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Genioglossus Response to Airway Occlusion in Apneic *Versus* Nonapneic Infants

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ABSTRACT. The ability to maintain pharyngeal patency is compromised in infants who have apneic episodes associated with airway obstruction. Since the genioglossus (GG) muscle is thought to be important in maintaining pharyngeal patency, we measured the GG EMG with sublingual surface electrodes during unobstructed breathing and in response to end-expiratory airway occlusion. Studies were performed in nine premature infants with mixed and obstructive apnea and in eight nonapneic control infants. Phasic GG EMG was usually absent during normal tidal breathing in both groups of infants, however, GG activity typically appeared during airway occlusion. The response of the GG muscle during airway occlusion differed between control and apneic infants. During the first three occluded inspiratory efforts, control infants had 42 ± 5, 74 ± 5, and 80 ± 5% (mean ± SEM) of their occlusions associated with a GG EMG response, respectively. In contrast, apneic infants had significantly fewer (13 ± 4, 38 ± 9, and 52 ± 9%) occlusions associated with a GG EMG response. There was a delay in onset of the GG EMG when compared to the onset of the diaphragm EMG and initial negative esophageal pressure swing, but this delay decreased with each subsequent appearance of the GG EMG in both infant groups. Infants with mixed and obstructive apnea thus have decreased activation of their GG in response to occlusion which may reflect their inability to recruit dilating muscles of the upper airway during spontaneous airway obstruction. (*Pediatr Res* 22: 683–687, 1987)

Abbreviations

GG, genioglossus
DIA, diaphragmatic
Ti, inspiratory time

Upper airway obstruction is a frequent component of apnea in adults with sleep apnea syndrome, in micrognathic infants, and in infants with apnea of prematurity (1–3). The site of airway obstruction is primarily pharyngeal (4) and thus the response of the major upper airway dilating muscle, the GG, has been a subject of recent investigation. The GG response to airway occlusion, hypercarbia, and hypoxia has been measured in adults, animals, and micrognathic infants by recording EMG activity with needle electrodes inserted into the muscle (2, 5–7). As this technique is unsuitable for the study of GG activity in healthy infants, we adapted the noninvasive sublingual surface electrode apparatus devised by Doble *et al.* (8) in adults to evaluate the GG response in a group of premature infants.

To test the hypothesis that infants with mixed and obstructive apnea are less able to initiate an upper airway dilator response to airway occlusion, we used sublingual surface electrodes to examine the GG response to induced end-expiratory airway occlusion in infants with and without mixed and obstructive apnea. Our data indicate that GG activity does differ between infants with apnea and healthy control infants.

SUBJECTS AND METHODS

A study population of 17 premature infants was selected. Nine infants with mixed and obstructive apnea and eight nonapneic control infants were studied. Infants with apnea had a (mean ± SD) gestational age of 28 ± 2 wk (range 26–31 wk), birth weight of 1165 ± 290 g (range 740–1675 g), and a postconceptional age of 32 ± 1 wk (range 31–34 wk). The control infants had a gestational age of 30 ± 2 wk (range 26–33 wk), birth weight of 1420 ± 310 (range 800–1630 g), and postconceptional age of 33 ± 1 wk (range 31–35 wk). The two groups were prospectively selected to be of comparable postconceptional age and this was confirmed by parametric and nonparametric unpaired *t* test. Birth weight did not differ between the two groups. The two groups, however, did differ in gestational age at birth when compared by the Mann Whitney test ($p = 0.04$).

None of the infants required supplemental oxygen and there was no evidence of tachypnea or radiographic lung disease at time of the study. Infants with a history of three or more bradycardias with or without apnea, as detected by electrocardiogram and impedance monitoring, and occurring 24 h prior to the study period, were selected for the apneic group. Bradycardia without detection of apnea by impedance monitoring was assumed to be representative of obstructive apnea. Apneic infants also had two or more mixed and/or obstructive apneic episodes lasting at least 10 s during the 2-h study period. No comparable apneic or bradycardiac episodes were observed in the control infants. Spontaneous apneic episodes were defined as: 1) obstructive if DIA EMGs and esophageal pressure swings persisted in the absence of nasal airflow for ≥10 s; 2) mixed if in addition to the obstructed efforts there were cessation of nasal airflow, absent esophageal pressure swings, and absent diaphragmatic EMG for at least 2 s with the entire episode lasting ≥10 s. Apneas without any obstructive components (central) of ≥10 s duration were not observed in either group of infants. Seven of nine infants with apnea and none of the control infants were receiving theophylline at the time of the study.

