	13	4.2	1-8	67	3.7	0-8
9	100	3.4	8.9	4	3.8	2-4	96	3.4	1-9
10	133	3.9	10.4	15	5.2	0-7	118	3.8	0-7
11	63	5.9	11.0	17	6.7	2-9	46	5.5	1-9
12	167	5.1	9.9	56	6.5	0-9	111	4.1	0-9
13	95	3.9	8.3	16	5.6	3-9	79	3.5	0-9
14	140	3.5	7.4	30	4.0	1-9	110	3.4	1-9
15	146	3.4	7.8	13	5.2	2-9	133	3.3	1-9
16	110	3.5	8.6	22	4.1	3-8	88	3.4	1-9
17	77	3.9	9.6	22	5.1	1-9	55	3.3	1-9
18	128	4.4	8.6	53	5.1	2-8	75	3.9	1-8
19	137	4.0	7.7	7	7.0	3-9	130	3.9	2-9
20	244	4.7	11.4	23	5.7	3-9	221	4.6	2-9
Mean	134.8	4.1	8.9	25.6	5.4		109.2	3.8	
SD	61.2	0.7	1.2	19.6	1.0		49.9	0.6	

n, number of arousals examined. SD, standard deviation.

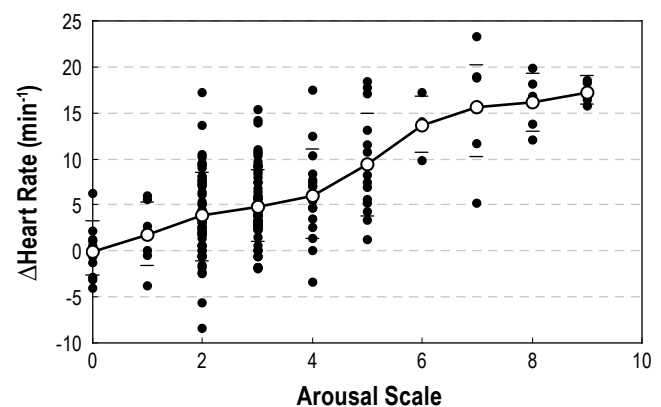


Figure 6—The change in heart rate with arousals of different intensities in a representative patient. Each dot represents one or more arousals. Horizontal bars are \pm standard deviation. The solid line represents the average response.

($r = -0.27$, $n = 9$). Average HR response with REM arousals was $7.6 \pm 3.4 \text{ min}^{-1}$, marginally higher than the response at the same arousal scales in NREM arousals in the same nine files ($5.7 \pm 2.3 \text{ min}^{-1}$, $P = 0.056$).

DISCUSSION

The main findings from this study are: (1) the intensity of arousals can be objectively quantified using the EEG signal's time and frequency characteristics; (2) arousals with and

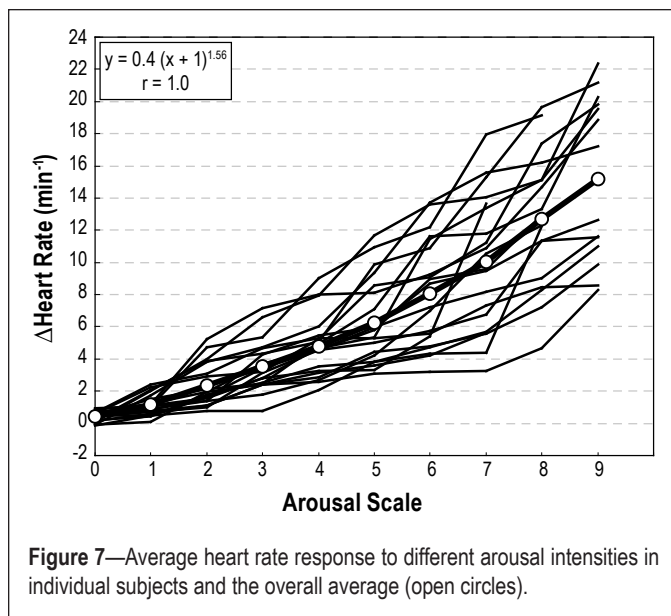


Table 3—Linear regression values of average change in heart rate at each arousal scale versus arousal scale

