Published in final edited form as:

Pediatr Neurol. 2015 September ; 53(3): 226–232. doi:10.1016/j.pediatrneurol.2015.05.012.

The Role of Sleep in the Modulation of Gastroesophageal reflux and Symptoms in NICU Neonates

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Abstract

Background—Newborns sleep about 80% of the time. Gastroesophageal reflux (GER) disease is prevalent in about 10% of NICU infants. Concurrent polysomnography and pH-impedance studies clarify relationship of GER with sleep.

Aims—To characterize spatio-temporal and chemical characteristics of impedance-positive GER and define symptom associations in sleep and wake states in symptomatic neonates. We hypothesized that frequency of impedance-positive GER events and their association with cardiorespiratory symptoms is greater during sleep.

Methods—Eighteen neonates underwent concurrent polysomnography with pH-impedance study. Impedance-positive GER events (weakly acidic or acidic) were categorized between sleep vs. wake states: Symptom Index = # of symptoms with GER/total symptoms*100, Symptom Sensitivity Index = # of GER with symptoms/Total GER*100 and Symptom Association Probability = [(1-Probability of observed association between reflux and symptoms)*100].

Results—We analyzed 317 GER events during 116 hours of polysomnography. During wake vs. sleep respectively, the median (interquartile range) frequency of impedance-positive GER was 4.9(3.1–5.8) vs. 1.4(0.7–1.7) events/hour ($P<0.001$), proximal migration was 2.6(0.8–3.3) vs.

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0.2(0.0–0.9)events/hour ($P<0.001$); Symptom Index for cardiorespiratory symptoms for impedance-positive events was 22.5 (0–55.3) vs. 6.1(0–13), $P=0.04$ while Symptom Sensitivity Index was 9.1(0–23.1) vs. 18.4 (0–50), $P=0.04$ though Symptom Association Probability was similar, ($P=0.68$).

Conclusions—Contrary to our hypothesis, frequency of GER in sleep is lesser; however, spatio-temporal and chemical characteristics of GER and symptom generation mechanisms are distinct. For cardiorespiratory symptoms during sleep, lower Symptom Index entails evaluation for etiologies other than GER disease, higher Symptom Sensitivity Index implies heightened esophageal sensitivity and similar Symptom Association Probability indicates other mechanistic possibilities.

Keywords

Gastroesophageal reflux; sleep; pH impedance; neonates; symptoms

Introduction

Sleep is a reversible physiological state, requiring aerodigestive protective functions to maintain homeostasis to prevent aspiration or acute life threatening events.^{1, 2, 3} Newborns may sleep up to 80% of the time and different sleep states emerge after 28 weeks gestational age.^{4, 5} Three stages of sleep are recognized in neonates: active sleep, quiet sleep and indeterminate sleep.^{6, 7, 8} Gastroesophageal reflux (GER) is a normal physiological phenomenon during which the passage of stomach contents into the esophagus occurs at frequency of 3–5 events per hour^{9, 10, 11}; whereas, GER disease relates to GER with troublesome symptoms. The distinction between GER and GER disease in the neonates can be challenging. The estimated prevalence of GER disease is about 10% in sick infants in Neonatal Intensive Care Unit (NICU).¹²

Coughing, grunting, arching, irritability, bradycardia, desaturation and emesis are symptoms commonly attributed to be due to GER disease. These reflux-type of symptoms can be classified into: cardiorespiratory, physical and sensory symptoms.¹³ These symptoms can also occur due to non-reflux causes such as chronic lung disease, intra-ventricular hemorrhage and apnea of prematurity, hence are nonspecific. Therefore, accurate diagnosis of the cause of the symptoms is critical since inappropriate, incorrect treatment is time consuming, wasteful and ineffective.^{12, 14, 15}

pH-impedance technique can detect both, acid and nonacid reflux in contrast to pH only technique which detects acid reflux only.^{16, 17} In order to validate the association between symptoms with actual reflux events, indices such as Symptom Index (SI), Symptom Sensitivity Index (SSI), and Symptom Association probability (SAP) have been developed (further defined in methods).^{16, 18, 19} Since infants sleep for a greater proportion of time, polysomnography along with pH-impedance has been used to detect cardiorespiratory symptoms associated with GER.^{17, 20}

