

Cardiac activation during arousal in humans: further evidence for hierarchy in the arousal response

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Abstract

Objectives: One major subject of discussion in sleep studies is whether bursts of K-complexes (K-bursts) and delta waves (D-bursts), expressions of a subcortical arousal, truly reflect an arousal response during sleep. To address this question we studied the changes in heart rate (HR) during spontaneous arousals in healthy subjects.

Methods: Twenty-seven healthy adults were examined. Arousals were graded in 4 levels, including the standard definition of a microarousal (MA), phases of transitory activation (PAT), D-bursts and K-bursts. HR was analyzed for 10 beats before and 20 beats during arousal. EEG spectral analysis was performed for all types of arousals, including in the analysis the 20 s period preceding the actual event.

Results: Each type of arousal was associated with HR changes consisting of a tachycardia followed by a bradycardia. Changes were more pronounced during MA and PAT. Detailed analysis of the HR response showed that HR always increased before MA and PAT onset, associated with a rise in delta, theta and fast EEG activities, and suggesting a cerebral activation.

Conclusions: Our data suggest that such subcortical arousals represent a real arousal response inducing cardiac activation similar to that found during MA and PAT. During MA and PAT, a rise in HR appears before the onset of the actual arousal associated with an increase in EEG slow and fast activity. The link between EEG and HR variation during MA and PAT and the fluctuations in HR during subcortical arousal suggest a continuous spectrum in the arousal mechanisms, starting at the brainstem level and progressing to cortical areas. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Current models of alertness regulation suggest that daytime sleepiness depends on the duration of prior sleep and on the presence of sleep fragmentation. Although sleep reduction produces an increase in sleepiness (Carskadon and Dement, 1982), several studies have shown that it is not so much the amount of sleep but the frequency of arousal that is important in the recovery functions of sleep (Williams et al., 1964; Stepanski et al., 1984; Bonnet, 1985, 1987; Philip et al., 1994; Roehrs et al., 1994). Evidence in favor of this hypothesis also comes from studies conducted in patients with sleep disorders such as obstructive sleep apnea (OSAS) (Roehrs et al., 1989) or periodic leg movements (PLMS) (App et al., 1990), in whom arousal density is the best predictor of daytime somnolence.

When we consider the processing of arousal response in clinical studies, definition of what constitutes *arousal* is critical, and criteria of detection and scoring are still controversial. Many studies have focused on microarousals (MA) (American Sleep Disorders Association, 1992; Boselli et al., 1998) and phases of transitory activation (PAT) (Schieber et al., 1971; Collard et al., 1996) corresponding to the largest periodical component of arousal response in humans. They are characterized by a combination of EEG desynchronization, appearance of alpha and low voltage EEG fast rhythms, and tachycardia, and thus they translate a '*cortical arousal response*' induced by endogenous or exogenous stimuli.

With the inclusion of more sophisticated methods of arousal detection, recent studies (Halasz and Ujjaszai, 1991; Halasz, 1993, 1998) opened the discussion of whether synchronized EEG sleep patterns might represent a form of arousal response in humans. By application of auditory stimuli, the authors found that stimuli-induced arousals consisted of transient EEG patterns, i.e. K-complex or delta bursts, without subsequent EEG desynchronization

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and associated with autonomic activation. These events, called ‘subcortical or autonomic arousal’ (Pitson et al., 1994; Martin et al., 1996), are intrinsic components of human sleep, appearing spontaneously as phases A1 of the cyclic alternating pattern (CAP) (Terzano et al., 1985; Parrino et al., 1998) and expression of levels of greater or lesser arousal.

To understand the exact influence of ‘subcortical arousals’, one must answer the question ‘Do K- or delta bursts directly cause sleep disruption; and are K- and delta bursts primary forms of an arousal response?’ There is now evidence supporting the concept of a common component in both MA and subcortical arousals in the ability to protect sleep against exogenous and endogenous stimuli (Terzano et al., 1985; Halasz and Ujjaszsi, 1991; Halasz, 1993). Responses to auditory stimulation in humans induce vasoconstriction (Williams et al., 1964), blood pressure variations (Rees et al., 1994), and increase in ventilation (Carley et al., 1996), concomitant with bursts of K-complexes or delta waves. Moreover, delta bursts occur in patients with upper airway resistance syndrome (Lofaso et al., 1998) and OSAS (Berry and Gleason, 1997) as an arousal response to airflow limitation.

Despite these findings, there is still controversy as to whether subcortical arousals truly reflect an arousal response. The most straightforward empirical method to determine an arousal response is to determine if concomitant phenomena occur in motor or autonomic systems. Measuring heart rate variation during a transitory event is one such approach. If the hypothesis that subcortical events are an arousal response from sleep is correct, the HR variation found during these arousals should be the same as that occurring during MAs and PATs. This study was undertaken to characterize the phenomenon of heart rate variations as indicators of the type of arousal response, i.e. cortical and subcortical arousals, in healthy subjects. A second goal was to obtain a more precise characterization of the EEG activity by means of spectral analysis to see whether EEG changes undetected by visual scoring could be seen before arousal onset and affect the cardiac response.