File	Intercept	Slope	r	P value	HR change at arousal scale of 5
1	-0.7	1.1	0.96	< 0.0001	3.8
2	-0.6	1.3	0.96	< 0.0001	5.0
3	-1.9	2.4	0.97	< 0.0001	9.9
4	0.5	1.8	0.96	< 0.0001	8.1
5	-3.0	2.4	0.94	< 0.0005	5.4
6	0.2	0.7	0.89	< 0.005	3.1
7	0.6	2.1	0.98	< 0.0001	9.4
8	-1.3	1.2	0.84	< 0.005	3.8
9	-1.5	1.5	0.85	< 0.01	3.3
10	0.1	0.7	0.98	< 0.0001	3.6
11	0.0	1.4	0.98	< 0.0001	6.0
12	-0.7	1.7	0.97	< 0.0001	7.1
13	-0.5	1.3	0.99	< 0.0001	6.0
14	1.4	0.8	0.98	< 0.0001	5.3
15	-1.3	2.1	0.96	< 0.0001	8.6
16	-0.6	2.4	0.98	< 0.0001	10.9
17	-1.8	1.6	0.94	< 0.001	4.2
18	-1.2	1.6	0.96	< 0.0001	5.8
19	-0.7	1.0	0.97	< 0.0001	4.4
20	0.2	2.1	0.99	< 0.0001	11.7
Mean	-0.6	1.6	0.95		6.3
SD	1.0	0.6	0.04		2.6

HR, heart rate; SD, standard deviation.

without leg movement are associated with a wide range of arousal intensities, but those with movement are, on average, more intense; (3) average arousal intensity varies considerably among subjects; (4) HR response to arousal appears to be most strongly related to arousal intensity; and (5) the increase in HR for a given arousal intensity varies considerably among subjects.

Evaluation of Arousal Intensity

Although all practitioners familiar with PSGs would agree that arousals that meet AASM criteria vary from barely visible to very intense (Figure 1), in clinical PSG arousals are scored as either present or absent without regard to their visual intensity. Few studies exist on the physiological and clinical consequences of arousal intensity. To our knowledge, there has been only one study in which arousals meeting standard criteria were classified according to their visual EEG intensity, and none that attempted to automate the scaling of arousal intensity. Younes¹² divided arousals into four categories based on the visual appearance of the EEG and found that the ventilatory overshoot following obstructive events increases with visual intensity, suggesting a physiological relationship between the two variables.

The current study is the first to describe a method for automating the measurement of arousal intensity. We found that the WT¹⁵⁻¹⁹ can duplicate the visual scaling of intensity, at least as determined by one expert observer. Validity of this method is supported by the fact that < 1% of arousals scored independently by experienced certified technologists were given a scale of zero and the average scale assigned to sham arousals was 0.4. The highly significant relationship between the scale assigned by this method and the increase in HR (Tables 3 and 4) not only supports the validity of the approach used but it also extends the earlier observation regarding ventilatory response to arousal¹² by showing that the HR response is also related to arousal intensity. Together, the current and previous study¹² suggest that quantifying the intensity of arousals, as well as their frequency, provides additional information that may improve our understanding of sleep disruption. Furthermore, the current approach provides a tool to investigate the clinical consequences of arousals both efficiently and without the inevitable interrater variability that may be expected with visual assessment.

