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Polysomnographic study of the autonomic nervous system in potential victims of sudden infant death syndrome

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To determine the influence of sleep stages and night-time distribution on cardiac autonomic activity, the polysomnographic recordings of 18 victims of sudden infant death syndrome (SIDS) and of 36 control infants were studied. Autoregressive spectral analyses of heart rate (HR), using both short-term and whole-night methods, were evaluated as a function of sleep stages. The two main peaks of normalized LF and HF were computed during the night and the sympathovagal balance (LF/HF) was determined.

In both NREM and REM sleep, SIDS infants were characterized by significantly lower normalized HF powers and higher LF/HF ratios. This finding was observed in both short-term and whole-night HR spectral analyses. In addition, SIDS victims were characterized by the presence of a high desynchronized peak of sympathetic tonus in the late hours of the night, a finding not seen in the control subjects.

This report adds further indirect evidence for a possible sleep-related impairment of autonomic controls in some infants who died of SIDS.

Keywords: autonomic nervous system, infant, sleep, sudden infant death syndrome.

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Introduction

The mechanisms responsible for sudden infant death syndrome (SIDS) remain largely unexplained [1,2]. Future SIDS victims exhibited symptoms during sleep that could be related to autonomic nervous system dysfunctions, such as high overall heart rate (HR), low HR variability [3–6], episodes of tachycardia [7], bradycardia [3], or prolonged Q-Tc indexes [8–9]. Some future SIDS infants were also characterized by profuse watery salivary and sweat production [1,2,10]. HR power spectral analysis in infants who eventually died of SIDS lead to varying conclusions, depending on data selection and recording techniques [11,18]. Most SIDS deaths occur in the early hours of the morning [19–21]. Infants who later succumb to SIDS show less waking, more sleep, and increased slow-wave activity during the early morning hours compared to age-matched control subjects [22,23]. It is not known whether SIDS victims could suffer from autonomic dysrhythmia in the later part of the night.

The present study was designed to evaluate the night distribution of sympathovagal balance in future SIDS victims during all sleep stages.

Methods

Patients

Between May 1992 and May 1995, all-night polygraphic recordings of 18 infants who later became victims of SIDS were collected from 13 Belgian sleep laboratories. The sleep studies were carried out as part of different sleep research programs on sleep characteristics in infants. None had a history of sleep problems or apnea. At the time of recording, no infant had signs of infection and none was receiving medication. Thirteen of the 18 SIDS infants were males. Five infants were prematurely born. Two preterm and 1 full-term infant had inappropriate weight for gestational age. One was a sibling of a SIDS victim. Three infants were monitored at home, two by means of cardiorespiratory monitors and one with a respiratory monitor. Because of caretakers' noncompliance, the children were not being monitored at the time of death. The 18 deaths were unexpected and remained unexplained despite complete postmortem studies. For each SIDS recording, recordings of two control infants were selected. Control infants were matched with SIDS cases for sex, gestational age, postnatal age, weight at birth, and body position during sleep. They had no family history of SIDS and survived the first year of life uneventfully. Data on the children's history and usual behavior were collected before sleep monitoring was carried out.

Polygraphic recordings

Similar recording techniques were used in the 13 sleep laboratories. The infants were admitted for a night monitoring session (8–9 hours). The data were collected on a computerized polygraph recording system (Morpheus system, Medatec, Belgium). The following variables were recorded simultaneously: two scalp electroencephalograms (EEG), two electrooculograms, an electrocardiogram (DII), a digastric electromyogram (EMG), thoracic and abdominal respiratory

movements by means of inductive plethysmography, and airflow by thermistors taped under each nostril and on the side of the mouth. Oxygen saturation was recorded continuously using a transcutaneous sensor (Ohmeda Box, USA). An actigram was placed on one arm to measure body movements.

Data analysis

Each infant recording was allocated a random code number.The code was disclosed after completion of the analysis. All recordings were analyzed visually. Two independent scores analyzed the sleep recordings to ensure reliability. Disagreements were discussed and codes subsequently agreed upon were used in data analysis. Thirty-second periods of the recordings were categorized as either non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), or wakefulness according to criteria recommended in the literature [24,25]. NREM refers to NREM II and III stages. Behavioral arousal was defined as opening of the eyes. Gross body movements were measured by actigrams and confirmed visually. Sleep efficiency was defined as the ratio of the total sleep time divided by the total recording time, expressed as a percentage. Sleep apneas were scored only if they lasted 3 seconds or more. A central apnea was scored when flat tracings were obtained simultaneously from strain gauges and thermistors. Periodic breathing was defined by the succession of more than two central apneas, separated from each other by less than 20 seconds of breathing. An obstructive apnea was scored when continuous deflections were obtained from strain gauges, while a flat tracing was recorded from thermistors. Mixed apneas were defined as central apneas followed directly by obstructive episodes and were scored together with the obstructive apneas.