2. Methods

2.1. Subjects

The subject sample was comprised of 27 healthy subjects, 10 men and 17 women, aged 28.8 ± 9.7 years (range 19–55 years). Subjects underwent a medical evaluation, including medical, psychiatric and sleep history, and a physical examination. They had no life history of cardiac disorder, and all were in good medical health. None was using medication that could affect heart rate, blood pressure or sleep structure. All volunteers participated in a 3 night sleep protocol, with the first night used for adaptation to laboratory conditions. Sleep data of the third night were used in the analysis.

2.2. Nocturnal sleep recording

Polysomnography included 5 EEG channels, an electrooculogram, an electromyogram of chin muscle and an electrocardiogram (ECG) recorded from a standard D2 lead.

Sleep stages were visually scored according to the criteria of Rechtschaffen and Kales (1968) using a 20 s epoch, and standard sleep parameters were computed for total sleep.

Recordings were analyzed with the ERA[®] software package (Phitools[®], Grenoble, France) for polysomnography and spectral analysis.

2.3. Data analysis

2.3.1. Visual EEG scoring

Arousals were categorized into 4 groups (Fig. 1) according to previously published criteria:

1. Delta bursts (D-bursts) as a sequence of delta waves, exceeding by at least 1/3 the amplitude of background activity in stages 3 and 4, and detectable on at least 3 EEG derivations (Parrino et al., 1998).
2. K-bursts as a sequence of two or more K-complexes without alpha activity, detectable on at least 3 EEG derivations. The K-complex was defined as a negative deflection, followed by a positive component with a minimum duration of 0.5 s, and a minimum peak-to-peak amplitude of 75 μ V (Paiva and Rosa, 1991).
3. Microarousal (MA) was defined according to ASDA criteria (American Sleep Disorders Association, 1992) as a return to alpha, theta or fast frequency, well differentiated from the background EEG activity. The duration was, however, extended to include MA lasting ≥ 1.5 and < 3 s (Martin et al., 1997). MA detection criteria for rapid eye movement (REM) sleep included an increase in submental EMG amplitude, in addition to a shift in EEG activity.
4. According to the criteria of Schieber et al. (1971), phases of spontaneous transitory activation (PAT) were defined as an acceleration of the background EEG activity with decreasing amplitude and apparition of alpha and beta activity associated with concomitant increase in EMG, appearance of muscular artifacts, acceleration of heart rate and, during REM sleep, transitory disappearance of rapid eye movements.

All 4 types of arousal were determined with all polygraphic data to define as accurately as possible the start of the event. An arousal index was calculated by dividing the number of each arousal type by the total sleep time.

For 10 subjects, arousal scoring was performed twice by the same scorer (E.S.), and the intrascore reliability was between 90% for K- and D-bursts and 96% for MA and PAT.