Objective Frequency Correlates of Arousal Intensity

It is difficult to objectively describe the visual correlates of arousal intensity, particularly because arousals that meet the AASM guidelines¹¹ vary greatly, not only in intensity, but also in the manner in which there is a “shift in EEG frequency”. Thus, some arousals may display primarily an increase in alpha rhythm whereas others display primarily an increase in beta rhythm. Often there is an increase in both rhythms, in slow waves, or a change in the primary rhythm from time to time during the same arousal. The analytical method used here made it possible to determine the EEG signal characteristics that correlated with what the scorer’s eye perceived as more intense which, fortuitously or not, turned out to be in strong agreement with the associated physiological responses. The wavelet features that correlated with subjective intensity were the relative increase (compared to prearousal baseline) in the power (P_{avg}) and MABS of frequencies > 16 Hz (D_1 and D_2) and, importantly, < 2 Hz (A_5), the increase in the ratio of absolute value in frequencies > 16 to the values in frequencies between 2 and 16 Hz (D_3 to D_5), as well as the increase in total variation in frequencies > 16 Hz (TV (D_1) and TV (D_2)). Within a given frequency range there were excellent correlations (> 0.85) between average power, MABS, and TV, so that the pattern of change of any of these features with arousal intensity

reflects the changes in other features. Figure 8 shows the changes in one of the features, MABS, in different frequency ranges as a function of visually scaled arousal intensity. All values are relative to prearousal baseline. A value of 1.0 means no change. The main changes with low arousal intensities (1 to 4) are modest increases in amplitude of all frequency ranges. The changes in amplitude in the beta range (D_2) are proportional to those in the alpha-sigma range (D_3), so that the ratio (D_2/D_3) remains unchanged or decreases slightly. Differences among scales 2 to 4 are small and consist mostly of a reduction in amplitude of theta waves (D_4/D_5) and in the ultra-low-frequency range (A_5). Beginning with scale 5, there is a sharp progressive increase in amplitude of beta waves and ultra-low-frequency waves, with little change in alpha amplitude or theta amplitude. As a result, the D_2/D_3 ratio increases progressively. The initial increase in ultra-low-frequency amplitude likely reflects true delta waves occasionally seen during low intensity arousal. The subsequent increase in this frequency range reflects the baseline undulations often seen in intense arousals (Figure 1, bottom panel).

It is important to note that the changes documented here in different frequency ranges do not necessarily reflect EEG changes. Some or all of the increase in beta activity (D_2) and in slow wave activity (A_5) seen with intense arousals may have originated from scalp muscle activity and movement artifacts, respectively. Thus, our findings apply strictly to surface recordings, as performed in clinical studies, and do not necessarily reflect what is happening inside the brain.

Factors That Influence Arousal Intensity

The files examined in this study provided an opportunity to identify some factors that affect arousal intensity. All subjects showed a wide range of arousal intensities. Arousals with or without leg movement covered a wide range of arousal intensities in all subjects (Table 2). However, average intensity was higher in arousals with movement than in those without movement. Arousal scale was also significantly correlated with arousal duration in all files. Because the digital scale reflects average intensity throughout the arousal period, this and the corresponding correlation between visual intensity and arousal duration suggest that absolute arousal intensity reaches higher levels as the duration increases.

An important finding in this study is that the overall average arousal intensity varied considerably among subjects (Table 2). A large number of factors might theoretically account for this variability, including age, sex, predominant sleep stage, medications, comorbidities, and mechanism of arousal. Further study on an appropriately large set of data is required to identify the determinants of average arousal intensity.

Arousal Intensity and Tachycardia

In straight correlations, and in agreement with previous studies,^{7,9} the increase in HR was strongly correlated with arousal duration and the presence of leg movements (Table 4,

