Influence of sleep state on frequency of swallowing, apnea, and arousal in human infants

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Don, Garrick W., and Karen A. Waters. Influence of sleep state on frequency of swallowing, apnea, and arousal in human infants. J Appl Physiol 94: 2456–2464, 2003. First published February 7, 2003; 10.1152/japplphysiol.00361.2002.—Apnea and arousal are modulated with sleep stage, and swallowing may interfere with respiratory rhythm in infants. We hypothesized that swallowing itself would display interaction with sleep state. Concurrent polysomnography and measurement of swallowing allowed time-matched analysis of 3,092 swallows, 482 apneas, and 771 arousals in 17 infants aged 1–34 wk. The mean rates of swallowing, apnea, and arousal were significantly different, being 23.3 ± 17 infants aged 1–34 wk. The mean rates of swallowing, apnea, and arousal were significantly different, being 23.3 ± 17 infants aged 1–34 wk. The mean rates of swallowing, apnea, and arousal were significantly different, being 23.3 ±

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Having recently developed a method for measuring airway pressure that permitted time-matched recording of airway pressures and sleep state, we used the data from this pressure catheter to document the occurrence of swallowing and thus to provide us with time-matched analysis of swallowing, apnea, and sleep state in human infants (7). We also wanted to determine whether our inability to document swallowing on routine polysomnography (PSG) effectively causes "artifact" in our analyses of PSG events. That is, if swallowing inhibits respiration, it is possible that a proportion of apneas documented on PSG are in fact related to concurrent swallowing. Alternatively, swallowing may have a distinctive pattern of PSG activity [e.g., chin electromyogram (EMG)] that would make it distinguishable on PSG.

Because respiratory rhythm is inhibited during swallowing activity, we postulated that swallowing would be associated with apnea on PSG and that swallowing would show the same modulation with sleep state as apnea. To evaluate this, we examined how the incidence and concurrence of apnea, arousal, and swallowing altered with sleep state in 17 human infants.

METHODS

Subjects were drawn from infants presenting to the Sleep Unit at the Children’s Hospital at Westmead (CHW). Reasons for presentation included an apparent life threatening event (n = 5), siblings who died from sudden infant death syndrome (n = 6), further investigation of witnessed apneas (n = 5), and a family history of central sleep apnea (n = 1). Four subjects had failure to thrive, and one suffered from the Robin sequence. The study was approved by the CHW Ethics Committee, and signed parental consent was obtained for each infant before their study.

From a total of 26 infants who were recruited, data from 9 infants were inadequate, leaving data from 17 infants for study. The mean age of the subjects was 15.6 ± 2.1 wk (range 1–34 wk). Six subjects were born prematurely with a mean gestation of 31.7 ± 2.0 wk (range 24–37 wk), 9 were male, and their postconceptional age at the time of study was 55.6 ± 2.1 wk.

PSG. Overnight PSG was performed on all subjects. Sleep studies were performed in the standard manner for the
laboratory, including channels for sleep staging [two electroencephalograms (EEG), two electrooculograms, submmental EMG] and respiratory analysis (diaphragm EMG, ECG, nasal airflow, chest and abdomen respiratory effort, arterial oxyhemoglobin saturation, and transcutaneous CO$_2$]. Nasal airflow was recorded via nasal cannulae (intermediate infant, no. 1615, Salter Laboratories, Arvin, CA) connected to a low-level pressure transducer referenced to atmospheric pressure (model MP45-4 \pm 2 cmH$_2$O, Validyne, Northridge, CA). Thoracic and abdominal respiratory effort were recorded by use of inductance plethysmography (Respitrace, Non-Invasive Monitoring Systems, Miami Beach, FL). Oxygen saturation was recorded on the hand or foot (arterial oxyhemoglobin saturation, Ohmeda Biox 3700e pulse oximeter, Datex-Ohmeda, Homebush, Australia), and transcutaneous CO$_2$ levels were recorded from the upper chest or abdomen (TINA TCM3, Radiometer, Copenhagen, Denmark).

PSG data were recorded by use of a digital PSG acquisition system (Compumedics, Abbotsford, Victoria, Australia).

Airway manometry. A triple-lumen, saline-filled catheter (Critchley Electrical Products, Sydney, Australia) was used to measure airway pressure fluctuations and variability. Standard-size apertures were cut in the separate inner lumens at 1.5, 12.5, and 16.5 cm from the sealed, distal end of the catheter. Each inner lumen was connected to a separate pressure transducer (Transpac IV, Abbot Critical Care), and patency was maintained with a total saline flow of 12.5 ml/h to prevent secretions from blocking the apertures. This catheter permitted quantification of respiratory efforts and documentation of swallowing in relation to apneas.