2.3.2. Heart rate analysis

The cardiac effect of arousing stimuli was quantified for

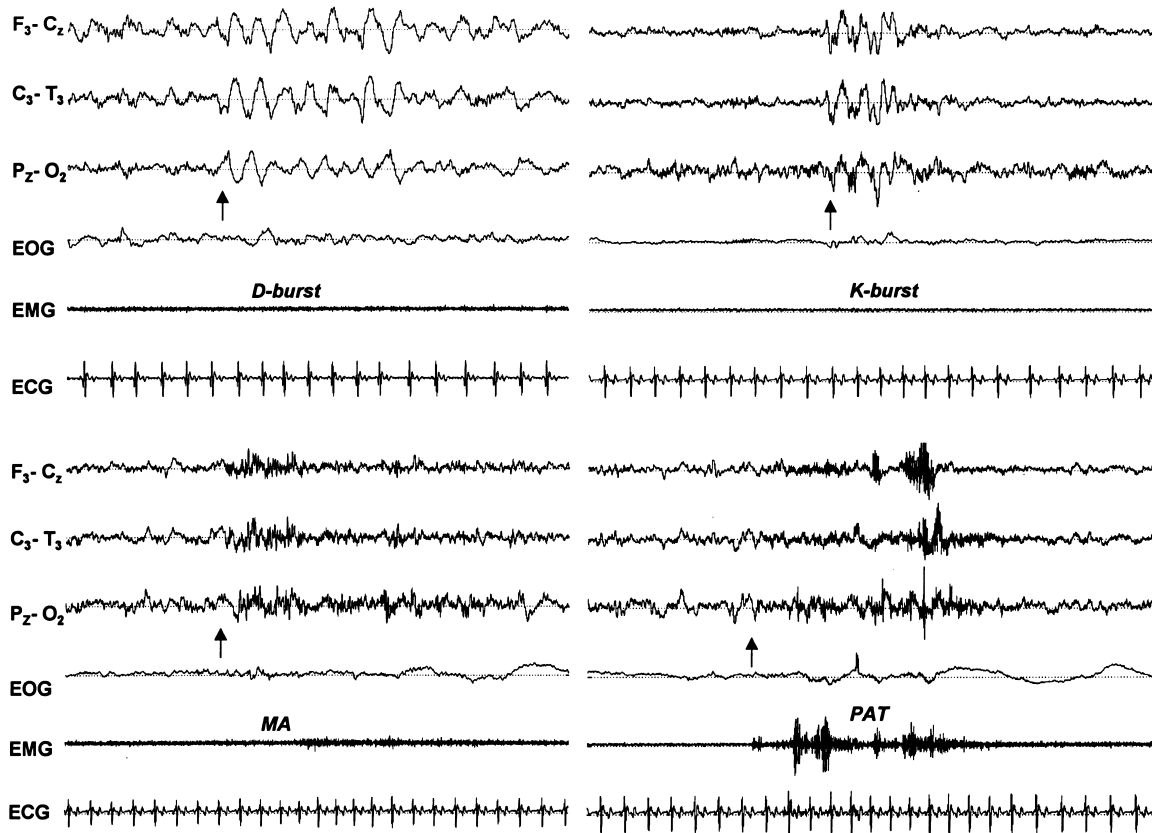


Fig. 1. Polygraphic examples of the 4 arousal types visually scored. Note that the timing of arousal was followed by a tachycardia and later bradycardia. Heart rate changes were less evident during D- and K-bursts than during microarousals (MA) or phases of transitory activation (PAT).

each arousal type throughout the sleep study. Arousal events during which the heart rate (HR) was affected by movements or artifact were not included in the analysis. The mean number of events for which HR fluctuations were measured was 265 ± 58 .

Pre-arousal HR values were measured during 10 beats occurring prior to arousal onset, and the event-related HR fluctuations were calculated during 20 beats after the arousal onset. Analysis was done for arousals separated for a minimum of 10 s in the same or contiguous sleep stages, and events were portioned throughout the sleep study. For HR analysis, QRS peaks were detected, and then the HR was calculated directly from the R-R interval.

As an index of sympathetic activation, we measured the ratio of the highest HR of the 20 beats after the onset of arousal over the lowest one recorded before arousal onset (HR ratio). The pattern of HR response (HR pattern) was calculated by examining the HR response during arousal. Measurements of HR were normalized by subtracting the mean value obtained over the 10 beats immediately preceding the arousal onset from each HR value before and after the onset of the arousal.

2.3.3. EEG spectral analysis

To test the hypothesis that subtle EEG changes may occur before the arousal onset, we measured EEG spectra bands

for 20 s before the arousal onset. Fast Fourier transform (FFT) was performed on the F3-CZ lead in 21 subjects, and on the C3-A2 lead for the others. EEG power spectra were computed for 2 s non-overlapping windows using a Hanning window. Seven frequency bands were defined: delta (1–4 Hz), theta (4.5–7.5 Hz), alpha (8–11 Hz), sigma (11.5–15 Hz), β_1 (15.5–18 Hz), β_2 (18.5–35 Hz), and gamma (35.5–45 Hz). For each band, the power within each 2 s window was then normalized by expressing their values as a percentage change from the mean 20 s pre-arousal value. This method was used in order to evaluate the magnitude of potential changes within a specific frequency band over time, and to compare, albeit individual differences, the changes in activity to that of other frequency bands. Analysis was done in 92% of the scored events after rejection of events showing EEG artifacts during the 20 s period of spectral analysis.

2.3.4. Statistical analyses

Data were expressed as means \pm SD and as percentage change \pm SD from baseline. Comparison of spectral EEG and HR changes for each type of arousal was made using a Wilcoxon paired signed-rank test with Bonferroni correction for multiple comparisons. One-way analysis of variance was used to detect differences in sleep stages upon cardiac and spectral EEG variables. If significance was found, a

post-hoc analysis was used to determine the source of significance. Significance was taken as a *P* value of ≤ 0.001 . All statistical analyses were performed with the SPSS statistical software package (SPSS for windows, 7.0, SPSS Inc., Chicago, IL).

3. Results

3.1. Polygraphic data and EEG arousal scoring

Details of sleep parameters and visual arousal scoring are given in Table 1. All subjects had polysomnographic parameters within normal limits for adults, and the 4 types of arousals were recorded in all patients. The total number of arousals, however, varied between subjects, with an average number of scored arousals of 269.5 ± 48.0 . MA represented 36.1% of the total events, and PAT 21.1%; 16.2% of arousals were defined as D-bursts, and 26.6% as K-bursts, occurring mostly in stage 2 and slow wave (SWS) sleep. MA and PAT occurred more frequently in light sleep and REM sleep, with only 2.1 and 6.6%, respectively, during deep sleep. Both arousal types tended to be longer in stages 3 and 4 (16.5 ± 5.3 s) than in light (12.4 ± 2.7 s) and REM sleep (10.9 ± 1.6 s) ($P < 0.0001$). The relation between the occurrence of PAT and hypnograms showed that in deep sleep 90% of PAT induces full awakening.

