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Developmental changes in upper airway dynamics

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Marcus, Carole L., Lucila B. Fernandes Do Prado, Janita Lutz, Eliot S. Katz, Cheryl A. Black, Patricia Galster, and Kathryn A. Carson. Developmental changes in upper airway dynamics. *J Appl Physiol* 97: 98–108, 2004. First published February 27, 2004; 10.1152/japplphysiol.00462.2003.—Normal children have a less collapsible upper airway in response to subatmospheric pressure administration (P_{NEG}) during sleep than normal adults do, and this upper airway response appears to be modulated by the central ventilatory drive. Children have a greater ventilatory drive than adults. We, therefore, hypothesized that children have increased neuromotor activation of their pharyngeal airway during sleep compared with adults. As infants have few obstructive apneas during sleep, we hypothesized that infants would have an upper airway that was resistant to collapse. We, therefore, compared the upper airway pressure-flow ($\dot{V}$) relationship during sleep between normal infants, prepubertal children, and adults. We evaluated the upper airway response to *1*) intermittent, acute P_{NEG} (infants, children, and adults), and *2*) hypercapnia (children and adults). We found that adults had a more collapsible upper airway during sleep than either infants or children. The children exhibited a vigorous response to both P_{NEG} and hypercapnia during sleep ($P < 0.01$), whereas adults had no significant change. Infants had an airway that was resistant to collapse and showed a very rapid response to P_{NEG}. We conclude that the upper airway is resistant to collapse during sleep in infants and children. Normal children have preservation of upper airway responses to P_{NEG} and hypercapnia during sleep, whereas responses are diminished in adults. Infants appear to have a different pattern of upper airway activation than older children. We speculate that the pharyngeal airway responses present in normal children are a compensatory response for a relatively narrow upper airway.

sleep-disordered breathing; critical pressure; infants; children; upper airway collapsibility

NORMAL CHILDREN ARE LESS LIKELY to snore than normal adults and rarely have any obstructive apneas during sleep (33). Consistent with this clinical finding, our laboratory (30) recently showed that the upper airway of normal children is less susceptible to collapse than that of adults. This could be due to structural differences in the upper airway or to functional differences in neuromotor tone.

In our laboratory's previous study (30), we found that upper airway collapsibility during sleep was modulated by the central ventilatory drive. The upper airway muscles are accessory muscles of respiration and, as such, are activated in response to increases in the central ventilatory drive (57). Children are known to have a higher ventilatory drive than adults (28); thus it is possible that they have increased activation of their upper airway muscles in response to differing stimuli. We, therefore, hypothesized that normal children have increased neuromotor activation of the pharyngeal airway compared with adults, resulting in a more patent upper airway.

Little is known about upper airway collapsibility and upper airway dynamic function in infants compared with older children and adults. We, therefore, included infants in this study. As infants have few obstructive apneas during sleep (23), we hypothesized that infants would have an upper airway that was resistant to collapse.

To test these hypotheses, dynamic upper airway responses were measured during sleep across the age span, from infancy through adulthood. Responses were tested in several ways. It has been shown that upper airway neuromotor activity is suppressed by continuous positive airway pressure (CPAP), resulting in relative hypotonia (56). In contrast, the upper airway is activated by the administration of subatmospheric pressure. This activation is not instantaneous but takes at least three breaths to develop (26, 47). Thus acutely dropping nasal pressure (P_N) from a positive level to a subatmospheric level for several breaths results in a relatively hypotonic upper airway, whereas maintaining subatmospheric pressure for longer periods of time results in activation of the airway. Therefore, in the present study, upper airway responses were tested by using both brief and prolonged applications of subatmospheric pressure. In addition, upper airway responses were tested in some of the children and adults by administering carbon dioxide during sleep.

METHODS

Upper airway, dynamic pressure-flow ($\dot{V}$) responses (PFR) during sleep were compared among normal, nonsnoring, nonobese infants, children, and adults. Children and adults first underwent baseline polysomnography on a separate night. As normal infants have a very low incidence of obstructive sleep apnea (23), their baseline data were obtained during the second half of the night after the PFR measurements were obtained, rather than during a separate night.

Study Group

The study group consisted of *1*) infants, *2*) children, and *3*) adults. The children were the same as those used for a simultaneous study evaluating upper airway responses in children with the obstructive sleep apnea syndrome (C. L. Marcus, J. Lutz, E. S. Katz, C. A. Black, P. Galster, and K. A. Carson, unpublished observations). Subjects were recruited from the community by means of advertisements. Subjects with habitual (nightly) snoring or other symptoms of apnea were excluded. All controls were nonobese, defined as weight <120%

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of the ideal weight for height for infants (25); body mass index <95% predicted for age, height, and race for children (43); and body mass index <30 kg/m^2 for adults (35). Infants were defined as being ≤1 yr of age. Infants with a history of prematurity, apparent life-threatening events, gastroesophageal reflux, or a family history of sudden infant death syndrome were excluded. The child group consisted of prepubertal school-aged children who were old enough to cooperate with testing (i.e., 5–13 yr of age). Children with a history of tonsillectomy and/or adenoidectomy were excluded, as the obstructive sleep apnea syndrome is now a common indication for adenotonsillectomy (42). Because tonsillectomies and adenoidectomies were performed so commonly in the past, this exclusion criterion was not applied to the adult group (aged ≥21 yr).

Written, informed consent was obtained from each subject or the parents or legal guardians. In addition, assent was obtained from children older than 5 yr of age. The study was approved by the Institutional Review Board of Johns Hopkins University, and studies were performed according to the Declaration of Helsinki.

Baseline Polysomnography

Polysomnographic studies were performed overnight. During polysomnography, the following parameters were measured and recorded continuously by using a computerized polysomnography system (Alice 3, Healthdyne, Marietta, GA): electroencephalogram (C_3/A_2, O_1/A_2); right and left electrooculogram; submental electromyogram (EMG); tibial EMG; electrocardiogram; chest and abdominal wall motion (piezoelectric transducers or respiratory inductance plethysmography); oronasal $\dot{V}$ (3-pronged thermistor); end-tidal P_{CO_2} ($P_{ET_{CO_2}}$), measured at the nose by infrared capnometry (Nellcor N-1000, Van Nuys, CA); arterial oxygen saturation (Sa_{O_2}) by pulse oximetry (Nellcor N-1000); and oximeter pulse waveform. Subjects were also monitored and recorded on videotape, by using an infrared video camera, and were continuously observed by a polysomnography technician. Sleep architecture and arousals from sleep were analyzed by using standard techniques (3, 5, 40). Cardiorespiratory parameters were scored by using pediatric standards; i.e., obstructive apneas of any length were scored (2). Hypopneas were scored if there was a qualitative decrease in oronasal $\dot{V}$ ≥50%, associated with a change in the $P_{ET_{CO_2}}$ waveform, paradoxical breathing and desaturation ≥3%, and/or arousal (6).

