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Original Article

Sleep architecture and attenuated heart rate response to arousal from sleep in patients with autonomic failure

Simon Freilich [a], Elizabeth A. Goff [a,*], Anura S.N. Malaweera [a], Gillian L. Twigg [a], Anita K. Simonds [a], Christopher J. Mathias [b,c], Mary J. Morrell [a]

[a] Clinical and Academic Unit of Sleep and Ventilation, Royal Brompton Hospital, Imperial College, London, UK
[b] Neurovascular Medicine Unit, Faculty of Medicine, St. Mary's Hospital, Imperial College, London, UK
[c] Autonomic Unit, National Hospital for Neurology and Neurosurgery, Institute of Neurology, Queen Square, University College Hospital, London, UK

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ABSTRACT

Objective: To determine if patients with autonomic failure have increased sleep disturbances and if multiple system atrophy (MSA) and pure autonomic failure (PAF) patients have frequent arousals from sleep associated with an attenuated heart rate (HR) response compared to healthy volunteers.
Methods: With informed consent, 10 autonomic failure patients and 10 healthy volunteers were studied. Sleep disturbances were scored using standard criteria. Arousals were identified from stage 2 sleep and differences in the R–R interval between groups were tested using a mixed-model regression analysis.
Results: Three MSA and one PAF patient had obstructive sleep apnoea compared to one volunteer. One MSA and three PAF patients had periodic limb movements. One MSA patient had REM behaviour disorder. The autonomic patients had significantly reduced total sleep time ($p = 0.007$) and sleep efficiency ($p = 0.003$). The HR response to arousal was smaller in autonomic failure patients compared to volunteers during the early phase of the arousal ($p = 0.047$), but not the later phase ($p = 0.67$).
Conclusion: Autonomic failure patients have increased sleep disturbances compared to healthy volunteers. The smaller HR response in autonomic failure patients suggests that an intact sympathetic nervous system is a key component of the HR response associated with arousal from sleep.

1. Introduction

Arousals from sleep produce acute surges in autonomic output that are associated with increases in ventilation, heart rate (HR) and systemic blood pressure (BP) in excess of metabolic requirements [1,2]. In patients with obstructive sleep apnoea, arousals from sleep occur at the termination of an apnoea and result in a 3-fold increased likelihood of developing hypertension over 4 years, independent of other risk factors [3]. The extent to which the cardiovascular response to arousal is mediated by central autonomic activity or an epi-phenomenon linked with the arousal-related increase in respiratory output is unclear. Previous studies in animals have shown that arousal from sleep is associated with acute increases in sympathetic drive and transient withdrawals of parasympathetic cardiovascular activity [2,4]. In the present study, we aimed to investigate the role of the autonomic nervous system in the acute cardiovascular response to spontaneous arousals from sleep by studying the heart rate (HR) response to arousal in patients with an impaired autonomic nervous system, specifically in patients with multiple system atrophy (MSA) and pure autonomic failure (PAF).

MSA is a neurodegenerative disease characterised by neuronal loss and widespread distribution of cytoplasmic inclusion bodies [5,6]. It is classified by its predominant clinical symptoms – either MSA-P with a Parkinsonian predominance, MSA-C with a Cerebellar predominance, or MSA-M with Mixed Parkinsonian and Cerebellar symptoms. Pontine involvement is thought to occur early in the disease and may account for the relatively high frequency of REM behaviour disorder that occurs in MSA [7,8]. MSA patients also have a high prevalence of periodic limb movements (PLMS) [9] and sleep-related respiratory dysfunction such as nocturnal laryngeal stridor caused by paradoxical vocal cord motion [10] and sleep apnoea [8,11]. These sleep-related respiratory and motor abnormalities are likely to disturb nocturnal sleep patterns and increase the frequency of arousals from sleep.

PAF is an idiopathic disorder characterised by significant autonomic deficits without other neurological features [5,6]. The cardinal symptoms are orthostatic hypotension and sudo-motor failure, but the spectrum of autonomic features can overlap with

* Corresponding author. Address: Clinical and Academic Unit of Sleep and Breathing, Royal Brompton Hospital, Fulham Road, London SW3 6NP, UK. Tel./fax: +44 (0) 20 7351 8911.
E-mail address: lizzygoff@hotmail.com (E.A. Goff).

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MSA. The lesions have been clinically shown to be peripheral and post-ganglionic [12]. Both MSA and PAF lead to a reduction in sympathetic activity. PAF patients, however, tend to have a greater reduction in residual sympathetic activity compared to MSA [13]. MSA patients often have earlier involvement of the parasympathetic nervous system. This is seen clinically by the earlier manifestation of parasympathetic symptoms such as constipation and severe urinary dysfunction [13]. Measurements of the cardiovascular response to spontaneous arousals from sleep in patients with MSA and PAF may therefore provide insights into the mechanisms associated with the autonomic response during arousal from sleep.

In the present study, we hypothesised that autonomically challenged patients would have more sleep disturbances compared to age and weight-matched healthy volunteers, that both MSA and PAF patients would have an increased frequency of spontaneous arousals from sleep, and that these events would be associated with an attenuated HR response.