The infants were studied in the neonatal pulmonary research laboratory in incubators maintained to approximate the infants' neutral thermal environment. Informed parental consent was obtained prior to each study. Measurements were performed

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during sleep, and no sedation was used. The apparatus used to record the GG EMG consisted of two silver, domed, 4-mm surface electrodes attached to flexible insulated wires and mounted on a moulded acrylic chin piece that was held in place by an elastic head band. The wires could be adjusted to allow a secure fit for each infant. The two surface electrodes were placed in an anterior sublingual position on each side of the frenulum (Fig. 1). The infants tolerated the apparatus well and were positioned with their head turned laterally and their neck in a neutral position. The DIA EMG was obtained from two adhesive surface electrodes (Medtronic Andover Medical, Lowell, MA) placed over the right subcostal margin between the mid- and anterior axillary line. The GG and DIA EMGs were amplified (Preamplifier, Coulbourn, Lehigh Valley, PA) and displayed on an oscilloscope. Raw EMGs were filtered from 30–300 Hz. For the DIA EMG, the electrocardiographic artifact was removed by gating (SB-1 EKG Blanker, CWE, Inc., Ardmore, PA). The raw DIA EMG was full-wave rectified and compared to a reference voltage that was adjusted to be triggered by the electrocardiogram. This signal was both stored undisturbed and sent to a delay circuit. The delayed signal was sent to the output until an electrocardiogram was detected. At this point, the delayed signal was replaced by the undelayed signal. Hence, the electrocardiogram was removed and replaced by an adjacent portion of the DIA EMG. This process introduced a delay of the DIA EMG of approximately 60 ms. The delay was always accounted for when timing calculations were performed using the DIA EMG. Both EMGs were averaged by a moving time averager (9) (MA-821 moving averager, Charles Ward Enterprises, PA) with a time constant of 100 ms. Esophageal pressure was measured by a dome transducer (Gould, Cleveland, OH), attached to a 5Fr fluid-filled catheter (Argyle, St. Louis, MO) placed in the mid-esophagus. Airflow and mask pressure were measured with a nasal pneumotachograph that had a linear flow up to 5 liter/min with a resistance of 8 cm $H_2O)\cdot liter^{-1}$ s and a dead space of less than 2.5 ml (10). The averaged GG and DIA EMGs, esophageal pressure, airflow, and mask pressure were recorded on a 6-channel Gould chart recorder.

A mean (±SD) of 13 ± 4 end-expiratory occlusions were performed per infant with 8 ± 3 performed in active sleep and 5 ± 3 in quiet sleep. After the nasal mask was manually occluded at end expiration, the occlusion was held until at least three occluded efforts were recorded or for a maximum of 10 s. Occlusions were separated by at least 60-s intervals and those resulting in behavioral arousal were not analyzed. Occlusions were only performed when oxygen saturation was at least 95% as measured by pulse oximetry (Nellcor-100, Nellcor Incorporated Haywood, CA). After ≥10 min of sleep, behavioral criteria were utilized to assess sleep state with active sleep being associated with rapid eye movements, body movements, and an irregular respiratory pattern. Quiet sleep was characterized by a regular respiratory pattern and the absence of rapid eye and body movements with the exception of occasional startles. Each infant exhibited three min of active or quiet sleep before occlusions were performed. Data were only collected and analyzed when there was no subsequent change in sleep state.

