Cardiorespiratory Events Recorded on Home Monitors

Comparison of Healthy Infants With Those at Increased Risk for SIDS

Rangasamy Ramanathan, MD
Michael J. Corwin, MD
Carl E. Hunt, MD
George Lister, MD
Larry R. Tinsley, MD
Terry Baird, MD
Jean M. Silvestri, MD
David H. Crowell, PhD
David Hufford, MD
Richard J. Martin, MD
Michael R. Neuman, PhD, MD
Debra E. Weese-Mayer, MD
L. Adrienne Cupples, PhD
Mark Peucker, BS
Marian Willinger, PhD
Thomas G. Keens, MD
for The Collaborative Home Infant Monitoring Evaluation (CHIME) Study Group

Context Home monitors designed to identify cardiorespiratory events are frequently used in infants at increased risk for sudden infant death syndrome (SIDS), but the efficacy of such devices for this use is unproven.

Objective To test the hypothesis that preterm infants, siblings of infants who died of SIDS, and infants who have experienced an idiopathic, apparent life-threatening event have a greater risk of cardiorespiratory events than healthy term infants.

Design Longitudinal cohort study conducted from May 1994 through February 1998.

Setting Five metropolitan medical centers in the United States.

Participants A total of 1079 infants (classified as healthy term infants and 6 groups of those at risk for SIDS) who, during the first 6 months after birth, were observed with home cardiorespiratory monitors using respiratory inductance plethysmography to detect apnea and obstructed breathing.

Main Outcome Measures Occurrence of cardiorespiratory events that exceeded predefined conventional and extreme thresholds as recorded by the monitors.

Results During 718 358 hours of home monitoring, 6993 events exceeding conventional alarm thresholds occurred in 445 infants (41%). Of these, 653 were extreme events in 116 infants (10%), and of those events with apnea, 70% included at least 3 obstructed breaths. The frequency of at least 1 extreme event was similar in term infants in all groups, but preterm infants were at increased risk of extreme events until 43 weeks' postconceptional age.

Conclusions In this study, conventional events are quite common, even in healthy term infants. Extreme events were common only in preterm infants, and their timing suggests that they are not likely to be immediate precursors to SIDS. The high frequency of obstructed breathing in study participants would likely preclude detection of many events by conventional techniques. These data should be important for designing future monitors and determining if an infant is likely to be at risk for a cardiorespiratory event.

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In the 1980s, a leading hypothesis related to sudden infant death syndrome (SIDS) was that prolonged apnea and bradycardia were markers for the susceptible infant and preceded the terminal event. The use of home monitoring subsequently expanded in the hope that timely recognition of apnea or bradycardia would lead to life-saving intervention.

In 1986, a National Institutes of Health Consensus Conference[1] concluded that although the effectiveness of home cardiorespiratory monitors in reducing infant morbidity or mortality remained to be established: "cardiorespiratory monitoring or an alternative therapy is medically indicated for certain groups of infants at high risk for sudden death. . . . These groups include infants with one or more severe apparent life threatening events (ALTEs) requiring mouth-to-mouth resuscitation or vigorous stimulation, symptomatic preterm infants, and siblings of two or more SIDS victims. . . ." For siblings of 1 SIDS infant, it was stated that available evi-

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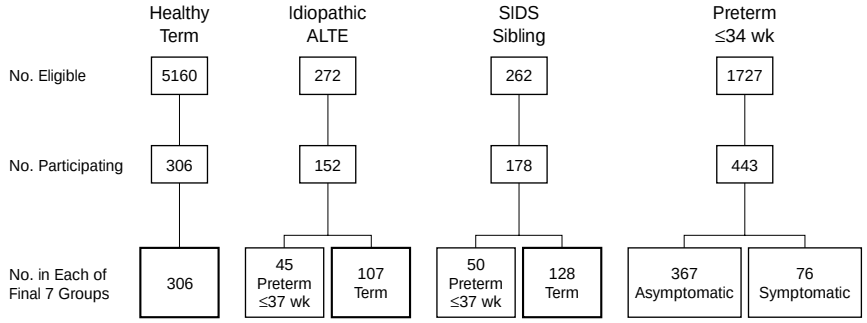
Author Affiliations and Members of the CHIME Study Group are listed at the end of this article.
Corresponding Author and Reprints: George Lister, MD, Department of Pediatrics, Yale Medical School, Box 208064, New Haven, CT 06520-8064 (e-mail: george.lister@yale.edu).

Figure 1. Distribution of Eligible and Participating Infants Among the Final 7 Study Groups



ALTE indicates apparent life-threatening event; SIDS, sudden infant death syndrome. See "Methods" for a description of the inclusion criteria.

dence was inconclusive and "the decision reached will be specific to the infant." Therefore, premature infants, siblings of infants who died of SIDS (SIDS-SIBs), and those who experienced an ALTE were commonly monitored at home because of these recommendations and their reported increased risk of SIDS (at least 2.5 times the general population, although data were sparse for infants with an ALTE[2-5]). However, it is important to recognize the unproven assumptions implicit in the following recommendations: (1) infants for whom home monitors are recommended are at increased risk for episodes of prolonged apnea or severe bradycardia; (2) such episodes are precursors to SIDS; and (3) home cardiorespiratory monitoring will warn caregivers in time for successful intervention. The Collaborative Home Infant Monitoring Evaluation (CHIME) study was designed to address the validity of the first assumption.

We specifically tested the hypothesis that preterm infants, SIDS-SIBs, and infants who have experienced an idiopathic ALTE have a greater risk of cardiorespiratory events than healthy infants, and risk is related to postconceptional age (PCA). We assessed the frequency and time course of events based on commonly used or conventional monitor alarm thresholds, but because these events are often not considered clinically relevant, we also assessed a subset of more severe events that we termed "extreme events." Although there were no means to establish the consequences of extreme events a priori, the event criteria defined a severity more likely to influence clinical management than commonly used thresholds. We selected a home monitor with extensive memory and one that also detected obstructed breaths to view the full range of respiratory abnormalities that might cause apnea.[2,5-7]

METHODS

Study Population

Infants were recruited from 5 clinical sites (see "Acknowledgment") between May 1994 and February 1998. The institutional review board at each site approved the study, and the parents of all subjects gave written informed consent.