Measurement of PFR

PFR were obtained during a separate, overnight polysomnogram (except for the infants, who were studied on the same night), by using modifications of previously described techniques (8, 30). Upper airway dynamics were measured under three conditions, in random order: *1*) stepwise, decremental, steady-state decreases in P_N, which was hypothesized to result in sequential activation of the upper airway ("gradual" technique); *2*) acute, transient, intermittent drops in P_N from a baseline holding pressure, which was hypothesized to result in a relatively hypotonic airway ("intermittent" technique); and *3*) decremental decreases in P_N during CO_2 breathing. CO_2 challenges were performed in the first 10 children and adults studied.

During PFR, routine polysomnographic parameters were measured as described previously. In addition, the subject breathed through a CPAP gel mask (Respironics, Pittsburgh, PA) attached to a heated pneumotachometer (Hans Rudolph, Kansas City, MO) and transducer (Validyne Engineering, Northridge, CA). P_N was measured within the mask by using a differential pressure transducer referenced to atmosphere. $P_{ET_{CO_2}}$ was measured via a port on the mask by using an infrared capnometer (Ametek, Paoli, PA). Transcutaneous P_{CO_2} was also measured (Radiometer, Paramus, NJ). A thermistor was placed at the mouth to detect oral breathing. Pressure and $\dot{V}$ signals, in addition to selected other polysomnographic channels, were acquired by using DATAQ Instruments (Akron, OH) hardware and WinDaq software and were simultaneously displayed on the Alice system. P_N was altered in either a positive or negative (subatmospheric) direction by using a device consisting of dual CPAP machines, one of which was modified by Respironics to provide subatmospheric pressure. A toggle switch allowed the subject to be switched rapidly between positive and negative pressure. The equipment was capable of delivering P_N over a range of +22 to −22 cmH_2O.

In infants, measurements were performed during quiet sleep (3). In children and adults, measurements were performed during non-rapid eye movement sleep, preferentially during slow-wave sleep. When measurements during slow-wave sleep were not possible (due to sleep stage transitions or lack of deep sleep in the instrumented, laboratory situation), measurements were performed during stage 2 sleep. Our laboratory has previously shown that PFR does not differ between stage 2 and slow-wave sleep (30). Pilot experiments attempting to obtain measurements during rapid eye movement sleep were unsuccessful due to arousal.

Gradual technique. Subjects were placed on a level of CPAP sufficient to abolish inspiratory $\dot{V}$ limitation (generally 2–4 cmH_2O). Inspiratory $\dot{V}$ limitation was considered to occur when $\dot{V}$ failed to increase, despite increasing respiratory effort, as demonstrated by the characteristic $\dot{V}$ waveform. The characteristic waveform pattern consisted of increasing inspiratory $\dot{V}$ followed by a midinspiratory plateau (11, 32). Once inspiratory $\dot{V}$ limitation had occurred, P_N was lowered in 2-cmH_2O steplike decrements every 30 s until $\dot{V}$ approached zero or an arousal occurred (Fig. 1).

Intermittent technique. Subjects were placed on a CPAP level sufficient to abolish inspiratory $\dot{V}$ limitation (the holding pressure). P_N was then decreased abruptly by 2 cmH_2O for three to five breaths, after which it was rapidly returned to the holding pressure. P_N was dropped repeatedly to incrementally lower levels, with a return each time to the holding pressure, until either $\dot{V}$ approached zero or arousal occurred (Figs. 1 and 2). Data from the first three breaths were analyzed.

Genioglossal EMG measurements during gradual and intermittent PFR were performed in five additional children during sleep by using an intraoral mouthpiece, as previously described (24).

CO_2 responses. CO_2 responses were performed while using the gradual technique. Subjects were placed on a CPAP level sufficient to abolish inspiratory $\dot{V}$ limitation. CO_2 was then introduced via a fine nasal cannula beneath the mask, sufficient to raise the transcutaneous P_{CO_2} by 3 Torr. The gel mask was able to make a seal around the cannula. In general, 0.4 l/min of 100% CO_2, blended with the $\dot{V}$ through the CPAP circuit, were required. This relatively mild degree of hypercapnia was chosen as larger amounts of CO_2, combined with the subatmospheric P_N, resulted in prompt arousal. Transcutaneous P_{CO_2} was measured rather than $P_{ET_{CO_2}}$, as the end-tidal waveform was lost during the administration of negative pressure. The response time of the transcutaneous CO_2 electrode to a step change increase in CO_2 was 35 s. The median time for the transcutaneous P_{CO_2} monitor to reach the goal of 3 mmHg above baseline was 91 s. Following 3 min of baseline CO_2 administration, P_N was decreased in a steplike fashion

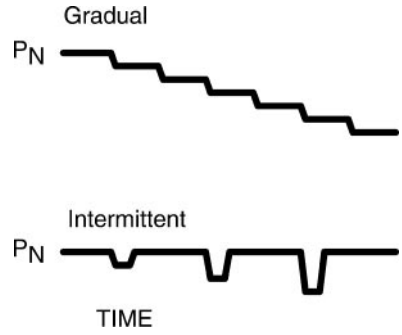

Fig. 1. Techniques for lowering nasal pressure (P_N) for the gradual and intermittent techniques are shown.

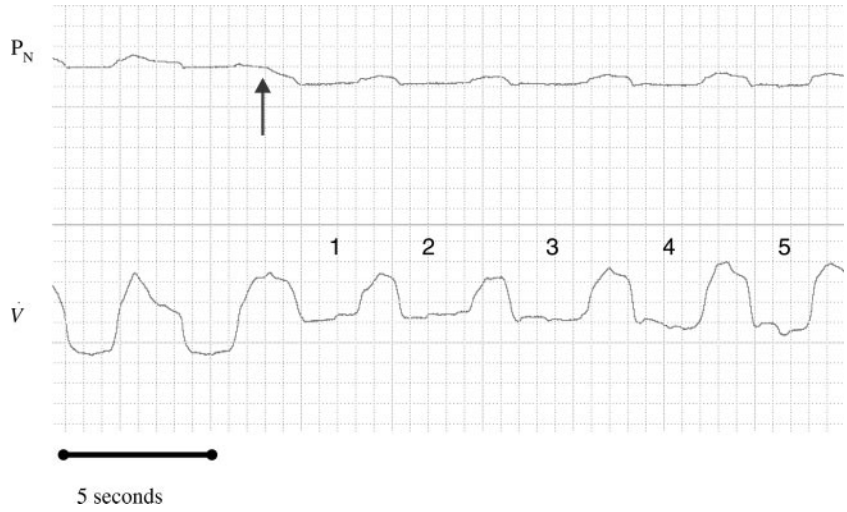

Fig. 2. P_N and flow ($\dot{V}$) tracings are shown from a child during the intermittent technique. Decreasing P_N (arrow) results in diminished $\dot{V}$. *Breaths 1–3* have small $\dot{V}$ values with a $\dot{V}$-limited pattern. *Breaths 4* and *5* are larger and show a transition to a non-$\dot{V}$-limited pattern, suggesting that activation of the upper airway is occurring at that point.

until $\dot{V}$ approached zero or an arousal occurred. CO_2 administration was continued throughout the challenge.

