BRUE and Apnea at Term, how do they relate?

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Apnea at Term

• Can it happen?
• How does it differ from apnea in the preterm infant?
• Is respiratory control fully mature at term?
• Are there discrete periods of vulnerability when apnea is more likely to occur?
• Does BRUE = Apnea?
Apnea at Term-Timeline and Periods of Vulnerability

Immediate postnatal period
0-3 days

Early Infancy
3 days-6 mo.

Late Infancy
6mo.-1 year
Apnea Definitions

• Central
  • Duration: 20 seconds
  • Shorter apnea/pauses if associated with hypoxemia or bradycardia

• Obstructive
  • Same duration parameters
  • Not detected by transthoracic impedance monitoring

• Mixed
  • A period of central apnea followed by a period of airway obstruction (most common form of apnea in preterm infants)
Other Definitions/Considerations

• Loss of 2 respiratory cycles
  • 3 seconds in neonate
  • 5 seconds in 5-6 month olds

• What makes apnea clinically significant?
  • Respiratory pause length?
  • When associated with a disturbance in other physiologic parameters?
Periodic Breathing (PB)

- Repetitive short cycles of respiratory pauses and breathing
  - ≥3 cycles of respiratory pauses, ≥3 seconds in length
  - Breathing duration between each pause ≤20 seconds
Periodic Breathing

- The most common form of breathing “instability”
- Peripheral chemoreceptors
  - Respond rapidly to changes in $\text{PaO}_2$, $\text{PaCO}_2$ and $\text{H}^+$
  - Carotid bodies ($\text{O}_2$ and $\text{CO}_2$ sensitivity increases over weeks to months)

Edwards BA. *Respiratory Physiology & Neurobiology* 185 (2013)
Maturation of Respiratory Control

• Components of the respiratory control system
  • Complex neuronal connections between brainstem and limbic systems
  • Neurotransmitters
  • Mechanoreceptors (lung volume)
  • Peripheral and central chemoreceptors (gas exchange)
Postnatal Maturation of Breathing

- Evidence that the brainstem is not fully mature at term
  - Incomplete myelination
  - Dynamic changes in neurotransmitter systems
  - Evolution of sleep/wake cycles and maturation of sleep states

- PB is the most common manifestation of immature respiratory control
  - Initially absent
  - Frequent at 2-4 weeks of age
  - Rare by 6 months
Cardiorespiratory Events Recorded on Home Monitors

Comparison of Healthy Infants With Those at Increased Risk for SIDS

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Carl E. Hunt, MD  
George Lister, MD  
Larry R. Tinsley, MD  
Terry Baird, MD  
Jean M. Silvestri, MD  
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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, 663 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.

JAMA. 2001;285:2199-2207
Table 2. Results of Cox Proportional Hazards Analyses for Risk of at Least 1 Event During a 180-Day Period

<table>
<thead>
<tr>
<th>Group</th>
<th>Events Exceeding Extreme Threshold (30sec)</th>
<th></th>
<th>Events Exceeding Conventional Threshold (20sec)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cumulative % for ≥1 Event†</td>
<td>Risk Ratio (95% CI)‡</td>
<td>P Value</td>
<td>Cumulative % for ≥1 Event†</td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>33.0</td>
<td>18.0 (6.2-53)§</td>
<td>&lt;.001</td>
<td>76.3</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>20.6</td>
<td>10.1 (3.7-28)§</td>
<td>&lt;.001</td>
<td>63.7</td>
</tr>
<tr>
<td>ALTE (n = 45)</td>
<td>19.2</td>
<td>7.6 (2.2-26)</td>
<td>.001</td>
<td>58.5</td>
</tr>
<tr>
<td>Sibling (n = 50)</td>
<td>17.2</td>
<td>5.6 (1.6-20)</td>
<td>.007</td>
<td>43.7</td>
</tr>
<tr>
<td>Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling (n = 128)</td>
<td>8.4</td>
<td>2.6 (0.8-8.7)</td>
<td>.11</td>
<td>64.5</td>
</tr>
<tr>
<td>ALTE (n = 107)</td>
<td>13.1</td>
<td>2.5 (0.66-9.2)</td>
<td>.18</td>
<td>34.4</td>
</tr>
<tr>
<td>Healthy (n = 306)</td>
<td>2.3</td>
<td>1 (Reference group)</td>
<td></td>
<td>43.2</td>
</tr>
</tbody>
</table>

*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.

