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Effect of Severity of Esophageal Acidification on Sleep vs Wake Periods in Infants Presenting with Brief Resolved Unexplained Events

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Objectives To describe the pattern of gastroesophageal reflux (GER) events in wake and sleep states with increasing acid reflux index (ARI) in neonates and to test the hypothesis that GER-related symptoms are frequent in ARI >7% in wake state.

Study design Infants underwent 24-hour pH-impedance studies with 6-hour concurrent video-polysomnography studies. Data were stratified based on the 24-hour ARI (% duration that esophageal pH is <4) into ARI < 3% (normal), ARI 3 ≥ to ≤7% (intermediate), and ARI >7% (abnormal). GER frequency, clearance mechanisms, and symptoms were distinguished during wake state and sleep state.

Results Total wake and sleep duration was similar ($P \geq .2$) in all ARI groups. Acidic events were frequent with increasing ARI in wake state vs sleep state ($P \leq .03$). The symptom index increased with increasing ARI ($P \leq .02$) in both wake state and sleep state. Acid clearance time increased with increasing ARI in wake state ($P \leq .02$). In ARI > 7% vs ARI ≤ 7%, frequency of acidic GER events was higher ($P \leq .02$) in wake state and sleep state; proximal migration of acid ($P = .03$) and acid clearance time were higher in wake state ($P = .0005$) only. Symptom index was higher in ARI >7% vs ARI ≤ 7% in wake state ($P < .0001$), comparable in normal vs intermediate ($P = .4$), and higher in abnormal vs intermediate ($P = .0004$) groups.

Conclusions Severe esophageal acid exposure (ARI >7%) is associated with increased reflux-associated symptoms in wake state. Sleep state appears to be protective regardless of ARI, likely because of greater chemosensory thresholds. Attention to posture and movements during wake state can be helpful. Scrutiny for non-GER etiologies should occur for infants presenting with life-threatening symptoms. *(J Pediatr 2016;179:42-8).*

More than 50% of infants younger than 3 months of age have some degree of gastroesophageal reflux (GER) symptoms,[1] and the prevalence of GER disease in infants in the neonatal intensive care unit is around 10%.[2] Magnitude of acidity (acid- and weakly acid exposure) and severity of esophageal acid exposure as measured by acid reflux index (ARI) are important considerations in the genesis of symptoms.[3] ARI is defined as the percentage of the entire pH recorded time that esophageal pH is <4.[1] ARI < 3% is considered normal, >7% is abnormal, and ARI 3≥ to ≤7% is considered intermediate.[1] ARI is reportedly an effective tool in predicting prognosis; symptoms at 1-year follow-up were higher in infants with high initial ARI.[4]

Sleep is a complex amalgam of modifiable physiological and behavioral processes.[5,6] Neurosensory processing and learning that are at their maximum during quiet sleep are disrupted by GER.[7] Esophageal distention or chemosensitive stimulation during GER events result in esophageal, pharyngeal, glottal, and laryngeal reflexes that protect the aerodigestive tract and prevent aspiration,[8-10] and are based in part on the degree of acidity of the reflux event.[11] However, the role of sleep or wake state on these mechanisms is not entirely clear.

Cardiorespiratory and physical symptoms have been associated with GER independent of activity states.[10] The relationship of ARI to symptoms in different vigilance states is not clear in neonates presenting with brief resolved unexplained events (BRUE), and the necessity to treat the intermediate ARI group has been uncertain. Therefore, our objective was to describe the pattern of GER events in wake and sleep states with increasing ARI in neonates, and to test the hypothesis that GER-related symptoms are frequent in ARI >7% in wake state.

ARI	Acid reflux index
BRUE	Brief resolved unexplained events
EEG	Electroencephalography
GER	Gastroesophageal reflux
LES	Lower esophageal sphincter
PSG	Video-polysomnography

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Methods

Twenty-five infants, referred for the investigation of suspected GER and BRUE, underwent concurrent pH-impedance and video-polysomnography (PSG) at The Neonatal and Infant Feeding Disorder Program and Sleep Disorder Center at Nationwide Children's Hospital. Presenting troublesome symptoms to parents and providers included life-threatening events (5), apnea (14), desaturations (10), bradycardia (11), cyanosis (8), individually or in combination. Informed consent was obtained from parent(s), and the study protocol was approved by the ethics committee at the Institutional Research Review Board at the Nationwide Children's Hospital Research Institute, Columbus, Ohio.