Previous studies have shown that frequency of GER is lower and clearance is prolonged during sleep state. However, in these studies sleep state was not defined by

polysomnography.^{21, 22, 23} Also, in some of these studies pH testing was done without impedance.²⁴ On the other hand, a recent study using polysomnography and pH-impedance in 25 healthy neonates showed that reflux episodes were greater in wake and that bolus migration was higher in active sleep but symptoms associations and characteristics of non-acid GER were not studied.²⁵ Few studies report the relationship of respiratory symptoms with GER disease in infants. Previously, we have studied the association of various types of symptoms (respiratory, sensory and movement) with GER in chronic lung disease as well as the association of nonacid GER with arousals and awakenings.^{1, 26} However, the relationship of sleep with GER and its symptoms remains unclear in infants in NICU. Hence, our aims were to test the hypothesis that GER as detected by pH-impedance and the symptoms due to GER are more frequent in sleep compared to wake period. We determined the prevalence of impedance-positive GER based on spatio-temporal and chemical characteristics as well as differentiation of symptom associations in sleep and wake states in symptomatic NICU infants undergoing concurrent polysomnography and pH-impedance studies.

Materials and Methods

Subjects—Eighteen NICU neonates (7 males), born at mean gestational age 34.6 ± 4.6 weeks (range 23–40 wk, median 36 wk) admitted with symptoms (apparent life threatening events, apnea, desaturations, bradycardia, cyanosis and stridor) suspected to be due to GER disease were evaluated between April 2012 to December 2013 with concurrent pH-impedance and polysomnographic monitoring at mean postmenstrual age (PMA) 41.5 ± 3.0 weeks (range 38–50 wk, median 41 wk). The study procedures were approved by the ethics committee at the Institutional Research Review Board at the Nationwide Children's Hospital Research Institute, Columbus, OH.

pH-impedance methods—Ambulatory pH-impedance recorder [Ohmega, Medical Measurement Systems Inc. Dover, NH, USA], along with 6.4 French pH-impedance disposable probes (Z1-1 or Z1-P-7R, MMS) with six impedance channels [1.5 cm spacing (for babies < 3.5 kg) and 2 cm spacing (for babies > 3.5 kg)] and one pH channel (antimony) was used. Prior to placement, catheter was calibrated with pH 4 and pH 7 buffer solutions.²⁷ It was passed nasally and placed such that the pH sensor in distal esophagus was at 87% of the distance from nares to the upper border of lower esophageal sphincter as described by us and others, and was confirmed using chest x-ray.^{26, 28, 29} Event markers were placed on the pH-impedance recorder at the onset of the symptoms by trained patient care assistants who were blinded to pH-impedance and polysomnographic methods. Infants were oral or tube fed every 3–4 hours during the study and if tube fed, tube was not removed during the study.

Polysomnography methods—Video polysomnography studies were scheduled for 6 hours in the NICU according to American Academy of Sleep Medicine standards.^{8, 30} Briefly, the Grass sleep system (Astro-Med; Grass Technologies, West Warwick, RI) with Twin polysomnography software was used. Standard infant montage (C3, C4, CZ, O1, O2, A1, and A2) was applied for electroencephalography and electrodes for bilateral

electrooculography, electromyography, and electrocardiogram were used. Respiratory inductance plethysmography was used to monitor thoracic and abdominal movements. An oral nasal polyvinylidene fluoride airflow sensor and end-tidal PCO₂ sensor were used to detect airflow. Pulse oximeter (Massimo) was attached to sole of the foot to measure blood oxygen saturation. Most of the studies were done in private rooms to avoid noise; however disturbances due to monitor alarms were unavoidable. During sleep study, we usually dim the lights irrespective of the time of the day to prevent photo-stimulation. Babies were placed in a supine position during sleep with minimal tactile stimulation. They were only handled at the time of cares and feeding usually at 3–4 hours intervals. Polysomnography data and pH-impedance were concurrent and synchronized (Figure 1A & 1B).