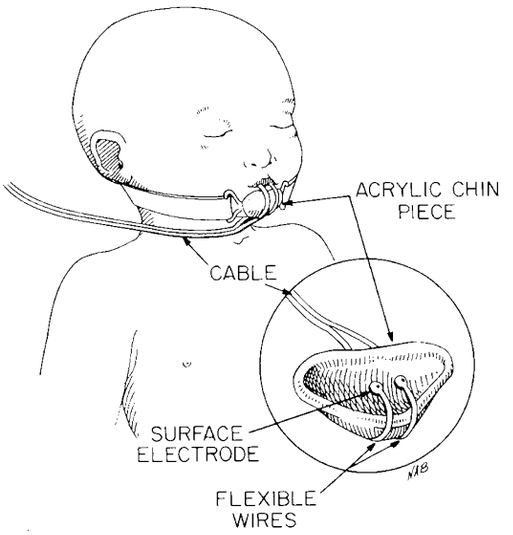

Fig. 1. Schematic illustration of the apparatus used to measure the genioglossus EMG via the sublingual electrodes used in the study.

Occlusions were analyzed with respect to: 1) the frequency of occurrence of phasic GG EMG activity associated with the first three occluded inspiratory efforts in active and quiet sleep; 2) the timing of onset of the DIA and GG EMG during the occluded inspiratory efforts, in relation to the initial negative deflection of the esophageal pressure swing; 3) the prolongation of inspiratory time of the first occluded effort as compared to the breath preceding occlusion; 4) the magnitude of the esophageal pressure deflection of the first occluded inspiratory effort. A mean response to occlusion was calculated separately for each infant and the combined means were then subjected to statistical analysis. Ti was measured from the onset to the peak of the esophageal pressure swing for both the unoccluded breath and the occluded inspiratory effort. The percent of inspiratory prolongation was calculated from the equation $[(Ti_{occl} - Ti_{unocel)/occl)}] \times 100$ where Ti_{occl} represents the first occluded effort and Ti_{unocel} represents the preceding unoccluded breath.

Results were analyzed by authors E.B.G. an J.M.D., one of whom was unaware as to which group the infants belonged. Statistical tests were analysis of variance with repeated measures and the Newman-Keuls procedure, the Student's paired and unpaired *t* test and Mann-Whitney U test as appropriate. Results are presented as mean ± SEM.

RESULTS

Sporadic bursts of phasic GG EMG were recorded during arousal, nonnutritive sucking, swallowing, and apnea. Spontaneously occurring phasic GG EMG associated with respiration was infrequent and not sustained in either group of infants. In contrast, occlusion usually elicited a brisk GG response. As the response of the GG to airway occlusion was comparable in both sleep states, the combined data are presented for each group of infants.

The frequency of phasic GG EMG differed between control and apneic infants during occlusion. A representative tracing from each group is shown in Figures 2*A* and *B*. In the control group 42 ± 5% of occlusions were accompanied by a phasic GG EMG on the 1st occluded inspiratory effort. The frequency of this response increased to 74 ± 5% ($p < 0.01$) and 80 ± 5% ($p < 0.01$) by the second and third occluded inspiratory efforts, respectively. In contrast, in the infants with apnea only 13 ± 4% of occlusions were associated with a phasic GG EMG on the 1st occluded inspiratory effort which increased to 38 ± 9% ($p < 0.01$) and 52 ± 9% ($p < 0.01$) by the second and third occluded inspiratory efforts, respectively. As indicated in Figure 3, the percent of occlusions with a GG response was less in the apneic as compared to the control infants ($p < 0.001$). When the data were subjected to analysis of variance with repeated measures, using gestational and postconceptual age as separate covariates, the GG response still differed significantly (both $p < 0.01$) between the two groups of infants.

The onset of the phasic GG and DIA EMGs during the occluded inspiratory efforts was compared to the onset of the esophageal pressure deflection for the first three occluded efforts exhibiting a GG EMG. A delay in onset of the GG EMG was typically observed during occluded inspiratory efforts. This delay decreased with each subsequent appearance of the GG EMG as demonstrated in Figure 2*A*. The control infants had a delay of

