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Effects of Aminophylline on Respiratory Center and Reflex Activity in Premature Infants with Apnea

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Summary

Fourteen preterm infants with apnea (body weight, 1052 ± 44 g; gestational age, 30.2 ± 0.5 wks; and postnatal age, 9.9 ± 1.5 days) were studied in an effort to evaluate the effects of aminophylline on respiratory center output and respiratory reflex activity in the preterm infant with idiopathic apnea. This was done by using the airway occlusion technique. The infants were studied before and 48 h after aminophylline was begun as a treatment for apnea. Occlusion pressure, which reflects respiratory center output, was measured at 100 msec after occlusion started (P100) and at its maximum (Pmo). P100 increased from 2.4 ± 0.2 to 3.1 ± 0.2 cmH_2O ($P < 0.005$), and Pmo from 6.1 ± 0.7 to 8.8 ± 1.0 cmH_2O ($P < 0.001$) after aminophylline therapy was started.

The % prolongation of inspiratory time during the occluded breaths, when compared to the unoccluded breaths increased from 26.2 ± 10.6 to 55.8 ± 12.5% ($P < 0.01$). This reflects a significant increase in the strength of the Hering Breuer reflex. Effective elastance, a measure of respiratory load compensation, was significantly higher during aminophylline treatment. It increased from 1.09 ± 0.14 to 1.33 ± 0.14 cmH_2O/ml ($P < 0.02$).

Abbreviations

E'rs, effective elastase of the respiratory system
Pmo, maximal occlusion pressure
Ti, inspiratory time
Tiocc, inspiratory time of the occluded breath
VT, tidal volume before occlusion

Aminophylline is widely used for the treatment of idiopathic apnea of prematurity without a full understanding of its mode of action. In two previous studies (10, 11) we showed that premature infants with apnea had decreased alveolar ventilation and hypercapnea. This was in part secondary to a large deadspace ventilation and a decreased respiratory center sensitivity to CO_2. Aminophylline increased ventilation in these infants by lowering respiratory center threshold to CO_2, without affecting lung function.

The purpose of this study was to evaluate in preterm infants with apnea the effect of aminophylline on respiratory center output, reflex influence on inspiratory timing, and effective elastance of the respiratory system. This was done by using the airway occlusion technique described by Grunstein *et al.* (13) and Olinsky *et al.* (23). The advantage of this method over measuring changes in minute ventilation is its decreased dependence on the mechanical properties of the respiratory system (4, 13). In addition, the airway occlusion technique allows the evaluation of the reflex influence on inspiratory timing (32, 35) and the effective elastance of the respiratory system (23). The latter has been used as a measure of the stability of the system when exposed to respiratory loads (19, 21, 23).

MATERIALS AND METHODS

Fourteen premature infants with severe idiopathic apnea were studied within the first 3 wk of life. The means ± S.E. for birth weight and gestational age of the study infants were 1052 ± 44 g and 30.2 ± 0.5 wk, respectively. Their postnatal age at the time of the study was 9.9 ± 1.5 days. This group of infants was the same as described in a previous publication (10). Apnea was defined as a cessation of breathing for more than 20 sec or for less time if accompanied by bradycardia (heart rate<100/min). The apneic episodes were detected by continuous monitoring (KDC IM300-4R, KDC, Orange, CA) and recording (Brush 220 recorder, Gould Inc., Cleveland, OH) of heart rate and respiration for a minimum of 12 h. Known causes of apnea were ruled out and all infants were in stable clinical condition except for their apneic episodes. The number of apneic episodes ranged from 21 to 45 per 24 h with a mean ± S.E. of 29.7 ± 2.7.

As described previously (10) the infants were studied while breathing from a continuous flow of gas through a nosepiece. Tidal volume (VT) was measured with a pneumotachograph attached to the outflow portion of the system. The signal given by the continuous stream of gas passing through the pneumotachograph was zeroed electronically. Esophageal pressure was measured using a latex balloon or a saline-filled feeding tube, which was placed in the midthird of the esophagus.

Airway occlusion was performed at the end of an expiration using a manual valve (deadspace 1 ml) placed between the nosepiece and the gas flow from which the infants breathed. Airway pressure was measured directly at the nosepiece, using a Statham TC283 pressure transducer (Statham Instruments, Inc., Oxnard, CA) and a Gould transducer coupler (Gould Inc., Cleveland, OH). The pressure signal was recorded on a Brush 260 recorder (Gould Inc., Cleveland, OH) simultaneously with inspiratory and expiratory flow, VT, and esophageal pressure. Occlusions that did not occur at the end of an expiration were excluded. Each patient had 5–10 well timed occlusions which were maintained for only one respiratory cycle. Because newborns are obligatory nose breathers, the airway pressure during occlusion was well transmitted to the nasal airways and the nosepiece. This was confirmed by the equal change in airway and esophageal pressure during the occlusion.