JAMA 2001;285
Reference values for respiratory events in infants aged 1 and 3 months

• 37 healthy infants
• Obstructive apnea: absence of air flow with chest and abdominal wall movement for at least 2 breaths
• Central apnea: >20 seconds or apnea for the duration of two breaths associated with hypoxemia and bradycardia
• Index = #events per hour of total sleep time

Brockman PE, Poets A. *Sleep Medicine* 2013
Fig. 1. Changes of respiratory indices between the ages of 1 and 3 months. Abbreviations: AHI, apnea-hypopnea index; MOAHI, mixed obstructive apnea-hypopnea index.
Apnea in the Otherwise Healthy, Term Newborn: National Prevalence and Utilization during the Birth Hospitalization

Jonathan C. Levin, MD¹, Jisun Jang, MA², and Lawrence M. Rhein, MD, MPH³,⁴

Objectives To describe the prevalence of apnea in otherwise healthy term newborns, identify attributable length of stay (LOS) and healthcare utilization (cost) of apnea, and measure hospital variation in attributable LOS and cost of apnea in this population.

Study design We conducted a secondary analysis of a national administrative dataset, the 2012 Kids’ Inpatient Database, which included 3.4 million newborn discharges in the US. The birth hospitalizations of approximately 2.6 million otherwise healthy, full-term newborns were included for analysis. Attributable LOS and cost of apnea were calculated using multivariate analyses.

Results Apnea was diagnosed in 1 in 1000 healthy full-term newborns. Multivariate analyses showed that newborns with apnea had 0.6 days longer LOS ($P < .001$) and $483 greater costs ($P < .001$) compared with healthy term newborns, per birth hospitalization. Newborns diagnosed with apnea plus hypoxia and/or bradycardia had 1.4 days longer LOS ($P < .001$) and $653 greater costs ($P < .001$). The attributable LOS and cost attributable to apnea varied between individual hospitals and differed by hospital region.

Conclusions Apnea is associated with higher LOS and cost in the newborn hospitalization, with variation in hospital practice. This suggests the need for better comprehension of the underlying physiology and standardization of practice in its management in the term newborn. (J Pediatr 2017;181:67-73).
## Characteristics of Term Infants with Apnea

### Table I. Demographic and hospital information for infants with apnea and those without apnea

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Apnea only (n = 2034)</th>
<th>Healthy (n = 2,618,278)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,050 (51.6%)</td>
<td>1,301,400 (49.7%)</td>
<td>.15</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>961 (47.2%)</td>
<td>1,268,899 (48.5%)</td>
<td>.23</td>
</tr>
<tr>
<td>Black</td>
<td>266 (13.1%)</td>
<td>314,841 (12.0%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>355 (17.4%)</td>
<td>492,838 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>277 (13.6%)</td>
<td>319,344 (12.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary payer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>985 (48.4%)</td>
<td>1,193,394 (45.6%)</td>
<td>.08</td>
</tr>
<tr>
<td>Private</td>
<td>920 (45.2%)</td>
<td>1,229,475 (47.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>126 (6.2%)</td>
<td>188,052 (7.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cesarean delivery</strong></td>
<td>837 (41.2%)</td>
<td>785,029 (30.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Hospital characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>330 (16.2%)</td>
<td>421,890 (16.1%)</td>
<td>.22</td>
</tr>
<tr>
<td>Midwest</td>
<td>481 (23.7%)</td>
<td>562,452 (21.5%)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>694 (34.1%)</td>
<td>991,281 (37.9%)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>526 (26.0%)</td>
<td>642,655 (24.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Teaching status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching</td>
<td>1,042 (51.2%)</td>
<td>1,234,372 (47.1%)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Apnea at Term: Triple Risk Model

- Vulnerable Infant
- Critical developmental Period
- Stressor(s)

Apnea
Apnea at Term

• What are the stressors?
  • **0-3 days:**
    • Perinatal events (hypoxemia, asphyxia)
    • ICH
    • Congenital anomalies (airway, CNS)
    • Sepsis
    • Maternal therapies
    • SSC (positioning, feeding)

• **3 days-6 mos.**
  • Gastroesophageal Reflux?
  • RSV, Pertussis
  • Bacterial infection
  • Seizure
  • Non-accidental trauma
  • Cardiac conduction abnormality
  • Cardiomyopathy
  • Metabolic disorder
Congenital Central Hypoventilation Syndrome
BRUE or BREW
Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants