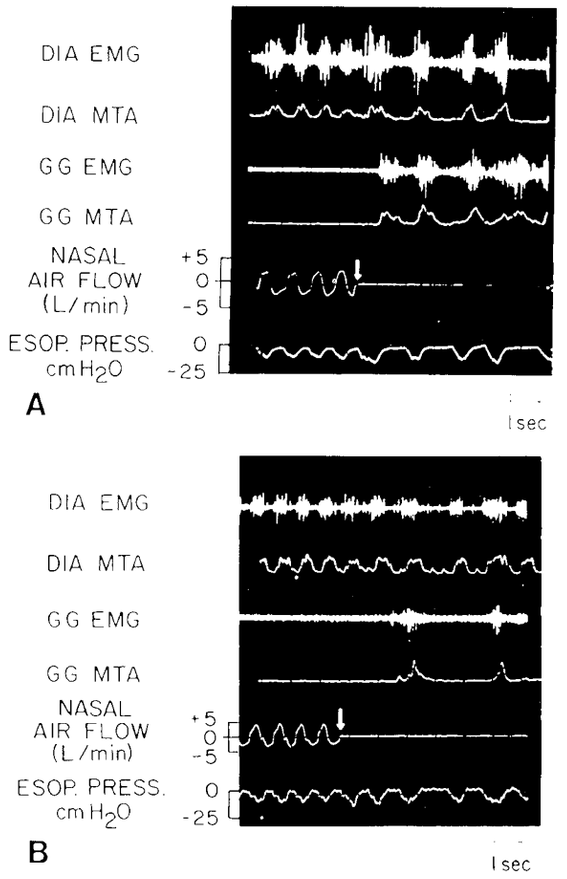

Fig. 2. *A*, typical response of the GG EMG in a control infant prior to and during occlusion. The *arrow* depicts the start of an end-expiratory airway occlusion. Both raw and moving time averaged (*MTA*) signals are presented for the GG and DIA EMGs. Each occluded inspiratory effort is associated with a GG EMG. *B*, typical response of the GG EMG in an apneic infant prior to and during occlusion. The GG EMG does not appear until the third occluded inspiratory effort and reappears with the fifth occluded inspiratory effort.

360 ± 50, 170 ± 40, and 50 ± 60 ms on the first three appearances of the GG EMG during occlusion, respectively. The infants with apnea had a comparable decrease of the delay from 350 ± 20, to 110 ± 60 and 90 ± 50 ms during occlusion. A significant decrease in this delay occurred from the first to the second appearance of the GG EMG in both groups of infants (Fig. 4). The DIA EMG was present with each breath or occluded inspiratory effort and preceded the onset of the esophageal pressure swing by 110 ± 5 ms in the control infants and 80 ± 10 in the apneic infants for the first three occluded inspiratory efforts that were associated with a GG EMG ($p > 0.05$).

The magnitude of the esophageal pressure deflection of the first occluded inspiratory effort was compared between the two groups. The control and apneic infants generated −9 ± 3 and −8 ± 2 cm H_2O), respectively ($p = 0.5$) during occlusion.

Inspiratory time of the first occluded effort was significantly prolonged as compared to the breath preceding the occlusion for both groups of infants (Fig. 5). The percent prolongation of inspiratory time for the control infants (35 ± 8%) did not differ significantly from that in the apneic infants (30 ± 6%, $p = 0.5$). The results were recalculated after omitting those occlusions when Ti_{occl} was shorter than Ti_{unocc}. This occurred in 11 ± 4% of the occlusions in the control infants and in 17 ± 4% of the occlusions in the apneic infants. The two groups of infants still had comparable percent prolongation of Ti, 41 ± 5% in the control and 40 ± 5% in the apneic group ($p = 0.9$).

DISCUSSION

We did not observe sustained phasic inspiratory GG EMG with unobstructed breathing in either of our infant groups. Phasic

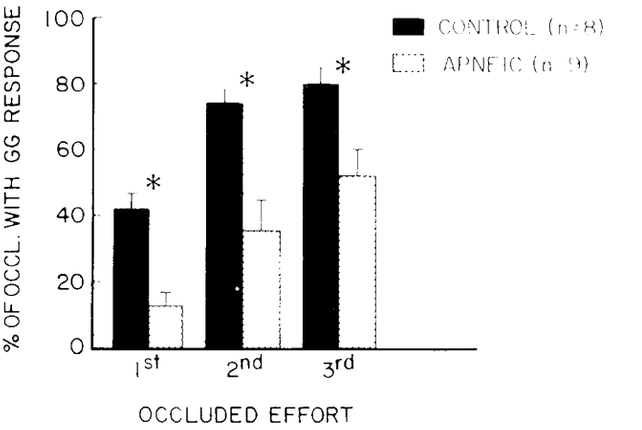

Fig. 3. Comparison of the percent of occlusions associated with a GG EMG on the first, second, and third occluded effort. There was a significant difference between the response of control and apneic infants (*$p < 0.001$).

