

Altered arousal response in infants exposed to cigarette smoke

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Aims: A failure of the arousal mechanism is a key feature in the apnoea theory for sudden infant death syndrome (SIDS). In infants studied at an age when the incidence of SIDS is highest, we evaluated whether in utero smoke exposed infants have altered arousal response to standardised auditory stimuli, and/or sleep pattern, as recorded on overnight complex sleep polysomnography.

Methods: A standardised sequence of audiology stimuli was applied binaurally to 20 in utero smoke and non-smoke exposed infants aged 8–12 weeks during a rapid eye movement (REM) and NREM epoch, in a controlled (temperature, position, pacifier use, noise) sleep environment. Infants were monitored for 10–12 hours using complex sleep polysomnography.

Results: Five infants exposed to in utero tobacco smoke did not have behavioural arousal response, whereas all non-smoke exposed infants aroused during NREM ($p = 0.016$). There was, however, no difference in REM sleep, and the groups did not differ in routine overnight complex sleep polysomnography parameters.

Conclusion: At the age when the incidence of SIDS is at its peak, infants of smoking mothers are less rousable than those of non-smoking mothers in NREM sleep; this may partly explain why such infants are more at risk of SIDS.

Sudden infant death syndrome (SIDS) is still the leading cause of post-neonatal deaths in previously well infants in many developed countries.^{1,2} The latest available report (2002) indicates that the incidence of SIDS in Australia is 63.2 and 39.5 per 100 000 for male and female infants respectively. The peak in SIDS events occurs between 2 and 4 months in full term infants.^{2,3} Although many diverse mechanisms have been proposed,⁴ a consistent finding is that exposure to tobacco smoke in utero significantly predisposes the infant to succumb to SIDS.⁵ It has been argued that 30% of deaths from SIDS are preventable by not exposing infants to smoke⁶; a dose response has been shown.⁷

A failure of the arousal mechanism is a key feature in the apnoea theory for SIDS.⁸ Smoking may influence the arousal mechanism as many pathways of the fetal nervous system are highly sensitive and can be modulated by noxious stimuli such as nicotine.^{9,10} It is not known how the arousal mechanism of smoke exposed infants is actually altered, and it is difficult to reproduce the events leading up to a sudden infant death. The ideal stimulus for assessing the arousal response would be a hypoxic challenge, which is ethically difficult in our setting. Diminished awakening hypoxic response in smoke exposed infants has been described.¹¹ An alternative stimulus is an audiology stimulus, as the sequence of movement arousal is similar and reproducible, regardless of the stimulus type.¹² Using auditory stimuli during rapid eye movement (REM) sleep, Franco and colleagues had previously shown that decreased arousability is found in infants in the prone position,¹³ who did not use pacifiers,¹⁴ and with in utero tobacco smoke exposure.¹⁵ To our knowledge there are no published data on arousability to audiology in both REM and non-REM (NREM) sleep during the age when the incidence of SIDS is highest. In this study, we applied standard stimuli to in utero smoke and non-smoked exposed infants aged 8–12 weeks. We hypothesised that the smoke exposed infants would have (1) an altered arousal response to standardised auditory stimuli and (2) an altered sleep pattern as recorded on overnight complex sleep polysomnography.

METHODS

Two groups of infants were recruited by approaching all available mothers consecutively on the postnatal wards on the days of recruitment and by asking mothers attending for their infants' routine six week check. Infants were eligible for the study if their mothers smoked either ante- and postnatally (smoke exposed, SE) or not at all (non-smoke exposed, NSE). The babies had to be full term with no perinatal complications and no significant cardiorespiratory disease, history of apnoea, or neurological problems. The study was approved by the local hospital's human ethics committee.

All infants were aged 8–12 weeks at the time of study (March to October 1999), free from intercurrent and recent (less than four weeks) infection, and not on any medication. Questionnaires were completed by a paediatrician (MH) and consisted of questions about the preconceptual and postnatal history, maternal and family medical history, family history of SIDS or apparent life threatening events (ALTEs), marital and social status, socioeconomic score (Daniel score) based on employment,¹⁶ maternal and paternal age, feeding practice, sleep position, and cigarette consumption of the father and mother, both ante- and postnatally. In addition the mothers all completed the Edinburgh postnatal depression screen.¹⁷ Each baby underwent a full paediatric examination and an overnight 10–12 hour complex sleep polysomnography study (sleep study). Studies were performed in a controlled sleep laboratory environment (including temperature control, 22–24°C) with continuous recording of electroencephalogram (EEG, C3–A2 left central lead and O2–A1 right occipital lead), electro-oculogram (EOG, left LOC–A2 and right ROC–A2), nasal airflow (Vacumetrics, USA), abdomen and chest wall