The catheter was inserted to a predetermined distance to position the three apertures in the nasopharynx, oropharynx, and thoracic esophagus (7). Pressures were recorded at these levels for a minimum of 3 h after sleep onset, on a digital data-acquisition system (Amlab v2.0, Amlab International, Lane Cove, Sydney, Australia) time matched to the PSG. After recording, the catheter was removed for the remainder of the study. The response time of the pressure system was <100 ms for all pressures tested up to 100 cmH$_2$O.

Data analysis. Each 30-s epoch of the PSG was analyzed to determine sleep state and to identify respiratory events. Sleep state was classified as quiet sleep (QS), indeterminate sleep (IS), or active sleep (AS), according to criteria set forth by Anders et al. (2). Apnea was defined as a \geq 80% reduction in airflow (nasal airflow) for at least two respiratory cycles, associated with \geq 3% blood oxygen desaturation and/or arousal. Respiratory cycles were defined on this same channel, which was recorded on both manometry and PSG systems. Obstructive and central apnea were respectively characterized by the presence or absence of respiratory efforts during the period of airflow reduction. Mixed apnea had obstructive and central components. Respiratory cycle time was defined according to the baseline respiratory rate of the preceding minute for central events or the number of ongoing respiratory efforts in the case of obstructive events (28).

Three types of arousal were defined for this study, namely “respiratory,” “full EEG,” and “movement.” A respiratory arousal was defined as a large change in at least two independent channels, without EEG disturbance, that lasted for \geq 1 s. A full EEG arousal was defined as a significant increase in EEG frequency or amplitude for a period of \geq 1 s, associated with increased submmental EMG activity and variability in respiratory effort and nasal airflow. A movement arousal was defined as an increase in at least two independent channels, not associated with a respiratory event, and with no apparent change in EEG (modified from Mograss et al., Ref. 20). In our analyses, arousals took precedence over apnea, and we did not mark an apnea if it occurred after the onset of (during) an arousal. We did not consider nonnutritive sucking, which is routinely identifiable on PSG from infants (Fig. 1).

The manometry record was examined for characteristic swallow peaks (29). A sharp pressure peak on the oropharyngeal channel identified a swallow. Nonpropagated swallows had no subsequent pressure rise on the esophageal channel, whereas an esophageal pressure peak after the oropharyngeal peak indicated a propagated swallow. The esophageal pressure wave had a much slower time course than the sharp oropharyngeal peak (3). Swallows during central (Fig. 2) and obstructive apneas (Fig. 3) showed the same features.

Events of interest were identified on the pressure manometry recording and on the PSG record for each infant. Nasal airflow was recorded on the manometry and the PSG systems and was used to time match the records from the two systems (manometry and PSG). Swallows were first identified on manometry, because they could only be identified on this recording, and the PSG record was subsequently reviewed at the time coinciding with that event. Apneas and arousals were then identified on the PSG, with respiratory cycle time as defined on the PSG nasal airflow signal. The manometry record was reviewed after PSG to determine coincidence of apnea and swallow events, because swallows could only be detected on the manometry system. Where respiratory or arousal events were coincident with swallows, the timing of the swallow was classified according to its relationship to the respiratory or arousal event (before or during). If the oropharyngeal spike occurred \leq 5 s before the initiation of the apnea or arousal it was classified as “before.” If the oropharyngeal spike occurred after the initiation of the apnea or arousal it was considered to have occurred “during” the event.

Statistical analyses. Data were analyzed for each subject, and then mean values were evaluated to provide group data. All analyses were undertaken by use of SPSS for Windows (SPSS v10.0 for Windows, SPSS, Chicago, IL). For comparison within apnea or arousal types, or for comparisons across events within sleep states, a one-way ANOVA was used, with post hoc analyses using Bonferroni’s test when the ANOVA showed significant difference. For comparisons between swallowing and apnea or swallowing and arousal, a Student’s $t$-test was used. To evaluate interactions among the events and/or with sleep state, multivariate analysis was used. Results are presented as means $\pm$ SE, unless otherwise stated. $P$ values $<0.05$ were considered statistically significant.

