Site and mechanics of spontaneous, sleep-associated obstructive apnea in infants

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Obstructive sleep apnea (OSA) occurs in infants as well as older children, but for infants in their first year of life OSA is not likely to be attributable to adenotonsillar hypertrophy. The exact prevalence of OSA in this age group (infancy) is not well documented because epidemiological studies have concentrated on older children (10). This may be due to the nonspecific nature of symptoms in infants or to difficulties in parental assessment of symptoms that have been present throughout the life of the infant. These include feeding difficulties, profuse sweating, and breath-holding spells (18). Known consequences of severe OSA in infancy include failure to thrive, chronic respiratory failure, and irreversible developmental delay (13). Recent studies suggesting that OSA may be linked with sudden infant death syndrome (42, 27) emphasize the potential importance of OSA during infancy and the need to recognize and to understand the pathophysiology of the disease.

Previous studies of upper airway obstruction in infants have not considered the palate as a potential site for obstruction (26, 34). However, the retropalatal region is a strong candidate as a site of airway collapse at any age, including infancy. It is a site of airway narrowing with little bony or cartilaginous support that is rendered prone to collapse when muscle tone decreases during sleep. The innervation of the palate is complex, involving at least five different neural centers (32). Palatal function in adults is affected by sleep, phase of respiration, and negative-pressure challenges. These factors may also influence the activity of paltoglossus and levator palatini, which are the muscles primarily responsible for palatal position (16, 30, 36, 37, 40). In adults with OSA, the frequency of palatal obstruction is approximately equal to that of retroglossal obstruction (15). Equivalent, detailed information regarding palatal information is not available in infants.

Early development is a period of rapid maturation in sleep patterns and of many respiratory reflexes. Infants have different reflex responses to many stimuli compared with older age groups, often with a predominance of inhibitory influences. Chemical responses are generally weak at birth and subsequently increase, whereas inhibitory reflexes are strong at birth and subsequently decline (42). The mechanics of spontaneous upper airway obstruction have been studied in adults (15), and many studies of airway collapsibility have been performed in older children (21). Few studies in infancy have, however, included the palate as a

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potential site of upper airway obstruction, so current literature suggests that the retroglottal region is the most common site of obstruction in this age group (35). Many changes occur in chemical and reflex responses during infancy, so it is likely that infants would exhibit differences in the pathophysiological mechanisms of, and responses to, upper airway obstruction. Examples of inhibitory influences on respiration include the strongly inhibitory laryngeal chemoreflex (4), inhibition of respiration during spontaneous sucking and swallowing (2, 22), and reduced activity of the genioglossus at the onset of obstructive events (44).

We hypothesized that the airway obstruction in infants could predominate at the level of the soft palate. In addition, we postulated that inhibitory responses would cause reduced respiratory effort in response to spontaneous airway occlusion and thus differ from the responses exhibited in older children and adults. Finally, we hypothesized that arousal would occur more commonly after obstructive than central apneas, when continued respiratory efforts during obstructive apnea were defined using an esophageal pressure channel.

To evaluate these hypotheses, a triple-lumen pressure catheter was inserted during overnight sleep studies of infants up to 8 mo of age. This permitted examination of the relative contributions of palatal and the retroglottal regions to obstructive apneas that occurred spontaneously during sleep in infants and permitted a detailed examination of mechanical responses to spontaneous airway obstruction in infants.

METHODS

Study Design

To determine normal values for the distance from nares to oropharynx, magnetic resonance images (MRIs) of the upper airway were recalled from a reference group of 70 infants and correlated with growth parameters. These correlations were used to assist placement of a triple-lumen catheter in a further 19 infants, who were then studied to evaluate the site and characteristics of upper airway obstruction in infants by measuring nasal, oropharyngeal, and esophageal pressure concurrent with polysomnography (PSG). Apneic events and arousals were identified by PSG criteria. Manometric data were analyzed for the period immediately before, during, and after each apneic event.

Evaluation of Oropharyngeal Distance

There is no published method available to provide a means for estimating the distance from nares to oropharynx in infants. Our study involved per nasal placement of a catheter in unsedated infants up to 8 mo of age. This required correct placement of an oropharyngeal pressure port while minimizing the amount of handling of the infant. To place the oropharyngeal lumen of the catheter, we evaluated MRIs to define the distance from the nares to the oropharynx in infants.