Joel S. Tieder, MD, MPH, FAAP, Joshua L. Bonkowsky, MD, PhD, FAAP, Ruth A. Etzel, MD, PhD, FAAP, Wayne H. Franklin, MD, MPH, MMM, FAAP, David A. Gremse, MD, FAAP, Bruce Herman, MD, FAAP, Eliot S. Katz, MD, FAAP, Leonard R. Krilov, MD, FAAP, J. Lawrence Merritt II, MD, FAAP, Chuck Norlin, MD, FAAP, Jack Percelay, MD, MPH, FAAP, Robert E. Sapién, MD, MMM, FAAP, Richard N. Shiffman, MD, MCIS, FAAP, Michael B.H. Smith, MB, FRCPCH, FAAP, for the SUBCOMMITTEE ON APPARENT LIFE THREATENING EVENTS
Rationale for Guideline

• Foster patient and family-centered approach
• Reduce unnecessary and costly medical interventions and evaluation/hospitalization
• Improve outcomes
• Support implementation of recommendations
• Provide direction for future research
Brief Resolved Unexplained Events, BRUE (formerly known as ALTE)

- Infant with ≥ 1 of the following
  - Cyanosis or Pallor
  - Absent, decreased or irregular breathing
  - Marked change in tone
  - Altered level of responsiveness
  - Absent, decreased or irregular breathing
Why not ALTE?

- First AAP clinical practice guideline that applies to patients who had a resolved, unexplained event
- Life-threatening as determined by who???
- History and physical exam are essential to diagnosis
- Lower vs Higher Risk
BRUE vs. ALTE

- BRUE has a strict age limit
- An event is only a BRUE if there is no other explanation after performing a thorough H&P
- BRUE is based on clinician’s evaluation and perception, NOT that of the care-giver
- Clinician should determine whether there is episodic cyanosis or pallor (turning red is not consistent with BRUE)
BRUE vs. ALTE

• BRUE expands respiratory symptoms beyond apnea
• Should determine whether there is marked change in tone
  • Hyper- or hypotonia
• Choking and gagging inconsistent with BRUE
• “Altered level of responsiveness” (new addition)
  • Episodic, but serious underlying disorder (cardiac, respiratory, metabolic, neurologic event)
Lower Risk

• >60 days
• GA ≥32 weeks and PCA ≥45 weeks
• First event
• <1 minute duration
• No CPR required by trained medical provider
• Benign history, reassuring physical exam
• Absence of identifiable risk factors
NOTE!

This guideline DOES NOT provide recommendations for the management of the higher-risk infant.
Potentially Serious Underlying Conditions at Risk for Recurrence

- Gastroesophageal reflux
- Respiratory tract infection (RSV), pertussis
- CNS disorder or seizure
- Child abuse
- Other (poisoning, bilirubin encephalopathy, structural heart disease, conduction defects/cardiac channelopathies, cardiomyopathies, arrhythmias, metabolic disorders, anaphylaxis, bacterial infections, anemia, causes of upper airway obstruction)
Rainbow Babies and Children’s Infant Apnea Program and Disposition of ALTEs 2010-2015

- Retrospective review
- 90 patients referred for pneumogram/pH-Impedance study
- ≥ 37 weeks
- Interventions extracted from discharge summaries
Rainbow Babies and Children’s Infant Apnea Program and Disposition of ALTEs 2010-2015

- Antacid/Anti-reflux (20)
  - Feeding Intervention (45)
  - No Intervention (30)
  - Home Monitor (12)
  - Other (8)

Antacid/anti-reflux
Feeding intervention
None
Apnea monitor
Other
Other....

• RSV
• Possible central hypoventilation syndrome
• Pneumonia
• UTI
• Possible mitochondrial disorder
• EKG abnormality
• Hyperinsulinism/hypoglycemia
Take Home Points

• Clinically significant apnea may occur in full term infants, but it is NOT physiologic
• True apnea at term requires a thorough history and physical and investigation for an underlying cause
• There are specific criteria for the diagnosis of BRUE
• The diagnosis of BRUE is assigned only when there is NO explanation for the event after completion of H&P
• The BRUE guidelines only provide recommendations for the Lower Risk infant population