

Precursors of Cardiorespiratory Events in Infants Detected by Home Memory Monitor

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Summary. In 1,079 infants monitored for >700,000 hr at home for apnea or bradycardia, we found an association between infants having multiple events exceeding conventional or a priori defined more extreme thresholds and less favorable developmental outcome at 1 year of age than infants with few or no events. If it is necessary to prevent such events to minimize risk for developmental morbidity, there is reason to determine whether there are disturbances in advance of the apnea or bradycardia that herald their onset. In the 85 infants with at least 1 extreme event and 1 conventional event, we hypothesized that apnea and bradycardia do not occur de novo but rather are preceded by cardiorespiratory and hemoglobin O₂ saturation changes. We compared recorded time intervals preceding these events, and we analyzed three preceding time intervals for each conventional and extreme event, and each non-event recording: Time-2 hr: up to 2 hr before; Time-1 hr: up to 1 hr before; and Time-75 sec: the 75 sec immediately preceding each event. O₂ saturation progressively decreased preceding both conventional and extreme events, and progressive increases occurred in heart and breathing rate variability. Duration of respiratory pauses and of periodic breathing progressively increased preceding conventional events, respiratory rate variability increased immediately preceding conventional events and at 1 hr preceding extreme events, and O₂ saturation decreased immediately preceding both conventional and extreme events. Thus, conventional and extreme events do not occur de novo but rather are preceded by autonomic instability of the cardiorespiratory system. **Pediatr Pulmonol.** 2008; 43:87–98. © 2007 Wiley-Liss, Inc.

Key words: apnea; bradycardia; sudden infant death syndrome (SIDS); hemoglobin O₂ saturation (SpO₂); prematurity.

INTRODUCTION

One of the prime purposes of The Collaborative Home Infant Monitoring Evaluation (CHIME) was to determine

whether infants who had cardiorespiratory monitoring due to perceived high risk for sudden infant death syndrome (SIDS), had prolonged apnea or bradycardia.¹ During >700,000 hr of home monitoring, we assessed the

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TABLE 1—Definitions for Each (A) Event Type and (B) Cardiorespiratory Variable¹

Event category	Definition
A	
Non-event (NE)	Routinely recorded physiologic data during the first 3 min of each clock-hour of monitor use
Conventional event (CE)	Apnea 20–29 sec (measured as duration of time with RIP sum channel amplitude <25% of baseline), or bradycardia (if <44 weeks PMA) <60 bpm for ≥5 sec or <80 bpm for ≥15 sec, or (if ≥44 weeks PMA) bradycardia <50 bpm for ≥5 sec or <60 bpm for ≥15 sec
Extreme event (EE)	Apnea for ≥30 sec (duration of RIP sum channel amplitude <25% of baseline), bradycardia (if <44 weeks PMA) <60 bpm for ≥10 sec, or (if ≥44 weeks PMA) bradycardia <50 bpm for ≥10 sec
Physiologic variable	Definition
B	
Median heart rate (beats/min)	Median of all heart rate values measured during each time interval. Computed using R-wave detection algorithm on beat-by-beat basis
Median breathing rate (breaths/min)	Median of all breathing rate values measured during each time interval. Computed on breath-by-breath basis
Median respiratory inductance plethysmography (RIP) Sum (%)	Median of all RIP Sum values measured during each time interval. Value for weighted Sum signal, as a percent (%) of baseline, calculated on a breath-by-breath basis. Proportional to tidal volume
Duration of respiratory pauses (sec/min)	Cumulative duration of pauses of 5–19 sec/min of recording, measured from the RIP Sum channel
Duration of periodic breathing (sec/min)	Sequence of at least three pauses >3 sec duration separated by less than 20 sec of breathing. Measured from beginning of first apnea to end of last apnea in sequence. Expressed as total duration per minute of recording
Median SpO ₂ (%)	Arterial hemoglobin oxygen saturation associated with normal pulse oximeter waveform (consistent systolic upstroke time)

See text and Refs. 1,5–8 for additional details.

¹Variability in respiratory and heart rates was quantified based on the IQR (see text).

frequency of apnea and bradycardia in the first few months after birth in 1,079 infants selected because they were either premature, a sibling of a prior SIDS (SIDS Sib), had an apparent life-threatening event (ALTE), or were a healthy term infant. We utilized a monitor that could detect apnea or bradycardia events based on “conventional” alarm thresholds commonly used at the time the study was initiated in the mid-1990s. In addition, because many of the conventional events (CE) were not necessarily considered clinically relevant we also assessed the frequency of a priori defined “extreme” events (EE), those with more severe bradycardia or apnea (see Table 1A for definitions). We recorded 6,933 conventional events in 445 infants, of which 653 were EE in 116 of the infants. Although heart rate and apnea were the signals used for

defining the events, we also determined that the more severe or prolonged the events the more likely and the more severe the associated hypoxemia.¹ During subsequent evaluation, we found that both the full term and preterm groups with multiple events had less favorable developmental outcome at 1 year of age than infants with few or no events, as assessed by the Bayley Scales of Infant Development.² These delays are not just related to prematurity since similar differences also occurred in the full term group. These data do not clarify the extent to which the events are causal or both the events and the developmental delays share a common underlying etiology.