A regression equation was determined from the measurement of nose to oropharynx on MRIs of a reference group of 70 infants. All digital records of cranial MRI available for infants aged 6 mo or less were recalled from the 4-yr period between 1994 and 1998, inclusive. Separate approval for this aspect of the study was obtained from the Ethics Committee of the Royal Alexandra Hospital for Children (RAHC), and this did not include the infants investigated with manometry.

The MRIs were acquired on a Phillips ACS-NT 1.5-T MRI unit (Powertrak 3000, software version 6.1.2). Images were analyzed using Siemens workstation and MagicView software (VA 31 C). This provided pixel-to-measurement correlations that were read in millimeters. Each MRI study was examined to determine whether a midline sagittal section showing airway structures was available, and, if so, the distances from nares to oropharynx were determined. The distance measured were from the nares to the posterior hard palate, from posterior hard palate to the inferior tip of the soft palate, and from the posterior hard palate to the superior tip of the epiglottis (Fig. 1). Adding these distances gave a minimum and maximum range for the oropharyngeal distance, and the midpoint was taken to be the distance from nares to oropharynx for each infant. The indications for MRI and physical characteristics of the infant at the time of the study were determined from the medical records.

The regression curve for age against the MRI measured distance was used to approximate the distance from anterior nares to oropharynx in 19 infants undergoing PSG with concurrent pressure measurements. Final analysis demonstrated that body weight was the best predictor for the oropharyngeal distance (Fig. 2). Observation of characteristic “swallowing spikes” on the oropharyngeal pressure channel was taken as confirmation that the catheter was placed in the oropharynx (38).

Analysis of Obstructive Apnea

Subjects. Infants presenting to the Sleep Unit at the RAHC, at least 36 wk postconceptional age and with a sufficiently normal upper airway to allow pressure recording, were invited to participate in this study. Of 45 infants eligible for study, 30 were recruited and 15 parents declined participation. There were 19 successful studies, 4 infants did not tolerate the catheter, and 7 studies failed because of technical difficulties. The 19 infants with successful studies were 15.9 ± 2.0 (SE) wk of age (range 1–36 wk) and included 10 male infants. Thirteen infants were born at term, and 6 were premature with a mean gestation of 31.7 ± 4.9 (SE) wk. Four infants were being investigated for suspected apnea after an apparent life-threatening event, five because a sibling had died from the sudden infant death syndrome, and five because of witnessed apneic events. The remaining five had clinically suspected OSA, four with failure to thrive (weight <3rd percentile for age and gender) and one with micrognathia. Approval for the study was obtained from the Ethics Committee of the RAHC, and signed parental consent was obtained before each study commenced.

PSG. All infants underwent multichannel overnight PSG, concurrent with airway pressure recordings. Sleep studies were performed in the standard manner for the laboratory. A minimum of five channels were included for sleep staging [2 for electroencephalogram (EEG), 2 for electrooculogram (EOG), and 1 for submental electromyogram (EMG)], and five channels were monitored for respiratory analysis [airflow, respiratory effort from chest and abdomen, arterial O2 saturation (SaO2), and transcutaneous CO2]. Surface electrodes were used to record EEG, EOG, submental and diaphragm EMGs, and electrocardiogram. Nasal airflow was recorded via nasal cannulas (intermediate infant, no. 1615, Salter Laboratories, Arvin, CA) connected to a low-level pressure transducer referenced to atmospheric pressure (model MP45–4 ± 2 cmH2O, Validyne, Northridge, CA). Thoracic
and abdominal respiratory effort were recorded using inductance plethysmography (Non-Invasive Monitoring Systems, Respitrace, Miami Beach, FL). \( \text{SaO}_2 \) was recorded on the hand or foot (Ohmeda Biox 3700e Pulse Oximeter, Datex-Ohmeda, Homebush, Australia), and transcutaneous \( \text{CO}_2 \) levels were recorded from the upper chest or abdomen (model TINA or TCM3, respectively, Radiometer, Copenhagen, Denmark). All sleep study data were digitally filtered and amplified and were recorded onto a digital data acquisition system (Compumedics, Abbotsford, Victoria, Australia), for later analysis. Nasal pressure signal was recorded on the manometry and the PSG systems to assist in accurate time matching of the respiratory events being analyzed.