Data Analysis

The average midinspiratory $\dot{V}$ was taken from the lowest two consecutive breaths at each level of pressure. Pressure-$\dot{V}$ curves were constructed by plotting maximal inspiratory $\dot{V}$ ($\dot{V}I_{max}$) of $\dot{V}$-limited breaths against P_N. P_N vs. $\dot{V}$ curves were fitted by least squares linear regression. The critical closing pressure (Pcrit) was defined as the *x*-axis intercept of the regression line ($\dot{V}I_{max} = 0$). Consistent with previous studies (30), many of the normal children in the present study did not have decreases in $\dot{V}I_{max}$, even at markedly subatmospheric pressures (Fig. 3). In these cases, the *x*-intercept could not be determined without extreme extrapolation, and, consequently, Pcrit could not always be determined. Therefore, the slope of the upstream pressure-$\dot{V}$ curve was also used to characterize the upper airway response (30). As our equipment allowed us to apply a maximum negative pressure of -22 cmH_2O, we arbitrarily elected to assign a threshold value of -25 cmH_2O to Pcrit data that were extrapolated to less than -25 cmH_2O. This allowed us to apply statistical methods to the Pcrit data. Note that Fig. 4 shows the raw Pcrit data without the arbitrary cutoff.

Statistical Analysis

Nonparametric methods were used as most data were not normally distributed. All results are expressed as median (range), unless otherwise specified. Differences were compared between groups by using the Kruskal-Wallis test. If the Kruskal-Wallis test was significant for the three groups, then pairwise group comparisons were performed. Differences between conditions for the same individual were compared by using the Wilcoxon signed-rank test. The mean difference in inspiratory $\dot{V}$ between individual breaths as a percentage of baseline $\dot{V}$ during the intermittent challenges was calculated for each patient and analyzed by using the Wilcoxon signed-rank test.

RESULTS

Study Population

Sixty-one subjects were recruited. Three adults and four infants did not sleep well enough to allow for meaningful PFR measurements, one child was excluded due to an abnormal baseline sleep study showing obstructive apnea, and one infant was excluded due to a history of central apnea associated with a respiratory syncytial virus infection. Thus 52 subjects competed the study: 17 infants, 22 children, and 13 adults. Of these, not all slept well enough to allow for all parts of the protocol to be performed. All subjects successfully completed the gradual responses. Intermittent responses were performed in 14 infants, 20 children, and 11 adults. CO_2 responses were tested in the first 10 children and 10 adults.

Subject demographics and baseline polysomnographic results are shown in Table 1.

Gradual and Intermittent Pressure-$\dot{V}$ Measurements

Our laboratory (30) has previously shown that normal children have a much less collapsible upper airway in the activated state than adults. This resulted in a very flat slope, such that Pcrit could not be determined without extreme extrapolation (30). We had similar findings in the present study using the gradual technique, with only 30% of the children having a determinable Pcrit (i.e., Pcrit greater than -25 cmH_2O). Indeed, a few children had such a flat PFR that there was actually a slightly negative tilt to the slope. However, the intermittent technique resulted in a steep slope in the children, in contrast to the flat slope seen with the gradual technique (Figs. 3 and 4). This resulted in a measurable Pcrit that fell within the range of P_N deliverable by our equipment in 50% of the children. We,

Table 1. *Study group*

	Infants	Children	Adults
n	17	22	13
Age, yr	0.5 (1–12 mo)	11 (6–13 yr)	40 (21–57 yr)
Males, *n*, %	11 (65)	14 (64)	5 (38)
BMI, kg/m^2	18 (14–23)	20 (15–27)	24 (20–29)
Height, cm	66 (53–83)	138 (121–179)	169 (158–193)
Apnea hypopnea index, no./h	0 (0–3)	0 (0–1)	0 (0–2)
Sa_{O_2} nadir, %	94 (90–98)*	96 (91–98)	95 (85–98)
Peak end-tidal P_{CO_2}, Torr	38 (31–46)†	49 (40–57)	45 (35–59)

Values are displayed as median (with range in parentheses), unless otherwise specified; *n*, no. of subjects. Statistical differences are shown only for polysomnographic parameters, as demographic parameters would be expected to differ between the age groups. BMI, body mass index; Sa_{O_2}, arterial O_2 saturation. *$P < 0.02$ for infants vs. children. †$P < 0.0001$ for infants vs. children and $P < 0.005$ for infants vs. adults.

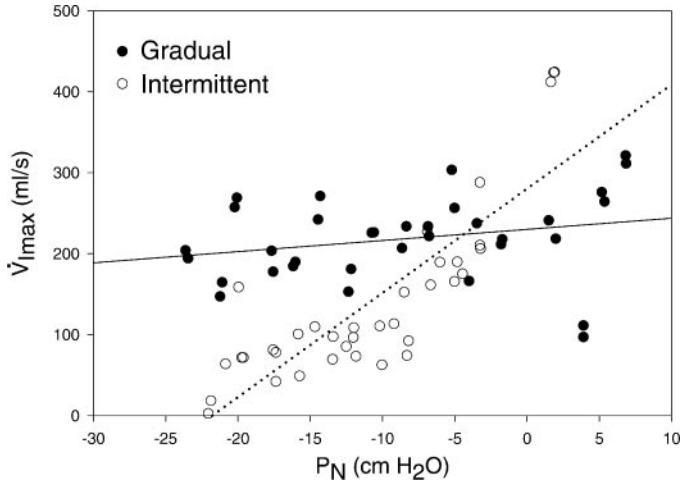

Fig. 3. Typical example of pressure-$\dot{V}$ relationships by using the gradual (●) vs. intermittent (○) techniques in a child is shown. The intermittent technique results in a more collapsible upper airway, with a steeper slope and a higher critical closing pressure. $\dot{V}I_{max}$, maximal inspiratory $\dot{V}$.

Table 2. *Nasal pressures during pressure-flow response testing*

Measure	Infants	Children	Adults
Holding P_N	2.0[a,b]	2.3	3.1
Intermittent	(0.2 to 2.6)	(1.0 to 4.0)	(1.4 to 4.8)
Gradual	1.9[b,c]	2.6	2.7
	(0.2 to 2.6)	(1.5 to 5.0)	(1.3 to 4.0)
CO_2		3.3[d]	3.3
		(1.8 to 4.6)	(2.2 to 4.5)
Flow-limited P_N	1.0[c]	−3.0	1.1
Intermittent	(−4.0 to 2.0)	(−6.0 to 1.0)	(−6.1 to 3.2)
Gradual	1.0	−3.0	1.0
	(−4.0 to 2.0)	(−5.0 to 5.0)	(−5.9 to 2.1)
CO_2		−3.7[e]	1.4
		(−5.6 to 1.0)	(−6.3 to 2.2)
Lowest P_N	−16.5[b]	−16.0[f]	−5.9
Intermittent	(−21 to −5.0)	(−22.0 to −6.0)	(−12.2 to −3.5)
Gradual	−16.0[b]	−13.5[f]	−8.1
	(−22.0 to −6.0)	(−22.0 to −5.0)	(−16.6 to −2.40)
CO_2		−15.8[g]	−8.7
		(−23.2 to −6.7)	(−15.1 to −3.0)

Values are shown as median (with range in parentheses). P_N, nasal pressure. Flow-limited P_N is the first P_N at which virtually all breaths are flow limited. Lowest P_N is the lowest P_N reached during a pressure-flow response challenge before the subject aroused or obstructed. [a]$P < 0.02$ for infants vs. children. [b]$P < 0.01$ for infants vs. adults. [c]$P < 0.01$ for infants vs. children. [d]$P < 0.02$ for children during CO_2 vs. intermittent responses. [e]$P = 0.01$ for children vs. adults. [f]$P < 0.01$ for children vs. adults. [g]$P < 0.05$ for children vs. adults.

therefore, chose to use the intermittent technique as the baseline to which other conditions could be compared.