Table 1
Sleep parameters and polygraphic characteristics of scored arousals^a

	Mean	SD	Range
Total sleep time (min)	487.5	33.8	400–537
Stage 1 (%)	7.6	2.6	3.3–14.7
Stage 2 (%)	50.7	5.7	37.7–63.8
Stages 3 + 4 (%)	17.3	5.8	8.2–34.2
Stage REM (%)	24.3	3.5	18.3–32.2
Sleep efficiency (%)	97.0	2.0	93–99
D-burst index (n/h)	5.5	3.4	0.9–9.2
K-burst index (n/h)	9.1	4.8	2.6–24.1
MA index (n/h)	6.9	5.1	2.9–17.9
PAT index (n/h)	6.8	3.6	1.4–16.9
D-burst duration (s)	5.7	0.6	4.6–6.8
K-burst duration (s)	3.9	0.3	3.2–4.6
MA duration (s)	8.3	2.2	4.0–12.2
PAT duration (s)	12.3	2.3	9.1–19.2
D-burst HR ratio (b/s)	1.17	0.07	1.07–1.41
K-burst HR ratio (b/s)	1.20	0.08	1.09–1.44
MA HR ratio (b/s)	1.31	0.10	1.19–1.51
PAT HR ratio (b/s)	1.46	0.11	1.30–1.64

^a D-burst, bursts of delta waves; K-bursts, bursts of K-complexes; MA, microarousal; PAT, phases of transitory activation.

3.2. Cardiac response analysis

Fig. 2 demonstrates the overtime evolution of heart rate for each type of arousal during the analyzed period of 30 heart beats. For each arousal, HR varied significantly

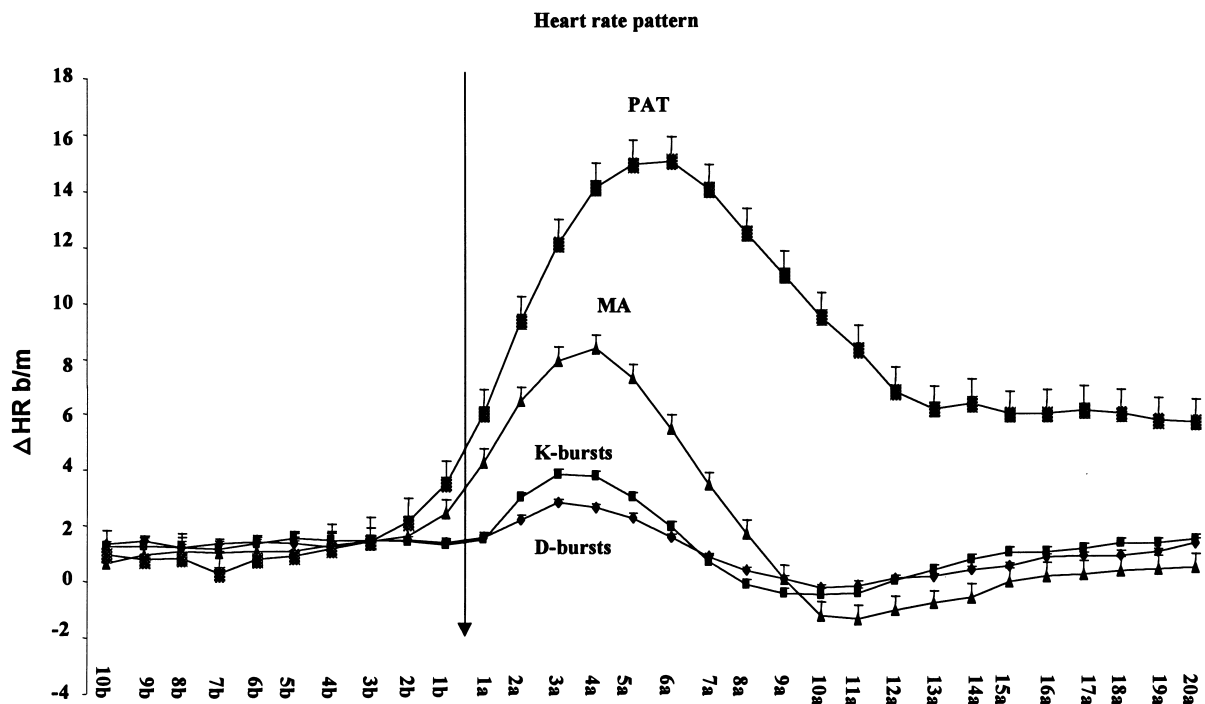


Fig. 2. Overtime heart rate changes in pre-arousal and post-arousal periods for the 4 types of arousal. The arrow indicates the onset of the arousal. For all 4 arousal types a typical pattern of heart rate response was seen, consisting of a tachycardia from the first to the sixth to seventh beats followed by a bradycardia. During MA and PAT, the rise in HR started at the first and second beats before the onset. The bradycardia was less evident during PAT, for which HR does not return to pre-arousal values.

compared to pre-arousal levels, consisting of a tachycardia followed by a bradycardia. While the pre-arousal mean HR value was identical for all types of arousal, the MA and PAT induced stronger tachycardia than K- and D-bursts. As reported in Table 1, the HR ratio rose from average values of 1.17 ± 0.07 and 1.2 ± 0.08 in D- and K-bursts, respectively, to values of 1.31 ± 0.10 and 1.46 ± 0.11 during MA and PAT, respectively ($P = 0.0001$), with the significantly highest rise during PAT.

Analysis of time-dependent fluctuations in HR during arousal showed differences between arousals during the post-arousal period. Compared to the first 5 beats preceding arousal, the pattern of HR response was similar for the D- and K-bursts with a significant rise in HR starting at the first two beats after the arousal onset and persisting until the fourth beat ($P < 0.001$). Then a bradycardia started, reaching significance after the eighth beat ($P < 0.0001$).