RESULTS

A total of 2,792 propagated and 234 nonpropagated swallows were identified by using the manometry record. The mean swallow rate was 23.3 $\pm$ 2.1 swallows/h. According to PSG criteria, 482 apneas [192 (39.8%) central, 67 (13.9%) mixed, and 223 (46.3%) obstructive] were identified. A total of 665 arousals were identified on PSG [240 (36.6%) respiratory, 344 (52.5%) full EEG, 71 (10.8%) movement]. Of all apneas, 30.8 $\pm$ 4.3% were terminated by an arousal. There was no significant correlation between the postconceptional age of the subject at the time of the study, and the frequency of swallows per minute ($R^2 = 0.12, P = 0.16$) or between postgestational age and swallow frequency ($R^2 = 0.16, P = 0.10$).

Swallowing and apnea. The mean proportion of swallows that occurred before (within 5 s of the com-
mencement) or during (after the onset of) apnea was 30.3 ± 5.1%. The type of apnea did not affect these results. Among all subjects, 34.2 ± 6.4% central apneas, 26.4 ± 7.9% mixed apneas, and 22.3 ± 6.9% obstructive apneas were associated with swallowing [not significant (NS), ANOVA]. However, it is important to note that only a minority (3.9 ± 1.0%) of all the swallows we observed occurred before or during any apnea.

By analyzing the timing of these events relative to one another, we evaluated whether swallows or apneas occurred first. Of the 131 (4.3%) swallows that coincided with apnea, 25.2 ± 7.9% occurred before and 74.8 ± 6.3% occurred during the apnea (P < 0.001, respectively). To examine whether there were observable distinctions between apneas with or without swallowing on the PSG recording, we evaluated the pattern of EMG activity associated with the swallowing events. Of the swallows that coincided with apnea, 101 (77.1%) were observed to coincide with a transient increase in submental EMG activity, but 15 (11.5%) showed no EMG increase. The latter often occurred during periods of high EMG activity, e.g., during an arousal (see below). No relationship was found between subject age (postnatal age, corrected for prematurity) and the coincidence of swallows and apnea.

Swallowing and arousal. Swallows occurred before or during 34.3 ± 4.9% of arousals. Among all subjects, a mean of only 7.0 ± 1.1% of swallows occurred before or during an arousal, and we did not find that the association with swallowing influenced the arousal type. When swallowing events were divided according to the type of arousal, mean values were 43.1 ± 7.1% respiratory arousals, 29.7 ± 5.4% full EEG arousals, and 39.5 ± 16.1% movement arousals, respectively (NS, ANOVA).

Of the 193 (6.7%) swallows that coincided with arousal, 35.7 ± 6.6 and 64.3 ± 6.6% occurred before or during the arousal, respectively (P < 0.001, 2-tailed). To examine whether there were observable distinctions between arousals with or without swallowing on the PSG recording, we evaluated the pattern of EMG activity associated with the swallowing events. Of the swallows that coincided with arousal, 59 (32.4%) were
observed to coincide with a transient increase in submental EMG activity, 21 (11.5%) showed no EMG increase, and 102 (56.0%) occurred during periods of high EMG activity already associated with the arousal. There was no relationship between subject age and the coincidence of swallows and arousals.

We used the mean values for apnea and swallow duration that were observed in these infants to evaluate the difference between the observed and the expected coincidence of events. With mean apnea duration of 5 s and mean swallow duration of 6 s, the two would be expected to be coincident during 5% of apneas. Thus the coincidence of swallowing during an apnea was greater than chance alone ($\chi^2, P < 0.001$). In contrast, the coincidence of apnea and arousal during swallows was not greater than expected. Our observed rates were not different from expected, being 1.2 (3.9%) swallow-apneas/h (expected = 1.2, or 5%), and 1.8 (7%) swallow-arousals/h (expected = 1.9, or 8%) ($\chi^2$, NS).

**Effect of sleep stage on swallowing, apnea, and arousal.** We examined the relationship between swallowing rate and sleep stage. The average swallowing rate during sleep, by sleep stage, was $21.7 \pm 2.7$ h$^{-1}$ in IS, $21.6 \pm 2.2$ h$^{-1}$ in QS, and $27.0 \pm 3.4$ h$^{-1}$ in AS, respectively (NS). The average apnea rate for all subjects was $2.6 \pm 0.9$ h$^{-1}$ in IS, $1.6 \pm 0.8$ h$^{-1}$ in QS, and $5.2 \pm 1.0$ h$^{-1}$ in AS, respectively ($P < 0.001$). The average arousal rate among all subjects was $5.7 \pm 1.5$ h$^{-1}$ in IS, $2.9 \pm 0.7$ h$^{-1}$ in QS, and $6.9 \pm 0.7$ h$^{-1}$ in AS, respectively ($P < 0.001$). Overall, the swallowing rate was significantly higher than both the arousal ($P < 0.05$) and the apnea rate ($P < 0.001$), and there was no significant difference between the rates of apnea and arousal ($P = 0.07$) (Fig. 4).