The nasal holding pressure, the first P_N at which virtually all breaths for that run were $\dot{V}$-limited (i.e., the P_N at which data began to be collected for each run) and the lowest P_N are shown in Table 2. Infants had a slightly lower holding pressure than children and adults, although the holding pressure did not differ between children and adults. This finding probably represented the difficulty in getting the infants to go to sleep with the nasal mask and bias $\dot{V}$ setup. Children had a tendency to become $\dot{V}$-limited at a lower P_N than adults or infants. Children and infants attained a lower P_N before arousal or obstruction occurred, compared with adults.

Figure 2 shows a typical pressure-$\dot{V}$ tracing from a normal child during an intermittent challenge. Following a drop in P_N, the first three breaths had low $\dot{V}$ values, with a $\dot{V}$-limited pattern to the waveform. *Breaths 4* and *5* were larger and showed a transition to a non-$\dot{V}$-limited pattern, suggesting that activation of the upper airway muscles occurred at that point. To quantitate this change, the mean difference in inspiratory $\dot{V}$ (as a percentage of baseline $\dot{V}$) between *breath 1* and *breath 2* following the drop in P_N was measured for each subject. Similarly, the differences between *breath 1* and *breath 3*, and *breath 1* and *breath 5*, were measured. In the children, there was no significant difference in $\dot{V}$ between *breath 1* vs. *breath 2* (median −1%, range −32–27%) or between *breath 1* vs. *breath 3*. However, there was a significant increase in $\dot{V}$ between *breaths 1* vs. *5* (median 15%, range −33–593%, $P < 0.05$). In infants, there was a highly significant increase in $\dot{V}$ rates by *breath 2* (median 5%, range −14–15%, $P < 0.03$ for *breath 1* vs. *breath 2*; and $P < 0.02$ for *breath 1* vs. *3*). Adults

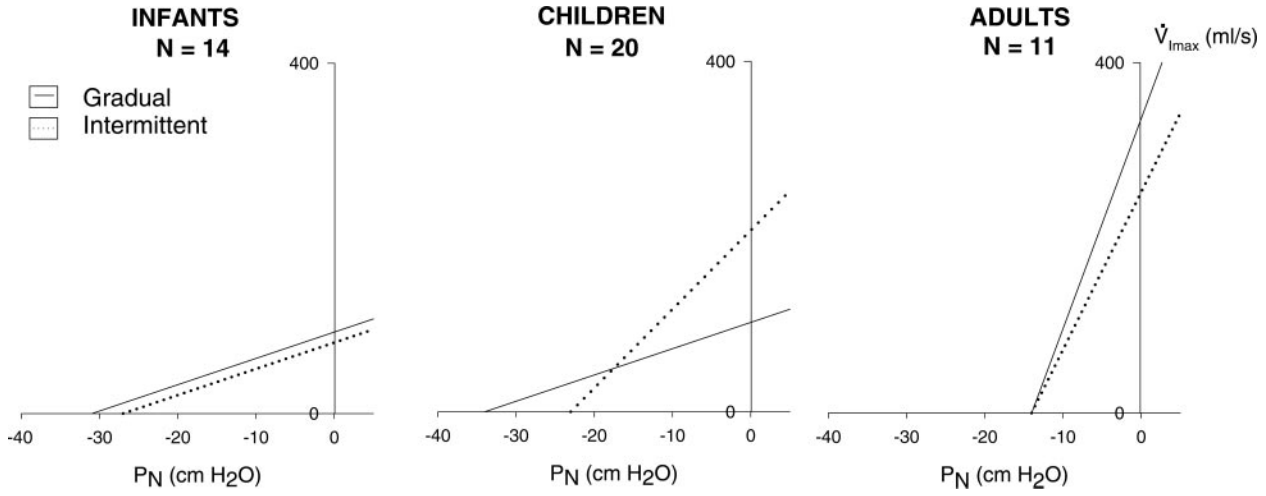

Fig. 4. Median group pressure-$\dot{V}$ data for the gradual (solid line) vs. intermittent (dotted line) techniques are shown for all subjects in whom paired data were available. Note that the figures show the raw critical closing pressure data without the arbitrary cutoff of −25 cmH_2O. See text for *P* values. *N*, no. of subjects.

had a nonsignificant decrease in $\dot{V}$ between *breaths 1* and *2* (median −20%, range −62–17%) and *breaths 1* and *3*, and a nonsignificant increase in $\dot{V}$ by *breath 5* (median 1%, range −83–197%).

Intraoral genioglossal EMG measurements were performed in five children during sleep. A typical example from an 11-yr-old boy is shown in Fig. 5. During gradual runs, there was a gradual increase in EMG activity as P_N became increasingly negative (Fig. 5*A*). In contrast, during the intermittent runs (Fig. 5*B*), the EMG activity was at a low level for the first three breaths of negative pressure and began to increase only by the fourth breath. For the group as a whole, there was an increase in EMG activity, measured as a percentage of baseline activity, for *breath 5* vs. *breath 1* ($P < 0.001$).

With the use of the intermittent technique, Pcrit was similar between infants and normal children (Table 3). This was not due to a floor effect, as it remained true even when an extrapolated Pcrit without a cutoff point was used. The intermittent Pcrit was significantly more negative in the pediatric groups compared with the adults ($P < 0.05$ for both infants and children vs. adults). The slope was flatter in the infants than in the children ($P < 0.001$) and was flatter in both the infants and children than the adults ($P < 0.0001$ and $P < 0.02$, respectively).

With the use of the gradual technique, both pediatric groups had a lower Pcrit and a flatter slope than the adults (Pcrit: $P = 0.001$ for infants vs. adults and $P < 0.0001$ for children vs. adults; slope: $P < 0.0001$ for both infants and children vs. adults); there was no significant difference between the infants and the children.

The group changes in slope for the gradual vs. the intermittent techniques are shown in Fig. 4. Eighty-five percent of children had a flatter slope with the use of the gradual technique compared with the intermittent technique ($P < 0.01$). In contrast, neither infants nor adults had a significant change between the two conditions (43 and 46%, respectively). There was no difference in Pcrit between the gradual and intermittent techniques in any of the groups. However, this may have been because many infants and children had a Pcrit cutoff of −25 cmH_2O applied to them in both states.

The effect of the PFR technique on gas exchange was evaluated by measuring the changes in Sa_{O_2} and transcutaneous P_{CO_2} from immediately before each gradual/intermittent run to just before arousal at the termination of each run. The median change in Sa_{O_2} was 0% for the intermittent technique and −1% for the gradual technique. The greatest individual change in Sa_{O_2} was −3%; no subject desaturated below 94%. The median change in transcutaneous P_{CO_2} was 0 Torr for all challenges; the greatest increase in P_{CO_2} for any individual was 2 Torr.