Abbreviations: ABR, auditory brain stem evoked response; ALTE, apparent life threatening event; EEG, electroencephalogram; EOG, electro-oculogram; NREM, non-rapid eye movement; NSE, non-smoke exposed; REM, rapid eye movement; SE, smoke exposed; SIDS, sudden infant death syndrome; SPL, sound phase level

Table 1 Demographics of infants studied

	Smoke exposed	Non-smoke exposed	p value
<i>Infant data</i>			
Male:female	2:8	6:4	0.36
Exclusive/predominant breast fed	8	9	0.5
Median birth weight, kg (range)	3.18 (3.13–3.80)	3.63 (2.49–4.28)	0.22
Median age at time of study, wk (range)	9 (8–12)	9 (8–11)	0.58
Median weight at time of sleep study, kg (range)	5.1 (3.86–6.42)	5.2 (4.56–5.82)	0.84
<i>Maternal history*</i>			
Cigarettes/day	17 (4–30)	0 (0)	0.00001
Maternal age	26.5 (19–35)	29.5 (29–40)	0.17
Alcohol consumed in pregnancy (number of persons)	5	7	0.33
Daniel score (median)	4.95	3.65	0.00001
Positive family history of SIDS	1	2	0.5
<i>Paternal history*</i>			
Paternal age	32 (24–41)	32 (27–35)	0.63
Smokers	6	2	0.05

*Results expressed as median (range) or number.

movement using respiratory inductance plethysmography (Respirace, USA), and pulse oxygen saturation (CSI Oximeter 504US, USA) on a computerised system (LaMont-NCI Systems, Sydney, Australia).

The infants slept alone in a cot, without a pacifier, in the supine position for arousal stimulus application. The first auditory stimulus was applied 10 minutes into the first epoch of NREM sleep and a minute after any obvious sigh or movement. The auditory stimulus of increasing intensity was applied by two speakers positioned exactly 20 cm from each ear. A warble tone oscillating in a sinusoidal waveform 10 times per second between 1200 Hz and 2800 Hz was applied for six seconds. The sound level was increased from 63 dB sound phase level (SPL) in seven steps to 86.2 dB SPL. The level of sound was calibrated with a Bruël and Kjaer sonometer at the same distance. The noise was activated away from the bed, ensuring no local movement/noise stimulus around the cot. The signal was recorded on the polysomnograph and continued through each step, with at least one minute between steps until full behavioural arousal occurred or until the maximum stimulus was applied. This protocol was then repeated 10 minutes into the next epoch of REM sleep. The subject was then left uninterrupted for the remainder of the study while data were collected. Auditory brain stem evoked responses (ABR) were obtained the day after the study using a conventional broad band click between 1 and 4 kHz (Navigator ABR unit, Biologic, USA). Both ears were tested separately and binaurally to thresholds. Infants were excluded if their ABR was above 30dB SPL. All studies were scored by an accredited sleep technician blinded to the smoking status of the baby, according to standard criteria.¹⁸

Definitions

Threshold responses (detectable changes for at least two consecutive stimuli within 10 seconds of the start of each stimulus) were determined for EEG (pattern change lasting at least three seconds), respiratory rate (20% change in respiratory rate compared with the average rate for two minutes prior to the onset of stimulus testing), and full behavioural arousal (eye opening and movement). Threshold responses for heart rate (10% change compared to the average rate for the two minutes prior to the onset of stimuli testing) were counted within 20 seconds after the onset of each stimulus to account for the time delay inherent in the averaging system for those parameters. Obstructive apnoea was defined as airflow cessation in the presence of respiratory effort lasting longer than the preceding two breaths in the presence of respiratory effort,¹⁹ and central apnoeas as cessation of respiratory effort

and therefore interruption of flow that lasted longer than the preceding two breaths in the absence of respiratory effort.¹⁹ A respiratory desaturation event was considered present when a respiratory event is associated with SpO₂ of <95%.

Statistical analysis

Statistical software package SPSS version 7.5 (Chicago, USA) was utilised. The Kruskal-Wallis test was used to compare data between the groups for continuous variables, and Fisher's exact tests for categorical variables. A two tailed p value less than 0.05 was considered significant.