Table 4—Correlation between Dheart rate and different arousal characteristics

File	n	Straight correlation			Multiple linear regression		
		Arousal scale	Arousal duration	Leg movement	Arousal scale	Arousal duration	Leg movement
1	140	0.50	NS	0.30	0.44	NS	NS
2	111	0.63	0.37	0.35	0.50	NS	NS
3	85	0.62	0.34	0.62	0.36	NS	0.38
4	320	0.44	0.32	0.26	0.30	NS	NS
5	157	0.69	0.46	0.44	0.52	NS	0.32
6	80	0.27	NS	NS	0.27	NS	NS
7	182	0.69	0.36	0.46	0.54	NS	0.19
8	80	0.40	0.37	0.29	0.24	NS	NS
9	100	0.34	NS	NS	0.35	NS	NS
10	133	0.51	0.32	0.30	0.38	NS	0.18
11	63	0.73	0.41	0.27	0.63	NS	NS
12	167	0.76	0.63	0.47	0.55	0.27	NS
13	95	0.61	0.29	0.48	0.49	NS	0.32
14	140	0.30	NS	0.18	0.24	NS	NS
15	146	0.60	0.28	0.35	0.50	NS	0.18
16	110	0.54	0.30	0.22	0.45	NS	NS
17	77	0.56	0.40	0.49	0.38	NS	0.31
18	128	0.54	0.30	0.22	0.54	NS	NS
19	137	0.50	0.26	0.40	0.40	NS	0.27
20	244	0.60	0.36	NS	0.51	NS	NS

n, number of arousals examined. Critical r is between 0.11 and 0.20 depending on number of arousals. NS, not significant.

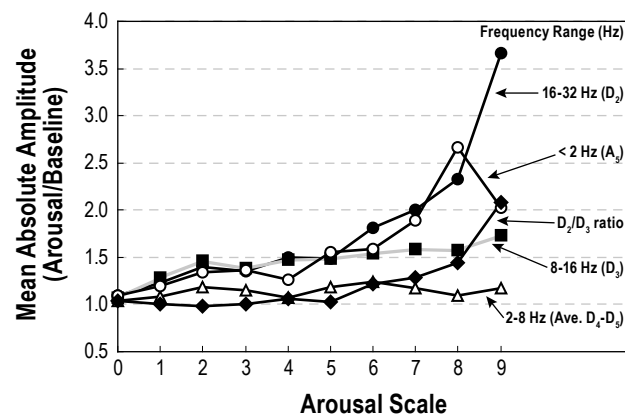


Figure 8—Changes in mean absolute amplitude (MABS) in different frequency ranges with different visually scored arousal intensities in the training file. The ratio of MABS (D_2) to MABS (D_3) is also shown (D_2/D_3) and this approximates the ratio of amplitude in the beta frequency range over the amplitude in the alpha frequency range. All values represent the change relative to prearousal baseline so that a value of 1.0 reflects no change from baseline.

left). However, the correlation between Δ HR and arousal intensity was considerably stronger in all subjects (Table 4, left). When all variables were examined by multiple regression, the correlation between Δ HR and arousal duration disappeared in all but one subject and a weak correlation remained between Δ HR and leg movement in only eight subjects (Table 4, right).

These findings suggest that Δ HR primarily reflects arousal intensity and that the earlier correlations observed with arousal duration⁹ and leg movement⁷ are largely secondary to their association with arousal intensity.

Although there was an excellent correlation between arousal intensity and Δ HR in each subject (Tables 3 and 4), the slope of the relationship varied considerably among subjects (Table 3). For a midintensity arousal (scale 5), average increase in HR ranged 3.1–11.7 min⁻¹. Differences between subjects may reflect different arousal responses and/or different HR responses to a given arousal stimulus. Thus, a high HR response slope may be due to a blunted cortical response to arousal stimuli or to an exaggerated HR response to arousal stimuli. There was no significant correlation between average arousal intensity in the different subjects and the corresponding HR response to arousal, whether the HR response to arousal was expressed as the slope of the relationship ($r = 0.027$) or the HR response at a scale of 5 ($r = 0.034$). Had the differences in slopes reflected different cortical responses to arousal stimuli, lower average arousal intensity in subjects with a high slope, and *vice versa*, would have been expected. This was not the case, thereby suggesting that the different slopes reflect different HR responses to arousal stimuli.