As a proportion of total sleep time, subjects spent an average of $33.2 \pm 2.6\%$ in IS, $31.0 \pm 2.7\%$ in QS, and $35.8 \pm 1.6\%$ in AS. There was a significant difference in the percentage of apneas between indeterminate or QS
vs. AS \( (P < 0.001) \), but not between indeterminate vs. QS \( (\text{NS}) \). The difference in percentage of arousals between indeterminate and QS was also significant \( (P < 0.05) \), with a highly significant difference between indeterminate or QS vs. AS \( (P < 0.001) \) (Fig. 5). The proportions of swallow-apneas and swallow-arousals were also higher in AS than QS \( (P < 0.01 \text{ for both}) \) (Table 1; Fig. 5). There was no significant difference between the percentage of swallows that occurred in each sleep state and no interaction between the proportion of swallows and the sleep state in which they occurred. If, in the latter analysis, we simply analyzed for the difference between the proportion of swallows in QS and AS \( (t\text{-test}) \), there was a significant difference at the \( P = 0.04 \) level (1).

Because apneas and arousals were highly influenced by sleep state, we evaluated the interaction of swallowing with apnea, and swallowing with arousal (that is swallow-apnea and swallow-arousal events). The rate of swallows coinciding with apneas was \( 1.3 \pm 0.5 \text{ in IS, } 0.5 \pm 0.2 \text{ in QS, and } 1.8 \pm 0.7 \text{ h}^{-1} \text{ in AS} \), respectively. The rate of swallows coinciding with arousals was \( 1.9 \pm 0.5 \text{ in IS, } 0.4 \pm 0.2 \text{ in QS, and } 3.1 \pm 0.7 \text{ h}^{-1} \text{ in AS} \). Whether considered as the proportion of all events or as the rate of events per hour, swallow-arousals and swallow-apneas were significantly different between QS and AS \( (P < 0.05) \) (Figs. 4 and 5).

Multivariate analysis confirmed, as above, that the proportion of apneas and arousals varied with by sleep state.
DISCUSSION

This study examined the interactions between swallowing, breathing, and sleep state in the first 6 mo of life in human infants. The most important finding of this study was that when swallowing was coincident with apnea and/or arousal, the swallow most often occurred during, rather than before, the apnea and/or arousal. In addition, the proportion of apneas that were associated with a swallow event was higher than expected. In contrast, apneas or arousals were rarely observed during swallowing, and the rate of coincidence was the same as that predicted by chance. Sleep state had a significant influence on the occurrence of apneas and arousals but not swallowing. Apneas and arousals were more frequent in AS compared with QS. In contrast, swallowing was frequent across all sleep states, and interactions observed between swallowing and sleep state were dominated by the coincidence of swallowing with apnea or arousal in this study.

With regard to the analysis of overnight polysomnograms, despite known inhibition of respiratory rhythm by swallowing, our results do not suggest that swallowing causes a significant interference with the analysis and occurrence of apnea and arousal in infants.

Coincidence of swallowing, apnea, and arousal. Our results consistently support the existence of a link between the occurrence of apnea or arousal and swallowing. First, ~30% of all apneas were associated with swallowing, and 34% of all arousals, which is higher than expected. Second, swallowing that was coincident with apnea or arousal was more likely to begin during the period of airflow cessation or during the arousal. Finally, although the rate of swallowing was unaffected by sleep state, the occurrence of coincidental swallow-apneas or swallow-arousals followed the pattern for apneas and arousals in any given sleep state, whether considered as rate (h⁻¹) or proportion (% of all events). These results suggest that once apnea or arousal has occurred, swallowing is likely, but the converse is not true; swallowing did not precipitate apnea and arousal.

If swallowing precipitated or even caused apnea or arousal, we expected a greater proportion of swallows to be associated with and/or precede the apneic and arousal events. Because the reverse was true, we suggest that the initiation of an apnea and/or arousal likely leads to the initiation of the swallow. Thus we suggest that apnea and arousal precipitate swallowing, for example, by triggering upper airway reflexes. The connection of apnea and arousal to swallowing may also be functional rather than due to a common initiating factor. Note that we were considering the types of apneas analyzed in sleep studies and not the prolonged apneic events previously described (18). In contrast to that study, we did not have a control period of observation before instrumentation, so we are not able to address this question with our present data set.