For purposes of analysis, infants were divided into 7 groups (FIGURE 1). Enrollment was relatively balanced by site, each contributing between 18% and 24% of subjects. The 7 groups of infants were derived from 4 initial categories of eligibility using stratification criteria that we thought a priori would influence outcome. These include the following:

Healthy Term Group. Criteria included: (1) 38 to 42 weeks' gestation at birth; (2) birth weight, 10th to 90th percentile; (3) 30 days or younger postnatal age; (4) clinically well (defined as Apgar score >4 at 1 and >7 at 5 minutes, not admitted to a special care nursery, discharge on or before date of maternal discharge, no medications, and no apnea or ALTE events based on clinical history or medical record); (5) no family history of SIDS in siblings; and (6) no other family history of SIDS in the last 10 years.

Idiopathic ALTE Group. Within the previous 30 days, an unexplained sudden episode of color change (cyanosis or pallor), tone change (limpness, stiffness), or apnea that required mouth-to-mouth resuscitation or vigorous stimulation.[1] Postnatal age had to be at least 12 hours but younger than 6 months when the ALTE occurred. The index event was identified by caretaker observation and occurred prior to the use of a home monitor. To establish an ALTE as idiopathic, an evaluation was performed based on the infants' initial presentation, and only those infants without an explained cause were enrolled. Based on whether or not they were born at 37 or less weeks' gestation, the infants with an ALTE were stratified into *term idiopathic ALTE* and *preterm idiopathic ALTE* groups.

SIDS-SIB Group. Criteria included: (1) full or half sibling of 1 or more previous SIDS infants (documented by autopsy), and (2) 30 days or younger postnatal age (<4 weeks after SIDS in a twin but <6 months' postnatal age). Based on whether or not they were born at 37 or less weeks' gestation, the SIDS-SIB infants were stratified into: *term SIDS-SIB* and *preterm SIDS-SIB* groups.

Preterm Group. Ineligible for other groups and (1) 34 or less weeks' gestation at birth, (2) birth weight less than 1750 g, (3) postnatal age younger than 120 days at time of discharge from the neonatal intensive care unit, and (4) 2 weeks or less since discharge. Based on whether staff in the neonatal intensive care unit observed apnea or bradycardia associated with cyanosis within 5 days of discharge, the preterm group was stratified into *asymptomatic preterm* and *symptomatic preterm* groups.

General Exclusion Criteria. Since our intent was to characterize cardiorespiratory events in infants for whom the cause was unknown, infants were

excluded if they had any of the following: current pneumonia confirmed by chest x-ray; home treatment with continuous oxygen, bronchodilators, diuretics, steroids, medications for gastroesophageal reflux or seizure; congenital heart disease except asymptomatic patent ductus arteriosus, atrial septal defect, or small muscular ventricular septal defect; ventricular-peritoneal shunt; congenital brain anomaly that would result in a non-SIDS diagnosis in the event of sudden death; chromosomal abnormality; midfacial hypoplasia or cleft palate; inborn error of metabolism; caregiver currently using illicit drugs; or parental inability to communicate (language barrier or no telephone).

Use of Home Monitor

Following enrollment, each infant had cardiorespiratory waveforms recorded in the home using the CHIME monitor (NonInvasive Monitoring Systems, Miami, Fla).[8] Rib cage and abdominal movement were recorded by respiratory inductance plethysmography (RIP) bands, and a third signal proportional to tidal volume was calculated from the weighted algebraic sum (sum channel). The monitor recognizes a breath whenever there is an excursion on the sum channel that is at least 25% of the amplitude determined during a calibration period (first 5 minutes each time the monitor is turned on). The monitor continuously measures the time following a breath. During each period of monitor-defined apnea (when there is no breath for a time exceeding a specified threshold) there may be (1) effort in which the rib cage and abdominal excursions are out of phase (consistent with obstruction) or (2) no respiratory effort (central apnea) (FIGURE 2).[9-11] Heart rate was determined by an R-wave detection algorithm using standard disposable infant electrocardiogram electrodes. Hemoglobin oxygen saturation by pulse oximetry (Spo_2)[12] (Ohmeda Minx pulse oximeter, Ohmeda Corp, Liberty Center, NJ) and transthoracic impedance signals (Aequitron Inc, Plymouth, Minn) were also monitored but were not used to define recording or alarm thresholds in this report.

The monitor had the capability to initiate recording and storage of physiologic data at a preset duration (threshold) for low heart rate and apnea; the duration for initiating an alarm was longer and could be set independently. All events stored in memory included the 75 seconds preceding onset of the event, the event, and 30 seconds after resolution of the event. The thresholds for recording physiologic events were identical for all groups of subjects: apnea (as defined above) at least 16 seconds in duration or a heart rate less than 80 or 60 beats per minute (bpm) for at least 5 seconds for infants less than 44 or 44 or more weeks' PCA, respectively.

In contrast to the recording thresholds, we varied the threshold for alarms. The alarm thresholds in the healthy term group were set at 40 or more seconds for apnea and less than 40 bpm for heart rate since they had no clinical indication for the audible alarm. For all other infants, the monitor was set to sound an audible alarm for apnea of at least 20 seconds (ie, 4 seconds beyond the threshold for recording), or a heart rate less than 80 bpm for at least 5 seconds for infants less than 44 weeks' PCA, or 60 bpm for those at least 44 weeks' PCA (same threshold as for recording). These alarm thresholds were equivalent to customary practice so that infants who would have been monitored absent our study received the same level of surveillance.

Families received standardized training and ongoing support of home monitoring and were instructed to use the monitor whenever the infant was sleeping or unobserved. Although parents were provided a form on which to note any observations or interventions related to cardiorespiratory events, these records were not consistently kept. Accordingly, only the recorded physiologic data are reported herein. The intended duration of home monitoring was through 66 weeks' PCA for the healthy term and SIDS-SIB groups, 56 weeks' PCA for the preterm groups, and 16 weeks from enrollment for the ALTE groups. In addition, infants continued to be monitored until they were free of events exceeding alarm thresholds for at least 12 weeks.