Mechanism of Association Between Arousal and Tachycardia

It is generally accepted that arousal from sleep is itself responsible for the associated tachycardia, hypertension, and increase in ventilation by virtue of the associated autonomic activation. This notion is based on the observations that the increase in these variables with arousal is greater than the difference between their sleep and fully awake values^{5,23,24} and on direct^{5,25} and indirect^{26,27} evidence of increased sympathetic discharge. Although these findings clearly indicate that arousal is associated with an active process that leads to activation of the sympathetic system, there is, to our knowledge, no evidence that such active process is the result of arousal, *per se*, as opposed to being the result of the stimulus that caused the arousal. Our data can be interpreted either way. Thus, it may be argued that a more intense arousal results in a stronger activation state, or that a more intense arousal is the result of a stronger arousal stimulus that caused the stronger activation state. Evidence exists to suggest that at least a component of the tachycardia is related to the stimulus that caused the arousal and not to arousal *per se*. Every stimulus that causes arousal when given with sufficient intensity causes tachycardia or hyperpnea (depending on which variable was examined) when given with subthreshold intensity. Thus, auditory stimuli that cause cortical arousal when delivered with threshold intensity are associated with an increase, albeit smaller, in HR when delivered in subthreshold intensities.²⁸ K complexes are associated with tachycardia even when they are not followed by cortical arousal.⁷ Obstructive events that are terminated spontaneously without arousal,²⁹ or are terminated deliberately before cortical arousal (by increasing CPAP),²² are followed by graded tachycardia in proportion to the severity of the preceding obstructive event. Although sympathetic nerve discharge is high at the end of obstructive events, the increase in discharge begins long before the arousal and is in fact abruptly terminated when arousal occurs.²⁵ Periodic

limb movements that are occasionally associated with arousal, tachycardia, and hyperpnea are also associated with tachycardia and hyperpnea when arousal is absent. Even spontaneous arousals are preceded by an increase in HR,⁷ indicating that the unknown stimulus can independently increase HR. It would seem reasonable to expect that when an excitatory stimulus (e.g., noise, asphyxia, pain) that is too weak to elicit cortical arousal results in tachycardia, the HR response would be greater when the stimulus is delivered at higher, threshold levels. By extension, a stronger suprathreshold stimulus should be associated with even more tachycardia and concurrently result in a more intense arousal. By this interpretation, arousal is not the mediator of the “fight or flight” response but is a component of the survival mechanism; the cardiopulmonary component prepares the organism for physical action while the arousal component allows the organism to deal more intelligently with threats. More studies are needed to determine the independent effect of arousal.

Limitations

The training file used to generate the automatic scales was based on the visual assessment of only one scorer. It is, however, reassuring that only one arousal of 2,695 arousals scored by the sleep technologists was assigned a scale of 0, and the scale given to sham arousals was on average 0.4. The excellent correlations between the automatic scales and HR responses also support the validity of the initial visual assessment, during which the scorer was blinded to HR. The analytical approach described here makes it possible for intensity scales to be generated based on custom training files generated by other investigators, or by a committee.

CLINICAL IMPLICATIONS

The clinical significance of arousal intensity was not established in this study. It is possible, however, that more intense arousals are more disruptive to sleep. As such, inclusion of arousal intensity among other variables that are commonly used to evaluate sleep quality (e.g., sleep efficiency, total sleep time, arousal index) may help explain instances of excessive daytime symptoms when other measures of sleep quality are relatively normal, and *vice versa*. It is worth noting that the most common arousal scale (scale 3) is associated with only small changes in HR (Figure 7) so that a large number of low intensity arousals may not be so clinically significant. Furthermore, to the extent that the slope of the relationship between HR and arousal intensity may reflect a more labile cardiovascular response to arousal stimuli, the slope may offer some predictive value for the development of cardiovascular complications. These possibilities require further study.

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