Data Analysis

pH-impedance Analysis—pH-impedance data was analyzed using MMS Software and visually verified. Impedance positive GER events and symptoms associations for symptoms categories were extracted from software analysis. GER events were classified as follows: *Impedance-positive* events, when impedance dropped 50% or more from baseline in two or more consecutive impedance channels, which were further classified into a) *acidic* events, when pH was ≤ 4 , b) *weakly acidic* when pH was > 4 and < 7 ; and c) and *weakly alkaline* when pH was ≥ 7 . All the spatiotemporal and chemical characteristics of GER were calculated for individual patient. Feeding periods were excluded from the analysis. *Bolus clearance time* as defined as the duration (seconds) from the onset of the drop of impedance below 50% of the baseline to the offset at which the impedance returns to 50% of the baseline value. *Proximal extent of refluxate* (bolus) was defined as impedance drop $\geq 50\%$ in most proximal impedance channel (pharynx).¹³ All reflux events and all symptoms were assigned the activity state in which they occurred by differentiating sleep and wake periods on pH-impedance tracings based on polysomnography.

Polysomnography Analysis—Polysomnography was initially scored in 30 seconds epochs by certified polysomnography technicians and further verified and confirmed by sleep board-certified pediatric physicians (Mark Splaingard and Abdul Khuhro) using standard criteria defined by American Academy of Sleep medicine.^{8, 30} Each epoch was assigned one of four categories: 1) *wake state* characterized by irregular heart and respiration with muscular activity and electroencephalogram (EEG) pattern, 2) *active sleep* characterized by rapid eye movements, muscular atonia, irregular respiration and EEG pattern, 3) *quiet sleep* characterized by non-rapid eye movements, axial muscle tone, regular respiration and EEG pattern and 4) *indeterminate sleep* when no other sleep stage could be assigned.^{8, 31} Data for active sleep, quiet sleep, and indeterminate sleep stages were combined to define overall sleep. According to AASM criteria the following definitions were applied to our study: 1) *Apnea* was defined as interruption of air flow lasting for the duration of 2 breaths, 2) *Hypopnea* was scored as 50% decrease in airflow or respiratory effort lasting at least two missed breaths from the end of last normal breathing amplitude associated with 3% or greater oxygen desaturation, 3) *Desaturation* was defined as change in oxygen saturation $\geq 3\%$ of the base line, and 4) *Periodic breathing* was defined if >3 episodes of apnea lasted for ≥ 3 second and were separated by no more than 20 seconds of normal breathing.^{8, 30}

Symptom Analysis—All symptoms were correlated with GER events. Symptoms were positively associated (correlated) with GER event if the GER event occurred within a two minute window before or after symptom onset as shown in analysis algorithm (Figure 2).³² Symptoms were grouped into cardiorespiratory (cough, gagging, choking, grunting, stridor, apnea, hypopnea, periodic breathing, bradycardia, desaturation), physical (arching, irritability, movement) and sensory (emesis, grimace, yawning, hiccough and sneezing).²⁶ SI [(# symptoms associated with GER events/total # of symptoms in that category)*100], SSI [(# of GER events associated with symptom/Total GER events in that category)*100] and SAP [(1-Probability of observed association between reflux and symptoms occurred by chance)*100] were calculated using the Medical Measurement System Inc. software for individual patient during sleep and wake periods. The software calculates the probability for SAP using Fisher's exact test in 2*2 contingency table with R+S+, R+S-, R-S+, and S-R- where S is symptom and R is reflux while '+' is positive and '-' is negative).^{16, 19, 33, 34}

Statistical Analysis—Group comparisons were performed using paired t-test for parametric data and Wilcoxon Rank test for nonparametric data. Data are presented as median [Interquartile range (IQR)] for non-normal and mean $\pm$ SD for normally distributed data. $P < 0.05$ was considered significant. The analysis was done using GraphPad Prism Version 6.03.

