ELSEVIER

Sleep Medicine 4 (2003) 569–577

SLEEP MEDICINE

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Original article

Autonomic responses to sighs in healthy infants and in victims of sudden infant death

Patricia Franco[a,b,*], Denis Verheulpen[a], Filomena Valente[c], Igor Kelmanson[d], Alain de Broca[e], Sonia Scaillet[b], José Groswasser[b], André Kahn[b]

[a]*Pediatric Sleep Unit, Hôpital Erasme, Brussels, Belgium*
[b]*Pediatric Sleep Unit, University Children's Hospital, Brussels, Belgium*
[c]*Department of Biostatistics, School of Public Health, Université Libre de Bruxelles, Brussels, Belgium*
[d]*Department of Pediatrics, University of St Petersburg, St Petersburg, Russia*
[e]*Department of Pediatrics, CHU Amiens, Amiens, France*

Received 2 January 2003; received in revised form 25 March 2003; accepted 27 March 2003

Abstract

Objective: Sigh, defined as an isolated breath with an increased tidal volume, can be associated with abrupt changes in heart rate (HR) or blood oxygenation. Sigh may be followed by a central apnea. As impairment of autonomic control was postulated in future SIDS victims, we hypothesized that their autonomic responses to sighs were different from those of healthy control infants.

Methods: Sighs followed by central apnea were studied in the sleep recordings of 18 infants who eventually died of SIDS and of 18 control infants. The infants of the two groups were matched for sex, gestational age, postnatal age, weight at birth and sleep position during sleep recording. HR autoregressive power spectral analysis was performed on RR intervals preceding and following sighs.

Results: In all infants, most sighs followed by an apnea were found in NREM sleep. Compared to the control infants, the future SIDS victims were characterized by a greater sympathovagal balance and a lower parasympathetic tonus before the sighs. Following the sighs, no more differences were found in NREM sleep.

Conclusion: Based on the present findings, it can be postulated that sighs contribute to reset autonomic tonus during NREM sleep.

Keywords: Autonomic nervous system; Infant; Sigh; Sleep; Sudden infant death syndrome

1. Introduction

Sighs are initiated by an inspiration-augmenting reflex arising in vagal afferents, probably from stimulations of rapidly adapting pulmonary mechanoreceptors [1] or of peripheral chemoreceptors [2]. The increased afferences to the respiratory brainstem system may also have an influence on the cardiovascular brainstem, reducing the vagotonus and causing acceleration of heart rate (HR) [3]. The apnea following sigh may be secondary to a rapid decline in carotid body chemoreceptor afferent discharge, due to a sigh-induced increase in arterial oxygen concentration and pH and a decrease in carbon dioxide [4,5]. During the ensuing apnea, the vagal inhibition is liberated.

These large breaths occur spontaneously or can induced by lung inflation or airway occlusion [6]. Sighs contribute to open collapsed alveoli, increase pulmonary compliance and functional residual capacity, and prevent atelectasis [7].

Study of autonomic response following a sigh could be a single tool for diagnosis of autonomic dysfunction. Using a Laser Doppler flowmeter to measure the cutaneous vasoconstriction after spontaneous sigh, Galland et al. confirmed a reduced autonomic activity in healthy infants positioned prone to sleep [8]. Changes in cardiac autonomic controls were seen in infants sleeping prone [8,9], prenatally exposed to cigarette smoke [10], or in high ambient

Abbreviations: ANS, autonomic nervous system; HF, high frequency; HR, heart rate; HRSA, heart rate power spectral analysis; LF, low frequency; LF/HF, low frequency to high frequency power ratio; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; SIDS, sudden infant death syndrome.

* Corresponding author. Pediatric Sleep Unit, Neuropediatrics Hôpital Erasme, Route de Lennik 808, 1070 Brussels, Belgium. Tel.: +32-2-555-43-45; fax: +32-2-555-66-56.

E-mail address: patricia.franco@skynet.be (P. Franco).

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doi:10.1016/S1389-9457(03)00107-2

temperature [11]. These conditions, known to increase the risk of sudden infant death syndrome (SIDS), were all associated with a reduced parasympathetic activity as measure on the infants' heart rate (HR) [12–15]. Evidences of changes in cardiac autonomic controls were collected in infants who eventually died of SIDS. Such changes included high baseline HR [16], small HR variability [17], prolonged Q-Tc indexes [18], low parasympathetic tone and/or high sympathovagal balance [19–21].

In future SIDS victims, the frequency of sighs followed by an apnea were reported to be reduced, compared to findings in healthy control infants, raising the possibility of lower peripheral chemoreceptor responses [22].

Based on the above observations, we postulated that autonomic responses to spontaneous sighs were depressed in future victims of SIDS.