Although the extreme cardiorespiratory events (EE) occurring in infants using the CHIME monitor were not immediate precursors to SIDS,¹ the association of multiple events with diminished infant development does suggest that such events may have important and clinically significant adverse effects independent of any potential mortality-related risk. If it is indeed necessary to prevent prolonged events in order to minimize risk for developmental morbidity, a first task is to determine if there are any indicators of an impending abnormality in cardiorespiratory control that can be detected prior to the events or whether such events occur suddenly and unpredictably.

The purpose of the present study was to determine whether there are physiologic disturbances occurring in

ABBREVIATIONS

ALTE	Apparent life-threatening event
CHIME	Collaborative Home Infant Monitoring Evaluation
CE	Conventional event
EE	Extreme event
IQR	Interquartile range
NE	Non-event
RIP	Respiratory inductance plethysmography
SpO ₂	Hemoglobin O ₂ saturation
SIDS	Sudden infant death syndrome
SIDS Sib	Sibling of a prior SIDS infant
T	Time

advance of the apnea or bradycardia that herald their onset and that precede the hypoxemia typically observed with prolonged apnea or bradycardia. The CHIME monitor was designed to record not only the events reaching threshold criteria for conventional events and the 75 sec preceding these events but also to automatically record physiologic data during the first 3 min of each monitor hour, hence yielding a large number of recorded intervals during which there was no event (non-events). To test the hypothesis that CE and EE do not occur de novo but rather are preceded by cardiorespiratory disturbances, we examined the pattern of cardiorespiratory function during time intervals up to 2 hr preceding EE and CE in comparison to intervals with non-events (NE).

MATERIALS AND METHODS

CHIME Study

Enrollment began in May 1994 and ended in February 1998. There were 1,079 infants enrolled who used the monitor, including 443 premature infants <1,750 g and <34 weeks postmenstrual age at birth, 152 infants with an apparent life-threatening event (ALTE), 178 SIDS Sibs, and 306 healthy full term infants.¹ The ALTE and SIDS Sibs groups collectively included 95 infants (29%) born preterm, 84% of whom were late preterm infants born at 34–37 weeks postmenstrual age.

Subjects

Our goal was to select that subset of infants whose home monitoring recordings included at least one EE, CE, and non-event (NE) (see Table 1A for definitions). This strategy permits comparison of physiologic variables preceding each event category in which each infant serves as his/her own control. Among the 1,079 infants, 116 infants had at least 1 EE (Fig. 1). After excluding infants for whom the EE did not include an SpO₂ signal, did not have an eligible CE, or did not have an eligible NE, 85 CHIME infants met the criteria for this analysis. The number of eligible EE ranged from 1 to 37 per infant, and the number of eligible CE ranged from 1 to 210 per infant.

Measures

We randomly selected one EE when more than 1 existed, and then selected one CE and one NE according to the following conditions:

- For all EE, CE, and NE, an SpO₂ signal had to be present.
- The selected EE had to be at least 2 hr away from a preceding EE. (Any subsequent EE occurring within 2 hr was considered part of the recovery from the preceding EE).

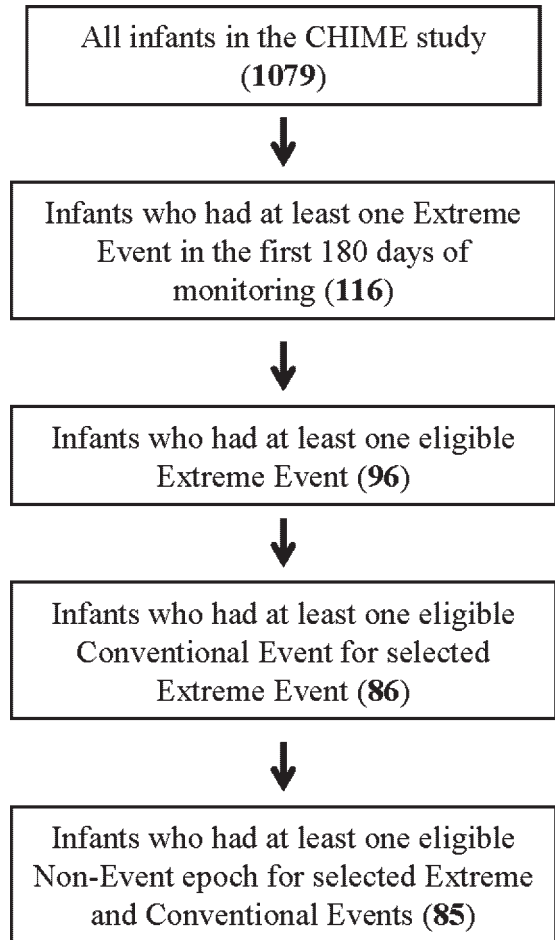


Fig. 1. Eligibility criteria and selection process for infants included in this analysis of onset characteristics.

- The selected CE had to be at least 2 hr after any preceding CE and the closest to the selected EE, but had to be at least 2 hr away from any EE.
- The selected NE had to be separated from any EE or CE by at least 12 hr.