The pH-impedance methods have been described in detail by our group.[10,12] Briefly, studies were performed using ambulatory pH-impedance recorder (Ohmega; Medical Measurement Systems, Inc, Dover, New Hampshire). pH-Impedance catheters (Medical Measurement Systems, Inc), 6.4 Fr, with 6 impedance channels and 1 pH channel were used. The catheter was first calibrated and then passed nasally so that the pH electrode was positioned at 87% of the distance from nares to the upper border of lower esophageal sphincter (LES) and position was confirmed by radiograph.[13]

Approximately 6 hours of bedside polysomnography concurrent with pH-impedance studies was performed according to American Academy of Sleep Medicine standards,[3,13] using the Grass Sleep system and Twin PSG software (Astro-Med; Grass Technologies, West Warwick, Rhode Island). All pH-impedance and polysomnography data were concurrent and synchronized.

Symptoms, such as movement, arching, grunting, and cardiorespiratory events, were visually recorded by trained patient care assistants blinded to the pH-impedance and sleep studies. Certified sleep laboratory technicians, blinded to GER events, documented apneas, bradycardia, desaturations, hypopnea, and periodic breathing on PSG.

pH-Impedance Analyses

pH-impedance data was analyzed using Medical Measurement Systems, Inc software (v 8.21.) and verified by trained researchers. ARI was defined as the percentage of the entire pH record time that esophageal pH was <4.[1] GER events were classified as follows: weakly acidic impedance events, when impedance dropped 50% or more from baseline in 2 or more consecutive impedance channels and pH was 4 and 7; acidic impedance events, when impedance dropped 50% or more from baseline in 2 or more consecutive impedance channels and pH was 4; acidic nonimpedance events, when pH was <4 and not accompanied by a drop in impedance.[14] Proximal migration was defined as an impedance drop ≥50% in the most proximal channel (Z1). Acid clearance time was defined as the time taken for the pH to normalize to ≥4 for ≥5 seconds.[10]

Polysomnography Analyses

Polysomnography was scored in 30-second epochs using standard criteria defined by American Academy of Sleep Medicine.[14-16] Sleep was classified into active sleep (rapid eye movement, muscular atonia, irregular respiration and heart rate, and continuous electroencephalography [EEG] pattern) and quiet sleep (nonrapid eye movement, axial muscle tone, regular respiration and heart rate, and specific EEG pattern). Wake state was characterized by irregular heart, respiratory activity with muscular activity, and changes in EEG pattern. Apnea was defined as interruption of air flow lasting for ≥2 breaths. Hypopnea was scored as 50% decrease in airflow or respiratory effort lasting ≥2 missed breaths from the end of last normal breathing amplitude associated with ≥3% oxygen desaturation. Desaturation was defined as a drop in oxygen saturation ≥3% from baseline. Sleep efficiency was the total sleep time that was effectively spent in sleep in bed,[17] and apnea-hypopnea index is the number of episodes of apnea and hypopnea per hour of total sleep time.

Symptom Analyses

Symptoms were positively associated with GER if the GER event occurred within 2 minutes before the onset of symptoms. Symptom index was calculated as the number of symptoms associated with GER/total number of symptoms in that category times 100,[18] with the limitation that increased GER increases the likelihood that a symptom could be associated with reflux by chance.[19] Symptom sensitivity index was calculated by formula (number of GER events associated with symptoms/total GER events in that category times 100).[20] Positive symptom sensitivity index (≥10%) when associated with a lower symptom index indicates that infant's esophagus is sensitive to reflux and non GER etiology of symptoms should be considered.[19,21,22]

Statistical Analyses

Data that were normally distributed were analyzed using unpaired *t* tests, and data that were not normally distributed were analyzed using the Wilcoxon rank sum test. Values are reported as mean ± SD or median (range) unless otherwise specified. A P value of < .05 was considered significant. Infants were categorized into normal (ARI < 3%), intermediate (ARI 3 ≥ to ≤7%), and abnormal (ARI > 7%) groups.[1] During the preliminary analysis, because of the comparable means between normal and intermediate groups (**Figure 1**), we combined the data from infants in these 2 cluster groups into ARI ≤ 7%, and then compared with ARI >7% groups. Data were analyzed using GraphPad PRISM 6 software (GraphPad Software, La Jolla, California).

Results

A total of 621 GER events during 163 hours of sleep study were analyzed. Infants were initially grouped into ARI < 3% (n = 10 subjects, median ARI 1.4 [0-2.8]), ARI 3 ≥ to ≤7% (n = 6 subjects, median ARI 5.3 [4.1-6]), and ARI >7% (n = 9 subjects, median ARI 16.4 [7.8-23]).

Three subjects had intraventricular hemorrhage (33.3%) in the ARI >7 group. Bronchopulmonary dysplasia was present in 4 (40%), 2 (33.3%), and 3 (33.3%) patients from the groups with ARI <3, 3 ≥ to ≤7, and >7 respectively (P = 1.0). Seven (70%) of those with ARI < 3, 3 (50%) in the ARI ≥3 to <7 group and 4 (44%) in ARI > 7 group were born preterm (P = .6).