2. Method

2.1. Patients

Between May 1992 and May 1995, a polygraphic sleep study was performed on 18 infants who later died of SIDS. These recordings were collected from 13 sleep laboratories. The sleep studies were conducted as part of different sleep research programs or to alleviate parental anxiety about sleep apnea. Two studies on autonomic tonus and autonomic responses after obstructive apnea were already published on this database [21,23]. Of the 18 SIDS, 13 infants were males and six were preterm infants. Two preterm infants had inappropriate weight for gestational age. One infant was a sibling of a SIDS victim. No infant was being monitored at the time of death. The 18 deaths were unexpected and remained unexplained despite complete postmortem studies. For each SIDS recording, a recording of a control infant was selected. Control and SIDS infants were matched for sex, gestational age, postnatal age, weight at birth and sleeping position during recording. All control infants were healthy, had no family history of SIDS and survived the first year of life. At the time of recording, no infant had signs of infection and none were receiving medication. Data on the children's history and usual behavior were collected using a standard questionnaire, before sleep monitoring was undertaken. The questionnaires were coded and analyzed together with the sleep recordings.

2.2. Polygraphic recordings

The infants were admitted for a night monitoring session that lasted 8–9 h. The data were collected on a computerized polygraph recording system (Morpheus system, Medatec, Belgium). The following variables were recorded simultaneously: eight EEGs, two electrooculograms, digastric electromyography, ECG (DII), thoracic and abdominal respiratory movements by inductive plethysmography, and airflow by means of thermistors taped under each nostril and on the side of the mouth. Oxygen saturation was recorded continuously using a transcutaneous sensor (Ohmeda Box, USA).

3. Data analysis

3.1. Sleep stages

Each record was allocated a random code number. The code was disclosed after completion of the analysis. Two independent scorers analyzed the sleep recordings to ensure reliability. The two scorers had not taken part in the collection of the data and analyzed the coded recordings without knowledge of the patient's identity. Disagreements were discussed and subsequently agreed upon codes were used in data analysis. Each 30-s period of the recordings was analyzed and categorized as either non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), indeterminate sleep, 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 the eyes. Sleep efficiency was defined as the ratio of the total sleep time divided by the total recording time, expressed as a percentage.

3.2. Cardiorespiratory parameters

Sleep apneas were scored only if they lasted 3 s or more. A central apnea was scored when flat tracings were obtained simultaneously from strain gauges and thermistors. An obstructive apnea was scored when continuous deflections were obtained from strain gauges, while a flat tracing was recorded from thermistors. To avoid artificial scoring due to thermistor displacement, obstructive apneas preceded by body movements, crying or sighs were rejected. Mixed apneas were defined as central apneas followed directly by obstructive episodes, and were scored with obstructive apneas.

A sigh was defined as a brisk and isolated increase in thoracoabdominal excursion with an amplitude at least twice superior to that measured during the 10 s that preceded the event. Non-specific body movements were distinguished from sighs by the presence of movement artefacts on thermistors and EEG tracings. When more than one sharp increase in respiratory and cardiac amplitude occurred in a row, the event was scored as a movement.

Pre-apneic sighs, sighs immediately followed by an apnea, were the variable of interest in this study. In both NREM and REM sleep, one to two pre-apneic sighs were selected in each SIDS infant and in each control subject for analysis. Median values of blood oxygen saturation were calculated for 10-s periods before each sigh, and the minimum values were noted during the sigh.

According to the methodology used by Eiselt in 1992 [3] (Fig. 1) the following changes in heart rate (HR) were evaluated. Basal median HR values were measured for 10 s preceding a sigh. Percent increase of HR was calculated as the maximum HR values during sigh divided by median basal HR values multiplied by 100. Median and minimum heart rate values associated with apnea following sigh were measured. Percent decrease of HR was calculated on the minimum values seen during apnea. Percent of changes corresponded to the difference between maximum HR values during sigh and minimum HR values during apnea following the sigh divided by median basal HR values multiplied by 100. Median heart rate changes were calculated after the end of apnea: 20 s following the end of a sigh divided into two successive groups of 10 s. To evaluate the speed of the return to basal HR, the percent changes in HR were calculated between the maximum HR values reached during each 10-s period and the minimum HR values during apnea following the sighs divided by median basal HR. The percent HR changes were calculated on the maximum HR values reached during each 10-s period and the median basal HR.