Protocol

For each selected event, we identified three time (T) intervals (Fig. 2): T-75 sec, the 75 sec immediately preceding the event of interest (for NE we used the 3 min recorded interval itself); T-1 hr, the 3 min automatically sampled interval recorded up to 1 hr before the event of interest; and T-2 hr, the automatically sampled 3-min interval recorded 1 hr before T-1 hr. Within each of the three time intervals, we identified the longest baseline time period in which it was possible to obtain clear measurements of breathing (shaded boxes in Fig. 2). These baseline periods had to be at least 15 sec beyond the beginning of the epoch, contain at least three breaths, be free of movement artifact and sighs, and had to be at least

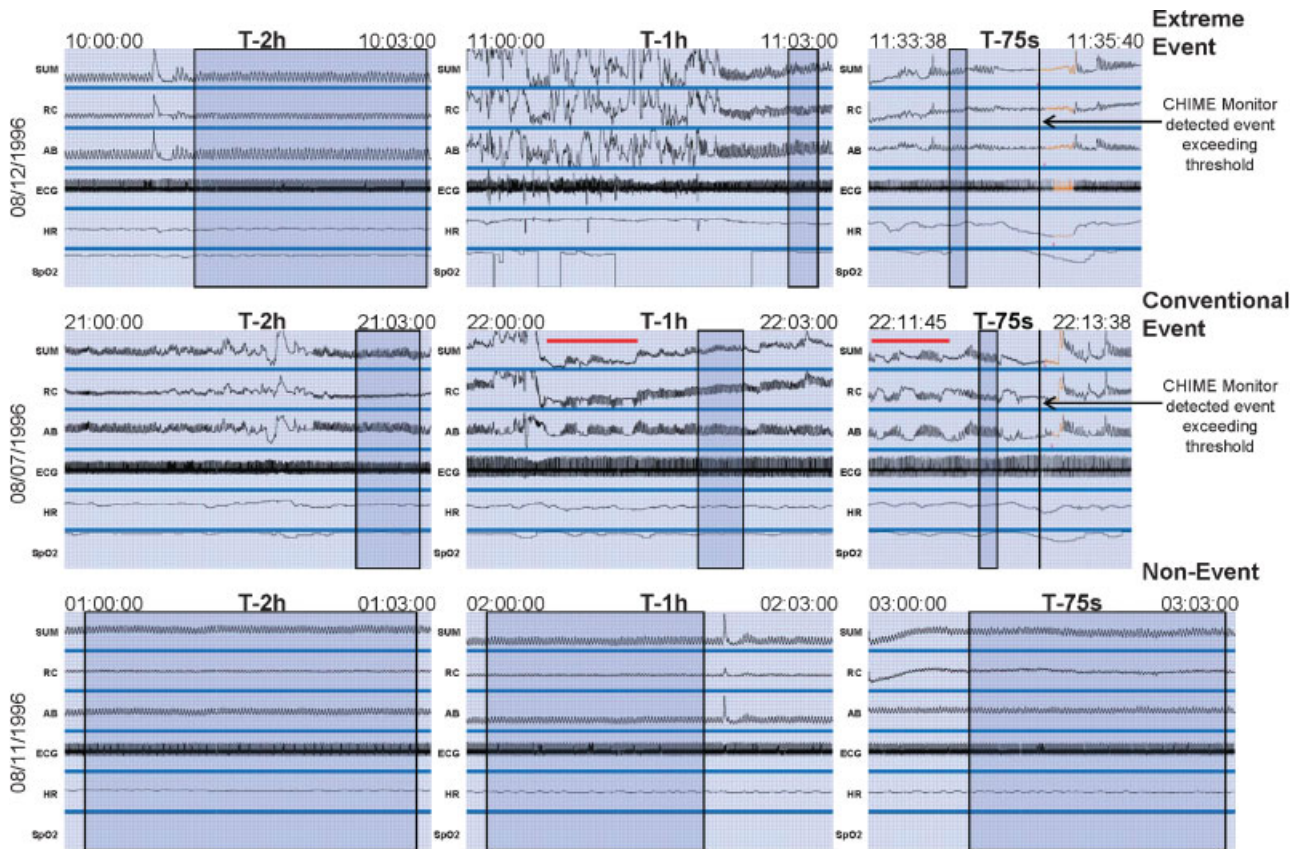


Fig. 2. Representative complete set of analyzed intervals in one infant. For each conventional and extreme event and each non-event epoch, 3-min automatically recorded segments were available up to 2 hr before (T-2 hr) and up to 1 hr before the event of interest (T-1 hr). The 75 sec interval immediately preceding the event of interest comprises T-75 sec. The shaded vertical boxes indicate segments with regular breathing from which percent of baseline RIP Sum channel amplitude, breathing rate, heart rate, and SpO₂ were obtained. Note that when the SpO₂ was at 100%, as in all three non-event epochs, the line showing the value is not visible. The red horizontal bars denote segments of the recording in which there was periodic breathing. See Table 1 for further details regarding each physiologic variable. SUM, the sum of the RC and AB tracings; RC, the rib cage waveform; AB, the abdominal waveform; ECG, a single-lead ECG waveform; HR, heart rate.