MA and PAT were characterized by a different pattern, consisting of an increase in HR starting two beats before the visual onset, reaching a peak between the fourth and sixth beats, and then progressively falling. Compared to the pre-arousal period, the HR rise of MA was significant from the second beat before arousal onset to the sixth beat after onset ($P \leq 0.001$), followed by a significant bradycardia from the tenth beat. During PAT, the rise also began at the first two beats before arousal onset but reached significance only at the first beat before onset. The HR rise then persisted until the eleventh beat ($P < 0.001$). Afterwards a fall was recorded, but the HR values persisted significantly higher ($P < 0.0001$) compared to pre-arousal values.

To consider the possible effect of sleep stage on the dependent variables, we analyzed the data of MA and PAT HR pattern response during light sleep (stages 1 and 2 NREM sleep), slow wave sleep (stages 3 and 4 NREM

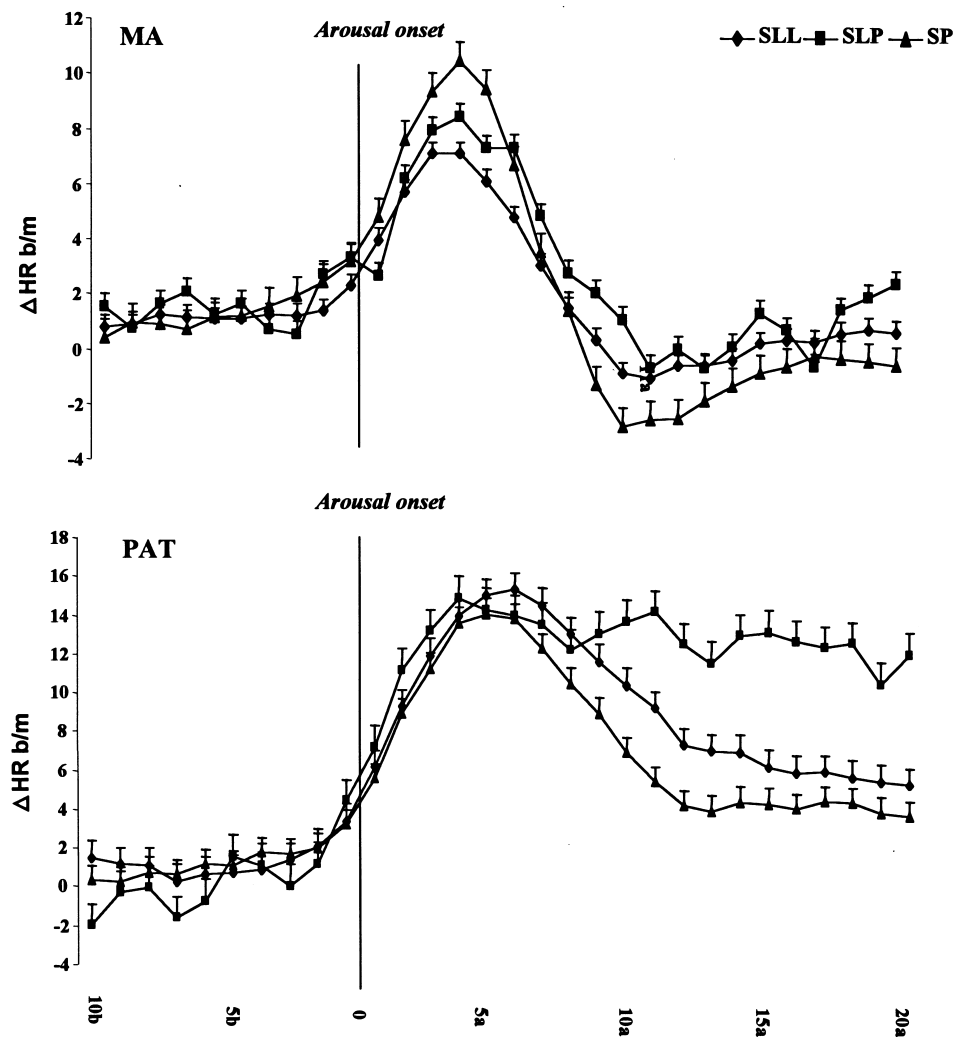


Fig. 3. Temporal evolution of HR fluctuations during light (SLL), slow wave (SLP), and REM sleep (SP). For MA events, the only significant difference was the greater tachycardia during REM sleep compared to other sleep stages. For PAT, the HR evolution was similar during light and REM sleep. During slow wave sleep, as a consequence of frequent transitions to the awake state and to longer PAT duration, the HR rise persisted in the post-arousal period.

sleep), and REM sleep. As shown in Fig. 3, there was no difference in HR pattern for MA during light, slow wave and REM sleep for both pre-arousal and post-arousal periods. Moreover, even though the HR ratio was greater during REM sleep (1.33 ± 0.10), the differences with light (1.30 ± 0.10) and slow wave sleep (1.29 ± 0.16) did not reach statistical significance. For PAT, comparison analysis demonstrated that sleep stage had a significant effect on HR ratio with significantly greater value in slow wave sleep than in REM sleep (1.54 versus 1.42) but the difference did not reach statistical significance ($P = 0.04$). As shown in Fig. 3, in slow wave sleep the HR pattern was different reaching a higher level and declining less and more slowly compared to other sleep stages ($P = 0.001$).