Each 30-s epoch of the sleep studies was analyzed to determine sleep state and the occurrence of respiratory and/or arousal events. Sleep staging was determined using standard infant criteria (1) for wakefulness, or quiet, active, and indeterminate sleep. Respiratory events were marked according to the standard criteria of the unit. That is, an apnea is marked if there is a reduction in airflow \( \geq 80\% \) for a period greater than or equal to two respiratory cycles (based on the respiratory rate of the preceding minute) and associated with a \( \geq 3\% \) blood oxygen desaturation, an arousal, or both. Significant apneas were typed as obstructive, mixed, or central on the PSG depending on the presence or absence of ongoing respiratory efforts during the period of airflow cessation, respectively.

Two types of arousal were defined for the use in this study: “full EEG arousal” and “respiratory arousal.” A full EEG arousal was defined as a marked increase in EEG frequency or amplitude for \( >1 \text{ s} \), associated with an increase in submental EMG tone and a marked variability in respiratory efforts and nasal airflow. A respiratory arousal was defined as a large change in two or more independent channels (e.g., the EMGs and respiratory-effort channels), without EEG disturbance, for \( >1 \text{ s} \). The incidence of full EEG and respiratory arousal after obstructive or mixed and central sleep

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Fig. 1. Midline magnetic resonance image of an infant sagittal head section showing the distances measured for this study. A, tongue; B, hard palate; C, soft palate; D, epiglottis; E, trachea.

Fig. 2. Raw data and regression line for body weight vs. distance from nares to oropharynx on magnetic resonance image. See text for details.
apnea was determined for each infant. The mean values were determined for the relevant group. Comparison between the incidence of arousals after central vs. obstructive apnea was used to clarify whether such arousals depend on common factors (such as desaturation) or features unique to obstructive events (such as stimulation of mechanoreceptors).

Airway manometry. A triple-lumen, saline-filled catheter (Critchley Electrical Products, Sydney, Australia) was used to measure airway pressure fluctuations at the nasopharynx, the oropharynx, and the midthoracic esophagus. Standardized 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 then connected to a separate pressure transducer (Transpac IV, Abbot Critical Care, Dublin, Ireland), and patency was maintained with a total saline flow of 12.5 ml/h to prevent secretions from blocking the apertures.

The catheter was inserted via the nasal route into the thoracic esophagus, with the insertion distance for the oropharyngeal lumen of the catheter predicted from the MRI regression equation. Catheter placement was confirmed by the observation of swallowing spikes on the oropharyngeal channel. Catheter apertures were thus placed in the nasopharynx, oropharynx, and intrathoracic esophagus, and pressure measurements were recorded for a minimum of 3 h after sleep onset. The catheter was left in place, without flow until the next full wakening, and then was removed for the remainder of the study. Recordings were made on a digital data acquisition system (AMLAB v2.0, AMLAB International, Lane Cove, Sydney, Australia) that was time matched to the PSG. Sections of the PSG recording with the catheter in place vs. removed were analyzed separately to examine for the effect of the catheter on the respiratory disturbance index (RDI).

Evaluation of apnea characteristics. Each apnea was identified on the PSG and then identified and analyzed on the manometry recording. Each respiratory event was characterized independently on the PSG and manometry recordings. For manometric analysis, pressure fluctuations were assumed to cease above the site of obstruction. Thus obstruction at the level of the palate would be indicated by absence of a nasal signal with continuing pressure fluctuations in the esophagus and the oropharynx (Fig. 3A). Retroglossal obstruction was indicated by continued pressure fluctuations only at the level of the esophagus, with no fluctuations above this level, including the oropharyngeal and nasopharyngeal sites (Fig. 3B). The use of a multichannel pressure catheter does not permit separation between obstruction isolated to the retroglossal region and obstruction occurring simultaneously at palatal and retroglossal regions, even when a laryngeal lumen is included (15).

The amplitude of respiratory efforts during obstructive and mixed apnea was calculated from the pressure recording in the esophagus. One or more obstructive events were seen in 16 (84%) of the 19 subjects, and the amplitude of the pressure swings was averaged for 5 breaths before and 5 breaths after each event. During the event, individual respiratory efforts were analyzed. Mean values were calculated for each infant and then for relevant groups.