Heart rate spectral analysis

Premature ventricular contractions and artifactual RR intervals due to gross body movements, apneas, sighs, or arousals were eliminated by visual analysis of the HR data. Spectral analysis was restricted to artifact-free segments. Short-term HR spectral analyses were performed during selected segments of NREM and REM sleep. To avoid the bias of segments selection and to increase the number of analyzed segments, the analysis was then computed during the whole night.

Short-term spectral analysis

The digitized ECG signals were sampled at 300 Hz. In each infant, two periods of 256 successive RR intervals were selected during both NREM and REM sleep, in the same period of the night for the two populations. An autoregressive power spectral analysis of the spontaneous beat-to-beat variabilities in RR intervals was performed [26,27]. Centre frequency and power of each spectral component were measured. Two major peaks were recognizable: a low-frequency component (LF) defined by a centre frequency of 0.1 Hzeq (0.04–0.15 Hzeq) related to sympathetic and parasympathetic activities and a high-frequency component (HF) defined by a centre frequency of 0.4 Hzeq (> 0.15–2 Hzeq) reflecting parasympathetic tonus [26]. Respiratory frequency during the selected period was measured manually after being printed on paper. For each 256 RR interval period, the major component in the LF band of the HR spectrum was related with the major component in the HF band corresponding to the mean respiratory frequency as determined by analysis of breath to breath intervals. The ratio of LF/HF powers for each episode was calculated as an index of the sympathovagal interaction [28]. Spectral components were represented as the RR intervals (in ms), power (in msec2), bandwidth (in Hzeq) [26,27], and normalized power obtained by dividing the power of the period by the total power component (in %), after subtraction of the direct current component [27]. The optimal autoregressive model order was determined by minimizing the value of the final predictor error [29]. Stationarity was confirmed by means of a pole diagram analysis [26,27]. The normalized powers were the major parameters of interest in this first part of the study. Normalized powers obtained by this method (major component of the band) were compared with the results obtained when the totality of the band was studied (LF band: 0.04–0.15 Hzeq; HF band: > 0.15–2 Hzeq).

Whole-night spectral analysis

HR spectral analysis was computed by periods of 256 successive RR intervals during the night. For each sleep stage period, mean HF normalized power (MHF) for the HF band (> 0.15–2 Hzeq), mean LF normalized power (MLF) for the LF band (0.05–0.15 Hzeq), and mean LF/HF power ratio (MLF/HF) were measured. The mean LF, HF, LF/HF normalized powers for each sleep stage period were the major parameters of interest in this second part of the study. For each patient, median and maximum values of MHF, MLF, and MLF/HF reached during the night in both NREM and REM sleep were calculated.

To evaluate autonomic activity through the night, recordings were divided into three 4-hour periods [22] (7:00 P.M. to 11:00 P.M., 11:00 P.M. to 3:00 A.M., and 3:00 A.M. to 7:00 A.M.). The two main peaks of MHF and MLF/HF reached during the night were classified within one of these three periods. The recordings of one future SIDS victim and those of the two matched control infants begun in the afternoon were excluded from this part of the analysis.

Statistic evaluation

The Friedman test was applied to compare SIDS and control cases. The Wilcoxon matched-pairs signed-ranks test was used to compare the SIDS case with each of the control cases and to compare the two control cases with each other. Statistical significance was defined by a level of 0.05 when comparing SIDS cases to control subjects and if there was no significant difference between each control case together [30–32]. The Wilcoxon matched-pairs test was used to compare values obtained during REM and NREM sleep for the two populations of infants. The median values of the control group presented in the tables are those obtained when the control cases were computed together.

Table 1. Major characteristics of the infants studied

	Future SIDS cases	Control infants
Number	18	36
Gender (M/F)	13/5	26/10
Gestational age (weeks)	38 (27–41)	38 (27–41)
Age at sleep study (weeks)	8 (8–19)	8 (5–19)
Birth weight (g)	2.925 (0.96–3.98)	2.865 (0.9–4)
Sleep position (prone/supine)	9/9	18/18
Preterm infants	6	12
Small for gestational age	4	8
Age at death (weeks)	13.5 (10–36)	—
Sibling of SIDS cases	1	0

The figures represent absolute, median, and range values. There were no significant differences between the two populations for any of the variables studied.

Results

General sleep characteristics

The general characteristics of the two groups of infants are shown in Table 1. Due to the study design, there were no significant differences for the following variables: sex, gestational age, postnatal age, weight at birth, and sleep position.