3.3. Spectral EEG analysis

Data in Fig. 4 show the mean profiles of EEG spectra in delta, theta, alpha and beta activities 10 s before arousal onset. For D- and K-bursts, the relative EEG power showed no significant change in any frequency band across the 20 s period analysis. Nevertheless, D-bursts were accompanied by a small and non-significant rise in theta and beta activity

2 s before the arousal onset. For MA and PAT, the pattern of EEG spectra changes was remarkably stable up to window 2, at which point both arousals displayed a clear EEG change. Delta and theta activities rose significantly during the 2 s before arousal onset, associated with a concomitant oscillation in fast activities. Although the pattern was similar, the two types of arousal differed in the magnitude of EEG changes. For MA, delta, alpha and beta activity increased significantly ($P = 0.0001$) 2 s before arousal onset. For PAT, EEG activity changed for all analyzed spectra, with a more pronounced rise in fast activities ($P < 0.0001$).

Spectral EEG analysis for MA and PAT during light, slow and REM sleep revealed that EEG changes before arousal onset were present only during NREM sleep. For MA, a rise in theta and delta activities was noted, starting 4 s before but reaching significance only 2 s before the MA onset (theta activity, $P = 0.0001$; delta activity, $P = 0.0001$). The increase on slow power was associated with a concomitant rise in alpha frequency ($P = 0.0001$). Similar changes were found before PAT onset, affecting delta ($P = 0.0001$), theta ($P = 0.0001$) and alpha activity ($P = 0.0001$). During REM sleep, the EEG response was blunted with no significant

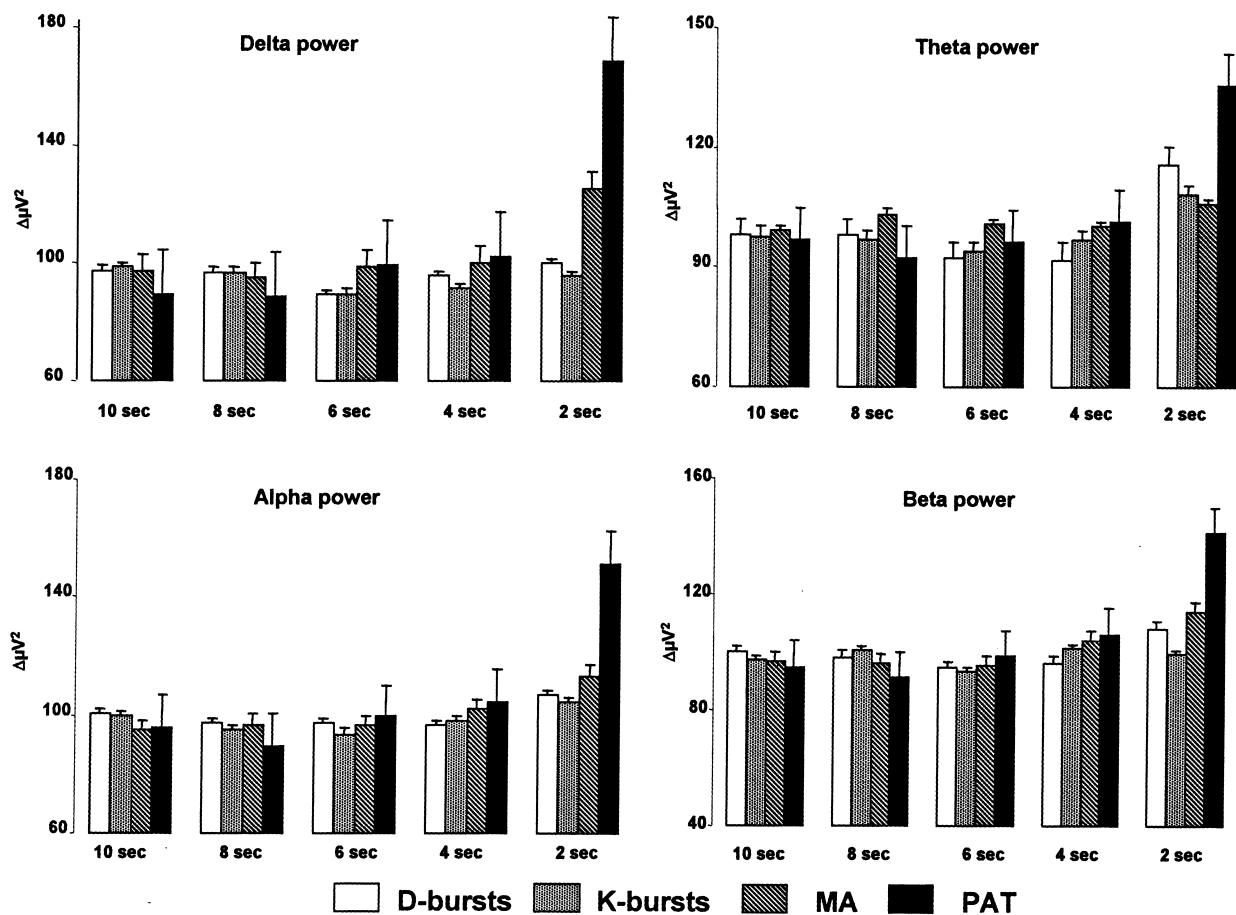


Fig. 4. Spectral EEG data (means \pm SEM) for the 10 s period prior to the onset of arousal. No changes in slow and fast activities were seen for D- and K-burst arousals. The appearance of MA and PAT was preceded by an increase in slow and fast activities, occurring 2 s before the onset.

change in slow frequencies compared to mean pre-arousal values. Compared to the pre-arousal period, a rise in beta and gamma power was observed, but differences did not reach significance ($P = 0.06$).