Statistical Analyses

All analyses were undertaken using SPSS for Windows (SPSS V9.0 for Windows, SPSS, Chicago, IL). For comparison of event numbers between groups, a Student’s t-test was used. For analysis of respiratory efforts during obstructive apnea, changes in successive breaths were evaluated by two-way ANOVA without replication followed by Bonferroni’s test when the ANOVA showed significant difference. The proportion of events followed by arousal was compared using Student’s t-tests for obstructive, mixed and central apneas. Results are presented as means ± SE, unless otherwise stated. P values <0.05 were considered statistically significant.

RESULTS

Evaluation of Oropharyngeal Distance

A total of 138 MRIs were recalled, and, of these, 70 could be used for airway distance measurements (41 = 59% male infants, 29 = 41% female infants). The cor-

Fig. 3. Manometric recording of obstructive apnea identified 2 ways. A: palatal obstruction characterized by a nasal signal with continuing pressure fluctuations in the esophagus and the oropharynx. B: retroglossal obstruction characterized by pressure fluctuations in the esophagus only.
rected age of the infants was 5.3 wk premature to 27.0 wk postterm [mean 11.7 ± 8.4 (SD) wk]. Length was rarely recorded, but weight was available for 55 subjects. The indication for the MRI included documented (e.g., seizures = 16%), or suspected neurological conditions (e.g., hyper- or hypotonia = 24%). Others conditions affected the cranial fossa but would not be expected to affect facial growth (e.g., documented or suspected hydrocephalus = 22%, suspected space-occupying lesions = 21%, or reduced cortical growth = 12%). Lesions affecting the face tended to be outside the airway (orbits or cheek = 4%). In two cases the MRI was undertaken to evaluate possible airway lesions, one for a suspected tracheal lesion and another for choanal atresia.

The mean distance from nares to oropharynx was 6.2 ± 0.35 cm. Regression analysis using weight in 55 cases (37 = 67% male infants, and 18 = 33% female infants) provided the best correlation with the oropharyngeal distance ($R^2 = 0.67$, $P < 0.001$; Fig. 2). Corrected age also correlated significantly, but less well ($R^2 = 0.56$, $P < 0.001$), and multiple-regression analysis did not improve the correlation. Using this MRI data, the best correlation for the distance to the oropharynx in infants up to the age of 27 wk postterm was

$$D_{OBO} = y = 1.21 \ln (x) + 4.14(R^2 = 0.67, P < 0.001)$$

where $x$ = body weight.

The catheter distance to the oropharynx ($D_{OBO}$) in the 19 study infants fell within the 95% confidence intervals of the weight vs. MRI equation for 79% of cases. This result is consistent with our final analysis demonstrating that weight provided the best estimate of nose-to-oralpharyngeal distance. In the four outliers, the regression equation tended to underestimate the distance from nose to oropharynx.

**PSG**

Infants with a minimum of four recorded obstructive apneas were grouped into two categories, according to the clinical recommendations following their study. Infants with few events (nontreatment) had an obstructive RDI (ORDI) <3 obstructions/h, and infants in whom treatment was instituted (treatment) had an ORDI >3 obstructions/h. Adequate manometry data were available for nine subjects, five in the nontreatment and four in the treatment groups. The proportion of obstructive events occurring at palatal and retroglossal regions was calculated for each subject, followed by group comparisons. Characteristics of infants are presented in Table 1 and their sleep studies in Table 2.

The RDI was not affected by the presence of the catheter [0.79 ± 0.2 vs. 0.72 ± 0.18 log10 RDI, catheter in place vs. catheter out, respectively; not significant (NS)], nor was the frequency of obstructive events (0.31 ± 0.2 vs. 0.31 ± 0.2 log10 ORDI catheter in place vs. catheter out, respectively; NS).

**Site and Characteristics of Upper Airway Obstruction**

The frequency of palatal and retroglossal obstructions is presented for individual infants in Table 3. Overall, the soft palate was the primary site of obstruction in 57 ± 9.5% of obstructions. Accordingly, in 43 ± 9.5% of obstructive apneas there was an obstruction at the retroglossal level with or without simultaneous palatal level obstruction. Infants in the nontreatment group had palatal obstruction in 38.6 ± 8.8% (SE) of events and retroglossal obstruction in 61.4 ± 8.8% of events (NS). In contrast, the majority of obstructive events in the treatment group occurred at the palatal level (80 ± 9.8%) compared with 20 ± 8.8% at the retroglossal level (NS). The differences in site of obstruction were significant between the treatment and nontreatment groups (treatment vs. nontreatment groups, $P = 0.02$ for palatal and for retroglossal obstruction; Fig. 4).