No significant differences were seen between the two groups of infants for the following variables: total recording time, total sleep time, sleep efficiency, NREM sleep, REM sleep, frequency of sleep stage changes, number of REM sleep epochs, number of NREM sleep epochs, movement frequency, or arousal duration.

Sudden infant death syndrome victims had significantly less RR artifacts than control infants during total sleep time (median of 0.63 minutes for SIDS infants; range 0.06 to 8.38 minutes, median of 2.21 minutes for control infants; range 0.03 to 11.15 minutes) ($p = 0.041$), and during REM sleep (median of 0.63 minutes for SIDS infants; range 0.06 to 7.79 minutes, median of 2.11 minutes for control infants; range 0.03 to 9.44 minutes) ($p = 0.047$).

After exclusion of RR interval artifacts, no significant differences were seen between SIDS victims and control infants for total sleep time, REM, and NREM sleep time.

Short-term spectral analysis

Table 2 provides a summary of the short-term spectral analysis of REM and NREM sleep. Compared to control subjects, SIDS infants were characterized during REM and NREM sleep by significantly lower HF powers and HF normalized powers, and higher LF/HF power ratios. The results were similar when the major components within the band or the totality of the spectral band were used. There were no significant differences in RR intervals, total power of the spectrum, LF values in REM and NREM sleep between the two populations.

Whole-night spectral analysis

Whole-night HR spectral analysis also significantly differentiated the two groups (Table 3). Compared to control subjects, SIDS infants were characterized by a lower median MHF and higher median MLF/HF in both REM and NREM sleep states.

Compared to control infants, SIDS infants had significantly lower maximum MHF and higher maximum MLF/HF during NREM sleep. The difference did not reach statistical significance during REM sleep.

Both SIDS victims and control infants had higher median and maximum MHF in NREM than in REM sleep. Median MLF/HF was significantly higher in REM than in NREM sleep in the two groups of infants. In contrast to control infants, future SIDS infants showed no statistical difference in maximum MLF/HF for NREM and REM sleep. There was no significant difference in MLF in REM and NREM sleep between the two populations.

Distribution across the night

There were no significant differences between the SIDS victims (Fig. 1A) and the control subjects (Fig. 1B) in the distribution of the main and second maximum MHF peaks or in the occurrence of the main maximum MLF/HF peak. These maximum values occurred between 11:00 P.M. and 3:00 A.M. For both SIDS and control subjects, the main MHF peak occurred during the second epoch of NREM sleep (range: 1–10). The main MLF/HF peak was in the same hourly range for both groups studied, and usually followed the HF peak (15/18 in future SIDS infants and 24/36 control infants [NS]). The main MLF/HF maximum peak occurred during REM sleep (12/18 SIDS infants and 33/36 control infants), usually during the third REM sleep epoch in the case of SIDS victims (range: 1–7) and the fourth REM sleep epoch for the control infants (range: 1–10) (NS). The only difference between the two groups was observed in the distribution of the second maximum MLF/HF peak. More SIDS victims had their second maximum MLF/HF peak in the third part of the night (62.5% of SIDS victims vs 36.6% of control subjects) (NS).

When the maximum MLF/HF values between SIDS victims and control infants were compared, the difference was greater for the second maximum peak than for the main peak (median values for the mean peak: 4.87% in SIDS cases (range: 1.3–8) versus 3.5% in control subjects (0.6–7.76) (NS); with median values for the second peak: 3.75% in SIDS (range: 1–7.5) versus 2% in control subjects (range: 0.43–7) ($p = 0.015$). In control and SIDS subjects, the two main MHF and MLF/HF peaks followed each other. In contrast to control infants, the two second MHF and MLF/HF peaks were desynchronized in future SIDS victims. When we studied the occurrence of the maximum MHF and MLF/HF peaks in the same hourly range, 5.5% of them were found in SIDS victims and 27.7% in control subjects for the main maximum peaks (NS), and 5.5% for SIDS victims compared with 33.3% in control subjects for the second maximum peaks ($p = 0.05$).