4. Discussion

The main goal of the present study was to determine whether cardiac changes occur during subcortical arousal, that is, during K-complex and delta bursts, and whether the pattern of variation was similar to that found during cortical arousals, i.e. MA and PAT. Using HR variation over time we found a significant change in HR during K- and D-bursts consisting of a tachycardia followed by a bradycardia, reflecting the changes seen during MA and PAT but to a lesser degree. Moreover, during MA and PAT a HR rise precedes the onset of the actual arousal mirrored by a shift in delta and fast activities in the 2 s pre-arousal period. Thus, subcortical arousals might represent the primary form of arousal response in sleep, preceding the appearance of a cortical arousal and implicating a common mechanism in the human arousal response.

Consistent with the models of cyclical changes in arousal level during sleep by Terzano et al. (1985) and Halasz (Halasz and Ujjaszsi, 1991; Halasz, 1993, 1998), we found that, whatever the type of arousal, the occurrence of the phasic events entrains oscillations in HR of a specific sequence pattern, with a maximal cardioactivation during the first 4–5 beats, and a bradycardia thereafter. Increased responsiveness of the arousal system would affect autonomic responses, since HR oscillations increased from D- to K-bursts, and from those to MA and PAT, being proportional to the associated EEG desynchronization. These results are comparable to those recently reported by Ferini-Strambi et al. (2000) and Ferri et al. (2000) showing higher sympathetic activity during phase A of the cyclic alternating pattern. Again these data are consistent with the notion that subcortical arousal translates a phase of greater arousability during sleep (Halasz and Ujjaszsi, 1991; Halasz, 1993), and may represent the primary form of arousal response in humans.

The time course analysis over 30 beats as opposed to just a single value provides a more detailed description of the shape of cardiac response for each arousal, and differences between arousals could be identified. Inspection of Fig. 2 clearly shows that despite the common features, statistical differences between arousals in the timing of cardiac response could be identified both for the pre-arousal and post-arousal periods. In the post-arousal period, a progressive fall in HR over the seventh to eighth beats after the arousal onset was present irrespective of arousal type. The inhibitory effect persisted following the arousal termination, since the heart rate remained reduced for several beats and then gradually recovered. This cardiac behavior may reflect a feed-back effect of arousal showing an 'inertial' effect

once the arousal stimulus is removed. An alternative hypothesis is that arousal and post-arousal periods produce a modulation of the autonomic system reflecting the activation–deactivation neuronal oscillations intrinsically regulated by the cyclic arousability of the sleepy brain (Schnall et al., 1999; Sforza et al., 1999; Ferri et al., 2000).

Although an inhibitory effect on HR was present for all types of arousal, including subcortical arousals, some differences were found in MA and PAT patterns. Instead of decreasing during PAT, as it did during MA, HR remained higher during PAT and declined more slowly. This pattern of cardiac response was present in all sleep stages, but was more evident in slow wave sleep (Fig. 3). Although many factors could influence this cardiac inhibitory mechanism during PAT, it is probable that the higher level of HR during PAT, its exponential evolution, and the slower decline reflect the associated body movement and the transition to an awake state as observed by the analysis of hypnograms.

Further insight comes from the timing of cardiac changes at the onset of visual arousal. Cardiac activation during D-bursts was similar to that of K-bursts with a latency in the cardiac activation of about one to two beats. The HR change during MA was similar to that of PAT with cardiac activation appearing prior to actual arousal, one to two beats preceding the arousal onset.

To understand the potential mechanisms of cardiac and cerebral coupling during arousal, we attempted to clarify the mechanisms of the cardiac activation during arousal by means of EEG spectral analysis. Our analysis of EEG activity before MA and PAT in NREM sleep revealed an overall change in cortical EEG activity which was consistent across subjects. The most consistent and robust response was seen in slow frequencies and in alpha and beta power, which significantly increased about 2 s before the onset of the visually scored arousal. Our analysis across the 20 s prior to arousal onset indicates that the delta power is always increased before arousal, and this change, nearly identical in MA and PAT, is associated with an initial autonomic response. This EEG response and the coupled pre-arousal HR rise may be indicative of a 'synchronized subcortical arousal' just preceding the cortical activation. This concept is in line with previous studies reporting that sympathetic activity precedes the initiation of a sleep event. Bonnet and Arand (1997), by analyzing HR spectral analysis, conclude that a heart rate acceleration precedes the visually detected arousal. Moreover, Muzet and Michel (1977) reported that PAT are preceded by an adjustment of the heart rate starting before the onset of the event, supporting the notion that variation in sympathetic activity precedes variation in the visual EEG activity. Potentially relevant to these observations are studies conducted in patients with OSAS (Rees et al., 1994; Lofaso et al., 1998) or periodic leg movements (Sforza et al., 1999; Winkelman, 1999) in whom a cardiovascular activation is associated with the appearance of slow wave bursts in spectral analysis.