The correlation between age and PFR was evaluated. For the study group as a whole, there was a significant correlation between age and both the intermittent and the gradual slope ($r = 0.66$, $P < 0.001$; and $r = 0.71$, $P < 0.001$, respectively; Fig. 6). Because it is possible that older subjects had a greater slope of the pressure-$\dot{V}$ curve (SPF) simply because they were larger and had a greater $\dot{V}$ rate, we evaluated the difference in SPF corrected for height (the primary predictor for $\dot{V}$ in pulmonary function testing) among the three age groups. There was no significant difference in SPF/height between children and infants ($P = 0.40$ for gradual SPF/height; $P = 0.20$ for intermittent SPF/height). Adults had a greater SPF/height than both the children and infants ($P < 0.001$ for adults vs. either infants or children for gradual SPF/height; $P < 0.02$ for intermittent SPF/height for adults vs. infants; $P < 0.03$ for intermittent SPF/height for adults vs. children).

The correlation between age and PFR was also evaluated within the individual age groups. Pcrit was not evaluated as it was not a continuous variable, due to the imposed cutoff of −25 cmH_2O. In the infants, there was a correlation between age and the intermittent slope ($r = 0.49$, $P < 0.05$) and a trend toward a positive correlation between age and the gradual slope ($r = 0.46$, not significant). Within the child and adult groups, there was no significant correlation between age and slope, and all of the correlation coefficients were very low.

CO_2 Responses

CO_2 responses were performed in children and adults by using the gradual technique. A few subjects who completed CO_2 runs did not successfully complete intermittent room air runs, although all completed gradual room air runs. Therefore, the CO_2 runs were compared with the gradual room air runs. In the children, median transcutaneous P_{CO_2} was 46 Torr before the challenge and 48 Torr by the end of the challenge. In the adults, transcutaneous P_{CO_2} was initially 45 Torr, increasing to 49 Torr by the end of the challenge.

In the normal children, hypercapnia resulted in increased $\dot{V}$ for a given P_N. A typical example is shown in Fig. 7. There appeared to be an interaction between the response to CO_2 and the response to negative pressure as P_N decreased. As a result of this interaction, there was a marked increase in $\dot{V}_{I_{max}}$ when the subject breathed CO_2 compared with room air at mild levels of subatmospheric P_N (e.g., −4 cmH_2O in Fig. 7). As the subatmospheric pressure decreased (became more negative, e.g., −14 to −18 cmH_2O in Fig. 7), there was a persistent but much smaller effect of CO_2 on $\dot{V}_{I_{max}}$. This suggests that, at high-pressure loads, the upper airway muscles were maximally activated in the normal children and could not increase their tone further, despite persistent stimulation by CO_2. However, this interaction made it difficult to analyze the pressure-$\dot{V}$ relationship. Therefore, data were evaluated by comparing $\dot{V}_{I_{max}}$ when subjects breathed room air vs. CO_2 at atmospheric pressure ($P_N = 0$ cmH_2O). As only $\dot{V}$-limited breaths were evaluated, changes in the amount of $\dot{V}$ were due to changes in upper airway properties, rather than changes in the overall ventilatory drive.

During CO_2 testing, $\dot{V}$ limitation began at a higher P_N in the adults than in the children. Adults had a greater $\dot{V}_{I_{max}}$ when breathing room air than the children (Table 4). However, the change in $\dot{V}_{I_{max}}$ when breathing CO_2 vs. room air, as a percentage of baseline (i.e., corrected for the differences in baseline values) was smaller in the adults than the children ($P < 0.05$). In the children, CO_2 resulted in a significant increase in $\dot{V}_{I_{max}}$, with 90% of subjects showing an increase during hypercapnia ($P < 0.01$). In contrast to the children, adults had a variable response, with only 50% showing an increase in $\dot{V}$ (not significant).

DISCUSSION

We have evaluated the dynamic upper airway responses to differing stimuli during sleep along the age spectrum. We found that *1*) upper airway collapsibility was increased in

