Changes in pulse transit time and pulse rate as markers of arousal from sleep in normal subjects

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INTRODUCTION

Two of the most important physiological variables requiring measurement in disorders of sleep and breathing are the inspiratory effort and the sleep disturbance. Increases in upper airway resistance during sleep lead to increased inspiratory effort, and this is thought to be the main arousal stimulus [1] in obstructive sleep apnoea and its variants (or upper airway resistance syndrome [2]). The recurrent brief arousals in this condition (often hundreds per night) are the main cause of the most debilitating symptom, excessive daytime sleepiness. As a consequence, the analysis of the sleeping EEG in this condition has moved away from the conventional epoch-based approach [3] towards the counting of microarousals [4], since these correlate best with daytime function rather than measures of the macro sleep architecture [5]. However, this approach still necessitates the measurement of an all-night EEG, which requires the placing of at least two head electrodes, a considerable recording capacity, as well as a prolonged manual analysis time, or very sophisticated computer processing.

Previous work has suggested that there could be other markers of arousal which are much easier to measure than EEG. For example, body movements correlate closely with short arousals [6], and the orienting reflex [7] is an autonomic response to external stimuli characterized by a rise in heart rate, blood pressure (BP) and skin vasoconstriction, both awake and asleep [8]. In obstructive sleep apnoea there are rises in BP and heart rate at the end of each apnoea. It was originally thought that these rises in BP were due to the attendant hypoxaemia [9]. However, more recent evidence suggests that they are due to the arousal itself [10, 11]. It has also been shown that the size of the systemic BP rises (about 6–12 mmHg) correlates with the length of EEG arousal, and that such rises can occur in response to external stimuli, even when there is no discernible EEG response [12, 13]. These rises in BP were measured with a non-invasive beat-to-beat method (Finapres; Ohmeda) and have been shown to be useful in identifying the sleep disturbance in sleep and breathing disorders [14].

Pulse transit time (PTT) is the time taken for the arterial pulse pressure (or shock) wave to travel from the aortic valve (at the moment of opening) to the periphery. PTT varies inversely with BP: as BP rises, arterial walls become tenser and stiffer so that the pulse wave propagates faster, and vice versa [15, 16]. As a method of measuring absolute beat-to-
beat BP, it is relatively inaccurate, partly due to the drift of the relationship between PTT and BP [17]. However, measuring very short-term changes in PTT is much less vulnerable to this problem. PTT can be measured easily using the time delay between the ECG R-wave, and the arrival of the pulse (detected photoplethysmographically) at the finger (about 250 ms). Measured in this way (PTT,,,,), it includes the cardiac pre-ejection period (PEP) which is the time delay between electrical depolarization and aortic valve opening (isometric contraction). The PEP may or may not change in the same direction as the true PTT when there are changes in the cardiovascular system. However, such a device can be made easily portable, unlike the Finapres device.

The purpose of this study was to assess the value of changes in PTT and heart rate as indirect markers of cortical arousal measured conventionally using EEG. In addition, we have measured the separate contributions of PEP and actual PTT (PTT,,,,) to the changes in PTT,,,, observed in response to an arousing stimulus.

METHODS

Subjects

Eight healthy subjects (six males, aged 19–30 years, mean 22 years) agreed to partake in this study. None had a history of sleep complaints or cardiovascular disease.

Techniques

Sleep recording. One channel of EEG was recorded (C3/A2) along with separate electro-oculogram (EOG) tracings for each eye and a single submental electromyogram (EMG). These were recorded on an MPA2 tape recorder (Oxford Medical, Abingdon, Oxon, U.K.) for later analysis and could be reviewed throughout the course of each study. Simultaneous audio and infra-red video recordings were also made.