Results

Overall, convalescing infants in the NICU underwent 116 hours of concurrent polysomnography and pH-impedance study, of which 71 hours (61%) were in sleep and 45 hours (39%) in wake. Details of subject demographics, time spent in different activity states, frequency of impedance-positive GER and symptoms per patient are shown (Table 1). At the time of study 15 infants were on full oral feeds and 3 were on gavage feeds. Four needed supplemental oxygen while the remaining 14 subjects were on room air at the time of study. Three infants had congenital anomalies (2 had Arnold Chiari malformation II with ventriculo-peritoneal shunts, and 1 had chromosome anomaly). Only one infant had grade 1 intra-ventricular hemorrhage.

Frequency distribution of GER events

Total impedance-positive GER events were 317. Among impedance-positive GER, 246 (78%) were weakly acidic and 71 (22%) were acidic. No weakly alkaline GER was identified among these subjects. Frequency of all impedance-positive events including weakly acidic and acidic GER events was greater in wake ($P < 0.05$) (Figure 3). Fifty two percent of all impedance-positive reflux events migrated to most proximal (pharyngeal) channel in wake while only 30% proximally migrated in sleep. Frequency of proximal migration (defined by impedance change in most proximal channel) of all impedance-positive, including weakly acidic and acidic GER events were greater in wake ($P < 0.05$) (Figure 4).

Clearance mechanisms of GER events

Bolus clearance time for impedance-positive reflux events in wake vs. sleep state was 10.0 (8.8–12.5) vs. 9.7(7.4–10.9) seconds, $P = 0.42$.

Symptom characteristics and relationships with GER events

Total symptoms (regardless of GER events) per patient per hour during study period were 7.8 ± 3.5 , (7.6, range 2.8 – 17.4), of which 10.3 ± 4.2 (10.1, range 4.4 – 18.2) occurred in wake and 6.8 ± 3.7 (5.9, range 1.6 – 17.2) in sleep ($P < 0.001$). Further analysis showed that cardiorespiratory symptoms were greater ($P = 0.005$) where as physical symptoms ($P < 0.001$) and sensory symptoms ($P = 0.03$) were lesser in sleep vs. wake (Figure 5). Eleven percent of symptoms were associated with impedance-positive GER events in sleep vs 30% in wake state. Overall 46% of impedance-positive GER events in wake and 43% in sleep states were associated with symptoms. Twenty-two percent of impedance-positive events during sleep resulted in change to wake state. Symptom correlations with GER between sleep vs. wake states using SI, SSI and SAP are given (Table 2). Of note, 6.1% of cardiorespiratory symptoms and 7.7% of physical symptoms were associated with GER as a proportion of all cardiorespiratory symptoms and physical symptoms in sleep state compared to 22.5% of cardiorespiratory symptoms and 25.9% of physical symptoms in wake state. Also 18.5% of reflux events in sleep state were associated with cardiorespiratory symptoms as a proportion of all impedance-positive GER events compared to 9.1% in wake state. However no significant difference was found in the symptom correlation on SAP between wake and sleep states with any symptoms categories.

Discussion

Troublesome symptoms resulting from GER, commonly defined as GER disease among convalescing neonates in the NICU, are a major conundrum for clinicians. Polysomnography concurrent with pH-impedance studies are performed to evaluate correlation of symptoms with GER with the underlying hypothesis that troublesome symptoms with GER are greater in sleep. In this regard, we investigated the role of different activity states in modulating impedance-positive GER events in relation to chemical characteristics and proximal migration of refluxate and temporal presence of refluxate in relation to symptoms. While we hypothesized that impedance and proximal migration during GER events are more frequent in sleep among NICU neonates and that symptoms related to GER are worse in sleep compared to wake state, we found the contrary.