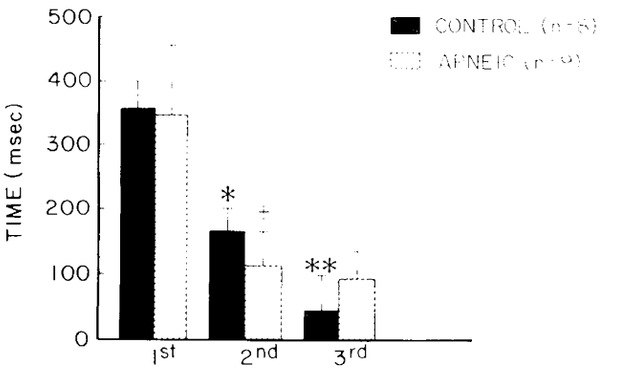

Fig. 4. Comparison of the time delay between onset of esophageal pressure deflection and onset of GG EMG for the first three occluded efforts exhibiting a GG EMG in the control and apneic infants. There was a significant decrease in this delay when the second effort was compared to the first effort (*$p < 0.001$, +$p < 0.01$) in both groups of infants and when the third effort was compared to the second (**$p < 0.05$) in the control group.

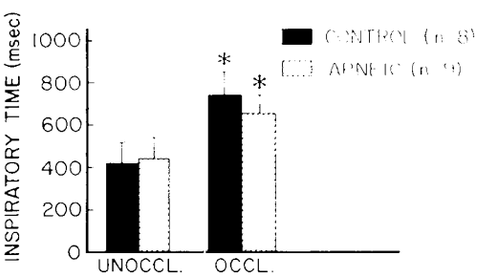

Fig. 5. Comparison of the inspiratory time between the first occluded inspiratory effort and the last unoccluded breath for the control and apneic infants (*$p < 0.05$). The prolongation of inspiratory time did not differ between control and apneic infants.

activity occurring with inspiration has been recorded from the GG, using intramuscular electrodes in adults with and without sleep apnea syndrome (1, 6, 11) although there is a paucity of data reporting the overall incidence of phasic GG activity during normal tidal breathing. Furthermore, it has been documented that sustained inspiratory activity of the GG during unobstructed breathing does not always occur in animals, children, or micrognathic or preterm infants (2, 5, 12–14). The activity of the GG is augmented, however, during hypercarbia, hypoxia, and end-expiratory airway occlusion (5–7, 13, 14). Our data in premature infants indicate that GG activity may be absent during unobstructed breathing but can be clearly elicited during occlusion.

We have shown that infants with apnea have less augmentation of their GG EMG during occlusion than nonapneic controls. Previous data suggest that lung inflation preferentially inhibits the activity of the upper airway muscles via a vagal reflex (Hering-Breuer) arising from pulmonary stretch receptors (15–17). Thus, the absence of lung inflation during end-expiratory occlusion may produce an increase in the activity of the upper airway muscles due to the release of this inhibition (2, 13, 17). Alteration in afferent activity from pressure or flow receptors in the upper airway may also contribute to augmentation of the GG during occlusion (18, 19). Esophageal pressure should reflect upper airway pressure provided the airway remains patent and this did not differ between the two groups of infants on the first occluded inspiratory effort. Therefore, it is unlikely that the decreased GG response in the apneic infants resulted from less negative pressure in the upper airway during occlusion.

