Risk Factors for Extreme Events in Infants Hospitalized for Apparent Life-threatening Events

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Objective To determine whether known risk factors for cardiorespiratory illnesses will help identify infants who could experience extreme events during an admission for an apparent life-threatening event (ALTE) or later at home.

Study design Retrospective cohort study of all patients admitted for ALTE between 1996 and 2006. Extreme events included central apnea >30 seconds, bradycardia >10 seconds, and desaturation >10 seconds at hemoglobin-oxygen saturation value with pulse oximetry <80%.

Results Of the 625 patients included in the study, 46 (7.4%) had extreme cardiorespiratory events recorded, usually within 24 hours of hospital admission. The most frequent diagnosis was upper respiratory tract infection (URTI, 30 infants). These factors increased the likelihood of having extreme events ($P < .0001$): post-conceptional age <43 weeks (5.2-fold increase), premature birth (6.3-fold), and URTI symptoms (11.2-fold). The most frequent events were extreme desaturations (43/46 infants), preceded by a central apnea. Seven infants had extreme events recorded later during home monitoring (4 with URTI); all 7 infants had sustained extreme events in the hospital.

Conclusion Extreme events were identified mostly in association with symptoms of URTIs, in infants born prematurely, and in infants <43 weeks post-conceptional age. Monitoring with a pulse oximeter should identify infants who sustain these events.
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An apparent life-threatening event (ALTE) is defined as an episode that is frightening to the observer, characterized by some combination of apnea (central or obstructive), color change, marked change in muscle tone, and choking or gagging.[1] A variety of diagnoses are identified after such events, such as an infection or a neurological condition.[2,3] In addition, some infants with ALTE have significant documented cardiorespiratory events when later monitored at home with cardiorespiratory monitors[4,5]; however, there is little information on the occurrence of such events in relation to the initial ALTE.

As the definition of significant cardiorespiratory events has evolved, events previously considered to be significant are now recognized as common in normal healthy infants. The Collaborative Infant Home Monitoring Evaluation (CHIME) study[5] showed that apnea lasting as long as 30 seconds and bradycardia lasting <10 seconds did occur in the group enrolled as "healthy term infants." The term "extreme events" therefore has been introduced for cardiorespiratory events that exceed the aforementioned limits for apnea duration and bradycardia. Data on what constitutes a drop in oxygenation that lies outside the reference range for infants and children is now available.[6-10]

We do not know with certainty what constitutes the risk factors for the occurrence and severity of cardiorespiratory events in infants experiencing an ALTE, whether while in the hospital or, later, at home. Being able to identify infants who are at high risk for extreme cardiorespiratory events would help clinicians who have to decide whether they would hospitalize infants who experienced an event at home. In the CHIME study,[5] the preterm infants were at increased risk of extreme events until 43 weeks post-conceptional age (PCA). Most of these infants, however, were not discharged home with a monitor because of a diagnosis of ALTE. A study conducted by our group between 1990 and 1995 showed that the presence of cardiorespiratory events in hospital was associated with an

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ALTE	Apparent life-threatening event	RSV	Respiratory syncytial virus
CHIME	Collaborative Infant Home Monitoring Evaluation	SpO_2	Hemoglobin-oxygen saturation value with pulse oximetry
IQR	Interquartile range	TTI	Transthoracic impedance
PCA	Post-conceptional age	URTI	Upper respiratory tract infection
PICU	Pediatric intensive care unit		

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increased risk of recurrence at home.[4] However, that study did not differentiate between conventional and extreme events, and data on oxygen saturations were often unavailable.

We therefore reviewed our past 10-year experience with infants who have ALTEs. Our objective was to determine whether known risk factors for cardiorespiratory illnesses can help to identify which infants will experience extreme events during an admission for ALTE or, later, at home. The potential risk factors we explored included prematurity (born at <37 weeks of gestation), PCA <43 weeks, male sex, symptoms of an upper respiratory tract infection (URTI), and winter months.