**Breathing Efforts During Obstructive Apneas**

The mean breath amplitude over five breaths before the apnea was not different between groups (−15.1 ± 1.0 vs. −16.2 ± 1.0%, nontreatment vs. treatment, respectively). The magnitude of respiratory efforts in-

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**Table 1. Subject characteristics in treatment and nontreatment groups**

<table>
<thead>
<tr>
<th></th>
<th>Nontreatment</th>
<th>Treatment</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>14</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age, wks</td>
<td>16.0 ± 1.8</td>
<td>15.6 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M:F)</td>
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<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>6.8 ± 0.4</td>
<td>5.5 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>0.3 ± 0.5</td>
<td>−1.4 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, %</td>
<td>55.5 ± 10.5</td>
<td>36.3 ± 21.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n$, no. of subjects. M, male; F, female; SDS, standard deviation score; NS, not significant.
increased with successive breaths during obstructive and mixed apnea (−11.4 ± 1.5, −15.0 ± 1.6, and −20.4 ± 2.7 cmH₂O for the first, second, and third respiratory efforts, respectively; Fig. 5A). After the apnea, respiratory efforts were greater in the treatment group (−16.2 ± 1.0 vs. −22.4 ± 2.9 cmH₂O, nontreatment vs. treatment, respectively; \( P = 0.02 \)). The first effort made during an obstructive event tended to have reduced amplitude compared with the efforts preceding the apnea (−11.4 ± 1.5 vs. −15.1 ± 1.0 cmH₂O, first obstructed breath vs. baseline, respectively; \( P = 0.002 \); Fig. 5B). We found no correlation between the amplitude of respiratory efforts at baseline with age, \( \log_{10} \) RDI, or \( \log_{10} \) ORDI.

### Arousal Frequency After Apneas

The occurrence of arousal at apnea termination was determined from the PSG recording. From a total of 341 obstructive and mixed events, full EEG or respiratory arousal followed 34 and 66 events, respectively. From 388 central apneas, 31 and 56 events were followed by a full EEG or respiratory arousal, respectively. Full EEG arousal therefore followed 22.9 ± 6.7% of obstructive and mixed vs. 7.3 ± 1.8% of central events (\( P = 0.04 \)). Respiratory arousal followed 14.1 ± 4.3% of obstructive and mixed and 20.5 ± 6.0% of central events (NS). When the two types of arousal were combined, there was no difference between the proportion of events terminated by arousal according to apnea type (37.0 ± 6.8 vs. 27.8 ± 6.2%, obstructive and mixed vs. central, respectively).

### Table 3. Location of upper airway obstruction in each subject

<table>
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<tr>
<th>Subject No.</th>
<th>ORDI,</th>
<th>Palatal, no.</th>
<th>Retroglossal, no.</th>
<th>Palatal, %</th>
<th>Retroglossal, %</th>
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<td>50</td>
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<tr>
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<td>19</td>
<td>2</td>
<td>90</td>
<td>10</td>
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</table>

Subjects are presented in ascending order of the obstructive apnea index (ORDI). Subjects 1–14 were not treated for obstructive sleep apnea and subjects 15–19 were. The ORDI was derived from polysomnography, but proportions of palatal vs. retroglossal obstruction were determined for events occurring during the period of the manometric recording. *This subject was not included in the group comparison because only 2 events could be analyzed on manometry.

### DISCUSSION

This study presents new data regarding measurements of the upper airway in infants on the basis of MRI. Triple-lumen pressure catheters were placed according to these measurements, to measure the site and characteristics of airway obstruction in infants. Our results demonstrate that the palate may be the primary site of obstruction in young infants with clinically significant OSA, a site that has not been implicated previously in infants with OSA. Use of this new investigative method also provided information about the responses of infants to airway obstruction, including initial inhibition of respiratory efforts and a tendency to EEG arousal after obstructive but not central apnea.

