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Brief Communication

Effect of respiration on heartbeat-evoked potentials during sleep in children with sleep-disordered breathing

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ABSTRACT

Objective: Heartbeat-evoked potentials (HEPs) in electroencephalogram (EEG) provide a quantitative measure of cardiac interoception during sleep. We previously reported reduced HEPs in children with sleep-disordered breathing (SDB), indicative of attenuated cardiac information processing. The objective of this study was to investigate the link between HEP and respiration.
Patients/Methods: From the overnight polysomnograms of 40 healthy children and 40 children with SDB, we measured HEPs during epochs of stage 2, slow-wave and rapid eye movement (REM) sleep free of abnormal respiratory events. HEPs were analysed with respect to respiratory phase.
Results: We observed a marked association between respiratory phase and HEP in children with SDB during REM sleep, but not in normal children. In children with SDB, HEP waveforms were attenuated during expiration compared to inspiration. Following adenotonsillectomy, expiratory HEP peak amplitude increased in the SDB children and was no longer different from those of normal children.
Conclusions: The expiratory phase of respiration is primarily associated with attenuated cardiac information processing in children with SDB, establishing a pathophysiological link between breathing and HEP attenuation.

Interoception refers to sensing of the internal physiological conditions of the body via ascending neuronal pathways to higher brain centres (particularly the insular cortex) and has been proposed to provide a basis of subjective feelings, emotions and self-awareness [1]. The study of interoception using the heartbeat has been established by Schandry et al. [2], who employed methods to quantify awareness of one's heartbeat and investigated relationship among interoceptive awareness, emotions and brain processes. Analysis of the heartbeat-evoked potentials (HEPs) in the electroencephalogram (EEG) enables objective quantification of cortical processing of afferent cardiac information and studies have suggested an association between altered cardiac interoception and mental disorders [3,4].

We recently utilised HEPs to study cardiac interoception during sleep in children as a tool to infer cortical information processing without disrupting sleep. This study was approved by the Women's and Children's Health Network Human Research Ethics Committee, South Australia, with parental consent and child assent obtained from all participants [5]. Heartbeat-aligned EEG was assessed for the presence of HEP in children within stage 2 non-rapid eye movement (NREM) sleep, slow-wave sleep (SWS), and rapid eye movement (REM) sleep; non-random HEPs were observed across all sleep stages analysed. HEP was most pronounced during REM sleep and its amplitude gradually decreased during stage 2 and SWS, respectively. In a group of children with sleep-disordered breathing (SDB), we were able to demonstrate significantly attenuated HEP during NREM sleep in comparison to a group of age-matched healthy children and observed a similar trend in REM sleep. Importantly, treatment of SDB with adenotonsillectomy appeared to reverse HEP attenuation, suggesting that adenotonsillectomy has a beneficial effect on cortical processing of cardiac information in children with SDB. The degree of HEP attenuation during baseline in children with SDB correlated with measures of behavioural problems, one of the important clinical complications of childhood SDB, along with development delay, learning difficulties, and other long-term effects [6]. However, mechanistic links between disordered breathing and cardiac interoception have not been elucidated yet.

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Here, we sought to pinpoint potential pathophysiological mechanisms that may link disordered breathing to cardiac interoception. Thus, we examined the effect of respiratory phase on HEP exploring the dataset of children with SDB used in our previous study.

From the overnight polysomnograms of 40 healthy children and 40 children with SDB, we measured HEP during epochs of stage 2, SWS, and REM sleep free of abnormal respiratory events, movement or artefact as described in detail previously [5]. In brief, EEG data were segmented with respect to the cardiac cycle, as indicated by the R-peak in electrocardiogram (ECG), and ensemble averages computed to obtain HEP curves. As these HEP curves are partially contaminated by the cardiac field artefact, we only considered that part of the curve that occurred after completion of the cardiac repolarisation phase, that is, the time window between 400 and 550 ms post R-peak in ECG. The upper limit of the window was chosen to avoid undesirable effects from subsequent heartbeats. For respiratory phase analysis, we used the respiratory inductance plethysmography (RIP) signal obtained from the thoracic excursion.

Respiratory cycles were divided into early/late inspiration (Ins1, Ins2) and early/late expiration (Exp1, Exp2) based on expiratory and inspiratory onsets and their midpoints located on the thoracic RIP signal. Knowing these time instances, cardiac cycles and their time-aligned EEG were assigned as corresponding to one of the four phases based on the time point of occurrence of the R-peak on the ECG. Within each group, R-peak-aligned EEG averaging was done to obtain individual sleep stage-specific, respiratory phase-specific HEP curves. HEP peak amplitude values were computed as the maximum values of the averaged HEP curve within the cardiac field artefact-free time window. HEP analysis was repeated during a follow-up study, which was conducted 32.4 ± 6.7 weeks post adenotonsillectomy in 32 SDB children and without any intervention in 36 healthy controls (28.0 ± 5.0 weeks later).

We observed a marked association between respiratory phase and HEP in children with SDB during REM sleep, while there was no apparent effect in normal children. In children with SDB, HEP waveforms in the low-cardiac field artefact window were attenuated during both segments of expiration compared to the two segments of inspiration. As HEP during inspiratory segments (Ins1 and Ins2) and the expiratory segments (Exp1 and Exp2) followed similar patterns, we used the combined average HEP peak values for inspiration and expiration, respectively, for further statistical evaluation. Two-way analysis of variance (ANOVA) revealed that during REM sleep the SDB children had (i) a significantly lower HEP peak amplitude during expiration compared to inspiration and (ii) a lower HEP peak amplitude during expiration compared to controls, which almost reached statistical significance (Fig. 1). Furthermore, following adenotonsillectomy, expiratory HEP peak amplitude increased in the SDB children and was no longer different from those of normal children. During NREM sleep, no significant respiratory phase effect on HEP was observed in either normal children or those with SDB.