Discussion

SIDS victims had lower values of HF normalized powers and higher LF/HF power ratios in all sleep stages compared

Table 2. Short-term heart rate spectral analysis*

	SIDS cases (36 periods)	Control infants (36 periods/group)	p Friedman
REM SLEEP			
HF Component			
Frequency components (Hzeq)	0.39 (0.19–1)	0.45 (0.17–1)	NS
Power (ms^2)	20.6 (0–259.1)	52.92 (6.1–703.4)	0.003
Normalized power (%)	5.7 (1–27.3)	8.85 (2.5–50.1)	0.003
Bandwidth (Hz)	0.15 (0.07–0.24)	0.13 (0.06–0.28)	NS
LF/HF power ratio (%)	8.02 (0–78.4)	3.82 (0–48.4)	0.019
HF band (>0.15–2 Hzeq)			
Normalized power (%)	11.1 (2.5–39.3)	20.65 (5.8–64)	<0.001
LF/HF power ratio (%)	3.71 (0–31.36)	1.64 (0–14.37)	0.009
NREM SLEEP			
HF Component			
Frequency components (Hzeq)	0.54 (0.24–1)	0.50 (0.18–1)	NS
Power (ms^2)	12.66 (2.7–127.3)	40.65 (4.7 –171.8)	0.040
Normalized power (%)	8.5 (2.3–58.2)	20.25 (3.4–66.4)	<0.001
Bandwidth (Hz)	0.13 (0.05–0.244)	0.095 (0.032–0.193)	0.013
LF/HF power ratio (%)	5.81 (0.33–37.88)	1.87 (0–19.48)	<0.001
HF band (>0.15–2 Hzeq)			
Normalized power (%)	22.7 (6.7–50.1)	40.6 (11.1–80.7)	<0.001
LF/HF power ratio (%)	2.86 (0.09–11.81)	1.05 (0–3.43)	<0.001

HF, high frequency; LF, low frequency; LF/HF, low frequency/high frequency ratio; NS, not significant.
*The figures represent median and range values.
Statistical analysis was performed using the Wilcoxon paired matched test, and the Friedman test with a level of significance <0.05.

with control subjects. The finding was seen in both short-term and whole-night analyses. It could reflect a greater sympathetic balance, or an impaired vagal tone, in infants who eventually died of SIDS. Such potential cardiac dysautonomia was already reported in clinical studies [3–6,33,34]. In a recent large prospective study, Schwartz *et al.* [35] demonstrated that prolongation of the Q-T interval was strongly associated with SIDS. It was suggested that a developmental abnormality in cardiac sympathetic innervation may result in prolongation of Q-T interval and could reduce the electrical stability of the heart [35–38] and precipitate ventricular fibrillation and sudden cardiac death [8,35, 39–41].

We do not know whether the presence of a high desynchronized peak of sympathetic tonus in the late hours of the night could further contribute to the death of SIDS victims.

We found fewer RR artifacts in both REM sleep and total sleep time in future SIDS victims than in control infants.

Table 3. Whole-night heart rate spectral analysis*

	Future SIDS cases	Control infants	p Friedman
HF: median values			
M (HF) NREM Sleep (%)	8.25 (4–11.5)	15.75 (3–30.5)	0.002
M (HF) REM Sleep (%)	3 (1–6)	5 (2.5–11)	0.020
P Wilcoxon	0.001	0.001	
HF: max. values			
M HF NREM Sleep (%)	14.5 (6–23)	23 (5–54)	0.005
M HF REM Sleep (%)	5.5 (1–19)	8.5 (2–38)	NS
p Wilcoxon	0.001	0.001	
LF/HF: median values			
M LF/HF NREM sleep (%)	1.24 (0.17–4.6)	0.54 (0.18–6.8)	0.002
M LF/HF REM sleep (%)	2.5 (0.62–4.22)	1.59 (0.4–5)	0.03
p Wilcoxon	0.004	0.003	
LF/HF: max. values			
M LF/HF NREM sleep (%)	3.05 (0.43–7.33)	1.1 (0.24–7.5)	0.004
M LF/HF REM sleep (%)	4.5 (3–8)	3 (0.71–13)	NS
p Wilcoxon	NS	0.018	

HF, high frequency; LF, low frequency; LF/HF, low frequency/high frequency ratio; M HF, mean of high frequency normalized power values during a sleep-stage epoch; M LF/HF; mean of low frequency on high frequency power ratio values during a sleep-stage epoch. NS; not significant.
*The figures represent median and range values.