The cardinal findings of our study were as follows: 1) The frequency of impedance-positive events including weakly acidic and acid reflux events reflux events were significantly less during sleep. 2) Proximal ascent of weakly acidic and acidic refluxate was also significantly less during sleep. 3) The frequency of physical symptoms (such as arching, irritability and movement) and sensory symptoms (such as sneezing and emesis) were significantly decreased during sleep. 4) The frequency of cardiorespiratory and physical symptoms associated with impedance-positive GER as a proportion of overall cardiorespiratory and physical symptoms respectively (SI) was significantly less during sleep as compared to wake. 5) The frequency of impedance-positive GER associated with cardiorespiratory and

physical symptoms as a proportion of all impedance-positive GER events (SSI) was significantly more during sleep as compared to wake. 6) Despite differences in SI and SSI between sleep and wake states, SAP was not different for cardiorespiratory, physical and sensory symptoms symptom for sleep and wake states. 7) No difference was found in the bolus clearance time during sleep and wake states.

Physiological explanation of our findings is described as follows. Increased frequency of GER events in the wake may be related to the frequent transient lower esophageal sphincter relaxation which is a predominant mechanism of triggering GER.³⁵ Similarly existence of higher postprandial gastric volume may distend the fundus evoking reflex relaxation of lower esophageal sphincter as well as favoring proximal ascent of the refluxate. These vagal-mediated responses to gastric distension typically occur during the 1st postprandial hour.^{35, 36, 37} On the other hand, vagal-mediated protective reflexes such as peristaltic reflexes and luminal clearance may minimize the proximal ascent thereby reducing severity of aerodigestive symptoms. Depending on the proximal extent of the refluxate and temporal clearance abilities, consequences can range from simple volume associated distention or chemical exposure to esophageal mucosal inflammation. During this process, the refluxate can exert its effects by several mechanisms including 1) direct mucosal contact,³⁸ 2) initiation of pharyngeal reflexes induced by esophageal distention or chemical exposure facilitating clearance,³⁹ 3) extra-esophageal effects involving esophago-glottal or pharyngo-glottal reflex interactions,⁴⁰ 4) activation of vagal parasympathetic cardiorespiratory regulatory reflexes,⁴¹ and 5) alteration of sleep states and arousal phenomena. Majority of the symptoms such as repetitive swallowing, coughing, sneezing, apneas, bradycardias and desaturations occur from the activation of afferent and efferent nerves involving esophageal or pharyngeal reflexes.

Contrary to our hypothesis, we noted that the frequency of GER events was lesser in sleep.^{35, 37} Sleep is associated with inhibition of reticular activating system resulting in elevation of sensory thresholds, and ascending sensory stimuli from stomach are modulated.⁴² During sleep, primary esophageal clearance mechanism is secondary peristalsis and UES contractile response limiting more proximal ascent.² Therefore, the infant is likely to process lesser ascending sensory stimulus spread manifesting in fewer somatic motor responses and preservation of sleep state.^{2, 42} Thus there are reductions in physical symptoms during sleep state. Sleep also modulates the recruitment frequency and type of aerodigestive reflexes slowing the clearance mechanisms.² Impairment of respiratory reflexes is also recognized during sleep with decreased coordination of cardiorespiratory homeostatic control.^{43, 44} Collectively these mechanisms may modulate autonomic responses resulting in more frequent cardiorespiratory symptoms during sleep. However, this phenomenon can be due to multiple sources of stimuli, rather than GER.