15 sec beyond any movement, sigh, or respiratory pause. Within each baseline period, we determined medians and interquartile ranges (IQR, difference between 75th and 25th percentiles) for heart rate, breathing rate, RIP sum channel amplitude, and SpO₂.¹ We also calculated the amount in each time interval of periodic breathing and respiratory pauses greater than 5 sec, and reported these apnea durations in sec/min of recording in order to account for variable durations of recording available for analysis in the intervals. The definitions for each variable are listed in Table 1B.

As part of the original CHIME protocol, each family was contacted weekly and a report generated regarding clinical symptoms and events, including those requiring a medical contact. For this analysis, these forms were reviewed to determine any reported occurrences of respiratory-related concerns within <7 days before or after the EE, CE, and NE of interest.

Data Analysis

We analyzed the longitudinal trends within subjects during the progression from T-2 hr through T-75 sec preceding NE, CE, and EE. Simple random-effects models were built, which included time as the only independent variable for each variable of interest.³ The time variable was calculated for each segment as exact time in hours between beginning of the interval and the beginning of T-75 sec. To be included in this analysis, we required that the pre-event period include an evaluable T-75 sec time interval, which was considered as the zero point on our time scale. Analyses were performed for 80 EE, 79 CE, and 79 NE, with 5 EE, 6 CE and 6 NE being excluded because they did not have an evaluable T-75 sec interval. We first built linear random-effects models with random slope and intercept accounting for within-infant correlation and between-infant variability (SAS

8.2 PROC MIXED).⁴ Analyses of infant-level residuals determined that they were non-normally distributed for the variable “duration of periodic breathing.” We then dichotomized this variable and used nonlinear mixed model with random slope and intercept (SAS 8.2 PROC NLMIXED and GLIMMIX macro) for longitudinal analysis.⁴

We also analyzed the three event categories (EE, CE, and NE) to determine if there were differences in the physiologic measures obtained during specific time intervals prior to event onset. Within each of the three time intervals preceding the events (T-2 hr, T-1 hr, and T-75 sec), paired within-infant Wilcoxon signed rank tests that accounted for non-Gaussian distribution of some of the nine variables (see Table 1), were used to compare EE to NE and CE to NE for each variable. For each time interval, the analysis was restricted to individuals in whom that interval could be evaluated prior to all three event categories. Hence, there were 35, 38, and 85 individuals who met this criterion during the T-2 hr, T-1 hr, and T-75 sec intervals, respectively. In addition, there were a small number of individuals in whom specific variables could not be evaluated, further reducing the sample available for the evaluation of that variable. The Kappa statistic was used to test the agreement in infant position by event category. In this analysis, the event categories are treated as raters and allow assessment of the extent to which infant position differs by event category (i.e., the greater the Kappa value the less variation in infant position in relation to event category).

All analyses were conducted with SAS 8.2.⁴ The alpha for all tests was set at 0.05.

RESULTS

Maternal and Infant Characteristics

The maternal and infant characteristics for the 85 subjects are summarized in Table 2. Racial/ethnic diversity and other characteristics are comparable to the overall CHIME study, including that the majority of EE (72%) occurred in the preterm group.¹ Twelve of the 24 subjects from the SIDS siblings and ALTE groups were <38 weeks postmenstrual age at birth, but almost all were late preterm infants (34–37 weeks). In comparing these 85 subjects to the other 31 infants with at least one EE not eligible for inclusion (Fig. 1), the two groups differed in regard to race, and the mean number of EE and CE.

The characteristics of the 85 CE, EE, and NE are summarized in Table 3. Comparable to the CHIME study overall, the majority of both CE and EE were apnea events (69% and 67%, respectively), approximately one-third were bradycardia events (28% and 32%), and <3% meet threshold criteria for both.¹ As confirmed by Chi square analysis, there was no difference ($P=0.58$) between the time of events (day or night) in the three event types

(CE, EE, and NE). The percent of events occurring in the supine and prone sleep positions was similar across the three event categories (Table 3). Frequency of the supine position was twice that of the prone position, with 40–47% and 16.5–21% of events occurring in the supine and prone sleep position, respectively. Infants tended to be in the same sleep position for the NE and CE as they were for the EE; Kappa agreement for NE/CE was 0.46 (moderate agreement), for NE/EE was 0.54 (moderate agreement), and for EE/CE was 0.61 (substantial agreement). The mean (SD) for the time between T-1 hr and T-75 sec was 0.63 (0.33) hr overall; the difference in hours was 1.00 (0.02) for NE, 0.48 (0.27) for CE, and 0.51 (0.30) for EE. The CE and NE for each subject were separated from the EE by a mean of about 3 days (SD 5.2–6.1 days). This difference in postmenstrual age is significant for EE–NE ($P=0.009$) and for CE–NE ($P=0.039$), but these small differences of <0.5 weeks are likely not clinically significant.

Event Analyses

Longitudinal Analysis

There were no longitudinal trends prior to NE. However, during the 2 hr prior to EE and CE there were significant increases in heart and breathing rate variability as indicated by increases in IQR, and a decrease in median SpO₂. In addition, median heart rate increased during the time leading up to EE and during the time prior to CE there were increases in duration of respiratory pauses and periodic breathing, and in median RIP sum (Fig. 3).