The memory monitor cartridges were downloaded every 2 to 4 weeks and waveforms were available for review locally if needed for clinical management. After infants completed home monitoring, waveforms were analyzed at the data coordinating and analysis center by technicians unaware of study group or clinical status. A software tool, which permitted magnification of the signal amplitude and time scale, was developed to facilitate the scoring procedures and analyses (Figure 2). We have previously reported a high level of interrater reliability using this tool.[8]

Data Analysis

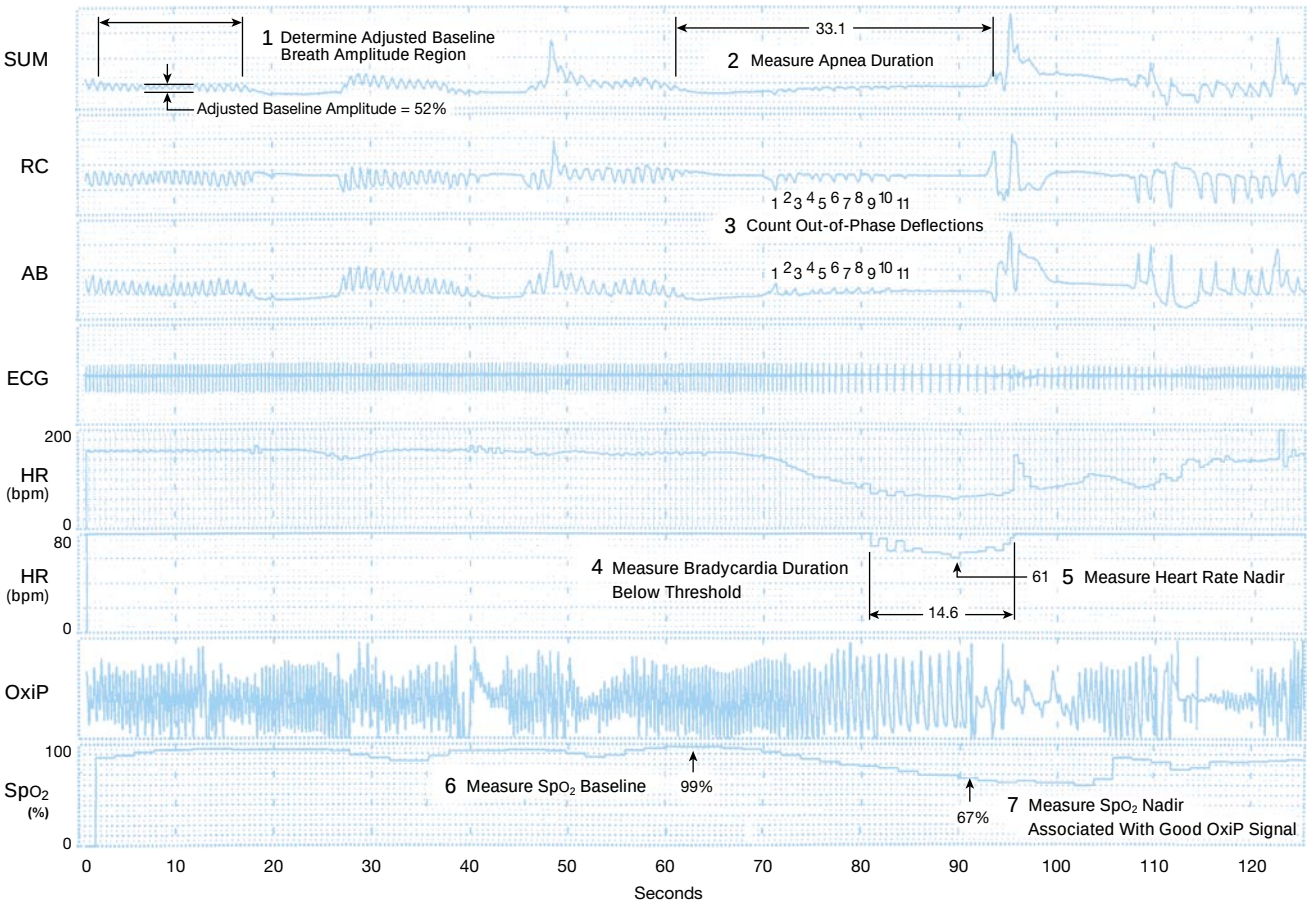
For the purposes of data analysis, events were categorized as exceeding, recording (see above criteria), conventional, or extreme thresholds. Conventional thresholds were defined as follows: (1) apnea of at least 20 seconds; (2) if less than 44 weeks' PCA, heart rate less than 60 bpm for at least 5 seconds or less than 80 bpm for at least 15 seconds; or (3) if 44 weeks' PCA, heart rate less than 50 bpm for at least 5 seconds or less than 60 bpm for at least 15 seconds. Extreme thresholds were defined as: (1) apnea of at least 30 seconds; (2) if less than 44 weeks' PCA, heart rate less than 60 bpm for at least 10 seconds; or (3) if at least 44 weeks' PCA, heart rate less than 50 bpm for at least 10 seconds.

We analyzed the frequency of events exceeding both conventional and extreme thresholds. For a primary comparison of the risk of at least 1 event by group, we calculated the time in days from beginning of monitoring to first event for those with events and the total time in the study ($\leq$180 days) for those without events. We calculated Kaplan-Meier survival curves and computed 1-minus estimates from these survival curves, thus accounting for variable days of monitor use.[13] The last date that subjects used the monitor be-

came a censoring date. Cox proportional hazards models were then used to obtain risk ratios (RRs) (with 95% confidence intervals [CIs]) of an event in comparison with the healthy term group.[14] These models also account for the variable monitoring duration. In the Cox models, we additionally accounted for variability in monitor use by adding total hours of actual monitor use to the models. The assumption of proportional hazards was tested by including a time-dependent variable in the model for each group.