The coincidence of swallowing and apnea was not dependent on the type of apnea, or the type of arousal. Although no previous data exist about the type of state, whether they occurred coincidentally with swallowing or not. Post hoc analyses showed that significant differences occurred in the proportion of these events occurring in indeterminate vs. QS (P < 0.001), and indeterminate vs. AS (P < 0.001) but not between indeterminate and QS (NS). There was no interaction between the proportion of swallows, apneas, or swallow-apneas and sleep state. Similarly, no interaction was found in the proportion of swallows, arousals, or swallow-arousals and the sleep state in which they occurred.
arousals and the coincidence of swallowing, other researchers have reported that a majority of swallows coincide with obstructive or mixed apnea (30, 18). Menon and coworkers (17, 18) observed an increase in the frequency of swallowing associated with apnea. They speculated that apnea and swallowing arise from a common mechanoreceptor, or chemoreceptor factor, rather than one event precipitating the other. Our results suggest that apnea is the primary event and show no significant relation between swallowing and apnea type. Despite the postulated differences in pathogenesis of central vs. obstructive apneas, it is possible that the inhibition of respiration within the dorsal and ventral respiratory groups (13). Indeed, it is thought that within the dorsal and ventral medulla that contain the swallowing and respiration central pattern generators, the neurons form a multifunctional pool, flexibly involved in the function of both central pattern generators (13). Given that respiration and swallowing are known to exhibit reflex inhibition of the other (19, 25), it is possible that the inhibition of respiration causing central apnea at least occurs simultaneously with the initiation of swallowing during the respiratory pause. It is therefore unclear why upper airway sleep state influences predominantly affect the initiation of apneas and arousals in these centers, because the motoneurons involved in swallowing are also in AS (5, 8, 12). Suggested reasons behind the increase in AS (9). This is supported by observations that responses to hypoxia and hypercapnia are lower in AS.
compared with QS of young infants (26). Arousal has also been noted to occur more often in AS infants compared with QS (21). Page and Jeffery (21) postulate that this respiratory vulnerability (lower responsiveness of chemoreceptors to hypoxia) of infants in AS compared with QS leads to arousal being evoked more often to prevent the prolonged apnea and bradycardia that would otherwise occur.

In these postterm infants, we found no significant difference between the spontaneous swallowing rates during IS, QS, or AS. Other differences include the overall frequency of swallowing rates, which was lower in our study (91.6 vs. 43%). The swallowing rate of our infants (25 h⁻¹) was equivalent to the lowest rate observed in term infants (30 h⁻¹ in QS for term infants) (14, 21). Possible explanations include the methods used and the age group in the study. Those studies were undertaken at term and used solid-state pressure transducers, with control study. Those studies were undertaken at term and used solid-state pressure transducers, with control data derived over 1 min preceding the test. We studied infants up to 7 mo of age, used a fluid-filled catheter, and sampled the entire spontaneous sleep period. Finally, the older age of our infants may well have contributed to the different results observed, although this seems unlikely in light of the absence of age-associated effects across our group.

Limitations of the study. The infants in this study were studied for clinical reasons and were therefore more likely to have respiratory abnormalities (apnea or increased respiratory distress) than normal infants. However, infants with respiratory distress show greater inhibition of respiration than those with normal respiratory status, so our results are likely to overestimate the concurrence of apnea and swallowing compared with equivalent observations in normal infants (24). Although our results are not consistent with the recent study showing a difference in swallowing with sleep state in lambs, the methods are different (25a). It is important to note that we did not examine nonnutritive sucking (Fig. 1) but examined swallowing by using an intraluminal catheter, so it remains possible that the two studies are examining different activities. The fact that the catheter was intraluminal (required instrumentation of the airway) and that we used a fluid infusion would likely have caused an elevation of the swallowing rate (18). It is not clear whether this would be an equal effect across sleep states.

In summary, we did not find a significant link between swallowing and sleep state. We also found that although links exist between the occurrence of swallowing and of apneas and arousals, the direction of the link was for apneas and arousals to be associated with swallowing but not the converse. Previous studies have shown that an increased swallowing rate is the most common response to pharyngeal stimulation. We speculate that the association between swallowing and apnea or swallowing and arousal occurs through swallowing being triggered by upper airway reflexes. We conclude that any sleep state influence on swallowing occurs in response to its association with apnea and/or arousal rather than as an independent effect at the site of the brain stem controller.

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REFERENCES