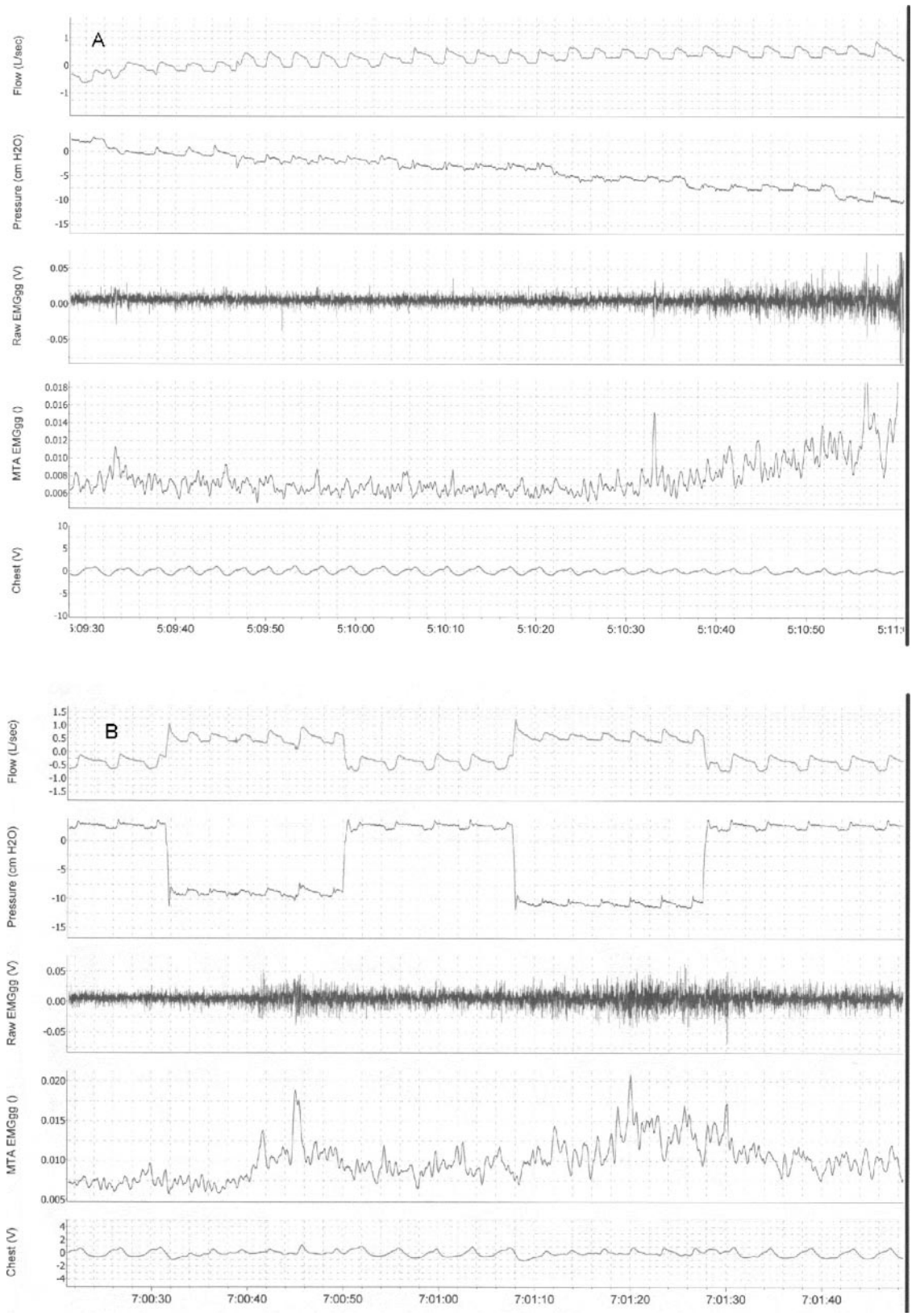

Fig. 5. $\dot{V}$, P_N, raw genioglossal electromyography (EMG_{gg}), moving average [moving time average (MTA)] of the EMG_{gg}, and chest wall motion are shown from a child sleeping while wearing an intraoral EMG mouthpiece. *A*: portion of a gradual run. *B*: portion of an intermittent run. During the gradual run, the EMG increases incrementally, whereas, during the intermittent run, the EMG typically begins to increase only by the 4th breath.

Table 3. *Gradual vs. intermittent pressure-flow relationships*

Measure	Infants	Children	Adults	*P* Value			
				Overall	Infants vs. Children	Infants vs. Adults	Children vs. Adults
Intermittent Pcrit, cmH_2O	−25 (−25 to −16)	−25 (−25 to −7)	−14 (−25 to −4)	0.02	0.40	<0.01	<0.05
Intermittent slope, $ml \cdot s^{-1} \cdot cmH_2O^{-1}$	3 (0 to 7)	9 (−5 to 26)	18 (4 to 45)	<0.0001	<0.001	<0.0001	<0.02
Gradual Pcrit, cmH_2O	−25 (−25 to −1)	−25 (−25 to −9)	−14 (−23 to −3)	<0.0001	0.39	0.001	<0.0001
Gradual slope, $ml \cdot s^{-1} \cdot cmH_2O^{-1}$	3 (−1 to 6)	4 (−9 to 21)	21 (10 to 56)	<0.0001	0.18	<0.0001	<0.0001

Values are shown as median (with range in parentheses). Pcrit, critical pressure.

adults compared with both infants and children, and *2*) children had active upper airway dynamic responses to both negative pressure pulses and hypercapnia during sleep. In contrast, adults did not have upper airway activation in response to the applied stimuli. Infants appeared to have a very rapid response to negative pressure.

Upper Airway Pressure-$\dot{V}$ Relationships

Our laboratory has previously used the Starling resistor model to objectively determine upper airway collapsibility (30, 32). This model, which has been well characterized for a number of biological systems, such as blood vessels (36) and the lower airways (39), has been shown to be applicable to the upper airway in both adults and children with obstructive sleep apnea syndrome (30, 32, 52). The model describes the major determinants of $\dot{V}$ in terms of the mechanical properties of collapsible tubes. According to this model, under conditions of $\dot{V}$ limitation, $\dot{V}_{I_{max}}$ is determined by the pressure changes upstream (nasal) to a collapsible locus of the upper airway and is independent of the downstream (tracheal) pressure generated by the diaphragm. In an isolated Starling resistor model, the sensitivity of the upstream pressure-$\dot{V}$ relationship is represented by the SPF. The Pcrit occurs at the *x*-intercept of the pressure-$\dot{V}$ curve (i.e., the pressure at which there is zero $\dot{V}$ due to upper airway closure). Pcrit provides an objective and reproducible method for evaluating upper airway collapsibility (48). In adults, it can differentiate between normal, snoring, hypopneic, and apneic subjects (13). Pcrit correlates with the severity of apnea in children (32) and decreases after treatment of obstructive sleep apnea (32, 46).

Although Pcrit is a useful measurement in the disease state in children, our laboratory previously showed that Pcrit could not be determined in normal children, as their upper airway was very resistant to collapse (30). This resulted in an extremely negative Pcrit, such that the *x*-intercept of the pressure-$\dot{V}$ curve could not be determined without extreme extrapolation. In addition, the pressure-$\dot{V}$ curve had a much flatter slope. This demonstrated a major difference in upper airway regulation between children and adults, and the Starling resistor model may not be applicable to normal children under activated conditions. We, therefore, utilized a relatively hypotonic technique, which allowed us to partition the neuromotor and structural determinants of upper airway collapsibility (47). In an isolated Starling resistor model, $\dot{V}_{I_{max}}$ is determined solely by Pcrit and the resistance of the upper airway upstream to the site of collapse. However, in the intact human, the upper airway pressure-$\dot{V}$ relationship reflects both upper airway structural factors and neuromotor control, as the upper airway is not merely a passive conduit affected by mechanical forces, but is also affected by activation of the upper airway muscles. The classic PFR performed in the past involved the application of increasingly more negative P_N (32). This resulted in increasing activation of the upper airway muscles. In the present study, we compared this activated technique to a hypotonic technique. Positive P_N suppresses upper airway tone (56), whereas reductions in P_N result in increased upper airway tone (26). Previous studies in adults have shown that this effect of negative pressure takes at least three breaths before the upper

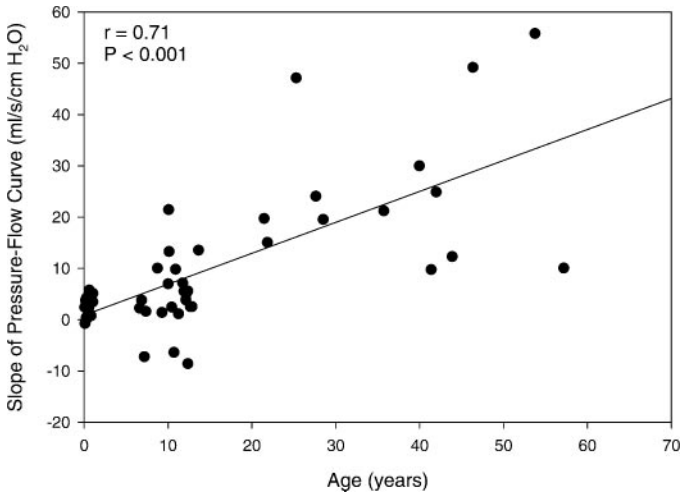

Fig. 6. Slope of the pressure-$\dot{V}$ curve, with the use of the gradual technique, is plotted against age. There is a significant correlation between slope and age.