METHODS

Patient Population

This retrospective cohort study included all patients admitted to the Montreal Children's Hospital for an ALTE between April 1996 and March 2006. Our institution is a tertiary pediatric center with, on average, 66 000 emergency department visits annually. Our search strategy consisted of using all the relevant international classification-of-disease codes that best describe the diagnosis of ALTE: "ALTE," "apnea," "blue spell," or "choking episode" and homemade code subdivisions used at our institution. We reviewed the medical records of all the patients identified with the aforementioned search parameters to determine their eligibility for inclusion. We excluded patients who had pre-existing control-of-breathing conditions (congenital central alveolar hypoventilation, myelomeningocele), airway anomalies, cyanotic heart diseases, arrhythmias, and patients already on cardiorespiratory monitors or patients with a tracheostomy. To qualify for inclusion, the reason for consultation had to have been an ALTE. The infant also should have apparently recuperated from the event when he or she was seen in the emergency department. When an infant was seen more than once for the same diagnosis, the first admission was counted as the relevant one.

To determine the proportion of infants coming to the emergency department for ALTE who were eventually admitted to the hospital, we extracted data from our emergency department database. The data, however, were available only from the end of 1999 (77 of the 120 months of the study). For the patients admitted to the hospital, we were able to match the data from the 2 sets on the basis of the medical record number, the admitting diagnoses, and the date of birth.

In-hospital Investigation

All infants admitted with a diagnosis of ALTE undergo a standard investigation[4] and are first monitored with a nonrecording cardiorespiratory monitor (detection of respiration with transthoracic impedance [TTI]) and, usually, a pulse oximeter also. The ward-attending pediatrician will then assess, on the basis of the perceived significance of the event, the need for documented monitoring (with an event-recording monitor), in consultation with the respiratory medicine consulting physician. When an event-recording monitor is used, it is used for the entire duration of the investigation (1 to several days), 24-hours per day. In addition, patients with recurrent clinical events or monitor alarms will have continuous hemoglobin-oxygen saturation recordings performed, with pulse oximetry (SpO_2).

Type of Monitor and Data Acquisition

We used the Smart Monitor 970S or the Smart Monitor 2 (Children's Medical Ventures, Respironics, Murrysville, Pennsylvania), both of which are TTI apnea monitors with memory capabilities to store events that violate the preset alarms. Respiratory and electrocardiographic waveforms were recorded 45 seconds before, and 45 seconds after, violation of the alarm thresholds. The monitor recorded any cessation of respiratory movements for ≥16 seconds and produced an audible alarm with a cessation of respiratory movements for ≥20 seconds and for an immediate drop in heart rate to 80 bpm (first month of life) or 60 bpm. When SpO_2 was to be recorded also, a pulse oximeter was connected to the cardiorespiratory monitor and the pulse oximeter memory was downloaded separately. For the early years of the study period, a Nellcor N200 pulse oximeter (Nellcor, Pleasanton, California) was used; we then used the Radical pulse oximeter with Masimo technology (Masimo Corporation, Irvine, California). With both monitors, the audible alarms were set at SpO_2 of 87%. For the last 2 years of the study, we used the Smart monitor 2PS (Children's Medical Ventures, Respironics, Murrysville, Pennsylvania), which is a thoracic impedance cardiorespiratory monitor with an integrated pulse oximeter that uses Masimo technology.

Data Extracted

All data relevant to the event leading to admission to the hospital, the risk factors, and the investigation undertaken were entered in a data base. For identifying infants who had symptoms of an URTI, we look for such a diagnosis made by the physicians or for the mention of a recent onset of rhinorrhea with or without cough and mild fever. We also collected data on follow-up, including home monitoring and further events, both clinical and documented. For all infants who had recordings in hospital and at home, we reviewed the original recordings to determine the precise duration of the recorded events. Two investigators did the scoring (H.A., A.C.). When the 2 investigators' scores did not correspond, they reviewed the tracings until an agreement was reached.

Definition of Extreme Events

We defined an "extreme event" according to the criteria of the CHIME study.[5] Thus, we defined an extreme apnea as a central apnea lasting >30 seconds and an extreme bradycardia as either a drop in heart rate to <60 bpm for at least 10 seconds for infants <44 weeks postconceptional age (PCA) or as a drop to <50 bpm for at least 10 seconds for infants ≥44 weeks PCA. We defined a significant drop in SpO_2 as a SpO_2