Paired Within-Infant Analysis for Each Time Segment

Comparing pre-EE time intervals to pre-NE time intervals, there were significant differences in several variables during the T-75 sec and/or T-1 hr intervals. These included: higher breathing rate IQR (T-1 hr and T-75 sec), lower median RIP sum (T-1 hr), longer respiratory pause duration (T-75 sec), and longer periodic breathing duration (T-1 hr and T-75 sec). When pre-CE time intervals were compared to pre-NE time intervals, significant differences were observed primarily in the T-75 sec interval (higher breathing rate IQR, longer respiratory pause duration and periodic breathing duration, lower SpO₂). During the T-1 hr pre-CE interval, only the RIP sum was significantly different (lower) compared to the pre-NE T-1 hr interval (Table 4).

For intervals where significant differences were present, the pre-EE and -CE intervals differed from the pre-NE intervals as follows: breathing rate IQR was approximately 50% wider (i.e., more variability), median RIP sum was approximately 25% lower, respiratory pause duration was approximately two times longer, periodic breathing duration was approximately three times

TABLE 2—Maternal and Infant Characteristics for the 85 Subjects Included in This Analysis and the 31 Ineligible Infants With at Least One Extreme Event (EE)

	Infants with EE included in this analysis	Infants with EE not eligible for inclusion
No. of infants	85	31
Maternal characteristics		
Age years (SD)	27.4 (7.2)	27.0 (6.5)
Education years (SD)	12.1 (3.6)	12.4 (3.3)
Race*		
White	34 (40%)	15 (48.4%)
Black	5 (5.9%)	10 (32.3%)
Hispanic	23 (27.1%)	4 (12.9%)
Asian	13 (15.3%)	2 (6.4%)
Other	10 (11.7%)	0 (0%)
Married	54 (63.5%)	14 (46.7%)
Pregnancy cigarette use	16 (18.8%)	7 (22.6%)
Pregnancy alcohol use	13 (15.3%)	1 (3.2%)
Infant characteristics		
Male	41 (48%)	10 (32.3%)
Group		
Healthy term	3 (3.5%)	1 (3.2%)
SIDS siblings	12 (14.1%)	4 (12.9%)
Idiopathic ALTE	9 (10.6%)	3 (9.7%)
Preterm	61 (71.8%)	23 (74.2%)
Postmenstrual age in weeks at start of monitoring		
Mean (SD)	37.0 (2.2)	38.5 (4.2)
Median	37	37
Max/min	42/33	57/34
Hours of monitor use		
Mean (SD)	1505.5 (1078.3)	1487.9 (2038.9)
Median	1388.9	872
Max/min	5290.4/64.8	9244.0/18.2
Extreme events** (EE) (total)		
Mean (SD)	578	75
Median	6.8 (15.2)	2.4 (4.4)
Max/min	2	1
Conventional events*** (CE) (total)		
Mean (SD)	94/1	25/1
Median	4,396	478
Max/min	51.7 (93.0)	15.4 (32.0)
Median	21	6
Max/min	545/1	132/0

See Fig. 1 for eligibility criteria.

* $P < 0.001$.

** $P < 0.05$.

*** $P < 0.0001$.

longer, and SpO₂ was approximately 2% lower than the corresponding measures in the pre-NE intervals.

For the T-2 hr intervals, the only significant differences observed were shorter respiratory pause duration and shorter periodic breathing duration preceding CE. These decreases were not in the direction expected and not observed in the pre-EE interval. The number of EE and CE were too small to permit separate analyses of apnea and bradycardia events, or of the apnea events according to distribution of obstructed breaths. A preliminary analysis, however (data not shown), did not suggest that our findings were associated with a specific event type or apnea type.

Upper respiratory infection (URI) requiring medical contact was reported in 11 subjects within 7 days before or after the EE, CE, or NE, including at least one infant from

each of the four infant groups (Table 2). URI not requiring medical contact was reported in another nine infants, including seven preterm and two full term infants. Fever requiring medical contact was reported in two preterm infants, one of whom also had a reported URI. Pneumonia and pertussis were reported in one full term infant in the <7 days before or after the EE, CE, or NE.

DISCUSSION

We analyzed cardiorespiratory function in the hours preceding CE and EE to determine whether there were physiologic abnormalities as related to respiratory or heart rate as compared to NE. We reasoned that antecedent cardiorespiratory changes would be manifest either by a

TABLE 3— Characteristics of the 85 Conventional Events (CE), Extreme Events (EE), and Non-Events (NE) Included in this Analysis

	Conventional events (CE)	Extreme events (EE)	Non-events (NE)
No. of events	85	85	85
Event type			
Apnea	59 (69.4%)	57 (67.0%)	n/a
Bradycardia	24 (28.2%)	27 (31.8%)	n/a
Apnea and bradycardia	2 (2.4%)	1 (1.2%)	n/a
Occurred			
Midnight to 8 am	42 (49.4%)	37 (43.5%)	33 (38.8%)
8 am to 4 pm	18 (21.2%)	22 (25.9%)	19 (22.4%)
4 pm to midnight	25 (29.4%)	26 (30.6%)	33 (38.8%)
Position			
Side	2 (2.3%)	5 (5.9%)	2 (2.3%)
Prone	18 (21.2%)	19 (22.4%)	14 (16.5%)
Supine	40 (47.1%)	35 (41.2%)	34 (40.0%)
Undetermined	25 (29.4%)	26 (30.6%)	35 (41.2%)
Hours to extreme event (SD)	73.6 (125.0)	n/a	72.2 (145.6)
Postmenstrual age in weeks at event (SD)	40.3 (5.1)	40.4 (5.1)	40.6 (5.0)

change in rate or an increase in variability, and we found evidence for both. When more than one method was used to assess variability, the results were consistent, indicating that these conclusions were not the result of a fortuitous choice of variables. Interestingly, both breathing frequency and heart rate become progressively more variable: the former was associated with increases in periodic breathing and pauses, and the latter was related to decelerations associated with respiratory variability. CE and EE therefore did not occur in isolation, but were preceded by progressive autonomic instability of cardiorespiratory systems.