3.3. Heart rate spectral analysis

Spectral analysis of the heart rates (HRSA) was done as follows. Digitized ECG signals were sampled at 300 Hz. Periods of 256 successive RR intervals were selected

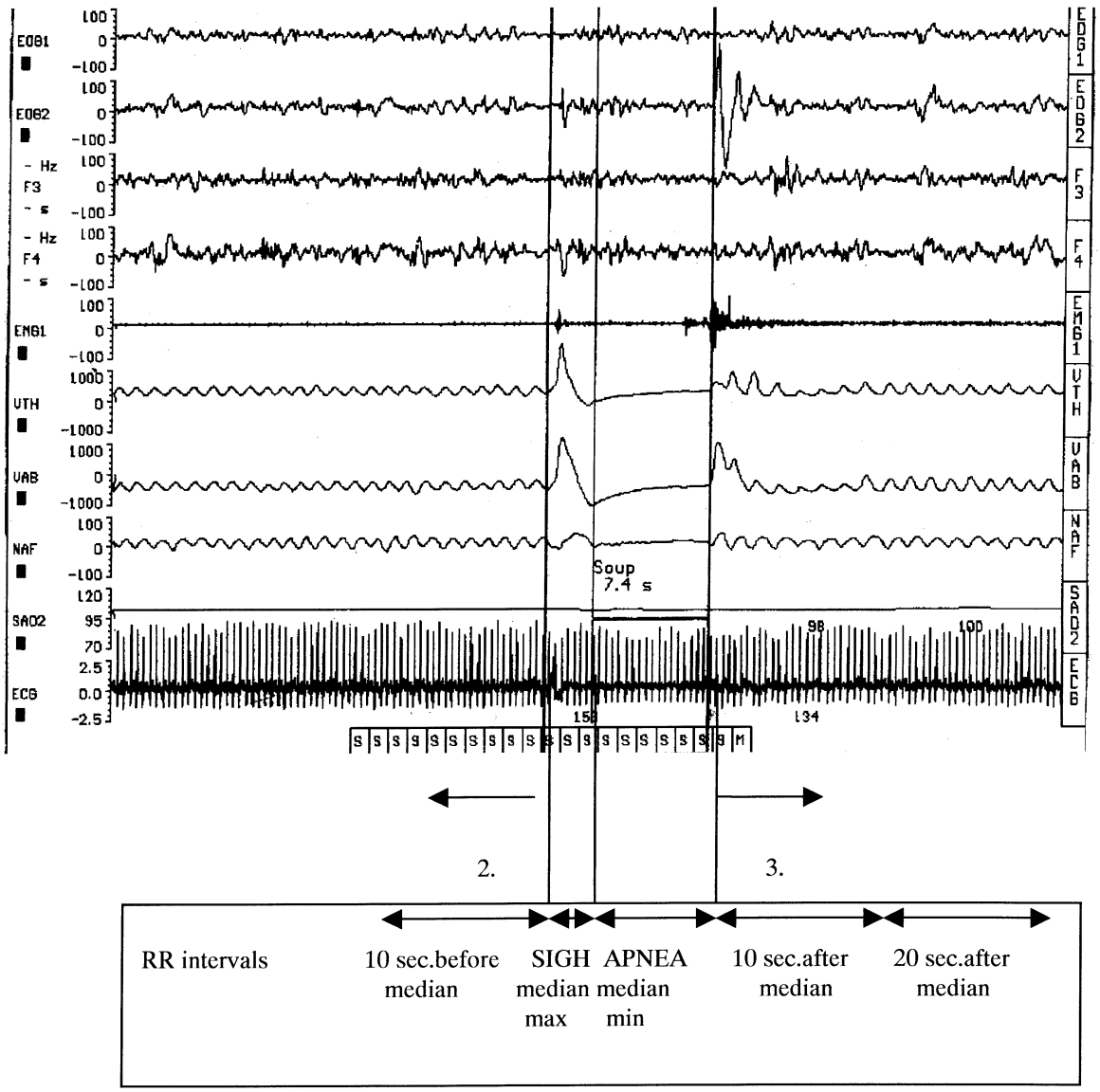

Fig. 1. Polysomnographic recording of a sigh. From surface electrocardiogram, HR spectral analyses of 256 RR intervals were calculated before (2) and after the end (3) of the apnea following the sigh. Calculation of heart rate changes during sigh: median value 10 s before; median and maximum values during sigh; median and minimum values during apnea; median values 10 and 20 s after sigh. ECG, electrocardiogram; EMG, electromyogram; EOG [1,2], electrooculogram [1,2]; F3-C3 and F4-C4, bipolar EEGs; VTH and VAB, thoracic and abdominal volumes; NAF, nasal thermistor; SAO2, saturation in oxygen.