Table I. Characteristics of the 625 infants

	Median	25th-75th percentile
Chronological age (days)	43	21-73
Gestational age (weeks)	39	37-40
PCA (weeks)	44.4	41.4-48.7
	N	**%**
Male	329	53
Prematurely born infants	128	21
Non-documented monitoring*	287	
Documented monitoring in hospital†	338	54
Cardiorespiratory and SpO_2	165	
SpO_2 alone	19	
Cardiorespiratory alone	154	
Patient discharged with a home monitor	88	14

*The equipment consisted of a non-recording cardiorespiratory monitor with a) detection of respiratory movement using transthoracic impedance; and b) ECG. The pulse oximeter was a non-recording pulse oximeter.
†Documented monitoring refers to the use of monitors with memory that allows the review of the recorded events.

level ≤80% for at least 10 seconds. This cutoff point was chosen because our review of normative data published for infants in the first few months of life showed this values to be well outside the reference range (fifth percentile limit).[7,8]

Home Monitoring

The criteria for using a home monitor was the presence of significant cardiorespiratory events in hospital or the history of a clinically significant ALTE with no treatable cause identified.

Data Analysis and Statistics

Because our data were not normally distributed, we expressed the variables with the median and an interquartile range (IQR). Group comparisons were done with analysis of variance on ranks. To compare proportions between the different groups, we used the χ^2 analysis or the Fisher exact test with Yates correction for sample size, as indicated. Relative risk ratios for the risk factors of interest were computed. Our study was approved by the appropriate review committee in our institution.

RESULTS

A total of 748 cases was retrieved with our search strategy. Of those, 123 cases were excluded because they did not fit our clinical criteria for ALTE (92 cases) or on the basis of pre-existing diseases (31 cases). We therefore retained 625 cases (Figure 1; available at www.jpeds.com). Table I lists the characteristics of these cases. During the period for which the data were available electronically from our emergency department, admissions for ALTE represented 71% of all consultations for that diagnosis.

Although all patients were continuously monitored with a cardiorespiratory monitor or a pulse oximeter (or both) during their hospital stay, 338 patients (54%) underwent continuous documented recording with a cardiorespiratory event recorder or SpO_2 monitor with memory. Of these, we identified extreme cardiorespiratory events in 46 patients (29 male infants), or 13.6% (Figure 1).

Extreme Events during the Initial Investigation

The diagnosis of extreme events was made early during hospitalization, within the first 24 hours in all but 7 of the 46 infants. For the infants in whom a diagnosis was made after the first 24 hours, it appears to have been the delay in initiating the documented cardiorespiratory monitoring (2 infants) or the documented monitoring of pulse oximetry (5 infants) that delayed the diagnosis; extreme events were identified within hours of the initiation of documented monitoring. A respiratory tract infection was the most often identified sole diagnosis (Table II; available at www.jpeds.com).

Most of the infants (41/46; 89%) did not appear to be sick on presentation to the emergency department; of these 41 infants, 26 were admitted to a regular ward and monitored, although they still did not appear sick. The other 15 infants were admitted directly to the pediatric intensive care unit (PICU). It was either the oximeter or the cardiorespiratory monitor alarms that alerted the health professionals to the events. Twenty-five of the patients with extreme events were eventually admitted to a PICU, and 16 of these patients were treated with mechanical ventilation and 2 were treated with nasal continuous positive airway pressure and supplemental oxygen. Sixteen of the 46 infants with extreme events were treated solely with supplemental oxygen.

The duration of the extreme events—as documented by recording—was brief for most infants. The median duration was 4 days (IQR, 3.0-7.8 days, n = 35). We could not, however, calculate the duration of events for either the infants who were receiving mechanical ventilation and had secondary complications or for the infants who were receiving oxygen for several days. Of the infants having a duration of events >7 days, pertussis was diagnosed in 2, whereas 1 had cardiac involvement with a metabolic disorder and severe bradycardia; the other infants had been born prematurely and came to the hospital with ALTE before the age of 43 weeks PCA.

Most extreme events (events in 43/46 infants, 94%) included a desaturation below the limit of 80% for >10 seconds, with most desaturations lasting ≥20 seconds (Table III). The extreme desaturations were most often preceded by a central apnea (Figure 2; available at www.jpeds.com); 27 infants had central apneas >30 seconds. If an oximeter had not been used, the diagnosis of extreme events would have been missed in 14 infants. Of these, 11 infants had documented events that did not exceed the threshold of 30 seconds for apnea and 10 seconds for bradycardia; the remaining 3 infants had clinically observed obstructive apnea (on repeated occasion while on the monitor), but with no bradycardia despite prolonged drops in SpO_2 <80%. A representative example is provided in Figure 3 (available at www.jpeds.com).