Our data suggest that children with SDB have impaired cortical cardiac information processing during sleep and that respiration may modulate HEP particularly during expiration in REM sleep. Potential respiratory phase effects in NREM may exist, but could possibly be masked by the inherently lower HEP amplitudes and thus lower signal-to-noise ratios.

We have previously shown slower respiratory rates in this same group of children with SDB, resulting from prolonged inspiration in all sleep stages and prolonged expiration in NREM sleep [7] as well as increased thoraco-abdominal asynchrony, suggestive of persistently higher respiratory effort during periods of sleep where no overt respiratory events were present [8]. Three-dimensional computed tomography of the airway in adult patients with obstructive sleep apnoea demonstrated that airway obstruction is a dynamic

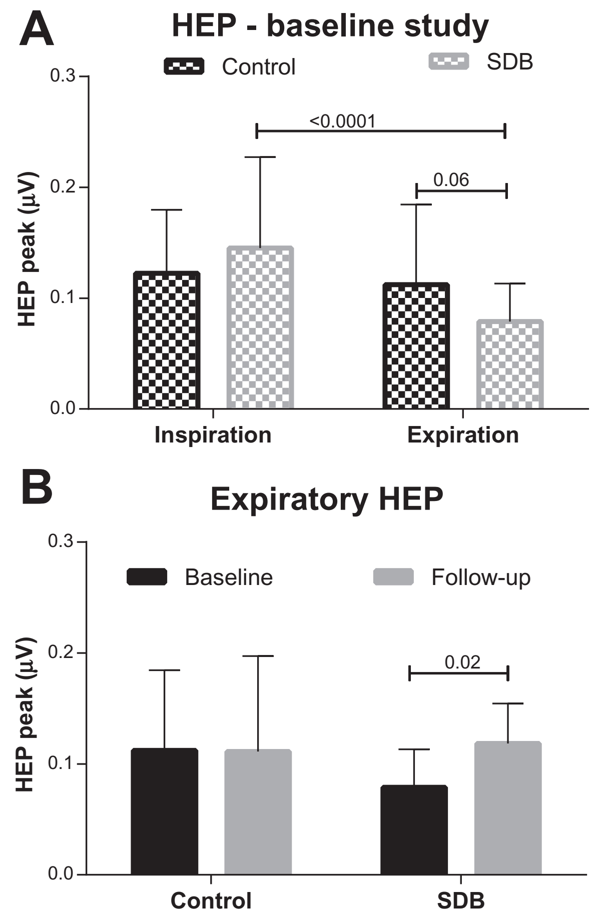

Fig. 1. A: HEP peak amplitude during REM sleep measured in SDB children and controls during inspiration and expiration in the baseline study. B: Comparison HEP peak amplitudes between controls and SDB children during expiration for baseline and follow-up study. Data are presented as group means and standard deviations and two-way ANOVA *p*-values.

process that occurs during inspiration as well as expiration [9]. Respiratory cycle-related EEG changes in our group children were more pronounced during REM sleep [10], indicative of neural and/or haemodynamic modulation of brain activity in children with SDB and of attenuation of the efferent cardiac response to spontaneous arousal [11].

There are several physiological mechanisms that could potentially be involved in the respiratory modulation of the HEPs; these could be predominantly mechanical or neural factors. Of the former, respiratory-related changes in the cardiac axis are an unlikely explanation due to the choice of an appropriate time window for our analysis. An alternative explanation is that afferent neural outflow from the heart to the cerebral cortex could be potentially affected/mediated by sensory signals from pulmonary afferents. As these are primarily active during inspiration, their involvement may be less likely. Respiratory gating of autonomic nervous system activity, on the other hand [12], is prevalent during expiration and may also involve cardiac afferents. Our finding may therefore be the result of altered autonomic nervous system activity in children with SDB, or the interaction could occur somewhere in the brainstem, starting from the nucleus tracts solitarius – a major sensory relay conveying to the brain afferent information from all visceral organs, including the heart [13], or even at the cortical level. Indeed, respiratory-related evoked potentials are extensively studied phenomena, and it has been recently reported that these evoked potentials are attenuated in children with SDB [14], similar to HEPs.

However, the SDB-dependent attenuation of the respiratory-related evoked potentials was reported to persist 4–6 months post-adenotonsillectomy [14], while our data suggest a reversal of HEPs after a similar time window. This may indicate that cortical interactions are less likely or that there are differences in SDB-related changes in processing of respiratory versus cardiac events.

In conclusion, respiration appears to modulate HEPs in children with SDB. Further research is needed to elucidate underlying pathophysiological pathways.

Author contributions

S.A.I. and M.B. contributed to the conception, design, analysis and interpretation of the data; the drafting and revision of the article; and final approval of the version to be published. Y.P and E.N. contributed to critical revision of the article for important intellectual content, and final approval of the version to be published. M.K. contributed to the collection of data, analysis, drafting and critical revision of the article and final approval of the version to be published. J.M. and D.K. contributed to revision of the article for intellectual content and final approval of the version to be published.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.02.528.

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