preceding and following the end of a sigh (Fig. 1). This method has already been used before and after obstructive apnea in future SIDS infants [23]. Premature ventricular contractions or artefact RR intervals due to gross body movements or arousals were eliminated by visual analysis of the HR data before HRSA was performed. A HRSA of the trendgram was calculated for each period, and center frequency and power of each spectral component were obtained [26,27]. Two major peaks were recognizable: a low-frequency component (LF) defined by center frequency of 0.1 Hz Eq (0.04–0.15 Hz Eq) and a high-frequency component (HF) defined by a center frequency of 0.4 Hz Eq (>0.15–2 Hz Eq) [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 to the major component in the HF band corresponding to the mean respiratory frequency as determined by analysis of breathing rate. Because of the possibility of variation of the breathing rate within the selected segment, we compared the normalized powers obtained by this method (major component of the band) with the results obtained when the totality of the band was studied: LF band: 0.04–0.15 Hz Eq, HF band: >0.15–2 Hz Eq. The ratio of LF/HF powers for each episode was calculated as an index of sympatho-vagal interaction [28]. Spectral components were represented as RR intervals (in ms), power (in ms^2), bandwidth (in Hz Eq), and normalized power values, obtained by dividing the power of the period by the total power component (in %) [26,27]. The optimal autoregressive model order was determined by minimizing the value of the final predictor error [29]. Stationarity was confirmed by a pole diagram analysis [26,27].

3.4. Statistical analysis

Wilcoxon matched-pairs signed rank test was used to compare the SIDS case with the matched control subjects. Wilcoxon non-paired matched test was applied to compare the spectral analysis values between the future SIDS victims and the control group. Chi-square test was used with 2×2 tables. Significance was evaluated with a level of significance of 0.05.

4. Results

The general characteristics of the infants studied are reported in Table 1. Due to the study design, no difference was seen between the future SIDS and the control subjects for sex, gestational age, postnatal age, weight at birth and sleeping position. Mothers of the future SIDS victims were younger than those of the control infants ($P = 0.022$). Only one infant died after 6 months of age at 36 weeks.

No significant differences were seen between the two groups of infants for the following sleep variables: total recording time (median duration 480 min; range: 330–510 min), total sleep time (median of 347 min for SIDS infants, 370 for control infants; range 210–478 min), sleep efficiency (median of 80.2% for SIDS infants, 77.3% for control infants; range 48–100%), percent of NREM sleep (median of 29.9% for SIDS infants, 32.6% for control infants; range 16.6–43.1%), percent of REM sleep (median of 46.1% for SIDS infants, 42.6% for control infants; range 22.7–69.8%), number of sleep stages changes (median of 15.5 for SIDS infants, 17 for control infants; range 11–23), percent of movements (median of 4.65% for SIDS infants, 4.00% for control infants; range 0–15.70%), percent of behavioral arousals (median of 15.4% for SIDS infants, 17.8% for control infants; range 0–46.60), frequency of central apneas per sleep hour (median of 6.6 for both SIDS and control infants; range 0.6–19.2), maximum duration of central apnea (median of 8 s for SIDS infants, 7 s for control infants; range 5.0–10.2 s), basal HR in NREM sleep (median of 133 bpm for SIDS infants, 125.5 bpm for control infants; range 110–155 bpm), basal HR in REM sleep (median of 136 bpm for SIDS infants, 131 bpm for control infants; range 111–156 bpm), basal breathing rate in NREM sleep (median of 39 breaths per min for SIDS infants, 28 breaths/min for control infants; range 22–62 breaths/min), basal breathing rate in REM sleep (median of 43 breaths/min for SIDS infants, 34 breaths/min for control infants; range 25–62 breath/min), oxygen saturation values (median of 93.7% for SIDS infants, 95.8% for control infants; range 86.5–98.6%).

Table 1
Major characteristics of infants studied

	SIDS infants	Control infants
No.	18	18
Gender (M/F)	13/5	13/5
Gestational age (weeks)	38 (27–41)	38 (27–41)
Age at sleep study (weeks)	8 (5–19)	8 (5–19)
Birth weight (g)	2.925 (0.96–3.980)	2.790 (1.090–3.840)
Sleep position (prone/supine)	9/9	9/9
Preterm infants	6	6
Small for gestational age	2	2
Age at death (weeks)	13.5 (10–36)	–
History		
Sibling of SIDS cases	1	0
Maternal smoking	4	2
Maternal age (years)[a]	24 (20–29)	27 (21–36)

The figures represent absolute, median and range values.
[a] Wilcoxon matched-paired test between SIDS cases and controls, $P < 0.05$.

As shown in Table 2, the frequency of obstructive and mixed sleep apneas was greater among the future SIDS than the control infants. No significant differences were found between the two groups for the duration of the obstructive or mixed apneas.

The frequency of isolated and pre-apneic sighs was not significantly different in the two groups of infants (Table 2).