PTT. PTT was measured between the ECG R-wave and the photoplethysmographically detected arrival of the pulse wave at both the right ear and the right index finger (RM10; Parametric Recorders, London, U.K.). This device measures PTT (typically 200–300 ms at the finger) to an accuracy of 2 ms. A rise in systemic BP of 10 mmHg produces a fall in PTT of about 10 ms. A new PTT value is obtained with every heart beat and is oversampled and stored at 5 Hz to ensure no values are missed. The stored values can be downloaded on to a computer at the end of the study for later analysis. A second EEG (C4/A1) was also stored on this recorder.

Sleep disturbance. Arousal stimuli were delivered from a vibrating box beneath the pillow (Vibrating pillow alarm, model VC1; Sarabec Electronics, Middlesbrough, U.K.), which was adapted to allow the delivery of variable length stimuli [12]. This system produced a combined auditory and vibratory stimulus. The timing of the arousal stimulus was accurately synchronized (within 1 s) with the MPA2 EEG recording.

Protocol. Each subject arrived at the sleep laboratory for the study at 21.00 hours. Each study was performed during spontaneous sleep, although subjects concerned that they would not sleep in the strange surroundings were asked to reduce their previous night’s sleep. They were asked to avoid xanthines and alcohol for 24 h before the study. After application of the sleep-staging electrodes and the two PTT devices, the subject was allowed to fall asleep. Once stage 3 or 4 sleep had been reached (defined by standard criteria [3]), arousal stimuli of different lengths were delivered in an attempt to produce various degrees of arousal. A repeat stimulus was given when sleep had returned to stage 2 or below for at least 30 s after the previous stimulus. The study was terminated when either a sufficient number and variety of arousals had been produced, or when the subject failed to return to sleep after an arousal stimulus. This was always before the first appearance of rapid eye movement sleep, and no study went beyond the first 2 h of sleep. Approval for the study was obtained from the Central Oxford Research Ethics Committee, and all subjects gave their informed consent.

Analysis

For each stimulus EEG, EOG and EMG recordings were printed out with a time interval of 25 s before, and 19 s after, the arousal stimulus. The point of the stimulus was marked and the subsequent arousal was graded, blind of the PTT data, into five arbitrary categories according to the following criteria: (Oa) no discernible change in the EEG or EMG; (Ob) an increase in the amount of slow waves; (1) increase in high-frequency EEG or EMG (or both) for <3 s; (2) increase in high-frequency EEG or EMG (or both) for >3 and <10 s; (3) increase in high-frequency EEG or EMG (or both) for >10 s. All these gradings were made in comparison with the previous 25 s of tracings. In addition, 10 'sham' stimuli were similarly analysed for each subject. These sham periods were 44 s epochs of stage 2, 3 and 4 sleep before a real stimulus, with an imaginary stimulus at the 25 s point: these were all equivalent to grade 0a arousals (no discernible change), as would have been expected.

The PTT data around the period of each arousal were first passed through a 4 s moving window average to remove the respiratory oscillations. A pre-arousal control PTT value was taken at the point 5 s before the stimulus. The response to the stimulus was taken as the lowest value of PTT seen within 15 s of the stimulus onset. The difference between this and the pre-arousal control value was
calculated, and was referred to as the arousal fall. The same analysis was performed on the sham stimuli tracings. Arousal fall data were available from both PTT devices, one on the ear and one on the finger. The device on the ear measures mainly the PEP (ECG R-wave to aortic valve opening, approximately 160 ms) due to the relatively short arterial pathway. The device on the finger provides a measurement consisting of both PEP and PTTnet (approximately 250 ms), due to the much longer arterial pathway.

In addition to the changes of PTTnet in response to sham and real arousal stimuli, we also logged the changes in heart rate. The typical heart rate response we observed after a brief arousal was a rise, followed by a fall that is sometimes greater. Thus there tends to be a small undershoot to a lower value than the pre-arousal value, due to the baroreceptor response to the rise in BP on arousal. We measured both the rise (baseline to peak) and immediate fall (peak to trough) in pulse rate.