Since PCA varied widely among groups, we also compared the groups regarding the number of infants with at least 1 event per 20 000 hours of monitor use during 4-week PCA periods. We chose 4-week PCA time periods to ensure that we would observe a sufficient number of infants with events for analysis. We expressed the rate of events per 20 000 hours of monitor use because this rep-

Figure 2. Procedure for Assessment of Events



Scoring procedures have been divided into 7 steps, as follows (note that in some instances channels were displayed in a montage for convenience or to assist in identifying artifact, even if not used directly in scoring): steps 1-3 (scoring respiratory variables): sum channel (SUM), rib cage (RC), abdominal (AB), and heart rate (HR); steps 4-5 (scoring heart rate variables): HR, electrocardiogram (ECG), SUM, and pulse oximetry (OxiP); and steps 6-7 (scoring saturation variables): hemoglobin oxygen saturation by pulse oximeter (Spo_2), OxiP, ECG, HR, and SUM. **Step 1:** Determine adjusted baseline breath amplitude region. The scorer places 2 cursor lines demarcating a region on SUM that contains deflections of "typical" size. The criteria for this region are: it precedes the event, contains at least 3 deflections, and is the longest segment that contains neither artifact nor sighs. The software automatically averages the amplitudes of all the breaths between the cursors to determine the adjusted baseline breath amplitude, which is then displayed and stored. **Step 2:** Measure apnea duration. The cursors are placed at the peak of the 2 deflections that represent the longest interval between deflections 25% of adjusted baseline breath amplitude. The software calculates and displays apnea duration; if 10 seconds, the duration is stored, otherwise the event is classified as false. **Step 3:** Count out-of-phase deflections. Eleven out-of-phase deflections are present and numbered. Out-of-phase deflections are defined as AB and RC signals that occur in opposite directions (ie, 180° out of phase) associated with a SUM deflection of 25% of adjusted baseline breath amplitude. If AB and RC signals are shifted in time in respect to each other, this shift can be no more than 25% or more of overall duration of breath (ie, 90°-270° out of phase) to be considered out of phase. The total number of out-of-phase deflections that are within the defined apnea is counted and manually entered into the system. **Step 4:** Measure bradycardia duration below threshold. The cursors are placed at the first decline in heart rate less than 80 beats per minute (bpm) and at the point of return to 80 or more bpm. The software tool determines and displays bradycardia duration whenever it is less than 80 bpm for at least 1 second. Similar procedures are used to measure bradycardia duration less than 60 bpm and less than 50 bpm. **Step 5:** Measure heart rate nadir. The cursors are placed on either side of the bradycardia. The software tool calculates, displays, and records the heart rate nadir. **Step 6:** Measure Spo_2 baseline. The cursors are placed on either side of the period of highest stable Spo_2 preceding the event. The software tool calculates, displays, and records baseline Spo_2. *Step 7:* Measure Spo_2 nadir associated with good OxiP signal. The cursors are placed on either side of the drop in Spo_2. The software tool calculates, displays, and records the Spo_2 nadir.

resents approximately the number of hours that 100 infants would be expected to use the monitor during a 4-week period (hence an estimate of expected number of infants with at least 1 event among 100 infants monitored for a 4-week period). We constructed smoothed plots for each group by calculating a moving average estimate at each week, using the 4-week window beginning at the week under consideration and the subsequent 3 weeks (eg, for week 35, we calculated the average of the rates from weeks 35-38). A formal comparison of the rate at which infants in each group had at least 1 event was conducted using Poisson regression with repeated observations for selected 4-week periods, adjusting for the number of hours monitored before the event for those with an event and the total number of hours monitored for those without events.[15,16] The reference rate chosen for these comparisons was that observed in the healthy term group during the 4-week PCA period from 42 to 45 weeks, the earliest 4-week PCA observation period for healthy term infants. Relative rates (and 95% CIs) were calculated for each group for successive, nonoverlapping 4-week PCA periods (ie, 34-37, 38-41, 42-45 weeks' PCA). From an assessment of data collected during the initial 2 years of the study, we estimated that events exceeding the extreme threshold would be observed in 1% to 2% of healthy term infants. To achieve a reasonably precise estimate of the event rate in the healthy term group, we set a goal of enrollment of at least 300 infants. With a sample of 300 healthy term infants, the upper 95% confidence limit for an observed rate of 2% is 3.6%.

RESULTS

Subject Characteristics

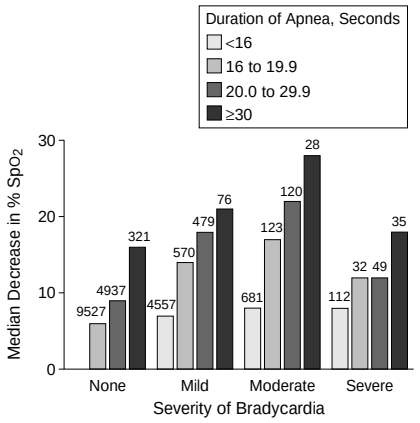
TABLE 1 provides the characteristics of the 1079 infants who participated in the