Table 2
Respiratory characteristics of SIDS cases and matched control infants

Respiratory events /h of sleep	Future SIDS Infants	Control Infants
Obstructive apneas*	0.60 (0–2.3)	0 (0–1.5)
Mixed apneas*	0.30 (0–2.5)	0 (0–0.6)
All obstructive events**	0.90 (0–4.8)	0.3 (0–1.9)
Isolated sighs	4.28 (0.7–13.2)	3.78 (0–19.1)
Pre-apneic sighs	2.60 (0.2–7.5)	2.3 (0.6–6.1)
In NREM sleep	4.24 (0.89–12.10)***	3.61 (0–13.48)***
In REM sleep	0.05 (0–0.11)	0.04 (0–0.15)

The figures represent absolute, median and range values. Wilcoxon matched-paired test between SIDS cases and controls: $*P < 0.05$; $**P < 0.01$. Wilcoxon matched-paired test between pre-apneic sighs in NREM and REM sleep in SIDS cases and in controls: $***P < 0.001$.

Pre-apneic sighs were preponderant in NREM sleep for future SIDS and control infants.

4.1. In NREM sleep

In NREM sleep, one to two pre-apneic sighs were selected in each SIDS infant (29 events) and in each control subject (30 events). No difference was seen between the two groups for the duration of the central apnea that followed the sighs (median of 6 s in future SIDS victims and 5 s in control infants; range 3.2–8.8 s). Likewise, no difference was seen for the time of the night of the selected sighs (median 5:01 AM in future SIDS victims and 4:28 AM in control infants; range 21:56–6:12 AM). Oxygen blood saturation values preceding the pre-apneic sighs were not statistically significant in the two groups (median of 97.5% in future SIDS victims; for 99% in control infants; range 95–100%). The minimum oxygen values during the sighs were not different for the two groups (median of 96% in future SIDS victims; range 89–100%; for 97% in control infants; range 94–98%).

As seen in Table 3, HR variations during sighs were smaller in the future SIDS victims than in the control infants (Fig. 2). Return to basal HR values was significantly slower in the SIDS infants than in the control infants.

When comparing the two groups of infants for HR spectral analysis preceding the sighs (Table 4), the future SIDS victims were characterized by significantly lower normalized HF values ($P = 0.013$), wider HF bandwidths ($P = 0.017$), greater normalized LF values ($P = 0.030$) and LF/HF ratios ($P = 0.030$). When comparing the SIDS and the control infants' HR spectral analysis following the sighs, no significant differences were found in these values. The results were similar when the major components within the band or the totality of the HF spectral band were studied.

Comparing the HR power values before and after each sigh, significantly increases in HF normalized band power ($P = 0.030$) and decreases in LF normalized values ($P = 0.030$) were measured in the future SIDS victims. The LF/HF power ratios tended to decrease in future SIDS victims ($P = 0.08$). No statistical differences were seen in control infants.

4.2. In REM sleep

In REM sleep, one to two pre-apneic sighs were selected in each SIDS infant (28 events) and in each control subject (29 events). No difference was seen between the two groups for the duration of the apneas, the time of the night of the selected sighs, oxygen blood saturation values preceding the pre-apneic sighs. HR variations during sighs were smaller in the future SIDS victims than in the control infants. These results did not reach statistical significance in this sleep stage.

When comparing the two groups of infants for HR spectral analysis preceding the sighs (Table 5), the future SIDS victims were characterized by significantly lower normalized HF values ($P = 0.005$) and greater LF/HF ratios ($P = 0.001$). When comparing the SIDS and the control infants' HR spectral analysis following the sighs, the difference persisted with lower normalized HF values ($P = 0.002$) and greater LF/HF ratios ($P < 0.001$). Comparing the HR power values before and after each sigh, no differences were seen in either future SIDS victims or control infants.

5. Comparison between REM and NREM sleep

In both future SIDS victims and control infants, comparing NREM sleep to REM sleep, the cardiac parasympathetic activity appeared to be significantly greater, as expressed by differences in high-frequency normalized powers, high frequency bandwidth and the sympathetic tonus lower reflected by LF normalized power and low/high power ratios (Tables 4 and 5). These results were found before and after the sighs. After the end of apnea following the sigh, the percent heart rate decrease was higher during NREM sleep than during REM sleep in future SIDS infants (median of 2.38% in NREM; range 0–12.28%; for 0.77% in REM; range 0–22.8%) ($P = 0.012$) and in control infants (median of 2.96% in NREM; range 0–16.28%; for 1.21% in REM; range 0.87–13.12%) ($P = 0.033$).

No differences were seen when the changes in HR spectral analysis associated with sighs were studied in relation to sleep position, sex, prematurity, age or maternal smoking.