The different HR response patterns and the EEG changes

occurring during arousal led us to propose a model of arousal response that described the progression of EEG and cardiac activation. In our group we noted that the variations in EEG slow activity and HR were coupled during all types of arousal. For example, a tachycardia and bradycardia were detected when D- and K-bursts were scored, and an increase in slow EEG activity occurred before the onset of MA and PAT with a concomitant rise in heart rate. Therefore, it can be postulated that these two responses may be driven by a common generator, presumably the brainstem systems. The continuous spectrum of arousal response from subcortical to cortical arousal may be explained if we consider the rhythmic brainstem activity (Koepchen et al., 1975; Langhorst et al., 1975; Lambertz and Langhorst, 1998), the stimuli transmission and the differential arousal threshold in cerebral areas (McGinty et al., 1979; Lijowska et al., 1997; McNamara et al., 1998). Substantial physiological evidence has reinforced the concept of the existence of a brainstem arousal center known since the 1950s (Moruzzi, 1954), in which coupling of autonomic and cerebral rhythms occurs (Berlucchi, 1997). Neurons of the reticular system and of the brainstem areas present an oscillatory rhythmic activity that is coupled with vascular, cardiac, respiratory and EEG delta-theta rhythms (Oakson and Steriade, 1982). These neuronal and autonomic rhythms indicate a functional link within brainstem structures that is able to adjust the system in case of an altered internal or external situation (Lambertz and Langhorst, 1998). Moreover, it has been demonstrated in experimental and human studies that brainstem neurons have a lower arousal threshold compared to cortical areas (McGinty et al., 1979; McNamara et al., 1998).

On the basis of these findings we suggest that when an arousal stimulus occurs during sleep, as a consequence of lower arousal threshold, brainstem centers may be activated firstly, driving tonic neuronal activity and inducing the appearance of a coupled rhythm expressed in tachycardia and synchronized EEG arousal. Afferent information from these neuronal structures is carried to the central nervous system leading to the EEG cortical changes visible in MA or PAT. Since the arousal threshold is higher in rostral cerebral areas (McGinty et al., 1979) when the arousal stimuli is of lower intensity or when sleep is deeper, the cortical areas might not be activated and consequently the arousal response might be translated only in autonomic activation and bursts of delta and K-bursts. When the stimuli intensity is greater or during light sleep, a delayed cortical activation would be present, determining the transition from slow to fast desynchronized EEG activity, i.e. MA and PAT, and an additional rise in HR. This hypothesis is in line with the Halasz model (Halasz, 1993), favoring the concept of a continuous spectrum in arousal response beginning with the signs of brainstem activation, that is, cardiac activation and D- and K-bursts, and ending with cortical EEG desynchronized activation. Some evidence in favor of this hypothesis comes from clinical studies showing that EEG synchronization rather than desynchronization occurs as a

response to stimulation. In patients with parasomnia arising from deep NREM sleep, macroarousal with slow wave synchronization (Halasz et al., 1985) and hypersynchronized delta wave bursts (Blatt et al., 1991) precede the onset of the motor phenomena. Thus, subcortical arousals, such as K- and delta bursts, may reflect a primary arousal processing for which conscious perception is not necessary, and preceding the onset of a physiological or pathological cortical arousal (Broughton, 1968).

We must point out that the validity of our study is critically dependent on visual analysis. Especially in normal subjects in whom K- and D-bursts can occur unassociated with a pathological phenomena, the appearance of a burst of K-complexes or delta waves may not be easily detected and may not be necessarily an expression of an arousal response. However, using criteria previously described we have an intrascore reliability of about 90% in our group, suggesting that inclusion of specific criteria, such as amplitude and number of K-complex and delta waves, may be a useful tool to visually detect these phasic events. Moreover, during subcortical arousal we found a significant rise in HR values with a pattern similar in evolution to that found during MA and PAT, indicating that the EEG and HR variations noted during these arousal cannot be explained by a simple random association. A second point that needs to be considered is that the onset of MA and PAT was defined by visual scoring and that very brief EEG changes were difficult to detect. Therefore, it could be argued that subtle modifications in EEG frequency, not detectable by visual inspection, may have occurred before the visually scored arousal onset. Even if this possibility cannot be ruled out totally, we believe that such a bias would occur for all types of arousal and would not explain why the HR rise before arousal onset was found only for MA and PAT.

In conclusion, our study demonstrates that EEG modification in cerebral synchronization may represent the primary form of arousal response in sleep. A continuum exists among arousal responses beginning with subcortical arousal patterns to arousal in fast EEG activation. The association between cardiac activation and EEG changes suggests the involvement of an active brainstem center regulating the arousal response. Even though in our study we were unable to determine whether sleep fragmentation revealed by our analyses contributes to the perceived differences in sleep quality and sleep restoration, our results suggest that subcortical arousals may be a useful tool to detect sleep fragmentation. Whether our approach has an impact in clinical practice will require future investigation.

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