Table 1. Maternal and Infant Characteristics*

	Term			Preterm ≤37 wk		Preterm ≤34 wk	
	Healthy Term (n = 306)	SIDS-SIB (n = 128)	ALTE (n = 107)	SIDS-SIB (n = 50)	ALTE (n = 45)	Asymptomatic (n = 367)	Symptomatic (n = 76)
Maternal							
Mean (SD) age, y	29.4 (6.3)	28.1 (5.9)	25.8 (6.4)	29.0 (5.3)	26.6 (8.0)	27.2 (6.5)	29.5 (6.3)
Mean (SD) education, y	13.0 (2.5)	12.6 (2.8)	12.8 (2.6)	12.3 (2.5)	12.2 (3.2)	13.9 (1.9)	14.5 (2.7)
Mean (SD) parity	3.2 (1.2)	2.2 (1.4)	3.7 (1.8)	2.4 (1.2)	2.0 (1.2)	1.7 (1.0)	2.2 (1.2)
Race, No. (%)							
White	166 (54.4)	82 (64.6)	55 (51.4)	21 (43.8)	24 (54.5)	130 (35.4)	24 (31.6)
Black	47 (15.4)	17 (13.4)	13 (12.1)	10 (20.8)	5 (11.4)	92 (25.1)	20 (26.3)
Hispanic	19 (6.2)	14 (11.0)	14 (13.1)	9 (18.8)	2 (4.5)	97 (26.4)	8 (10.5)
Asian	26 (8.5)	6 (4.7)	9 (8.4)	7 (14.6)	5 (11.4)	27 (7.4)	12 (15.8)
Other	47 (15.4)	8 (6.3)	16 (15.0)	1 (2.1)	8 (18.2)	21 (5.7)	12 (15.8)
Married	244 (80.0)	103 (81.1)	75 (70.8)	37 (77.1)	26 (59.1)	265 (72.2)	58 (76.3)
Used cigarettes in pregnancy	50 (16.3)	37 (29.1)	46 (43.4)	15 (31.3)	15 (34.9)	80 (22.0)	18 (23.7)
Used alcohol in pregnancy	63 (20.6)	23 (18.1)	26 (24.5)	13 (27.7)	6 (14.3)	45 (12.4)	10 (13.2)
Infant							
Male, No. (%)	160 (52.3)	68 (53.1)	55 (51.4)	23 (46.0)	24 (53.3)	183 (49.9)	42 (55.3)
Mean (SD) gestational age at birth, wk	39.5 (1.0)	39.7 (1.0)	39.6 (1.1)	35.0 (2.7)	35.5 (1.7)	29.7 (2.5)	29.6 (2.2)
Mean (SD) birth weight, g	3311 (304)	3520 (403)	3367 (427)	2532 (750)	2610 (568)	1252 (319)	1241 (306)
Mean (SD) PCA at start of monitoring, wk	41.8 (1.8)	40.4 (1.9)	46.9 (6.4)	37.9 (4.4)	41.5 (4.5)	37.0 (1.9)	36.6 (1.7)
Infant-preterm only							
Received supplemental oxygen, No. (%)	NA	NA	NA	11 (22.9)	10 (22.7)	311 (84.7)	67 (88.2)
Received mechanical ventilation, No. (%)	NA	NA	NA	6 (12.5)	5 (11.4)	255 (69.5)	57 (75.0)
Mean (SD) PCA at newborn-hospital discharge, wk	NA	NA	NA	36.0 (2.1)	36.2 (1.3)	35.2 (3.4)	35.8 (2.8)
Mean (SD) monitor use, h							
Total per infant	373 (468)	1089 (866)	683 (663)	958 (904)	867 (896)	671 (727)	768 (746)
Use by PCA, wk							
34-37	NA	NA	NA	3355 (n = 36)	1320 (n = 8)	32 046 (n = 264)	9571 (n = 56)
38-41	5335 (n = 150)	11 349 (n = 111)	2461 (n = 27)	9279 (n = 43)	4805 (n = 25)	61 093 (n = 306)	15 896 (n = 64)
42-45	19 547 (n = 261)	24 866 (n = 109)	10 575 (n = 59)	8106 (n = 35)	6058 (n = 27)	47 852 (n = 238)	11 574 (n = 53)
46-49	22 222 (n = 190)	23 770 (n = 95)	12 336 (n = 68)	7331 (n = 32)	6956 (n = 29)	38 076 (n = 204)	7935 (n = 42)
50-53	21 893 (n = 160)	22 669 (n = 93)	12 866 (n = 66)	6505 (n = 29)	6168 (n = 26)	31 749 (n = 173)	6351 (n = 33)
54-57	19 003 (n = 135)	21 478 (n = 90)	11 563 (n = 66)	5925 (n = 25)	5450 (n = 24)	22 754 (n = 148)	4816 (n = 30)

*Continuous variables expressed as mean (SD), categorical variables as number and percentage. There were a small number of missing values for some variables. SIDS-SIB indicates siblings of infants who died of sudden infant death syndrome; ALTE, apparent life-threatening event; PCA, postconceptional age; and NA, not applicable.

Figure 3. Decrease in Percent Hemoglobin Oxygen Saturation (SpO_2) in Infants Experiencing Apnea or Bradycardia



Median baseline saturation was 98% to 99% for all event types. The numbers on the bars denote the total number of events with the specified combination of apnea and bradycardia. The height of the bar shows the median fall in SpO_2 for those events for which an adequate saturation signal was obtained (approximately 70% of all events). Apnea duration categories included 30 seconds or longer (based on extreme threshold of 30 seconds), 20.0 to 29.9 seconds (based on conventional threshold of 20 seconds), 16.0 to 19.9 seconds (based on the record threshold of 16.0 seconds), and 0 to 15.9 seconds (not identified). Bradycardia categories were "severe" (met extreme threshold), "moderate" (met conventional threshold), "mild" (met record threshold), and "none" (none identified). Because an event needed to be triggered by apnea or bradycardia, there were no events in which neither disturbance occurred (far left).

study. Each of the 7 groups included racial/ethnic diversity and had characteristics representative of the target populations for this study. Although there were some small differences between participants and eligible nonparticipants with respect to marital status, education, and ethnic group, we were unable to discern a meaningful trend.

Six infants died during the study, but none was being monitored at the time of death. The cases were independently reviewed by an expert panel, which included the medical examiners or pathologists at each CHIME site. There were 2 SIDS cases, including an infant in the healthy term group who died at 17 weeks and an infant in the preterm group born at 28 weeks' gestational age who died at 20 weeks. There were 2 cases for which the autopsy and medical history were consistent with SIDS, but there was no information on the death scene, including a term infant in the SIDS-SIB group who died at 7 weeks of age and an infant in the preterm group born at 32 weeks' gestation who died at 12 weeks of age. One infant in the term ALTE group, who was also a SIDS-SIB, died suddenly and unexpectedly at 32 weeks of age and was designated "undetermined" because of uncertainty regarding the SIDS diagnosis. One infant in the preterm group born at 32 weeks' gestation, who was also a SIDS-SIB, died at 41 weeks of age, and the cause of death was homicide.

Event Characteristics

The CHIME monitor was used for a total of 718358 hours, with wide differences in usage within and between groups, which necessitated analytic approaches that accounted for individual time monitored.