6. Discussion

Compared to the control infants, future SIDS victims had lower values of HF normalized powers and higher LF/HF power ratios in all sleep stages. These differences were, however, not seen following the sighs in NREM sleep. It can

Table 3
Heart rate changes during sighs in NREM

	SIDS	Controls
No of sighs	29	30
Before Sighs (basal)		
Median HR 10 s	134 (114-151)	129 (118–151)
During sighs		
Median HR	142 (119.5-157.5)	141 (126–155)
Max HR	142 (125-160)***	142 (130–160)***
% Max HR/basal HR†	5.96 (−3.01-28.21)	8.80 (1.32–29.66)
During apnea		
Median HR	130 (98.5-150)	123 (109–148)
Min HR†	122 (90-148)***	115 (90–141)***
% Min HR/basal HR†	8.27 (−0.85–21.40)	12.20 (0–29.32)
% HR changes/basal HR‡	14.93 (1.5–38.43)	22.22 (6.35–53.39)
After apnea		
Median HR 10 s	130.5 (100-151)***	127 (108–142)***
% HR changes/min HR	5.26 (0–28.89)	7.50 (0–47.78)
% HR changes/basal HR	2.38 (−2.56–12.28)	2.96 (−12.71–16.26)
Median HR 20 s	133 (101-153)***	129 (112–144)**
% HR changes/min HR†	6.03 (0–21.67)	10.43 (−0.76–54.44)
% HR changes/basal HR	2.38 (−2.56–11.40)	1.55 (−17.8–13.18)

The figures represent absolute values, percentages, or median and range values. Wilcoxon non-matched-paired test between sigh characteristics in SIDS cases and controls: †$P < 0.05$; ‡$P < 0.01$. Wilcoxon matched-paired test between basal HR to Max HR, to Min HR, to HR 10 s after sigh and to HR 20 s after sigh: **$P < 0.01$, ***$P < 0.001$.

be hypothesized that autonomic reactions following the sighs were different in NREM and REM sleep. The sighs could thus contribute to reset the autonomic tonus in NREM sleep.

We must admit several limitations to the present study. First, we could not measure tidal volume to score the sighs. Body movements were, however, carefully excluded during scoring [3]. Second, it was hypothesized that before and following sighs, the HR varied in a sinusoidal fashion, a prerequisite for the application of Fourier analysis. For this reason, an autoregressive spectral analysis method was used, being well suited for the analysis of short time series [21]. Third, no spectral analysis was performed on respiratory movements, and cross-spectral analysis of respiration and HR changes were not evaluated [21]. The major component in the HF band corresponding to the mean