The Hering-Breuer reflex is thought to contribute to the prolongation of the first inspiratory effort in response to airway occlusion in infants (20, 21). The intercostal phrenic reflex may also influence inspiratory time as chest wall distortion during inspiration may shorten inspiratory time (22), especially during occlusion. Therefore, in response to occlusion two opposing mechanoreceptor reflexes, the Hering-Breuer and the intercostal phrenic reflex, may be affecting inspiratory duration in premature infants. When the occlusions associated with shortening of inspiratory time were removed from the analysis, the two groups of infants still had comparable inspiratory prolongation. Thus, our data indicate that the strength of the Hering-Breuer reflex does not appear to differ between apneic and nonapneic infants. This is in contrast to the findings of Gerhardt and Bancalari (23) who observed significant differences in the prolongation of inspiration following occlusion in apneic *versus* nonapneic premature infants. Our study had 80% power to detect a difference of 30% or more in the percent prolongation of inspiratory time between the two groups with group sizes of nine and eight, at $p < 0.05$. The infants reported by Gerhardt and Bancalari (23) had a mean postnatal age of 8 days while our infants had a mean postnatal age of 3 and 4 wk for the control and apneic infants, respectively. This difference in postnatal age may have contributed to the contrasting findings between these two studies. Our data indicate that the decreased response of the GG during occlusion in the apneic infants cannot be explained by a difference in mechanoreceptor influence on the activity of the upper airway muscles.

We speculate that the decreased GG response during occlusion in the infants with apnea may result from an overall decrease in efferent output to the muscles of the upper airway. Gerhardt and Bancalari (24) demonstrated decreased CO_2 sensitivity in apneic infants when compared to controls at a mean gestation of 30 wk, and speculated that the infants with apnea had an abnormality in the central control of breathing. In addition, studies evaluating brainstem evoked potentials have also found prolonged brainstem conduction times in apneic infants suggestive of immature brainstem function (25). Contrary to adult and animal data, when the phasic GG EMG appeared during occlusion it did not precede the DIA EMG or the onset of the corresponding inspiratory effort (5–7). Both groups of infants, however, had an earlier appearance of the GG EMG with each subsequent firing of the GG during occlusion. It is possible that the sensitivity of the surface electrodes did not allow us to detect the true onset of EMG activity. However, the electrodes were placed directly over the origin of insertion of the GG, and this position was the optimal placement of recording EMG activity with needle electrodes as described by Sauerland and Harper (11). In addition, Doble *et al.* (18) reported good correlation between sublingual surface electrodes and intramuscular electrodes in adults. The use of surface electrodes, however, may have limited our ability to detect very low level phasic activity. It is likely that the upper airway muscles are inhibited during unobstructed breathing (13, 15, 16). The delay in activation of the GG during occlusion may be secondary to release of this inhibition or stimulation that occurs after the onset of the occluded inspiratory effort. The progressive decrease in this delay with each subsequent appearance of the GG EMG during occlusion is probably the effect of increased chemoreceptor and/or mechanoreceptor stimulation.

Although the two groups were of comparable postconceptional age, and the difference in the response to occlusion between the two groups was still present when the data were subjected to an analysis of variance with gestational age used as a covariate, the relative immaturity of the apneic infants at the time of birth may have still influenced our results. Seven of the nine infants in the apneic group were being treated with theophylline. Theophylline has been shown to be a central respiratory stimulant (26). Therefore this is unlikely to have contributed to the decreased GG response to occlusion in the apneic infants.

We conclude that the GG is usually not active during unobstructed breathing in premature infants. During end-expiratory airway occlusion, there appears to be release of the inhibitory control with resultant augmentation of the GG. However, premature infants with mixed and obstructive apnea have less augmentation of the GG during induced occlusion than control infants, possibly due to an overall decrease in central output to the muscles of the upper airway. Our findings suggest that infants with mixed or obstructive apnea are less apt to recruit their upper airway dilating muscles in response to spontaneous obstruction, thereby prolonging the airway obstruction and its consequences.