It remains to be determined whether frequent apnea or bradycardia events were the cause for the developmental delays observed in a previous report or rather the consequence of an underlying abnormality causing both the events and the delays.² However, the importance of our findings in the current study is that that knowledge of these subtle pre-event changes may help focus future research efforts directed at detecting infants at risk for apnea or bradycardia early enough in advance of events sufficiently prolonged to cause intermittent hypoxemia to consider intervention or to better understand factors that contribute to developmental risk.

The studies using the CHIME memory monitor and extensive database^{1,5-8} are unique in comparison to other studies⁹⁻¹³ because the CHIME monitor provides data for substantially longer periods of time preceding events, and for periods when there are no events. Across a broader range of postmenstrual and postnatal ages, the CHIME data base includes not only a substantial number of events exceeding the threshold for a CE but also a subset of more severe or extreme events (EE) of potentially greater clinical significance (Table 1A). Finally, the CHIME monitor detects breaths using respiratory inductance

plethysmography (RIP) so as to identify obstructive breaths as well as central apneas.⁵

Although it is not possible to compare directly these results to other studies, it is nevertheless important to consider the extent to which our results may be consistent with prior studies or may enhance our knowledge regarding apnea and bradycardia-related events in at-risk-for-SIDS groups. As recently reviewed, numerous studies have been conducted in infants born premature, SIDS-sibs, and ALTE infants, and have included comparisons with healthy full term infants.⁹⁻¹⁵ These earlier studies indicate evidence of impaired autonomic regulation of cardiorespiratory systems, including increased frequency of mixed and central apneas and respiratory pauses, periodic breathing, differences in resting respiratory or heart rate, and altered heart rate variability or decreases in sustained heart rate changes to respiratory events. Although our threshold criteria for defining a bradycardia event were more stringent than what is typically used to trigger a monitor alarm for bradycardia, heart rate decelerations or more brief bradycardias associated with shorter periods of apnea were not ignored since they were included in the analyses of each recorded event. SIDS Sibs have also been observed to have increased heart rate variability.¹³

There was no apparent acute morbidity resulting from these CE and EE. However, most of the CE and likely all of the EE resulted in a monitor alarm and potentially in caretaker intervention. It is thus unknown to what extent more CE might have persisted beyond the EE threshold absent a monitor alarm-related arousal, or to what extent EE might otherwise have resulted in greater acute or long term adverse clinical consequences.

There are alternative strategies that could have been selected for this analysis of cardiorespiratory changes preceding events of interest. However, the particular