RESULTS

Twenty infants were studied, 10 each from the SE and NSE groups. Three infants from the SE group had unilateral conductive hearing loss, but all had normal binaural thresholds and none were excluded. Nine of the 10 smokers smoked throughout pregnancy and continued to do so postnatally. The tenth smoker smoked for the first trimester and then reduced to occasional cigarettes until delivery when she increased to prepregnancy intake levels. There was no significant difference in demographics of infants or paternal characteristics (table 1). Mothers of NSE infants were significantly more affluent as defined by the Daniel score. There was no difference between the groups for maternal age, alcohol consumption, family history of SIDS, or depression score (only one smoking mother scored positively on the questionnaire).

Not all infants had detectable change in the various outcome measures (change in respiratory rate, heart rate, EEG, behavioural response) after the maximum stimulus was applied (table 2). In NREM sleep five infants from the SE group did not have a behavioural arousal. This group were significantly less likely to have behavioural arousal after application of maximal stimuli when compared to the NSE infants (p = 0.016). However, no difference between groups was found in REM sleep. There was also no difference between the groups for change in EEG, heart rate, or respiratory rate. In infants where a change in EEG, heart rate, and respiratory rate were present, there was no significant difference between the groups in the SPL required to produce the threshold changes.

In routine sleep study parameters, no difference was found between the groups in central apnoea index, obstructive apnoea index, time in REM sleep, total sleep time, and respiratory desaturation index in both REM and NREM sleep phases (table 3).

DISCUSSION

In this study of infants at an age when the incidence of SIDS is highest, it has been shown that infants exposed to in utero

Table 2 Arousal thresholds; threshold of sound phase level (SPL) in dB (range) and number (n) with no response to maximum SPL for changes in outcomes

Outcomes	Smoke exposed*	Non-smoke exposed*	p value
<i>REM sleep</i>			
Behavioural arousal	69.2 (63–75.0), n=2	63.0 (63–86.2), n=1	0.5
EEG	65.0 (63–86.2), n=0	63.0 (63–86.2), n=1	0.29
Heart rate	64.0 (63–73.3), n=4	68.2 (63–86.2), n=2	0.31
Respiratory rate	63.0 (63–65), n=1	63.0 (63–73.3), n=3	0.29
<i>NREM sleep</i>			
Behavioural arousal	75.8 (63–77.4), n=5	79.5 (73.3–86.2), n=0	0.01
EEG	69.2 (63–81.5), n=2	73.3 (63.0–86.2), n=0	0.21
Heart rate	70.4 (63–86.2), n=6	77.4 (63.0–86.2), n=3	0.5
Respiratory rate	63.0 (63–75.8), n=1	65.0 (63.0–81.5), n=1	0.77

*Median (range).

Table 3 Sleep polysomnography details

Variable	Smoke exposed*	Non-smoke exposed*	p value
Central apnoea index	11.45 (1.5–15)	8.9 (2.6–41.8)	0.68
Obstructive apnoea index	13.3 (1.5–30.4)	10.8 (3.4–45)	0.79
<i>REM sleep</i>			
Central apnoea index	10.5 (4.4–56.4)	14.8 (4.4–56.4)	0.74
Obstructive apnoea index	37.7 (9.5–71.9)	39.4 (25–64.5)	0.85
<i>NREM sleep</i>			
Central apnoea index	5.1 (0.7–22.8)	4.2 (1.1–25.7)	0.74
Obstructive apnoea index	4.1 (1.5–12)	5.5 (0.5–21)	0.85

*Median (range).

tobacco smoke have reduced arousal response when compared to infants not exposed to in utero smoke during NREM but not REM sleep. However, the groups did not differ in routine overnight complex sleep polysomnography parameters.

SIDS is the single most common cause of post neonatal death in previously well infants.¹ In utero smoke exposure is also associated with altered respiratory physiology in infancy, such as reduced airway calibre and increased airway responsiveness,^{20,21} and decreased awakening response to hypoxic stimulus but not altered ventilatory response to hypercapnia or hypoxia.^{11,22} The arousal response is a protective mechanism by which infants increase their activity to prevent life threatening asphyxia, for example, movements to sustain access to fresh air.¹² Studying newborns and 41 infants aged 4–17 weeks, Franco *et al* showed that during REM sleep, infants of smokers had reduced arousability (median threshold in smoked exposed was 70 dB (range 50–100) versus 60 (50–90) in non-smoke exposed infants).¹⁵ They did not, however, study the NREM phase and used a higher maximum auditory stimulus of 100 dB placed closer and unilaterally to the infant's ear (3 cm, in contrast to our study, which used 20 cm). In our study, infants of smoking mothers were less likely to fully behaviourally arouse despite maximal auditory stimuli (86.2 dB SPL) than non-smoke exposed infants. However in contrast to other studies we did not show an increased threshold to arousal in those smoke exposed infants who did behaviourally arouse. This may reflect our relatively small numbers of subjects as only five infants of smokers aroused.