Based on CHIME criteria, we analyzed 21647 events that exceeded recording thresholds. Of these, 6993 events exceeded conventional thresholds in 445 (41%) of the 1079 infants, and 653 events exceeded extreme thresholds in 116 (10%) of the 1079 infants. Because SpO_2 values were available and of sufficient quality for assessment in 84% and 67% of events that exceeded conventional and extreme thresholds, respectively, we were able to examine the relationship between these events and hypoxemia (FIGURE 3). Apnea without bradycardia represented 5258 (75%) of 6993 events exceeding conventional thresholds (≥20 seconds) and 321 (49%) of 653 events exceeding extreme thresholds (≥30 seconds). Bradycardia without apnea of at least 20 seconds represented 948 (14%) of 6993 events exceeding conventional thresholds and 144 (22%) of 653 events that exceeded extreme thresholds. In general, the degree of hypoxemia increased with increasing duration of apnea or bradycardia. When severe bradycardia coexisted with apnea, however, there was slightly less hypoxemia, but fewer events with SpO_2 values of sufficient quality for assessment. Of all extreme events, 25% were associated with a decrease in SpO_2 of less than 10%. Using RIP, we also assessed the proportion of apnea events that met criteria for obstructed breaths, which correlate well with obstructed breaths on polysomnographic studies.[9-11] Among all extreme events with apnea of 30 seconds, 70% included at least 3 obstructed breaths. Among all conventional events with apnea of at least 20 seconds, 50% of the apneas included at least 3 obstructed breaths.

Risk of Events

TABLE 2 provides RRs for each study group compared with healthy term infants for the occurrence of at least 1 event exceeding the extreme threshold and at least 1 event exceeding the conventional threshold during the first 180 days of monitoring (Cox proportional hazards model). Only the 4 preterm groups had significantly increased risk of an extreme event. The 2 highest RRs occurred in the symptomatic and asymptomatic preterm groups (18.0 and 10.1, respectively), and these 2 RRs declined over time ($P<.01$). For example, at day 7 of monitoring, the RRs were 34 and 17 for symptomatic and asymptomatic preterm infants, respectively, while by day 28 of monitoring, the RRs had declined to 14 and 8 for symptomatic and asymptomatic preterm infants, respectively. For both groups, the risk of at least 1 extreme event remained significantly higher than the healthy term group for approximately the first 7 weeks of monitoring (ie, up to 43 weeks' PCA). Similarly, the symptomatic and asymptomatic preterm groups also had the highest RRs for events exceeding conventional thresholds. However, the occurrence of at least 1 event exceeding conventional alarm thresholds was very common (cumulative incidence, 43%) in all groups including the healthy term group. For events exceeding conventional thresholds, as with events exceeding extreme thresholds, the RRs for the preterm groups declined with time, and by 7 weeks of monitoring were no

longer significantly higher than the healthy term group.

Risk for Recurrence of Event

We next assessed the pattern of recurrence of extreme events among the 116 infants who had at least 1 extreme event. We combined the groups since, except for the preterm group, the numbers of infants were too few for separate analysis. A second extreme event occurred in 60 (51.7%) of the 116 infants, a third occurred in 35 (57.3%) of the 60, and a fourth was observed in 28 (80%) of the 35. In each case, almost all the subsequent events occurred within 6 weeks of the prior event.

Relationship of Events to PCA

The above analyses assess occurrence of extreme events in relation to the number of days an infant was monitored at home. However, the PCA at onset of home monitoring varied considerably. Analyses of the effect of increasing PCA on occurrence of extreme events in each group of infants (Poisson analyses, FIGURE 4) indicate the number of infants in each group experiencing at least 1 extreme event per 20 000 hours of monitoring during successive 4-week PCA intervals. The likelihood of experiencing at least 1 extreme event decreased as PCA increased until about 43 weeks' PCA, after which all groups had similarly low rates of having at least 1 extreme event. During the 4-week period from 34 to 37 weeks' PCA, only the symptomatic (Figure 4, point A) and asymptomatic (point B) preterm infants had a sufficient number and hours of monitoring for analysis. Compared with the healthy term group at 42 to 45 weeks' PCA, the number of infants having more than 1 extreme event per 4 weeks of monitoring time was 19.7 ($P<.001$) and 10.5 ($P=.002$) times higher for the 34 to 37 weeks' PCA symptomatic and asymptomatic preterm groups, respectively. At 38 to 41 weeks' PCA, all 4 preterm groups also demonstrated significantly higher rates than the reference. At 42 to 45 weeks' PCA and thereafter, no group had a rate that was significantly higher than the reference rate.

COMMENT

This is the first large, longitudinal study comparing incidence of cardiorespiratory events among infants monitored at home with that of healthy term infants. Based on more than 700 000 hours of monitor use, we determined that events previously described as "pathologic"[1] are actually quite common, even in healthy term infants. Furthermore, we identified groups that, when compared with healthy term infants, have higher risks of extreme events that are likely to influence clinical management. Our data indicate an increased risk of at least 1 extreme event only in preterm infants and only until about 43 weeks' PCA. Although our choice of RIP for breath detection limits direct comparison to data based on customary impedance monitoring, the high frequency of obstructed breaths in our subjects strongly suggests that many events would have been missed by techniques commonly used in clinical practice.

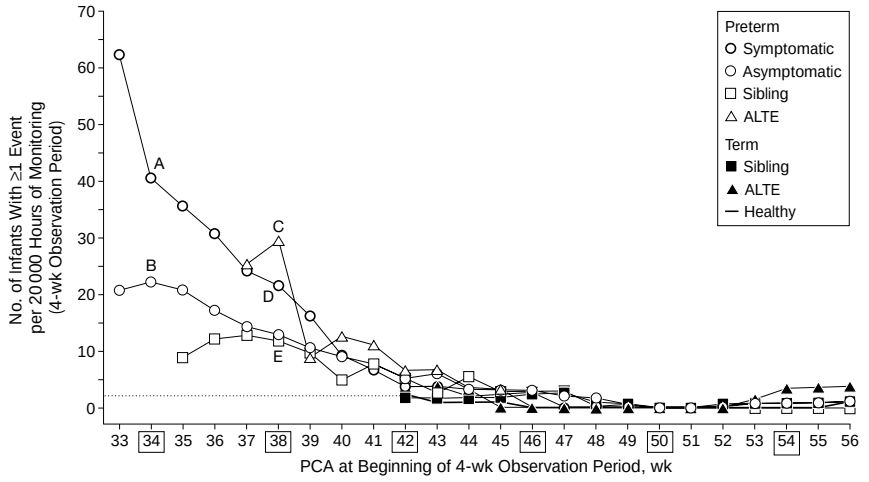
There are several aspects of the CHIME study that are important to consider. First, although the threshold used to define extreme events is much higher than commonly used, our study does not have the means to delineate the pathologic nature of extreme events. Because it is not possible to determine a priori how long apnea or bradycardia can be tolerated without injury, it is only possible to raise the threshold for detection of events in an iterative fashion. Second, since many conventional and extreme events caused a monitor alarm, it is possible that the duration of some events in the risk groups was shortened by either an alarm-induced auditory arousal or by caretaker intervention. The use of conventional alarm thresholds in these groups was a design compromise to be consistent with current practice in infants perceived to be susceptible to life-threatening events, but they could have resulted in an underestimate of extreme events in risk groups and hence reduced ability to detect differences compared with healthy term infants. In addition, subsequent clinical management of infants who experienced events may have influenced their risk for subsequent events. Third,