Table III. Type and association of events in 46 patients with extreme events

Event	N
Isolated events*	
Isolated central apnea >30 s	2
Isolated bradycardia >10s	1
Isolated SpO_2 <80% for >10 s	3
Combination of events	
Conventional central apnea or bradycardia with SpO_2 <80% for >10 s	11
Central apnea >30 s with SpO_2 <80% for >10 s, no bradycardia	15
Central apnea >30 s with bradycardia >10 s and desaturation >10 s, <80%	12
Bradycardia >10 s with SpO_2 <80% for >10 s, no central apnea	2

*To qualify as an isolated event, the events were not associated with another one that made it qualified for the definition of extreme events. For instance, the isolated central apnea >30 seconds, when associated with either a drop in heart rate or in SpO_2, will not have the bradycardia or the desaturation qualifies as extreme.

Table IV. Relative risk of having an extreme event, infants on recording monitors*

Risk factor	Relative risk	95% CI	*P* value
Male sex	1.2	0.71-2.2	.443
Winter months	1.6	0.89-2.7	.121
PCA <43 weeks (males and females)	5.2	2.6-10.3	<.0001
Males with PCA <43 weeks	8.7	2.7-27.8	.0001
Females with PCA <43 weeks	2.8	1.09-7.3	.033
Prematurity†	6.3	3.6-11.0	<.0001
Symptoms of URTI‡	11.2	6.7-18.9	<.0001

*For the evaluation of relative risk, we are using the group of 338 infants who had documented monitoring. The same analysis was done for the whole group and yielded similar results.
†There was no sex difference in the relative risk of having an extreme event for infants born prematurely.
‡There was no sex difference in the relative risk of having an extreme event for infants with symptoms of an URTI.

Predictive Factors of Extreme Events

Three factors—being born prematurely, being <43 weeks of PCA, and having symptoms of an URTI on admission—increase the risk of extreme events in infants admitted for ALTE who were on a recording monitor (338 cases; Table IV). However, symptoms of URTI did develop within 24 to 48 hours in some infants with no symptoms of URTI on admission. These infants were not included as "having symptoms of URTI on admission." Male sex and winter months were not found to increase the risk for extreme events. Male sex, however, did increase the risk of extreme events in infants <43 weeks PCA, although not in infants born prematurely or having symptoms of URTI. Both male and female infants born prematurely had an increased risk of extreme events; similarly, both male and female infants with symptoms of URTI had an increased risk of extreme events.

Because not all infants were on recording monitors during their hospital admission, we evaluated the presence of the risk factors in infants who had cardiorespiratory recordings, with and without an oximeter, and infants who did not (Table V; available at www.jpeds.com). The non-recorded group and the group that had recording (but with no extreme events identified) were very similar, and both were different from the group with extreme events.

We evaluated the usefulness of a single-risk factor or a combination of risk factors in predicting which infants would experience extreme events. However, the only factor with a 100% negative predictive value and 100% sensitivity was "being <48 weeks PCA"; however, 72% of the infants in our study were aged "<48 weeks PCA." For male infants <48 weeks PCA, born prematurely, and having symptoms of an URTI, the negative predictive value was 97.4% (95% CI, 95.8%-98.6%), but with a sensitivity rate of only 67.4%. If these combined factors had been used as criteria for hospital admission, 15 infants with extreme events would have been missed. Other combinations did not improve either the negative predictive value or the sensitivity.

Follow-up at Home

A total of 88 infants were sent home with a monitor. This number included all infants except 7 who presented with extreme events. These 7 infants not monitored at home were American Indian or Inuit infants who lived in the far north. They were monitored until free of events for 1 month, either in our institution or in a hospital near their place of residence. All other infants were monitored via a home cardiorespiratory monitor, except 3 infants for whom we used a pulse oximeter because the events were characterized by a decrease in SpO_2 without prolonged central apnea or bradycardia. Two infants were sent home on supplemental oxygen.