### Catheter Placement

The cephalocaudal growth gradient of cranial structures is far advanced during infancy and early childhood, with these structures nearer to final adult size than other parts of the body (5). There is a paucity of data regarding the distance to the oropharynx, with some addressing childhood (12) but none assessing the early period of exponential growth in infancy. Previous physiological studies in infants do not provide predictive estimates of the distance a catheter should be inserted but rely entirely on the observation of swallowing spikes during the physiological recordings of neonates (2, 3, 20). The infants in our study were older (up to age 8 mo) and were not sedated. In contrast to adults (15), it is not possible to directly visualize the
oropharyngeal aperture of the catheter in infants because of the anatomic characteristics of their oral airway and the inability of infants to cooperate with the examination.

To minimize the need for repositioning andrefixing the upper airway catheter, we evaluated a new method of predicting the distance from the external nares to the oropharynx. In our physiological studies, catheter placement was predicted from the MRI data then confirmed by observation of swallowing spikes on the oropharyngeal pressure trace. Thus noninvasive, predictive estimate derived from MRI data achieved the goals of expediting catheter placement and minimizing the handling required for each infant as well as avoiding the need for imaging studies. Body weight is a readily available growth parameter, which is particularly important when proposing tools for clinical studies. If a pressure catheter is being used, it remains advisable to confirm catheter placement by the observation of characteristic swallowing pressure waves, at and below the level of the oropharynx (43).

Site and Response to OSA in Infants

The palatal region has not been implicated previously as the site of spontaneous upper airway obstruction in infants. This study has shown that the soft palate can be a primary site of upper airway obstruction and that for a group of infants with clinically significant OSA it is the most common site of obstruction. Previous evidence suggests that inhibitory reflexes are strong in preterm infants and may contribute to the pathophysiology of the obstruction itself (10, 11) and that arousals are infrequent in young infants after apnea (26). Our data show initial inhibition of respiratory efforts after the onset of obstruction but progressively increasing amplitude of respiratory efforts during the event, with the efforts exceeding baseline before termination of the obstruction. We also found predominance of arousals with an EEG component after obstructive events compared with central events but no overall difference in the frequency of arousals when EEG criteria were not included (27).

The demonstration that palatal obstruction occurs in infant OSA is supported by adult studies using equivalent techniques showing that obstruction occurs at the level of the palate and at the retroglossal region (15, 19). Most infants in this study had some obstruction at palatal and at retroglossal levels. However, infants also tended to show a predominant site of obstruction, and the incidence of palatal obstruction in the treated group was higher than that reported for adult disease (17, 44). The predominance of palatal obstruction in infants with a higher obstructive RDI suggests that palatal dysfunction plays a role in the increased rate of obstruction experienced by those infants.

Obstructive events with retroglossal obstruction may have included collapse (occlusion) of the palatal region as well. Thus the incidence of palatal obstruction may have been even greater than reported, and such events would involve a larger segment of the upper airway. If this were the case, infants with more severe OSA would be expected to have more retroglossal than palatal events, and intrathoracic pressures at the termination of the obstruction would be expected to be greatest after retroglossal events. Given that neither of these sequelae is supported by our data, we conclude that obstruction tended to occur at one or the other site. More extensive pressure catheters (more pressure sites) may still not help to clarify this issue (15), so that imaging (e.g., rapid MRI; Ref. 38) would be

Fig. 5. A: Amplitude of respiratory efforts during obstructive apnea. The efforts were increasing during successive breaths \( P < 0.05 \). B: mean change in esophageal pressure amplitude compared with the mean of the 5 breaths preceding the apnea (100% amplitude). The pressure swing initially fell but exceeded baseline by the third obstructive effort.
required to distinguish isolated palatal from mixed palatal and oropharyngeal collapse.

The pattern of respiratory efforts by these infants during obstruction suggests that they have less respiratory inhibition in response to spontaneous airway obstruction compared with preterm infants. Preterm infants show reduced amplitude or respiratory efforts throughout spontaneous obstructive episodes (9), but the group in the present study exceeded baseline respiratory efforts by the third attempted breath. Externally imposed upper airway occlusion stimulates a different pattern of respiratory effort as measured by diaphragmatic EMG (9), so it is not clear whether the inhibition seen in older children in response to an external load reflects the same inhibitory reflexes (22).

In this study, the first effort made during an obstructive event tended to have reduced amplitude compared with the efforts preceding the apnea (Fig. 5B). However, the infants went on to make substantial, and increasingly greater, efforts against their spontaneous upper airway obstruction (Fig. 5, A and B). Thus postterm infants show active mechanical responses to airway obstruction, whether the obstruction has occurred at the palate and/or the retroglossal region.