2. Methods

2.1. Subjects

Patients with autonomic failure were recruited from a national database held at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. Selection criteria were that patients had a confirmed diagnosis of either PAF or MSA. The clinical diagnosis of MSA and PAF was established using the standard National Hospital for Neurology and Neurosurgery Autonomic Testing and Imaging Protocols and Accepted Criteria [12,14]. Tests included MRI, blood pressure and HR stress testing (including orthostatic and prandial challenges) and clonidine/catecholamine studies. All patients were ambulant and had to be well enough to undergo the study. Patients with stridor were excluded and this symptom was clarified with both the patient and his/her partner or carer.

Twenty-three of 62 patients based in London fulfilled our inclusion criteria and were contacted, 12 agreed to participate. Healthy volunteers, matched to the patient group for age, gender and body mass index (BMI) were recruited from a database of healthy volunteers held at the Royal Brompton Hospital. The study was approved by the Local Ethics Committee and all participants gave written informed consent.

2.2. Measurements

Electroencephalograms (EEG: C3/A2, C4/A1 and O1/A2), electrooculograms (EOG: right and left) and electromyograms (EMG: submentalis and anterior tibialis) were recorded overnight (SOMNOscreen, S-Med, UK). Breathing was monitored via recordings of nasal pressure and respiratory effort (thoracic and abdominal effort belts). Oxygen saturation was recorded using finger pulse oximetry. HR was measured from the R–R interval of a two lead electrocardiogram (ECG). The sampling frequency for the ECG was 256 Hz (SOMNOscreen, S-Med, UK). In 5 of the 10 healthy volunteers, the ECG was sampled using a different data acquisition system (Spike 2, Cambridge Electronic Design, UK); on this system the ECG was sampled at a higher rate of 1000 Hz. Subjective sleepiness was assessed with the Epworth Sleepiness Scale (ESS) [15].

2.3. Protocol

Patients were studied for one night in their own home ($n = 9$) or in the hospital ($n = 3$, PAF patients) according to their preference. All control subjects were studied at the Sleep Laboratory at the Royal Brompton Hospital. Subjects were discouraged from drinking caffeinated or alcoholic drinks for at least 6 h prior to the study. Medications were taken as prescribed. On the night of the study, two researchers attended the patient's home between 20:00 and 22:00 h. Following informed consent, a clinical history was taken and the ESS was completed. Polysomnography equipment was attached and the subject was left to sleep for as long as he/she wished (maximum recording time 10 h). One of the researchers returned the next morning to remove the equipment.

2.4. Data analysis

Sleep stages and arousals from sleep were manually scored in accordance with standard criteria [16,17]. All respiratory events were manually scored; apnoeas were defined as a cessation of airflow lasting $\geqslant 10$ s and hypopneas as a >50% reduction in airflow lasting $\geqslant 10$ s, associated with a 4% drop in oxygen saturation or an arousal. PLMS were scored in accordance with the American Academy of Sleep Medicine Criteria [18].

The HR responses to spontaneous arousals from stage 2 sleep were investigated. The arousals included in these analyses were $\geqslant 3$ s, but <15 s in duration and preceded by a minimum of 3 min of stable stage 2 sleep (i.e., no respiratory disturbances or periodic limb movements). Each arousal was independently confirmed by a second investigator blinded to the status of the participant (i.e., patient or healthy volunteer) and the cardiovascular variables.

The HR responses to the spontaneous arousals from sleep were identified from the change in the R–R interval. R waves were manually detected, and measurements of the R–R interval were made using data collected via the SOMNOscreen (S-Med, UK) system or Spike 2 (Cambridge Electronic Design, UK) data acquisition software. The group mean (SEM) for the mean R–R interval was calculated for four time periods: one pre-arousal time period (60 s preceding the start of arousal, termed baseline) and three post-arousal time periods (0–3 s, 3.1–9.9 s and 10–20 s). We chose these time periods because we were particularly interested in the immediate acute HR response to arousal (0–3 s), the peak response to arousal (3.1–9.9 s), and the recovery response following arousal (10–20 s). The duration of the periods were based on earlier work from our laboratory [19,20]. For statistical analysis, the post-arousal time periods were classified as the Response phase (0–3 s through to 3.1–9.9 s) and the Restitutional phase (3.1–9.9 s through to 10–20 s).

2.5. Statistical analysis

We aimed to detect a mean difference of 10% in the HR responses to arousal between the autonomic failure patients and healthy volunteers with 80% power, p-value < 0.05, and a common standard deviation of 5%. This difference was similar to that measured during PLMS-related arousals in patients with MSA vs. controls [9]. Our power calculation indicated that we needed to study five patients in each group. Sleep parameters were tested using independent t-tests. The null hypothesis was rejected when $p < 0.05$. Analyses were performed using STATA 9.2 (StataCorp, Texas). The arousal responses were measured in each patient, and each patient contributed equally to the group mean response. The group mean arousal responses were tested using a mixed-model linear regression. The baseline measurements (pre-arousal) were entered as a covariate, and each patient was declared as a random effect. In order to investigate the difference between groups during the biphasic arousal response, the change R–R interval over two post-arousal time periods were statistically analysed; the Response phase: mean R–R change from baseline at 0–3 s through to 3.1–9.9 s, and the Restituitional phase: mean R–R