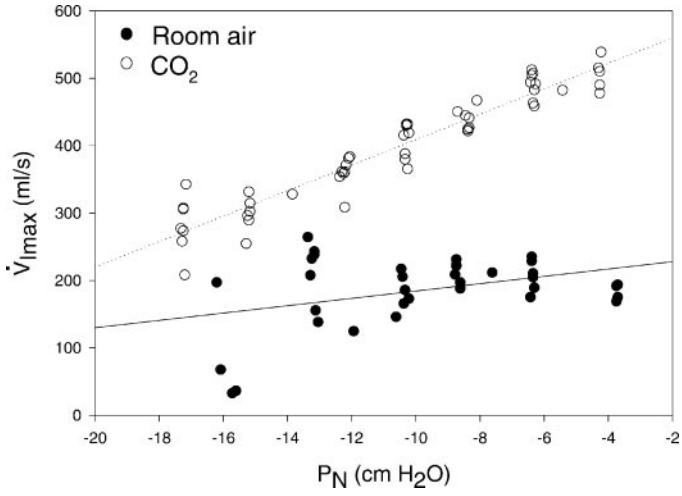

Fig. 7. Typical example of pressure-$\dot{V}$ relationships during room air (●) vs. hypercapnia (CO_2; ○) in a child is shown. Hypercapnia resulted in increased inspiratory $\dot{V}$ at each pressure level. However, this effect was more marked at low levels of subatmospheric pressure.

Table 4. *Effect of CO_2 on maximal inspiratory flow at atmospheric pressure ($P_N = 0$) during sleep*

	n	$\dot{V}_{I_{max}}$ on Room Air, ml/s	$\Delta\dot{V}_{I_{max}}$ (CO_2 vs. Room Air), %baseline	Subjects With Increased $\dot{V}_{I_{max}}$ on CO_2, %
Children	10	154 (44–232)*	+85 (−33–64)†‡	90
Adults	10	229 (159–562)	+14 (−20–67)	50

Values are shown as median (with range in parentheses). $\dot{V}_{I_{max}}$, maximal inspiratory airflow; Δ, change. *$P < 0.01$ for children vs. adults. †$P < 0.05$ for children vs. adults. ‡$P < 0.01$ for children breathing room air vs. CO_2.

airway is activated; our data support a similar response in children older than infancy (26, 47). Thus maintaining positive P_N and then acutely dropping to negative pressure for a few breaths results in a relatively hypotonic airway. This hypotonic technique can be used to construct PFR curves for a functionally denervated upper airway, which can then be compared with PFR curves constructed for the activated airway.

Neuromotor Control of the Upper Airway

Neuromotor factors are important in maintaining upper airway stability. Studies using denervation of upper airway dilating muscles or postmortem measurements have shown that, when upper airway muscle function is decreased, the upper airway is more collapsible (9, 60). Conversely, stimulation of the upper airway muscles decreases collapsibility (49, 50). The factors modulating upper airway tone include sleep state, chemoreceptor afferents (57), upper airway pressure receptors (37), and tracheal traction (54). The upper airway response to subatmospheric pressure has been intensively studied. It is thought to be a centrally mediated reflex, as suggested by *1*) functional magnetic resonance imaging studies showing activation of central nervous system centers in response to upper airway loading (15), *2*) the fact that the upper airway response to disparate stimuli such as hypercapnia and inspiratory loading is similar (34), *3*) the rapid timing of the response compared with voluntary activation (18), and *4*) changes in the response to loading during sleep compared with wakefulness (7). The upper airway contains pressure receptors in the mucosa of the nasopharynx and larynx (44). These negative pressure receptors appear to be the same as those for CO_2 (4), although they are separate from receptors for other stimuli, such as cold, $\dot{V}$, and irritants (44). Afferent stimuli are conducted along the trigeminal, glossopharyngeal, and vagal nerves (16). Central pathways have not been clearly delineated but are thought to involve the locus coeruleus, caudal raphe, mesopontine tegmentum, and medullary reticular formation (59). Stimulation of these subatmospheric pressure receptors results in both inspiratory and expiratory activation of numerous upper airway dilator muscles (16).

It is possible that factors other than activation of the upper airway muscles played a role in the change of the $\dot{V}$ profile. This change was not due to arousal, as the EEG was monitored, and runs were terminated if arousal occurred. During CO_2 and negative pressure administration, it is most likely that the change in inspiratory $\dot{V}$ pattern was due to activation of the central nervous system, resulting in augmented upper airway muscle activity (19, 29, 57). This is considered most likely as subjects showed similar changes in SPF and Pcrit with the use of two very different techniques: pulses of subatmospheric pressure and CO_2 inhalation. In addition, during CO_2 challenges, it is possible that the inspired CO_2 diminished fluctuations in chemical stimuli to the brain, thereby decreasing the gain of the respiratory controller and reducing central nervous system oscillations and their subsequent effect on the upper airway (27). Other factors that may have an effect on the $\dot{V}$ waveform include changes in negative airway pressure (1) and changes in lung volumes due to changes in P_N (1, 54); lower lung volumes are associated with increased Pcrit. The latter was unlikely to have been a major factor in the present study. Although lung volumes were not measured, it is likely that lung volumes would be lower during the long gradual runs, during which continuous subatmospheric pressure is applied, than during intermittent runs, during which the subject is placed on positive pressure between the five breath runs. Thus, if lung volume played a major role, it would be expected that subjects would have a more collapsible airway during the gradual than the intermittent runs, yet in the children the opposite result was noted.

Developmental Changes in Upper Airway Collapsibility

Infants and children have a narrower upper airway than adults. Nevertheless, they snore less and have fewer obstructive apneas (33). This could be due to either structural differences or differences in neuromotor regulation of the upper airway.

In the activated state, using the gradual technique, the children had a markedly more negative Pcrit and flatter slope than the adults. Upper airway neuromotor responses in adults have been reported in detail in the literature. During wakefulness, both CO_2 and negative pressure result in increased upper airway activity (58). However, these responses are markedly diminished during sleep (38, 58). This was confirmed in the adults in our study. However, we found a significant difference between children and adults in this regard, with the normal children having preservation of upper airway responses to both negative pressure and hypercapnia during sleep. This may be due to a difference in central nervous system regulation of upper airway function. Normal children have a higher ventilatory drive than adults (14, 28, 53). It has been shown that there is a relationship between the occlusion pressure in 100 ms (a measure of ventilatory drive) and PFRs during sleep (30). Thus normal children may have increased upper airway dynamic responses during sleep due to the effect of an increased central ventilatory drive on the upper airway musculature. It should be noted that the stimuli used in this study were very subtle (i.e., a 3-mmHg increase in CO_2 and a 3-breath pulse of negative pressure). It is possible that adults would have shown a response to a larger or more prolonged stimulus.

To determine whether the intermittent technique truly resulted in hypotonia, we compared the difference in $\dot{V}$ between *breath 1* following the drop in P_N and the subsequent breaths. In the children, we typically noted a change to a non-$\dot{V}$-limited

pattern following *breath 3* (Fig. 2). $\dot{V}$ did not change between *breaths 1* and *breaths 2* and *3* but increased significantly by *breath 5*. This indicates that upper airway activation typically occurred after three breaths in the normal children. This was confirmed by EMG measurements in several children. Thus analyzing the first three breaths at each pressure drop did allow for the assessment of a relatively hypotonic airway.