Seven monitored infants (8.0%) had extreme events recorded at home, and all had had extreme cardiorespiratory events recorded in hospital. Pertussis was diagnosed in 2 of these infants; 4 infants had a recurrence of events (central apnea >30 seconds with desaturation) with an URTI (1 with respiratory syncytial virus [RSV]). The last infant had persistence of desaturation events for months (only a few events met the criteria for extreme events); she had been noted as being mildly hypotonic at the initial admission, and later nemaline rod myopathy was diagnosed.

Five of the 7 infants with extreme events at home were readmitted to the hospital. None of the readmitted patients needed intensive care, and all were treated with low-flow oxygen for a few days. These recurrent events occurred at a median PCA of 46.5 weeks (IQR, 42.4-49.7 weeks). The median duration of illness was brief at 3 days (IQR, 2-6 days).

DISCUSSION

The occurrence of extreme cardiorespiratory events in infants admitted to the hospital for ALTE was seen only in infants <48 weeks post-conception. A post-conceptional age

<43 weeks, a premature birth, and symptoms of an URTI were associated with an 5.2-fold, 6.3-fold, and 11.2-fold increased risk of extreme events, respectively. Furthermore, although recurrence at home was infrequent, extreme cardiorespiratory events did occasionally occur at home, but only in infants who had extreme events in the hospital.

We explored the occurrence of cardiorespiratory events in infants admitted for ALTE in a large cohort of infants in a 10-year period. We used the definition of "events that are truly outside the normal range," as determined by the CHIME study,[5] a study in which prolonged recordings were made at different ages throughout the first 6 months of life. In addition, our data take into consideration the level of SpO_2 and the duration of low-oxygenation events.

It is not surprising to find that cardiorespiratory events occur in the youngest of infants. We know that for some weeks, even after a term birth, there is still immaturity of the respiratory centers,[11-13] arousal mechanisms,[14,15] and airway reflexes.[16-18] Nor is the finding that male sex carries a higher risk than female sex in the youngest infants unexpected, because there is evidence of sex differences in control of breathing and in neurotransmitter modulation of this control in infants.[19-21]

Most infants with extreme events in our study (65%) had symptoms of URTI. The occurrence of prolonged apnea associated with URTI has been well documented for RSV infection since the 1970s[22-24]; in 1 of these early studies,[24] age <2 months was the strongest independent risk factor for RSV-associated apnea. More recently, Willwerth[25] identified "PCA of less than 48 weeks" for infants born preterm, and "age less than 1 month" for term infants as risk factors for apnea associated with bronchiolitis. Stimulation of the laryngeal chemoreceptors has been postulated as the mechanism leading to prolonged apnea.[26,27] However, viral infections other than RSV can lead to prolonged central apnea and low oxygenation, which is less well known and less documented in the literature. Poets et al[28] have reported some marked episodes of low oxygenation (prolonged SpO_2 drops <80%) in association with central apnea in a few preterm infants during a viral infection. In the present study, as was also shown in a different cohort,[29] we are also reporting episodes of a marked decrease in SpO_2 that occurred before the symptoms of a viral infection.

Physicians are often confronted with the need to decide whether to admit infants who do not look sick, but have had an event at home that qualifies as an ALTE.[30,31] The review of studies with identified risk factors for significant events has produced some conflicting results. For instance, Davies and Gupta (n = 65 infants)[32] and De Piero et al (n = 150 infants)[33] identified "age at presentation over 2 months" as a risk factor for a serious diagnosis, such as lower respiratory tract infection needing mechanical ventilation, supplemental oxygen, or both, or a seizure disorder. De Piero et al also identified "prematurity" as a risk factor for a more serious diagnosis.[33] In contrast, Claudius and Keens, in a small prospective cohort study (n = 59 infants), identified "age >30 days" as a low risk factor.[30] However, in these small studies, chronological age was used instead of PCA to estimate the risk of a serious disease. Therefore, some infants >2 months were likely at a PCA <48 weeks. Also, none of these studies specifically looked at cardiorespiratory events, and no data are available for in-hospital cardiorespiratory and oxygenation recordings.