Table 2. Results of Cox Proportional Hazards Analyses for Risk of at Least 1 Event During a 180-Day Period*

	Events Exceeding Extreme Threshold			Events Exceeding Conventional Threshold		
Group	Cumulative % for ≥1 Event†	Risk Ratio (95% CI)‡	*P* Value	Cumulative % for ≥1 Event†	Risk Ratio (95% CI)‡	*P* Value
Preterm						
Symptomatic (n = 76)	33.0	18.0 (6.2-53)§	<.001	76.3	4.3 (3.0-6.3)§	<.001
Asymptomatic (n = 367)	20.6	10.1 (3.7-28)§	<.001	63.7	2.7 (2.0-3.6)§	<.001
ALTE (n = 45)	19.2	7.6 (2.2-26)	.001	58.5	1.5 (0.86-2.5)	.16
Sibling (n = 50)	17.2	5.6 (1.6-20)	.007	43.7	1.2 (0.69-2.0)§	.56
Term						
Sibling (n = 128)	8.4	2.6 (0.8-8.7)	.11	64.5	1.4 (0.97-2.0)	.07
ALTE (n = 107)	13.1	2.5 (0.66-9.2)	.18	34.4	1.1 (0.71-1.7)	.75
Healthy (n = 306)	2.3	1 (Reference group)		43.2	1 (Reference group)	

*CI indicates confidence interval; ALTE, apparent life-threatening event.
†Values provided are based on Kaplan-Meier plots that account for variable monitoring time.
‡Risk ratios are adjusted for the number of hours of monitor use.
§These risk ratios declined with age. Values were calculated assuming a constant risk over the 180 days.

Figure 4. Rate of Infants With 1 or More Events Exceeding the Extreme Threshold During 4-Week Postconceptional Age (PCA) Periods



Each point indicates the number of infants in a given study group who experienced at least 1 event exceeding the extreme threshold, per 20 000 hours of monitor use during a 4-week observation period beginning at the specified PCA week. Poisson analyses were used to calculate relative rates for nonoverlapping 4-week periods (beginning at the PCA weeks enclosed in a box) compared with the reference group of healthy term infants observed from 42 to 45 weeks' PCA. Significantly higher relative rates were observed in (A) preterm symptomatic group at 34 to 37 weeks (relative rate, 19.7; 95% confidence interval [CI], 4.1-94.0; $P<.001$); (B) preterm asymptomatic group at 34 to 37 weeks (relative rate, 10.5; 95% CI, 2.4-47.0; $P=.002$); (C) apparent life-threatening event (ALTE) preterm group at 38 to 41 weeks (relative rate, 14.3; 95% CI, 2.6-80.1; $P=.002$); (D) preterm symptomatic group at 38 to 41 weeks (relative rate, 10.2; 95% CI, 2.2-47.8; $P=.003$); (E) preterm asymptomatic group at 38 to 41 weeks (relative rate, 6.0; 95% CI, 1.4-26.5; $P=.02$); and the siblings of infants who died of sudden infant death syndrome preterm group at 38 to 41 weeks (relative rate, 5.7; 95% CI, 1.0-31.1; $P=.05$).

our definitions for extreme and conventional events took into account apnea, bradycardia, and combinations. It is possible that the results would have been different had we chosen alternative criteria. Fourth, the procedures, tools, and criteria used for scoring can have a substantial impact on the events identified. To limit variability in data analysis, high scoring reliability was attained.[8] Furthermore, we have confirmed a high level of concordance between apnea detected by the monitor and apnea detected by polysomnogram recordings.[9] Fifth, we excluded infants who had diagnoses commonly associated with cardiorespiratory events, recognizing that the frequency and nature of events thus may have been different. Sixth, due to limited sample size, 95% CIs for RRs were relatively wide, especially in the term risk groups. The upper limits of the 95% CI for term SIDS-SIBs and term infants with idiopathic ALTE, for example, were 8.7 and 9.2, respectively. However, even these upper limits are well below the RRs observed for the preterm infants.

We considered describing apnea events as obstructive, central, or mixed, but recognized early that such categorization obscures the wide range of variability in these events. The high proportion of apnea containing at least 3 obstructed breaths exemplifies the value of using RIP, which can identify obstructed breaths.[9-11] For this reason, transthoracic impedance, which detects effort during obstruction, would not detect many of these apneas, and currently available home monitors would have detected less apnea than we observed. Thus, the distribution of events might vary between our subjects and those reported using other technology.[17-22] Although detection of bradycardia might provide an alternative opportunity to detect events, fully half of extreme events had no bradycardia, even when associated with desaturation.

The CHIME study was not designed to address the important question of whether infants who experience extreme cardiorespiratory events are more likely to die of SIDS. The 6 deaths among study participants are too few to derive conclusions. However, the highest rates of extreme events were observed among infants who were 43 or less weeks' PCA, whereas the peak incidence of SIDS generally occurs at older mean PCAs of 44.2, 46.8, and 52.7 weeks for infants born at 24 to 28, 29 to 32, and 37 weeks, respectively.[23] These differences in timing suggest that extreme events are not likely to be immediate precursors to SIDS, although it does not eliminate the possibility that they are markers of vulnerability.

The CHIME study was also not designed to determine whether use of a monitor decreases the rate of SIDS. The finding that preterm infants 43 weeks' PCA exhibited more extreme events than healthy term infants does not resolve the debate whether such infants would benefit from monitoring. The observation that 20% of asymptomatic preterm infants experienced 1 extreme event highlights the need to determine clinical relevance of extreme events. Until then, however, it is not possible to refute or support the recommendations of the NIH Consensus Development Conference that monitoring or an alternative therapy is medically indicated for symptomatic but not asymptomatic preterm infants.