Lower SI during sleep can be due to an increase number of symptoms during sleep (denominator) and/or decreased number of GER events (numerator). On the other hand, higher SSI during sleep can be due decrease in number of GER events during sleep (denominator) and/or an increase in total number of symptoms during sleep (numerator).^{16, 13} In our study, decrease in SI for cardiorespiratory symptoms in sleep could be due to increased number of symptoms and decreased GER events, and the increased SSI

for cardiorespiratory symptoms during sleep could be due to decreased number of GER events and increased number of cardiorespiratory symptoms during sleep.¹⁶ Though SI and SSI showed significant difference in cardiorespiratory and physical symptom association, SAP showed no difference in symptom associations between sleep and wake states. This is because of the reasons explained earlier about SI and SSI giving false positive results depending upon the absolute number of symptoms and/or GER events.^{16, 19}

Few studies have been done in the past to assess the differences in sleep and wake states in NICU neonates in relation to GERD-type of symptoms. Our findings however, are in agreement with that of Vandenplas et al who reported in infants (1.5 to 4.5 months) and Schilter et al who reported in children (14 days to 19 years old), that the frequency and clearance of GER is more in wake and the duration of GER was prolonged in sleep.^{21, 22} Cresi et al found prolonged acid reflux duration during wake in term neonates.²³ Jeffery & Heacock observed higher frequency of GER episodes in wake as well as prolonged duration of acid reflux in active sleep in term healthy infants.²⁴ Machado et al showed that nonacid GER plays significant role in association of GER with arousals and awakenings.⁴⁵ Previously, Jadcherla et al have shown that 73.5% of GER events were associated with arousals. Esophageal provocation during spontaneous GER events in sleep significantly modifies sleep state and respiratory patterns and causes arousals. GER arousals are associated with prolonged esophageal motility and clearance.¹

In conclusion, ours is the first study in neonates which correlated the spatio-temporal and chemical characteristics of impedance-positive GER and its associations with different symptom categories during sleep and wake states. Only 6.1% of cardiorespiratory symptoms in sleep were associated with GER events. Though there were differences in SI and SSIs, no difference was found on Fisher's exact test (SAP) in symptom association during sleep and wake state thus highlighting the need to assess for other non-GERD etiologies related to cardiorespiratory symptoms. This also supports the view that only SI and/or SSI are not sufficient for correlating the symptoms with reflux events. On the other hand, more physical symptoms related to GER during wake state suggest activation of polysynaptic pathways due to more proximal extent of refluxate or of other unrelated etiologies. Thus, mechanisms of symptom generation and adaptation are dissimilar in sleep and wake states underscoring the differential ability of infants to perceive esophageal sensitivity during sleep.

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Figure 1.

Concurrent polysomnography (upper panel) and pH-Impedance (lower panel) demonstrating gastroesophageal reflux in wake (A, continuous EEG pattern) and sleep (B, discontinuous EEG pattern with theta burst). Note weakly acidic GER (minimal pH change and decrease in impedance) with retrograde refluxate movement (solid arrow) and anterograde clearance (dotted arrow).

Figure 2.

Data analysis algorithm: pH Impedance tracing of weakly acid GER (impedance drop associated with pH remaining above 4.0) with reference to symptom. Symptoms were positively correlated with GER event if the GER event occurred within a two minute window either before or after the onset of symptom.

Figure 3.

Frequency of GER events in wake and sleep states. During wake state, note the significant increase in impedance positive, weakly acidic and acidic events. Data are shown as median (interquartile range) and mean.

Figure 4.

Frequencies of GER events ascending to the most proximal impedance channel are shown. During wake state, note the significant increase in proximal migration of impedance positive, weakly acidic and acidic GER events. Data are shown as median (interquartile range) and mean.

Figure 5.

The frequency of symptoms in sleep and wake states. Significantly, during sleep, cardiorespiratory symptoms are increased whereas physical and sensory symptoms are decreased. Data reported as median (interquartile range) and mean.