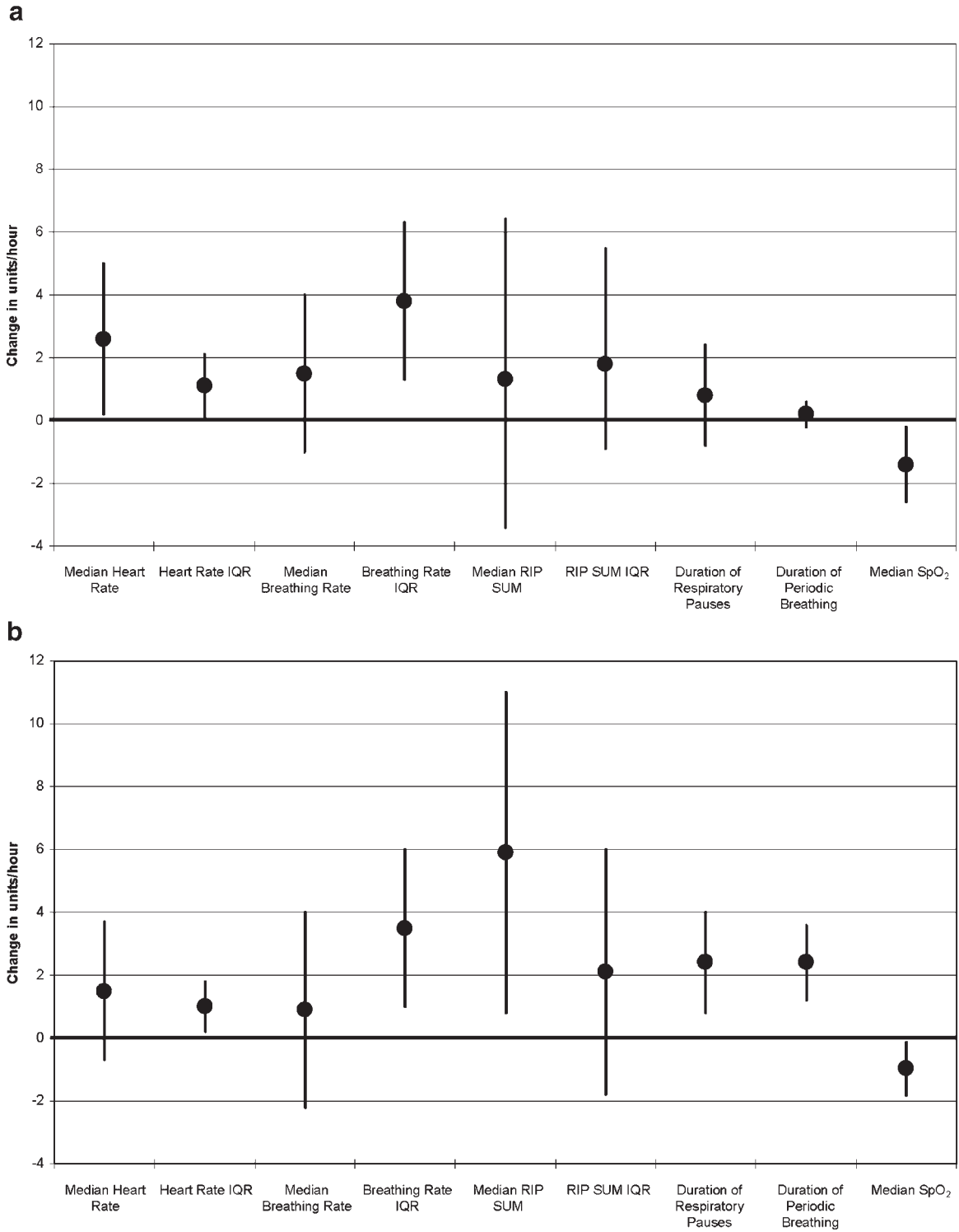


Fig. 3. Longitudinal changes during the progression from T-2 hr through T-75 sec, expressed as change in units/hour for each variable (e.g., bpm for respiratory rate, % for SpO₂) during intervals preceding extreme events (a) and preceding conventional events (b). See Table 1 for further details regarding each variable. The vertical bars indicate the 95th percentile confidence interval (CI) for that variable. Whenever the vertical bar does not cross the zero line, the change from T-2 hr through T-75 sec is significant ($P < 0.05$).

TABLE 4—Paired Within-Infant Analysis for Each Time Segment

Variable	Interval T-2 hr			Interval T-1 hr			Interval T-75 sec		
	EE	CE	NE	EE	CE	NE	EE	CE	NE
Heart rate (bpm)									
Median	149.7 (13.7)	152.6 (15.0)	149.3 (13.9)	148.7 (17.3)	150.2 (19.2)	148.3 (15.9)	149.4 (20.6)	151.5 (18.9)	147.6 (17.3)
Interquartile range (IQR)	7.5 (3.0)	7.5 (4.1)	7.3 (3.0)	9.6 (4.2)	8.9 (4.6)	7.5 (3.5)	11.0 (8.8)	8.8 (5.4)	8.1 (4.8)
Breathing rate (bpm)									
Median	54.1 (14.4)	55.8 (15.8)	57.0 (15.8)	55.3 (17.4)	56.3 (16.1)	55.9 (15.9)	56.6 (21.1)	55.8 (19.4)	54.0 (17.4)
IQR	15.3 (8.7)	16.3 (8.4)	17.4 (9.9)	22.7 (10.9)**	18.8 (10.0)	17.0 (8.6)	24.8 (17.9)*	23.6 (14.4)**	17.7 (10.7)
RIP Sum									
Median (%)	81.5 (24.7)	83.3 (30.7)	83.1 (24.2)	76.9 (22.1)**	81.9 (36.4)*	101.3 (46.7)	86.1 (29.4)	82.9 (34.0)	86.8 (41.0)
IQR (%)	27.0 (12.9)	28.5 (15.9)	27.7 (14.2)	30.8 (14.6)	26.6 (14.3)	35.8 (24.2)	32.2 (17.4)	31.9 (20.4)	32.3 (25.6)
Respiratory pauses									
Duration (sec/min)	2.6 (3.3)	1.4 (2.2)*	3.4 (5.5)	6.6 (8.9)***	4.1 (6.4)	2.4 (5.9)	7.7 (8.6)***	7.7 (8.7)***	3.9 (6.5)
Periodic breathing									
Duration (sec/min)	2.6 (8.9)	1.1 (4.6)**	5.3 (11.5)	10.9 (18.0)*	6.4 (15.4)	3.1 (10.5)	13.8 (19.2)***	12.5 (17.6)**	5.9 (14.8)
SpO ₂									
Median (%)	96.3 (2.9)	96.2 (3.4)	96.1 (3.5)	95.5 (4.6)	95.4 (4.1)	95.7 (4.0)	93.7 (8.3)	94.3 (5.5)*	96.0 (3.9)

The Means (SD) are shown for each cardiorespiratory variable in each time interval prior to extreme events (EE), conventional events (CE), and non-event epochs (NE). See Table 1 for definitions. bpm beats/min or breaths/min for heart rate and breathing rate, respectively.