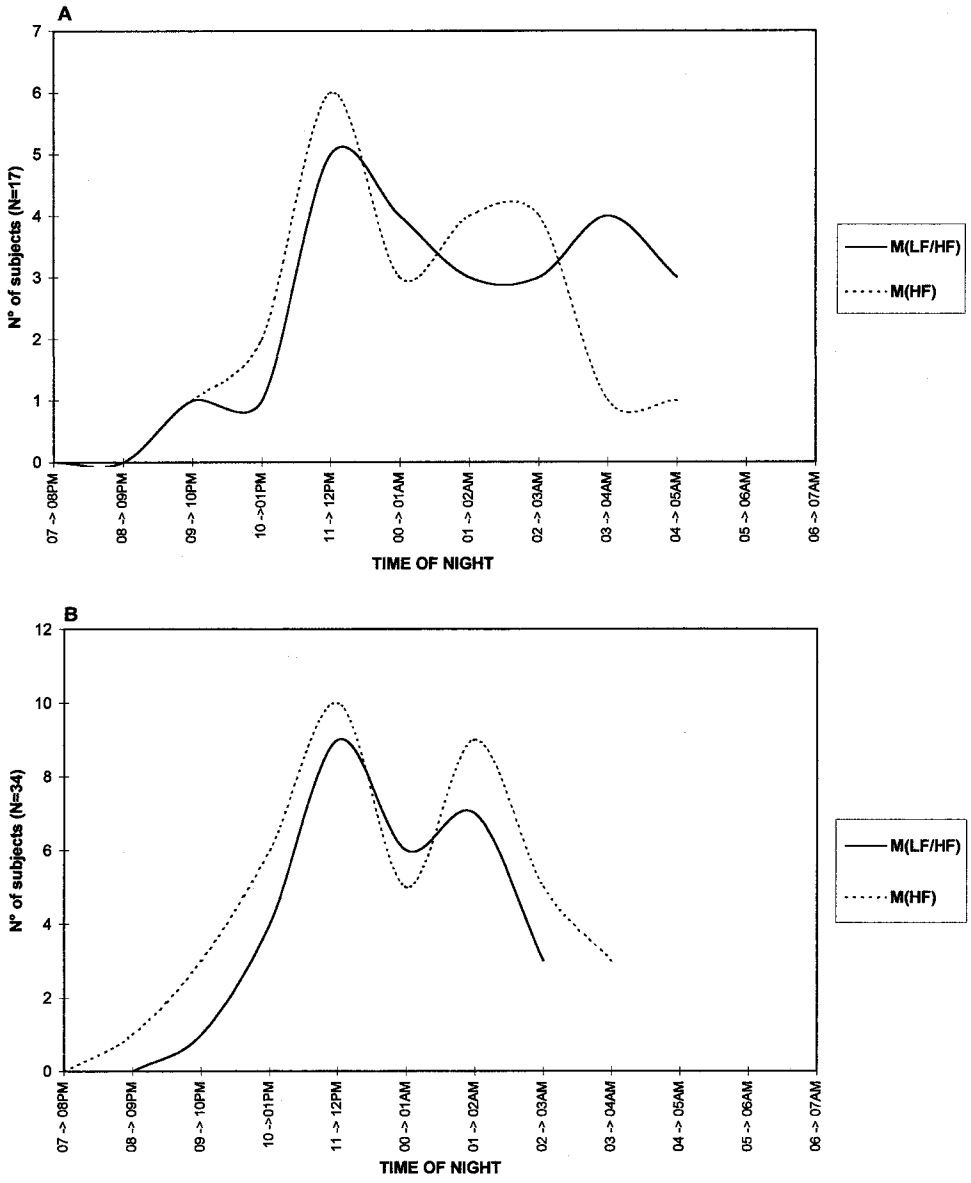

Figure 1. Distribution of first and second maximum peaks of M (HF) and M (LF/HF) throughout the whole-night in sudden infant death syndrome (SIDS) victims **(A)** and control infants **(B)**.

Similar findings were reported for future SIDS victims and were attributed to reduced mobility [22] and high arousal thresholds [42,43].

We must admit that several limitations impinged on our study. Firstly, the limited number of infants studied may contribute to a failure to obtain significance in some analyses. Secondly, the analyses were carried out in a laboratory with sleep analysis fittings (strain gauges and thermistances) that could have disturbed sleep or the autonomic status of infants. Such effects would, however, have influenced both SIDS and control subjects. There was no difference in nursing care, type and time of feeding, ambient temperature, or sleep body position [44] in the two populations studied. Thirdly, no spectral analysis was performed on respiratory movements, and cross-spectral analysis of respiration and HR changes were not evaluated [11,14,15]. A decreased HF energy was measured in all sleep stages when comparing future SIDS victims to the control groups. These results are similar to those reported by authors who used a cross-spectral analysis of respiration and HR changes [11].

Conclusions

Our findings indicate that potential SIDS victims are characterized by high sympathetic HR controls during all sleep stages and by the presence of a high desynchronized peak of sympathetic tonus in the late hours of the night. The present report adds further indirect evidence of a possible sleep-related impairment of autonomic control in some infants who eventually die of SIDS. Our findings, however,

do not permit prospectively identifying an infant at higher risk for SIDS.

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