To explore the changes in PTT and heart rate across the arousal grades and between subjects, we used analysis of variance (SAS Institute, Cary, NC, U.S.A.) with Duncan’s multiple range test to establish which groups were significantly different from others.

RESULTS

All eight subjects completed the study. Arousal ability varied considerably between subjects, so that it was not possible to obtain consistent numbers of each grade of arousal, grade 1 being the hardest to achieve. On average there were 4.5 arousals per subject in each arousal category (and 10 in the control category). However, in four subjects no grade 1 arousals were achieved and the larger SEM values for grade 1 results reflect this. Of the total of 176 arousals analysed, 80% were delivered during stage 3/4 and the rest in stage 2. There was no significant difference in the proportions of each grade of arousal achieved in stage 2 versus stage 3/4 (P > 0.2, χ²).

PTT

Analysis of variance showed that there were small, but significant (P < 0.001), differences between subjects in the overall size of the falls in PTTnet at the finger in response to arousal. However, grade of arousal accounted for a greater proportion of the overall variance (r² = 0.44, P < 0.0001, Fig. 1a). Duncan’s multiple range test showed that all five arousal grades, including 0a, were significantly different from control, and that grades 0a and 0b were significantly different from grades 1 and 3. The average fall in PTT for all arousal grades was 15.1 (SEM 1.4) ms.

The falls in PTTnet at the ear were very much less, in both absolute (Fig. 1b) and percentage terms. This indicated that the fall in PTTnet seen at the finger in response to arousal is due mainly to rise in BP, rather than a shortening of the cardiac PEP. The proportion of overall variance explained by the arousal grade was only just significant (r² = 0.28, P = 0.036) and only grade 2 arousals were different from control.

Pulse rate

Pulse rate rises. Analysis of variance again showed that there were small and significant differences between subjects in the overall rise in pulse rate in response to arousal (P < 0.001). Grade of arousal accounted for a significant proportion of the overall variance (r² = 0.50, P < 0.0001, Fig. 1c). However, unlike PTTnet changes at the finger, Duncan’s multiple range test showed that the changes at grade 0a were not significantly different from control, although those at 0b and above were. The average rise in pulse rate for all grades and subjects was 10.3 (SEM 1.2) beats/min.

Pulse rate falls. Overall, after an arousal, the fall in pulse rate was larger than the initial rise, 12.5 (SEM 1.2) versus 10.3 beats/min (P < 0.003), thus confirming the tendency to a small undershoot. Analysis of variance showed that grade of arousal accounted for a significant proportion of these changes (r² = 0.41, P < 0.001, Fig. 1d). As with pulse rate rises, Duncan’s multiple range test showed that only arousal grades 0b and above were significantly different from control.

DISCUSSION

This study has shown that falls in PTTnet measured at the finger, and both rises and falls in heart rate, are sensitive indicators of external arousing stimuli. As has been observed in studies looking
specifically at beat-to-beat BP [12], these falls in PTT measured at the finger can occur even when there is no discernible change in the superficial cortical EEG. This implies that external stimuli can influence the brain stem cardiovascular centres without being passed further up and arousing the cortex. The 0b 'arousals' consisted of an increase in slow waves and yet were attended both by a fall in PTT and by changes in pulse rate, compared with control. This perhaps suggests that runs of slow waves following an increase in slow waves rapidly replaced by a full arousal presumably 'breaking through'. Others have also observed transient spontaneous changes in BP, with resetting of baroreceptors, in association with K complexes [18], suggesting that these too may be associated with brain stem 'arousal' or activation.

The main limitation of this study was the relatively crude grading of arousals from the EEG and EMG. The point at which EEG high-frequency starts and ends, even with the benefit of 25s prior tracing, is to some extent subjective. However, all tracings were analysed by one person (J.R.S.) blind to the PTT data. Not all grade 1 and 2 arousals did have an associated EMG rise; thus there are differences even within grades. It is not possible currently to truly quantify an arousal other than by simply attempting to measure its length. Therefore, although there is a trend to increasing falls in PTT from 0a to 3, we would not claim that PTT used in this way 'quantifies' arousals. Of more importance is its sensitivity to even the smallest 'arousals', undetectable on cortical EEG.