Significant differences in arousability to behavioural awakening were only present in NREM and not in REM sleep. It is unknown which epoch is the best to test arousability, and it is also unknown which sleep state is more important as a risk factor for SIDS. Transient brain activity is seen more readily in response to auditory stimulation in REM sleep than in other sleep states,²³ but when looking at failure to arouse it may be more relevant to study periods of low arousability. We studied

both REM and NREM epochs, testing in NREM first so as to decrease sleep disruption and awake time during the study as a whole. Reasons for our negative findings in REM include possible influence of habituation²¹ as we had started the auditory stimulation sequence in NREM sleep, and the small sample size. We also found no difference in arousals measured by heart rate, respiratory rate, or EEG change. Likewise, Franco *et al* also did not show any difference between infants of smokers and non-smokers in these polygraphic arousals.¹⁵

We used a different sequence of stimulus to other groups.^{15,24} Although any stimulus produces a similar sequence of movement arousal regardless of type,¹² care must be taken to avoid additional stimuli during testing. We chose an auditory stimulus calibrated and delivered at a distance of 20 cm from the level of the infant's ears and operated from a computer distant to the infant to minimise such errors. It is more difficult to standardise air jets into the nostrils and auditory stimuli delivered very close to the ear, as both require proximity of the tester. While airjet delivery can be standardised, it is difficult to assure standardised flow and/or pressure at the receptor level as the infant's nasal anatomy and patency will influence physical characteristics of airflow delivered. Furthermore, auditory stimuli delivered to one or other ear at random may heighten inequalities in hearing between each ear. Three of our 20 babies had unilateral conductive hearing loss, probably secondary to secretory otitis media. Our method of testing, however, required only binaural functioning which was normal in all three of these infants. Unless auditory brain stem testing screened both ears separately and binaural thresholds, errors may be introduced if single ears are used for auditory stimuli.¹⁵ Findings in studies that fail to test auditory brain stem responses may reflect only an increased incidence of conductive hearing loss, as there is a strong relation between smoking and incidence and duration of secretory otitis media.²⁵

Some studies have shown higher rates of obstructive apnoeas in smoke exposed infants^{26,27} which we did not find.

However, arousal is said not to be important in the termination of obstructive and central events in children with obstructive sleep apnoea.²⁸ The criticism with many studies involving polysomnography in infants is the difficulty in interpreting results from infants of a wide age range, as sleep characteristics and arousability change markedly over the first six months of life.^{8 29-31} Some studies have used premature babies who are at an increased risk of SIDS, but who also pose difficulties when deciding whether to use postnatal or post-gestational age, as neither corresponds to the full term equivalent. We have used a narrow age range of infants during a period when the risk of SIDS is highest. Our infants were all full term, without any perinatal illness, were studied in a temperature, noise, and light controlled environment during specified sleep states, and their mothers were not depressed. None were sleep deprived, slept prone during the study, received sedation, or used a pacifier, all of which have been shown to alter arousability.^{13 31-35} Other studies have not controlled for all these factors.

SIDS is strongly associated with maternal smoking, with a dose response effect.³⁶ This risk remains significant after controlling for other confounders such as age of mother, parity, prematurity, low socioeconomic status, sleep position, and protective effect of breast feeding.^{36 37} In addition, studies confirm that postnatal household exposure has an independent additive effect.³⁷ Most hypotheses relating SIDS to maternal smoking discuss an effect of maternal smoking on fetal oxygenation and fetal brain development.⁹ 3[H]-nicotine binding sites in mid-gestational fetuses are heavily concentrated in the tegmental nuclei, which are involved in cardiopulmonary integration, arousal, attention, REM sleep control, and somatic motor function.³⁸ This study adds to the body of evidence that in utero smoke exposure is detrimental to the infant's neurorespiratory system, which governs arousals. We conclude that at the age when the incidence of SIDS is at its peak, infants of smoking mothers are less rousable than those of non-smoking mothers in NREM sleep, and this may partly explain why such infants are more at risk of SIDS.

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