The difference between children and adults using the intermittent technique was not as marked as that with the gradual technique. Nevertheless, even with the intermittent technique and a relatively hypotonic airway, the children had a lower Pcrit and a flatter slope than the adults. There are two possible explanations for this. One is that there are structural differences in the upper airway between children and adults. It is possible that the narrower upper airway in children is less compliant than in adults, or that adults have more laxity of the connective tissue and mucosa. Another explanation is that the intermittent technique did not result in total atonia of the airway in the children. Both theories are supported by data from Isono et al. (20). They studied upper airway collapsibility in anesthetized, paralyzed children, i.e., children with a totally flaccid upper airway. The mean closing pressure under those conditions was -8 ± 5 cmH_2O, which was higher than that demonstrated in our subjects by using the intermittent technique (-25 cmH_2O). Measurements from the two studies may not be directly comparable, as different techniques were used. However, in the study by Isono et al., as in ours, the children had a lower closing pressure than adults studied with the same technique, suggesting that structural differences do play some role.

Adults may have a greater SPF simply because they are larger and have a greater $\dot{V}$ rate. However, this cannot explain all of our results. Although adults had a greater SPF/height than either infants or children, there was no significant difference in SPF/height between infants and children, despite the fact that the height difference between these two groups was far greater than between the children and adults (Table 1). Furthermore, differences in body size cannot account for the differences in Pcrit between the groups. In addition, differences in body size between groups cannot explain why children show a much greater response to negative pressure and hypercapnia than adults.

As with the older children, the infant upper airway was resistant to collapse, with a low Pcrit and a flat slope. However, in the infants, there was little difference in upper airway collapsibility between the gradual and the intermittent techniques. In addition, there was little variability between individual infant subjects. There are several possible reasons for the similarity of responses between the gradual and the intermittent techniques. In contrast to the older children, infants had rapid activation of the upper airway in response to negative pressure, occurring as early as the second breath after the drop in P_N. This correlates very well with the work of Gauda et al. (12), who showed that an EMG response to upper airway occlusion occurred by the second breath in 74% of trials in premature neonates, and by the third breath in 80%; Carlo et al. (10) found similar results. Thus it is most likely that the infants had active upper airway responses during sleep but that the mechanism and timing of these responses differed from those of the older age groups. Other studies suggest the presence of active upper airway neuromotor responses in infants. Roberts et al. (41) examined the closing pressure in normal young infants and found it to be -4 ± 3 cmH_2O. The same group found that the upper airway closing pressure in infant cadavers was -1 ± 2 cmH_2O (60). Different techniques were used for the two studies, which makes it difficult to directly compare the results of these studies to each other or to our data. Nevertheless, these data suggest that, in the postmortem or paralyzed state, where there is no neuromotor activation, the infant upper airway is more collapsible than in the intact state. Thus the literature supports the contention that the infant upper airway remains patent during sleep due to continued activation of upper airway muscles. In the present study, we did not test hypercapnic responses in the infants, as infant testing was difficult due to frequent arousals in response to subatmospheric pressure. However, further studies that use other techniques to evaluate infant upper airway responses would be desirable to confirm our speculations. An alternative explanation would be that the infants' flat slope and low Pcrit were due to structural changes, i.e., that the infant upper airway was smaller and stiffer than that of older subjects. This would be surprising. In general, infants have decreased muscle tone compared with older subjects. We are not aware of any direct comparisons of upper airway muscle tone between infants and other age groups. However, the muscles of the head and neck, such as those supporting head control, are clearly weaker in infants. Similarly, the cartilaginous structures of the upper airway in infants tend to be floppy, frequently giving rise to tracheomalacia and laryngomalacia. Furthermore, a study of anesthetized, paralyzed infants showed that the upper airway in this totally atonic state was more collapsible than that of older children (20, 21). Finally, structural changes would not explain the differences in *breaths 1* and *2* following negative pressure in the infants.

We evaluated the relationship between PFR parameters and age. We confirmed our previous finding showing that the gradual slope correlated with age (30). We also found a similar relationship between the intermittent slope and age. Isono et al. (21) previously showed an inverse correlation between upper airway collapsibility and age in the anesthetized, paralyzed state in infants. We found contradictory results in the infants. In the present study, there was a positive correlation between age and the intermittent slope in the infants, as well as a trend toward a correlation between age and the gradual slope. The difference between the two studies is most likely due to the differences in techniques. Isono et al. studied a totally passive airway, i.e., an anesthetized and paralyzed preparation. As a result, their closing pressures reflect anatomic changes. In contrast, we studied infants during natural sleep, when some neuromotor tone was present. This suggests that younger infants have increased upper airway neuromotor activity during sleep than older infants.

Methodological Limitations

In this study, upper airway dynamics were assessed by evaluating changes in $\dot{V}$ during $\dot{V}$-limited breaths. Upper airway EMG measurements were obtained in only a few subjects. It is difficult to obtain EMG measurements in children undergoing research protocols, as invasive techniques cannot be used. Although intraoral EMG measurements have been made in neonates, it was not practical to add intraoral mouthpieces to the onerous equipment (nasal mask, negative pres-

sure, CO_2 and monitoring electrodes) used in this research protocol and expect these young children to have sustained, natural sleep. Furthermore, EMG signals are hard to quantitate and compare between individuals, especially in children too young to cooperate with specific calibration maneuvers (34). In addition, changes in EMG signals do not necessarily correspond to changes in muscle function (i.e., changes in muscle length). Therefore, to verify that the intermittent technique did, in fact, represent a relatively hypotonic airway, we analyzed the breath effect of changes in $\dot{V}$ following acute drops in P_N. This confirmed differences in neuromotor activation between the age groups. Nevertheless, future studies including more comprehensive EMG measures would be desirable.

Analysis of the gradual Pcrit was difficult in the infants and children, due to some of the very flat slopes generated. We, therefore, evaluated the gradual PFR in two ways: *1*) by determining the slope of the response and *2*) by arbitrarily assigning a Pcrit cutoff of -25 cmH_2O. This cutoff point was chosen as it was just below the most negative pressure deliverable by our equipment. The alternative was to extrapolate data far beyond what was actually measured. This did not seem reasonable, as some of the slopes were extremely flat, so that extrapolated Pcrit values were as low as -165 cmH_2O. However, assigning a cutoff point resulted in minimizing differences between the pediatric groups and the adults. Nevertheless, although the cutoff point resulted in smaller absolute differences between the groups, the relationship between groups was not altered compared with the use of the extrapolated data (see Fig. 4). Use of the cutoff level may have resulted in a floor effect that prevented us from determining significant differences between the infants and the children.

It is possible that the gradual technique resulted in upper airway activation by causing hypoxemia or hypercapnia, rather than as a direct effect of subatmospheric pressure. However, in view of the minimal changes in Sa_{O_2} and P_{CO_2} during the challenges, it is unlikely that chemoreflexes played a major role. Even if this were the case, it would still be an indication of upper airway neuromotor activation.

Conclusion

We have shown that normal infants and children have a less collapsible upper airway than adults, consistent with the clinical finding that snoring is less common in the pediatric age groups. Our data suggest that this decrease in collapsibility is due primarily to the preservation of upper airway neuromotor responses in normal children during sleep. The timing and degree of upper airway neuromotor activation differ over the course of development. Further study is required to elucidate the mechanisms involved in maintaining airway patency in infants.

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