It is not clear whether adults and older children show this pattern of initial inhibition in response to airway obstruction, although they do exhibit progressively greater respiratory efforts during externally induced airway occlusion (6). Possible mechanisms for this increase in respiratory effort include hypoxia, hypercarbia, and stimulation of mechanoreceptors by the airway occlusion itself (29, 33, 34). Infants with clinically significant OSA had greater amplitude of respiratory efforts, and infants with externally imposed airway occlusion also demonstrated an increased amplitude of diaphragmatic EMG after the event (9). It remains possible that mechanoreceptor-induced responses were stronger in infants with more severe OSA.

Our study provides new data, quantifying the amplitude of efforts among postterm infants before, during, and after apnea. There was no evidence that the infants had persisting upper airway obstruction (“upper airway resistance”) between the discrete obstructive events. Older children clearly demonstrate increased work of breathing between the periods of discrete obstruction (14). The lack of correlation between the amplitude of respiratory efforts at baseline with age, log_{10} RDI, or log_{10} ORDI is consistent with data in term infants, suggesting that maturation of the response to later obstructed breaths is due to maturation of chemoreflexes (8, 25) and not to pressure generation or the occurrence of paradoxical respiration. We did not measure acute changes in the SaO_2 or CO_2, but we found no differences in average SaO_2 or CO_2 values of the treatment vs. nontreatment groups to explain the increased amplitude of postobstructive efforts (Table 2).

These infants showed few arousals at apnea termination, consistent with other studies examining arousal responses (26). Arousal is so common at apnea termination in adults that the two responses are often dealt with interchangeably (17), and arousal from sleep is deemed an important mechanism in averting potentially dangerous situations, such as hypoxia or hypercapnia (28). We found that obstructive events were more likely to precipitate arousals with EEG disturbance than central apnea. We found a higher arousal index than previous studies, but, importantly, the apneic events in the present study were selected on the basis of the fact that they terminated with arousal or desaturation (rather than duration). In addition, an important new finding was that there was no overall difference in the proportion of central or obstructive apneas terminating in arousal when the definition of arousals included disturbances without EEG shifts. The higher proportion of arousals after respiratory events in this study is almost certainly due to the same methodological difference and inclusion of arousals without EEG shifts. The triggering mechanism for apnea termination may be hypoxia, hypercapnia or airway occlusion (3, 33, 34). Gleeson and associates (11) suggest that the point of apnea termination is determined by the amplitude of the respiratory efforts being made. Our results support the concept that termination of apnea is independent of arousal in infants and confirm that it is unlikely that arousal has a fundamental role in apnea termination in infancy (26). The information regarding respiratory efforts in this study suggests that, after term, apnea termination may be related to the amplitude of the respiratory efforts or other mechanoreceptor pathways.

Small pressure fluctuations were sometimes seen above the site of obstruction, which may have reflected some persisting airflow (see Fig. 1), but because the apnea was defined as a fall to ≤20% of the baseline this does not preclude definition of the event as an apnea. These and other pressure changes observed during the study period were not due to transmission through the catheter wall between the apertures, confirmed by measurement of catheter compliance and the demonstration that this was negligible up to 100 cmH_2O. In addition, the presence of the catheter did not affect the rate of apnea (including obstructive events). These were measured for the periods with the catheter in place and without the catheter and did not change. Thus we confirmed that the presence of the catheter or of saline flow did not impact on the rate or site of upper airway obstruction observed in this study.

Summary

A regression equation was derived from MRI measurements of the upper airway and was used to assist the placement of a nasal catheter into the oropharynx of infants. Pressure measurements from a triple-lumen catheter indicated that the soft palate is the most common site of obstruction in infants with clinically significant OSA, suggesting that palatal dysfunction contributes to the disease in infants. During spontane-
ous airway obstruction of infants <1 yr of age, the first respiratory effort had reduced amplitude compared with baseline, but unlike preterm infants the amplitude of subsequent respiratory efforts returned to and then exceeded baseline. Termination of apnea was associated with greater amplitude of respiratory efforts in the treatment group compared with infants with few events. However, apnea termination was accompanied by arousal in the majority of events, and there was no evidence of increased amplitude of respiratory efforts between the discrete events. We speculate that termination of apnea in infants is due to upper airway mechanoreceptor pathways or chemoresponses, regardless of their interaction with arousal centers.

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REFERENCES