* $P < 0.05$ based on paired within subject Wilcoxon signed rank test comparing EE to NE and CE to NE.

** $P < 0.01$ based on paired within subject Wilcoxon signed rank test comparing EE to NE and CE to NE.

*** $P < 0.001$ based on paired within subject Wilcoxon signed rank test comparing EE to NE and CE to NE.

approach we selected had a number of strengths including: (1) The paired within-subject analysis of the three time intervals for the CE, EE, and NE allowed us to address changes over these 2 hr with equal representation of subjects; (2) Our selection strategy for event inclusion prevented close proximity to a prior CE or EE, increasing the likelihood that we were identifying antecedents of events and not the consequence of impaired or delayed resolution of previous events; and (3) The total time span of just a few days between the three analyzed events in each subject was sufficiently short to preclude any confounding by maturational changes.

There are several potential study limitations. We were limited by having only 85 infants in the CHIME dataset with an EE and with paired CE and NE meeting our selection criteria. Analysis of additional EE would have required including multiple events from the same infants, and the group results might then be biased by a few subjects not representative of the group. An analysis of more events might also be limited by potential influences of other events in close proximity or by maturational changes with increasing age. Although not likely affecting this analysis of antecedent events, it is of note that the 85 infants included were more likely to be Hispanic and less likely to be Black, and to have more EE and CE than the infants with EE not eligible for inclusion (Table 2). It might have been informative to include more events from the full term groups, but EE were much more frequent in infants born preterm and were rare in the healthy term group.¹ Although regression analysis on all outcome variables by event category shows that postmenstrual age is an independent variable, time interval or segment is also an independent variable and it is this analysis of the by-time interval progression of changes preceding EE, CE, and NE that is the primary focus of this report. In our analyses, each infant serves as his/her own control; although we do not have sufficient numbers of subjects to conduct a quantitative comparison of preterm versus full term subjects, there is no qualitative indication that the changes occurring preceding events in preterm infants differ from events preceding events in full term infants.

The 75 sec duration of recording immediately preceding the event of interest was significantly longer than the 30–45 sec typically possible with other home memory monitors, but a longer pre-event duration might have been even more informative. Although the availability of non-event epochs up to 2 hr before the event of interest is also unique to CHIME, additional insights regarding longitudinal trends might have been achievable had these NE epochs been longer or more frequent preceding the events of interest. Although likely not affecting the results, T-1 hr and T-2 hr were not precisely 1 and 2 hr before the event of interest due to random variability in the timing of the event of interest relative to the last NE. Once selecting the 85 EE and matched CE and NE for each subject, we

were limited by missing data or excessive artifact in some of the individual time intervals. We may therefore not have had sufficient power to more fully characterize cardiorespiratory instability antecedent to the events of interest. We did not have sufficient power to assess the relative potential impact of apnea and bradycardia events on the findings. We also might have identified important antecedent changes in autonomic regulation of heart rate had we been able to perform more robust analyses of heart rate variability than feasible using the memory monitor recordings.¹⁶ Most of the long apneas were mixed and included at least three obstructed breaths, and it therefore was not possible to evaluate to what extent the progressive changes may differ preceding central as compared to obstructive apnea.¹ We did not include 20 infants with an EE due to lack of a valid SpO₂ signal, but cannot exclude the possibility that such infants were more severely affected preceding the EE and hence had too much artifact to permit analysis.

Finally, our results are limited by absence of additional physiologic data in the CHIME dataset that would yield any mechanistic insights. Our results are descriptive in nature and hypothesis-generating, but additional studies need to be conducted to test these hypotheses and better clarify underlying pathophysiologic mechanisms. In this respect, it would likely be informative to have more detailed clinical information regarding respiratory symptoms and diagnoses more immediately related to the analyzed EE, CE, and NE instead of just the information derived from the weekly parental reports. It is not surprising that 20 of 85 infants (23.5%) had at least mild respiratory symptoms, but it is also noteworthy that most of the EE and CE we analyzed were thus not associated with respiratory-related symptoms. As part of a future study, it would be likely be informative to analyze all weekly parental reports and determine the frequencies with which all of the recorded EE and CE were related to acute respiratory events during the same week and perhaps gain some insight as to the extent to which these respiratory events may be causal. The abrupt onset and very brief duration of these EE and CE (measured in seconds) would seem to preclude “peripheral” causes related to lung disease or low lung volumes or to be directly attributed to a change in state or sleep position. However, we cannot fully exclude a “peripheral” contribution to the autonomic dysregulation evident in our analyses.

We conclude that conventional and extreme events detected by the CHIME monitor during infancy did not occur in isolation but rather were heralded by relatively subtle cardiorespiratory instability and decreased SpO₂ in the 2 hr preceding a CE and especially preceding an EE. We speculate that these findings are progressive and culminate in the conventional and extreme events. These heart rate decelerations and associated respiratory pauses

including periodic breathing thus may not be benign to the extent they indicate increased vulnerability for a CE or especially an EE, and to the extent that a CE and especially an EE may increase risk for adverse clinical consequences. Additional studies are needed to clarify the potential clinical implications of these relatively small and subtle antecedent changes that indicate autonomic dysregulation of the cardiorespiratory system.

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