Subject's demographics, time spent in different activity states, total symptoms and frequency of Impedance positive gastroesophageal reflux

Table 1

Subjects	GA* (wks)	Age (wks)	PMA [†] (wk)	Concurrent Recording Time (min)	Wake Time min (%)	Sleep Time min (%)	Indeterminate Sleep min (%)	Quiet Sleep min (%)	Active Sleep min (%)	Total Symptoms (#/Patient)	Impedance Positive events (#/Patient)
1	37	1	38	364	123 (34)	241 (66)	0 (0)	122 (51)	119 (49)	19	27
2	30	9	39	345	89 (26)	256 (74)	0(0)	102 (40)	154 (60)	26	17
3	34	16	50	362	125 (35)	237 (65)	1(0)	132 (56)	105 (44)	37	15
4	31	11	43	355	182 (51)	173 (49)	0(0)	99 (57)	75 (43)	19	17
5	38	3	41	363	151 (42)	212 (58)	0(0)	112 (53)	100 (47)	34	6
6	37	3	40	416	162 (39)	254 (61)	11(4)	80 (36)	163(64)	23	20
7	23	18	41	365	108 (30)	257 (70)	14(5)	116 (45)	127(50)	20	2
8	38	6	44	373	113 (30)	260 (70)	6(2)	174 (67)	81(31)	64	45
9	40	1	41	406	160 (39)	246 (61)	0(0)	107 (43)	140(57)	16	19
10	39	1	40	361	126 (35)	235 (65)	1(1)	135 (57)	100(43)	43	16
11	39	2	41	388	128 (33)	260 (67)	2(1)	113 (43)	146(56)	79	9
12	29	17	46	593	320 (54)	273 (46)	2(1)	139 (51)	132(48)	47	33
13	35	7	42	345	100 (29)	245 (71)	0(0)	120 (49)	125(51)	22	10
14	38	3	41	344	158 (46)	186 (54)	0(0)	116 (62)	71(38)	28	16
15	32	6	38	442	290 (66)	152 (34)	1(1)	100 (64)	52(34)	14	16
16	39	5	44	367	156 (43)	211 (57)	6(3)	133 (63)	72(34)	32	14
17	33	10	43	361	96 (27)	265 (73)	26(10)	117 (44)	122(46)	29	15
18	30	14	44	414	117 (28)	297 (72)	47(16)	142 (48)	108(36)	14	20
Mean	34.6	7.4	41.5	387	150 (39)	237 (61)	6 (2)	120 (51)	111 (47)	31	18
Median	36	6	41	364	128	246	1	117	113	27	16
Range	23–40	1–18	38–50	344–593	89–320	152–297	0–47	80–174	52–163	14–79	2–45

* GA, gestational age;

[†] PMA, postmenstrual age

Table 2

Differences in Symptom related indices, categorized by symptom types characterized according to wake and sleep states for impedance positive events

Symptom Characteristics	Wake	Sleep	<i>P</i> -values
	Median (IQR [*])	Median (IQR [*])	
<i>Symptom Index</i>			
All Symptoms	29.7 (20.2 – 33.3)	10 (3.2 – 15.4)	0.001
Cardiorespiratory	22.5 (0 – 55.3)	6.1 (0 – 13)	0.04
Physical	25.9 (15.1 – 38.5)	7.7 (0 – 17.8)	0.03
Sensory	0 (0 – 100)	3.9 (0 – 20.7)	0.50
<i>Symptom Sensitivity Index</i>			
All Symptoms	38.5 (31 – 70.9)	46.1 (23.8 – 85)	0.66
Cardiorespiratory	9.1 (0 – 23.1)	18.4 (0 – 50)	0.04
Physical	25 (15.4 – 44.3)	20 (0 – 42.2)	0.04
Sensory	0 (0 – 16.7)	2.2 (0 – 76.1)	0.99
<i>Symptom Association Probability</i>			
All Symptoms	85.8 (72.1 – 93.3)	82.6 (64.2 – 95.7)	0.68
Cardiorespiratory	65.3 (0 – 85.7)	67.7 (0 – 84.3)	0.68
Physical	80.3 (0 – 90.5)	0 (0 – 96.6)	0.41
Sensory	0 (0 – 91.1)	30.7 (0 – 83)	0.50

* IQR, interquartile range