Controversies regarding who should be monitored notwithstanding, the CHIME data are responsive to an identified gap in our knowledge by defining risk of occurrence and timing of extreme events during early postnatal development.[1] These data also document a high frequency of obstructed breathing within events. Our choice of RIP for breath detection does limit direct comparison to all prior (transthoracic impedance–based) data, but it is important to note that commercially available monitors would likely have missed many CHIME events due to the high frequency of obstructed breaths. These results should be important for design-

ing future monitors and determining if an infant is likely to be at risk for a cardiorespiratory event.

Author Affiliations: Department of Pediatrics and Neonatology, University of Southern California School of Medicine, Women's and Children's Hospital, Good Samaritan Hospital, and Childrens Hospital Los Angeles, Los Angeles, Calif (Drs Ramanathan and Keens); Departments of Pediatrics and Epidemiology and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, Mass (Drs Corwin and Cupples, Mr Peucker); Department of Pediatrics, Medical College of Ohio, Toledo (Drs Hunt and Hufford); Department of Pediatrics, Yale University School of Medicine, New Haven, Conn (Dr Lister); Department of Pediatrics, University of Hawaii at Manoa, Kapiolani Medical Center for Women and Children, Honolulu (Drs Tinsley and Crowell); Department of Pediatrics, Case Western Reserve University School of Medicine, MetroHealth Medical Center, Cleveland, Ohio (Dr Baird); Department of Pediatrics, Rush Medical College of Rush University, Rush Children's Hospital, Chicago, Ill (Drs Silvestri and Weese-Mayer); Department of Pediatrics, Case Western Reserve University, Rainbow Babies and Children's Hospital, Cleveland, Ohio (Drs Baird and Martin); Department of Obstetrics and Gynecology, Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio (Dr Neuman); Pregnancy and Perinatology Branch, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md (Dr Willinger). Dr Neuman is now with the Joint Program in Biomedical Engineering, University of Memphis and University of Tennessee, Memphis.

Author Contributions: *Study concept and design:* Ramanathan, Corwin, Hunt, Lister, Tinsley, Baird, Silvestri, Crowell, Martin, Martin, Neuman, Weese-Mayer, Willinger, Keens.
Acquisition of data: Ramanathan, Hunt, Tinsley, Baird, Silvestri, Crowell, Hufford, Martin, Neuman, Weese-Mayer, Keens.
Analysis and interpretation of data: Corwin, Hunt, Lister, Tinsley, Silvestri, Crowell, Neuman, Weese-Mayer, Cupples, Peucker, Willinger, Keens.
Drafting of the manuscript: Ramanathan, Corwin, Hunt, Lister, Tinsley, Baird, Silvestri, Martin, Weese-Mayer, Cupples, Keens.
Critical revision of the manuscript for important intellectual content: Ramanathan, Corwin, Hunt, Lister, Tinsley, Baird, Silvestri, Crowell, Hufford, Martin, Neuman, Weese-Mayer, Peucker, Willinger.
Statistical expertise: Corwin, Cupples, Peucker.
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Study supervision: Ramanathan, Corwin, Hunt, Lister, Baird, Silvestri, Crowell, Martin, Neuman, Weese-Mayer, Willinger.

Participants in the CHIME Study Group (* indicates Principal Investigator, and †, Study Coordinator): Clinical Sites: Department of Pediatrics, Case Western Reserve University School of Medicine, MetroHealth Medical Center, Cleveland, Ohio: Terry M. Baird, MD* (currently at Rainbow Babies and Children's Hospital, Cleveland); Rainbow Babies and Children's Hospital: Richard J. Martin, MD, Lee J. Brooks, MD (currently at The Children's Regional Hospital at Cooper, Robert Wood Johnson School of Medicine/UMDNJ, Camden, NJ), and Roberta O'Bell, RN†; Department of Pediatrics, Medical College of Ohio, Mercy Children's Hospital, and Children's Medical Center, Toledo, Ohio: Carl E. Hunt, MD* (currently at the National Center for Sleep Disorders Research, National Institutes of Health, Bethesda, Md), David R. Hufford, MD, and Mary Ann Oess, RN†; Department of Pediatrics, Division of Respiratory Medicine, Rush Medical College of Rush University, Rush Children's Hospital at Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill: Debra E. Weese-Mayer, MD*, Jean M. Silvestri, MD, and Sheilah M. Smok-Pearsall, BSN, RN†; Department of Pediatrics, John A. Burns School of Medicine, University of Hawaii at Manoa, Kapiolani Medical Center for Women and Children, Honolulu: David H. Crowell, PhD,* Larry R. Tinsley, MD, and Linda E. Kapuniai, DrPH†; Department of Pediatrics and Neonatology, USC School of Medicine, Los Angeles County & USC Medical Center, Women's and Children's Hospital, and Good Samaritan Hospital, Los Angeles, Calif: Toke T. Hoppenbrouwers, MD*, Rangasamy Ramanathan, MD, and Paula Palmer, MA, PhD†; Childrens Hospital Los Angeles: Thomas G. Keens, MD, Sally L. Davidson Ward, MD, and Daisy B. Bolduc, MBA, RPFT, Technical Coordinator.
Clinical Trials Operations Center: Department of Obstetrics and Gynecology, Case Western University School of Medicine and MetroHealth Medical Center, Cleveland, Ohio: Michael R. Neuman, PhD, MD* (currently at the University of Memphis, Memphis, Tenn), Rebecca S. Mendenhall, MS.†
Data Coordinating and Analysis Center: Departments of Pediatrics and Epidemiology and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, Mass: Michael J. Corwin, MD*; Theodore Colton; Sharon M. Bak, MPH†; Mark Peucker, BS, Technical Coordinator; Howard Golub, MD, PhD, Physiologic Data Biostatistician; and Susan C. Schafer, RNC, MS, Clinical Trials Coordinator.
Steering Committee Chairman: Department of Pediatrics, Yale University School of Medicine, New Haven, Conn: George Lister, MD.
National Institutes of Health: Pregnancy and Perinatology Branch, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md: Marian Willinger, PhD.

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