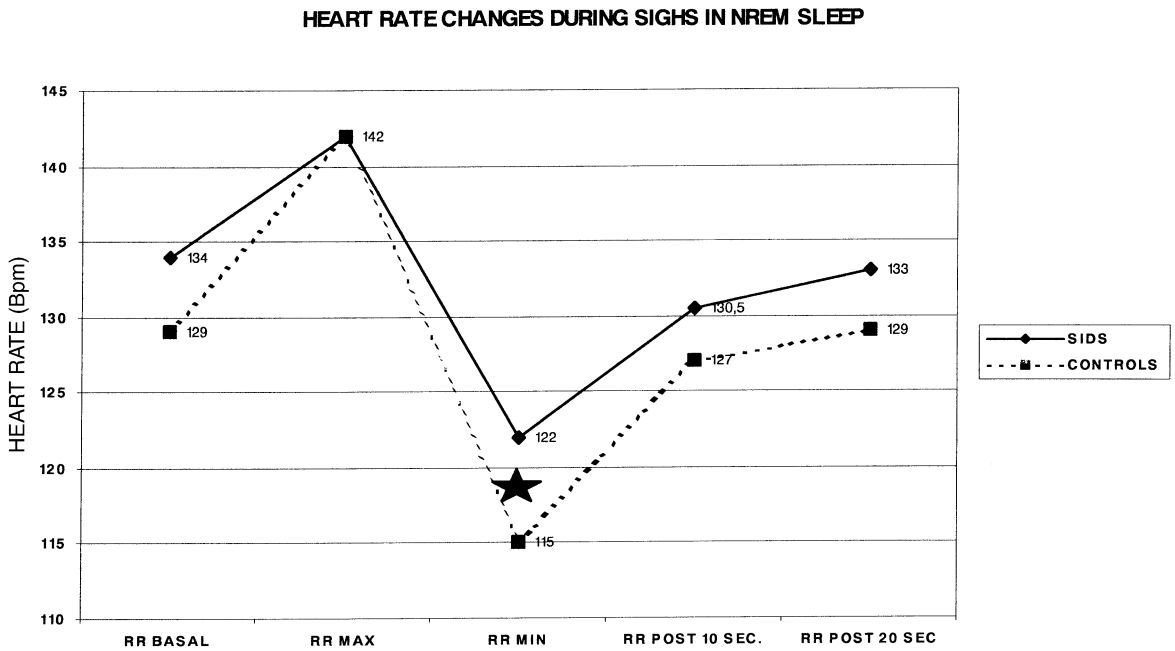

Fig. 2. Sigh-related heart rate changes. Heart rate changes during periods with sighs during NREM sleep in future SIDS victims (solid line) and control infants (dashed line). HR variations during sighs were smaller in the future SIDS victims than in the control infants (★). Return to basal HR values was significantly slower in the SIDS infants than in the control infants.

Table 4
Heart rate spectral analysis before and after pre-apneic sighs in NREM

	SIDS infants	Control infants
No of sighs	29	30
Before pre-apneic sighs		
LF Normalized power (%)†	73.00 (49.90–92.10)	64.30 (8.40–90.80)
HF Normalized power (%)†	10.60 (3.10–27.20)	18.25 (4.30–66.40)
HF band (0.15 to >2 Hzeq)†	27.00 (7.90–50.10)	35.70 (9.20–91.60)
HF bandwidth (Hzeq)†	0.13 (0.04—0.28)	0.08 (0.02—0.19)
LF/HF power ratio (%)†	2.70 (1.00–11.66)	1.80 (0.09—9.87)
After apnea		
LF Normalized power (%)	65.80 (36.80–91.20)*	65.85 (19.70–88.40)
HF Normalized power (%)	13.10 (5–36.70)	15.50 (3.60–63.40)
HF band (0.15 to >2 Hzeq)	34.20 (8.80–63.20)*	34.15 (11.60–80.30)
HF bandwidth (Hzeq)	0.11 (0.03–0.19)	0.09 (0.01—0.17)
LF/HF power ratio (%)	1.92 (0.58–10.36)	1.93 (0.25—7.62)

The figures represent median and range values. HF, high frequency; LF, low frequency; LF/HF, low frequency/high frequency ratio; Wilcoxon non-matched-paired test between spectral analysis in SIDS cases and controls: $^{\dagger}P < 0.05$. Wilcoxon matched-paired test before and after sighs in SIDS cases and controls: $^{*}P < 0.05$.

respiratory frequency was studied, as well as the HF band to consider the breathing variations within the selected segment. In our previous studies comparing future SIDS victims with control infants, our results were similar to those of Kluge who used cross-spectral analysis of respiration and heart rate changes [16]. Fourth, the interpretation of the LF/HF ratio is complex [30]. Within the low frequency range, the HR fluctuations depend on both sympathetic and parasympathetic controls. The band under 0.09 Hz represents fluctuations of vasomotor or thermal origin [28]; the mild frequency band (between 0.1 and 0.15 Hz) has been related to baroreceptor control [31]. The power in these two frequency bands usually merges into one wide peak. The respiratory peak has been shown to be mainly vagally mediated [32]. The vagal efferent fibers could not originate in a common brainstem structure. The HF peak, which corresponds to the respiratory sinus arrhythmia, would reflect only the part of the vagal efferent system from the nucleus ambiguus [33]. Spectral HR techniques cannot permit us to evaluate the influence of the other branch of the parasympathetic system from the dorsal motor nucleus [33], although it was suggested that competition between the two branches of parasympathetic system could be responsible for autonomic dysfunction [33].

We failed to confirm the previously reported observation that future SIDS victims had fewer sighs followed by an apnea than control infants [22]. The discrepancy could result from the selection of a different SIDS subpopulation, considering the possible heterogeneity of causes leading to SIDS. However, other retrospective and prospective studies failed to show a difference in the frequency of all types of sighs [21,34,35].

Heart rate oscillations with respiration are well known. They are attributed to vagal reflex mediated by lung receptors [36]. HR changes more during a sigh than during a normal breath, because of the greater associated lung

Table 5
Heart rate spectral analysis before and after pre-apneic sighs in REM

	SIDS infants	Control infants
No of sighs	28	29
Before pre-apneic sighs		
LF Normalized power (%)‡	89.35 (46.60–97.50)***	80.25 (46.60–94.30)***
HF Normalized power (%)‡	4.70 (1.00–19.30)***	7.70 (1.90–22.30)***
HF band (0.15 to >2 Hzeq)‡	10.65 (2.50–53.70)***	19.75 (5.70–53.40)***
HF bandwidth (Hzeq)	0.15 (0.05–0.22)*	0.14 (0.07–0.30)***
LF/HF power ratio (%)‡	8.42 (0.86–39.00)***	4.42 (1.07–16.54)***
After apnea		
LF Normalized power (%)†	88.00 (30.30–98.10)***	80.50 (43.90–92.40)***
HF Normalized power (%)‡	5.10 (0.50–41.20)***	9.55 (2.10–26.10)***
HF band (0.15 to >2 Hzeq)†	12.00 (1.90–69.70)***	19.50 (7.60–56.10)***
HF bandwidth (Hzeq)	0.13 (0.01–0.26)**	0.14 (0.02–0.23)***
LF/HF power ratio (%)†	7.34 (0.43–51.63)***	4.13 (0.78–12.16)***