Our study therefore adds important information for physicians taking care of infants with ALTE and having to decide on admission and investigation. Because most infants with extreme events documented did not appear sick on arrival at the hospital, we recommend that infants <48 weeks PCA be monitored during the first day of observation with a pulse oximeter or a cardiorespiratory monitor, ideally a monitor with memory capability, so any extreme events can be documented. Clearly, however, the pulse oximeter has advantages when compared with the cardiorespiratory monitor, because events in 14 infants would likely have been missed if oxygen saturation had not been recorded. The pulse oximeter would also alert the clinicians in the event of a prolonged obstructive apnea if associated with hypoxemia.

Not all infants in our study were receiving the surveillance of recording monitors; indeed, it is possible that some events may have been missed. We do not think this is likely, however, because all the infants studied were on standard cardiorespiratory monitors or pulse oximeters during their hospital stay; thus recurrent severe events should have been picked up. We acknowledge, however, that prolonged cardiorespiratory events can be missed by standard monitors.[34,35] We were reassured that the group with no recording done was similar, in age and risk-factor prevalence, to the groups having had no extreme events while continuously undergoing surveillance with recording monitors. We acknowledge, however, that obstructive events have been missed, especially when these were not associated with drops in SpO_2.

We do not think that our population of infants differs from the usual population of infants presenting to hospital with ALTE. When compared with data from other studies, the proportion of infants seen in our emergency facility with ALTE—at 1%—is similar to that of other, albeit much smaller, published series.[30,32,33,36] Also, similar to other centers, the proportion of infants seen for ALTE who were admitted to the hospital was high. Finally, both the age distribution and the identification of causes yielded very similar results, compared with other large studies from different regions of the world.[2,3] We therefore think that the conclusions of our study would be applicable to the populations of other regions.

Finally, none of the risk factors studied, either alone or in combination, were sufficiently sensitive to identify most infants who later sustained extreme events, while eliminating infants not likely to have events. Our results, however, could serve to design a prospective study to better test the usefulness of using these risk factors in combination with other risk factors for infant morbidity, such as exposure to passive smok-

ing, lack of breastfeeding, or unsafe sleeping environment, to mention only a few.

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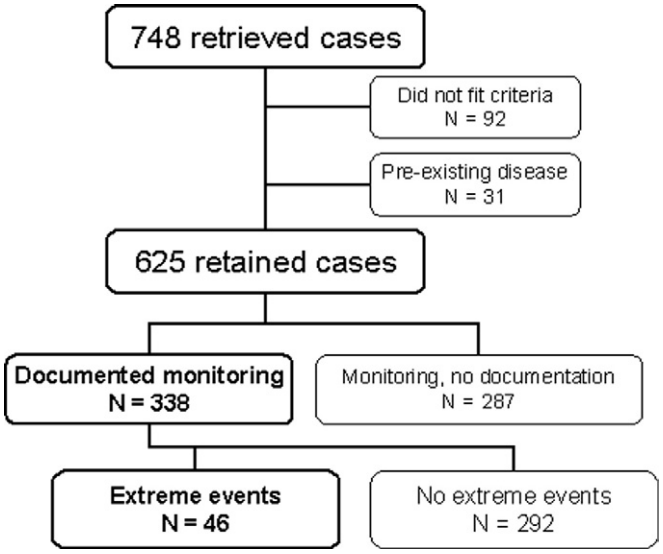

Figure 1. Ascertainment and classification of patients admitted for ALTE.

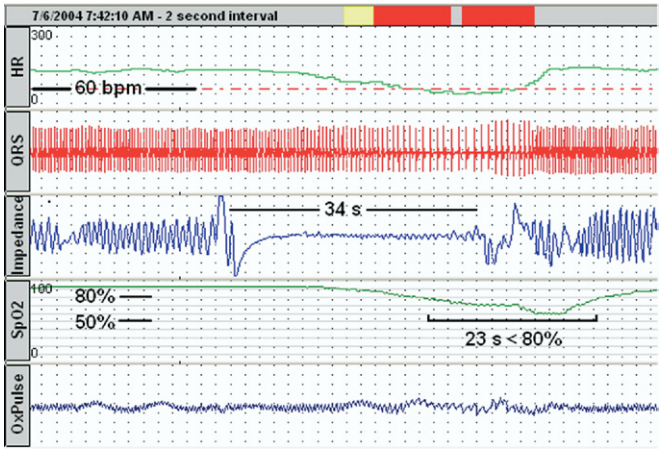

Figure 2. Representative example of the most common event classified as an extreme event. Note the 34-second central apnea with the associated desaturation below the level of 80%. The drop in heat rate did not reach <60 bpm for >10 s. The apparent small respiratory movements on the impedance channel during the apnea correspond to cardiogenic artifacts. *HR,* Heart rate; *QRS,* QRS wave of the electrocardiogram; *impedance,* respiratory movements detected by transthoracic impedance; o*xypulse,* plethysmographic wave obtained from the pulse oximeter.