A potential problem could have been that changes in PTT were simply a consequence of changes in heart rate, for example due to a change in pulse waveform at faster heart rates. The fact that 0a 'arousals' significantly altered PTT, but not heart rate, is against this, and indeed including change (or absolute) heart rate first in the analysis of variance did not remove the significant relationship between PTT changes and arousal grade.

A confounding factor in this study might have been time-of-night effects, but since all stimuli were delivered during the first sleep cycle (and also not beyond 2h into sleep), the later and generally lighter periods of sleep were not used. Since only 20% of stimuli were delivered during stage 2 sleep (the rest during stage 3/4), and the arousal grades obtained were not significantly different in proportion to those obtained during stage 3/4, it is also unlikely that the stage of sleep present before the stimulus delivery is another confounding variable in this study.

The control changes in PTT were significantly different from zero. This is a consequence of our manual technique specifically looking for a fall in PTT within 15s of a particular point. Because PTT has spontaneous fluctuations, there will nearly always be a small fall, unless by chance the baseline point was synchronous with a trough.

Arousal is associated with an increase in sympathetic tone [19], presumably responsible for the rise in BP. One might have expected PEP to shorten as left ventricular contraction becomes more vigorous in response to this sympathetic stimulation. The trivial fall in PEP may mean that those rises in sympathetic tone are either too brief, or alternatively it might be that the rise in BP increases left ventricular afterload, therefore tending to lengthen the time the ventricle takes to open the aortic valve after electrical depolarization. This lengthening could cancel any shortening effects from increased left ventricular contractility. Whatever the explanation, changes in PTT at the ear are poor markers of arousal compared with those at the finger.

Johnson and Lubin [7] explored the orienting reflex, measuring heart rate changes, peripheral blood flow, skin resistance and EEG in response to fixed-volume audio tones delivered approximately every 40s throughout the night. These stimuli rarely produced full arousals, with about half having no discernible EEG response and the other half having evoked K complexes. There was a significant heart rate speeding, that habituated to a small extent, across the night, and which was greater in the presence of an evoked K complex (6.8 beats/min) compared to without (3.5 beats/min, P=0.01). On the other hand, Ringler et al. [11] did not find a significant rise in heart rate in response to noise (delivered during nasal continuous positive airway pressure treatment in patients being treated for obstructive sleep apnoea), although this group did find a rise in BP under the same circumstances, but did not look at the relationship with the degree of EEG arousal.

Whether falls in PTT or rises in pulse rate are a useful clinical tool to measure transient arousals largely depends upon whether they represent events that have symptomatic consequences. We know from experimental studies in normal subjects that the shorter arousals are, the less they influence subsequent daytime functions [20]. However, we do not know whether hundreds of these 'autonomic arousals' every night for long periods might produce daytime sleepiness or other symptoms. Most experimental studies have only used, at most, a few nights of sleep fragmentation compared with years, as has usually been present in patients with sleep-related breathing disorders. To answer these points requires clinical trials comparing the relationship between symptoms and both conventional (EEG) micro-arousals, as well as these markers of 'autonomic arousal'.

PTT and heart rate can be measured using only three ECG electrodes and a finger probe, similar to that used with pulse oximeters. The absence of head EEG electrodes, and the smallness of suitable digital recorders, makes it possible that these autonomic
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markers of arousal could be valuable signals during unattended domiciliary sleep studies that require a measure of sleep disturbance. PTT may be better than heart rate for this purpose, not only because we have found it to be a little more sensitive, but also because it can be used concurrently to measure the degree of inspiratory effort [21].

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REFERENCES