The figures represent median and range values. HF, high frequency; LF, low frequency; LF/HF, low frequency/high frequency ratio; Wilcoxon non-matched-paired test between spectral analysis in SIDS cases and controls: $^{\ddagger}P < 0.01$; $^{\dagger}P < 0.001$. Wilcoxon non-matched-paired test between spectral analysis in REM and NREM in SIDS cases and controls: $^{*}P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.001$.

inflation [4]. As already reported in infants, sighs immediately followed by an apnea occurred mainly in NREM sleep [5,7]. At the end of the apnea following the sighs, the HR decrease was greater in NREM than in REM sleep. HR deceleration during NREM is the main difference between sigh-related heart rate changes in both sleep states [3]. The mechanisms responsible for these differences in NREM sleep are not known. This difference may be related to differences between states concerning the tonic innervations of muscles [37] or to different responses to pulmonary stretch receptor stimulations [38,39]. During REM sleep, both sensory and motor functions are impaired that result in postsynaptic inhibitions of motoneurons producing postural hypotonia and contribute to the impairment of ventilatory responses [37]. Inflation reflex is practically abolished during REM sleep in dogs and human infants [38,39]. As usually reported, cardiac parasympathetic tone was significantly lower and orthosympathetic activity higher in REM than in NREM sleep [30,40,41]. The increase of sympathetic activity in REM sleep is essentially due to the high incidence of phasic events with accompanying pulses of sympathetic activity [40]. An attenuated vagal or increased sympathetic activity could reduce behavioral adaptation to internal or exogenous stimuli [42].

The decreased HR responses during sighs in future SIDS victims could result from an impairment of autonomic controls, as postulated to occur in these infants [16–21]. The future SIDS victims had lower values of normalized HF powers and higher values for LF/HF power ratios, than the control subjects [19–21]. As already observed, the future SIDS victims had also less sustained HR changes [43] and decreased cardiac autonomic responses to obstructive apneas [23]. In response to sighs, future SIDS victims had smaller and more prolonged reactions than control infants in NREM sleep, permitting the return of autonomic tonus to normal values. These changes resulted in an increase in parasympathetic tone and a decrease in sympathetic activity.

As already reported, increases in the frequency of obstructive apneas were seen in future SIDS infants [34,44]. At postmortem investigations, some future SIDS infants showed gliosis of the brainstem and hyperplasia of pulmonary neuroendocrine cells, considered to be secondary to repeated episodes of hypoxia and to a possible impairment in upper airway breathing controls [45–47]. Basal oxygen saturation values in our study tended to be lower in future SIDS victims than control infants but did not reach statistical significance.

Repeated investigations have provided evidence of subtle brainstem injury in SIDS victims [48–52]. Such changes could impair cardio-respiratory and autonomic controls in the infants at risk [52]. Although it is not possible at this state to establish which sleep states, REM or NREM represents a more vulnerable period for the infant. During NREM sleep, sighs could play a role of regulation by resetting the autonomic tonus in conditions of autonomic imbalance, such as appear to occur in future SIDS victims. The relation with changes in cardiac autonomic controls associated with the sighs could result from the complex control mechanisms for sighs, which include a medullary network [53] and forebrain structure [4].

In conclusion, sighs could be involved in autonomic control. It remains to be evaluated whether the present findings contribute to our understanding of the physiological mechanisms of sighs and their role in some cases of unexpected infant deaths during sleep.

Acknowledgements

The authors gratefully acknowledge the physicians of the 12 other sleep units for their collaboration: F. Alu (St. Elizabeth), F. Ravet (Citadelle), F. Lemmens (St Jans Ziekenhuis), M. Foulon (Hôpital Civil), Y. Vandeplas (AZ VUB), F. Van Horebeke (Onze Lieve Vrouw), R. Vinckx (Imelda Ziekenhuis), J. Barillari (Kiniek Maria Midelares), R. Marien (HZ St Augustinus), F. Deneyer (Vilvoorde Ziekenhuis), J. Van Egemont (UZ Gent), F. Michel (Cliniques St Pierre).

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