REFERENCES

1. Remmers JE, deGroot WJ, Sauerland EK, Anch AM 1978 Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 44:931–938
2. Roberts JL, Reed WR, Mathew OP, Thach BT 1986 Control of respiratory activity of the genioglossus muscle in micrognathic infants. J Appl Physiol 61:1523–1533
3. Milner AD, Boon AW, Saunders RA, Hopkin IE 1980 Upper airways obstruction and apnoea in preterm babies. Arch Dis Child 55:22–25
4. Mathew OP, Roberts JL, Thach BT 1982 Pharyngeal airway obstruction in preterm infants during mixed and obstructive apnea. J Pediatr 100:964–968
5. Haxhiu MA, van Lunteren E, Mitra J, Cherniack NS 1984 Responses to chemical stimulation of upper airway muscles and diaphragm in awake cats. J Appl Physiol 56:397–403
6. Onal E, Lopata M, O'Connor TD 1981 Diaphragmatic and genioglossal electromyogram responses to CO_2 rebreathing in humans. J Appl Physiol 50:1052–1055
7. Patrick GB, Strohl KP, Rubin SB, Altose MD 1982 Upper airway and diaphragm muscle responses to chemical stimulation and loading. J Appl Physiol 53:1133–1137
8. Doble EA, Leiter JC, Knuth SL, Daubenspeck JA, Bartlett D Jr 1985 A noninvasive intraoral electromyographic electrode for genioglossus muscle. J Appl Physiol 58:1378–1382
9. Evanich MJ, Lopata M, Lourenco RV 1978 Analytic methods for the study of electrical activity in respiratory nerves and muscles. Chest 70(suppl 1):158S–162S
10. Anderson JV Jr, Martin RJ, Lough MD, Martinez A 1982 An improved nasal mask pneumotachometer for measuring ventilation in neonates. J Appl Physiol 53:1307–1309
11. Sauerland EK, Harper RM 1976 The human tongue during sleep: electromyographic activity of the genioglossus muscle. Exp Neurol 51:160–170
12. Jeffries B, Brouillette RT, Hunt CE 1984 Electromyographic study of some accessory muscles of respiration in children with obstructive sleep apnea. Am Rev Respir Dis 129:696–702
13. Carlo WA, Miller MJ, Martin RJ 1985 Differential response of respiratory muscles to airway occlusion in infants. J Appl Physiol 59:847–852
14. Parisi RA, Neubauer JA, Frank MM, Edelman NH, Santiago TV 1987 Correlation between genioglossus and diaphragmatic responses to hypercapnia during sleep. Am Rev Respir Dis 135:378–382

15. van Lunteren E, Strohl KP, Parker DM, Bruce EN, Van de Graaff WB, Cherniack NS 1984 Phasic volume-related feedback on upper airway muscle activity. J Appl Physiol 56:730–736
16. Kuna ST 1986 Inhibition of inspiratory upper airway motoneuron activity by phasic volume feedback. J Appl Physiol 60:1373–1379
17. Brouillette RT, Thach BT 1980 Control of genioglossus muscle inspiratory activity. J Appl Physiol 49:801–808
18. Mathew OP, Abu-Osba YK, Thach BT 1982 Genioglossus muscle responses to upper airway pressure changes: afferent pathways. J Appl Physiol 52:445–450
19. Mathew OP, Abu-Osba YK, Thach BT 1982 Influence of upper airway pressure changes on genioglossus muscle respiratory activity. J Appl Physiol 52:438–444
20. Olinsky A, Bryan MH, Bryan AC 1974 Influence of lung inflation on respiratory control in neonates. J Appl Physiol 36:426–429
21. Thach BT, Frantz ID III, Adler SM, Taeusch HW Jr 1978 Maturation of reflexes influencing inspiratory duration in human infants. J Appl Physiol 45:203–211
22. Knill R, Bryan AC 1976 An intercostal-phrenic inhibitory reflex in human newborn infants. J Appl Physiol 40:352–356
23. Gerhardt T, Bancalari E 1984 Apnea of prematurity: II. Respiratory reflexes. Pediatrics 74:63–66
24. Gerhardt T, Bancalari E 1984 Apnea of prematurity: I. Lung function and regulation of breathing. Pediatrics 74:58–62
25. Henderson-Smart DJ, Pettigrew AG, Campbell DJ 1983 Clinical apnea and brainstem neural function in preterm infants. N Engl J Med 308:353–357
26. Eldridge FL, Millhorn DE, Waldrop TG, Kiley JP 1983 Mechanism of respiratory effects of methylxanthines. Respir Physiol 53:239–261