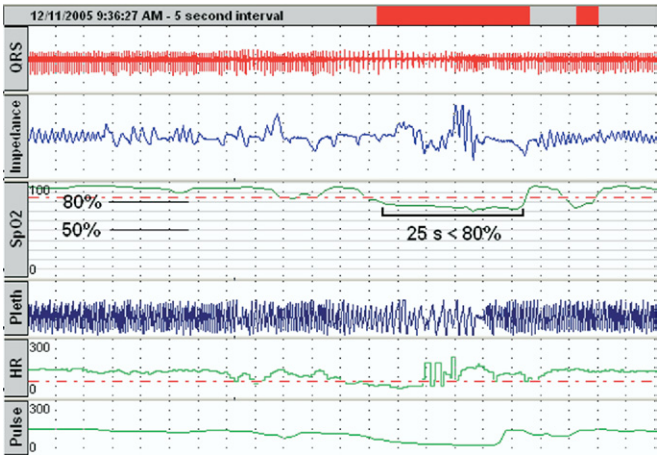

Figure 3. Representative example of a desaturation event classified as an extreme event. Note the 25-second drop in SpO_2 level <80%. There are irregular breathing movements on the impedance channel. This infant had anterior nasal stenosis and was witnessed to have repeated obstructive events. *Pleth,* Plethysmographic wave obtained from the pulse oximeter; HR, heart rate; *pulse,* heart rate derived from the pulse signal of the pulse oximeter.

Table II. Identified causes for the extreme events

Diagnosis	N
Respiratory infection	30 (65.9%)
RSV	7
Pertussis	3
Para-influenza	1
Non-identified	19
Gastroesophageal reflux*	5
Metabolic disorder	1
Upper airway obstruction†	1
Pallid syncope‡	1
No cause identified§	8
Total	46

*These infants had clinical manifestation compatible of gastroesophageal reflux during the events, abnormal results on a 24-hour pH recording, and the events stopped after initiation of treatment.

†This infant had anterior nasal stenosis.

‡Pallid syncope was defined as loss of consciousness with intense pallor. These events were witnessed in hospital and associated with bradycardia on the recording monitor. No cause was found.

§Two infants, in addition to the extreme events, had numerous desaturation episodes and low baseline values; they were eventually sent home on supplemental low-flow oxygen.

Table V. Comparison of age and presence of risk factors as a function of cardiorespiratory and pulse oximetry recording status

	Infants on recording monitors				
	Extreme events	No extreme events		No extreme events	
	CR monitor + oximeter 46 infants	CR monitor + oximeter 138 infants	CR monitor 154 infants	No recording monitor 287 infants	Significance
Age*	**Median (IQR)**				
Chronological (days)	32 (26-49)	46 (18-79)	42 (21-73)	44 (21-77)	NS
Gestational (weeks)	35.0 (33.7-37.0)	39.0 (37.5-40.0)	39.0 (37.9-40.0)	39.0 (37.4-40.0)	$P < .001$
Postconceptional (weeks)	41.0 (38.7-42.0)	44.7 (41.3-49.3)	44.9 (41.7-48.7)	44.7 (41.6-49.3)	$P < .001$
Factor†	**N (%)**				
PCA < 43 weeks	37 (80)	56 (30)	57 (37)	113 (39)	$P < .001$
Prematurity	31 (67)	29 (16)	24 (16)	243 (15)	$P < .001$
URTI	30 (65)	14 (8)	19 (12)	59 (21)	$P < .001$
Male sex	28 (61)	76 (41)	84 (55)	141 (49)	NS
Winter months	15 (33)	26 (14)	39 (25)	81 (28)	NS

CR, Cardiorespiratory; *NS,* not significant.

*Analysis of variance on ranks; the 3 groups that experienced no extreme events as compared with the group with extreme events.

†χ^2 (2×4 contingency tables, "yes" or "no" for each factor).