The peak of the negative airway pressure recorded during the occluded breath was used to calculate the effective elastance of the respiratory system (E'rs) according to the formula:

$$E'rs = \frac{Pmo}{VT}$$

where Pmo is the lowest airway pressure during occlusion and VT is the tidal volume preceeding the occlusion (19, 23). Occlusion pressure was also measured at 100 msec after the airway was occluded (P100), as this may more accurately reflect the respira-

tory center's activity in case the occlusion elicits a voluntary response (4).

The inspiratory duration of the unoccluded breath (Ti) was measured from the inspiratory flow tracing preceeding the occluded breath. The inspiratory duration of the occluded breath (Tiocc) was calculated from the airway pressure tracing. This was done by taking the time when airway pressure becomes negative as the beginning, and the point when the pressure was lowest as the end of inspiration. The % prolongation of the inspiration during occlusion is considered to reflect the activity of the Hering Breuer Reflex (22, 23) and was calculated using the formula:

$$\frac{\text{Tiocc} - \text{Ti}}{\text{Ti}} \times 100$$

This formula differs from that used by other authors (22, 32), and was chosen because it describes % prolongation of inspiration as a linear function of Tiocc (9).

All tests were performed 45–60 min after feedings with 5–8 ml/kg of formula and while the infants were supine and asleep in their incubators. The infant's skin temperature was controlled at 36.5°C using the incubator's servocontrol mechanism. Airway occlusion was performed only during regular respiration and at least 5 min after any apneic episode.

After the first set of tests was completed the infants were treated with aminophylline 2 mg/kg intravenously every 6 h. The same tests were repeated after 48 h of treatment under identical conditions, and therefore each infant served as his own control.

The results are given as mean ± standard error (SE).

This study was approved by the Committee for the Protection of Human Subjects at the University of Miami. An informed consent was obtained from the parents of each infant studied.

RESULTS

Table 1 lists the individual values for P100 before and during aminophylline treatment. The increase in respiratory center activity during aminophylline administration is reflected by a 40% rise in P100, which increased from 2.4 ± 0.24 to 3.1 ± 0.24 cmH_2O.

The results of inspiratory time (Ti), inspiratory duration of the occluded breath (Tiocc), and % prolongation are given in Table 2. Whereas, the inspiratory time of the nonoccluded breath did not change significantly during aminophylline medication, the inspiratory time of the occluded breath did increase significantly. During treatment, the % prolongation of the occluded breath more than doubled as compared to the unoccluded inspiration.

Table 3 lists the individual values and the means for the maximal occlusion pressure (Pmo), the tidal volume preceeding the airway occlusion (VT), and the effective elastance of the respiratory system (E'rs). The maximal occlusion pressure increased significantly during aminophylline therapy. This change was similar in magnitude to the rise in P100. The increase in VT was also significant. As Pmo increased more than VT, E'rs was significantly higher during aminophylline treatment than before.

Table 1. *Occlusion pressure (cmH_2O) at 100 msec (P_{100})*

Pt. No.	Before	During aminophylline	% Change
1	1.9	3.0	58
2	4.0	3.1	−22
3	3.1	3.5	13
4	2.7	5.1	89
5	2.2	2.6	18
6	3.0	3.5	17
7	3.3	3.4	3
8	1.5	2.0	33
9	1.9	2.9	53
10	3.3	4.1	24
11	2.3	3.3	43
12	1.3	1.7	31
13	2.1	3.7	76
14	0.8	1.8	125
Mean ± S.E.	2.4 ± 0.24	3.1 ± 0.24	40 ± 11
$P <$		0.005	

Table 2. *Inspiratory time (Ti), inspiratory time of the occluded breath (Tiocc) and % prolongation before and during aminophylline treatment*

	Before aminophylline			During aminophylline		
	Ti (sec)	Tiocc (sec)	% Prolongation	Ti (sec)	Tiocc (sec)	% Prolongation
1	0.28	0.21	−25	0.31	0.50	61
2	0.40	0.36	−10	0.31	0.43	39
3	0.42	0.36	−14	0.54	0.47	−13
4	0.45	0.61	36	0.45	0.98	118
5	0.34	0.32	−6	0.27	0.28	4
6	0.35	0.40	14	0.30	0.34	13
7	0.31	0.48	55	0.32	0.57	78
8	0.35	0.27	−23	0.48	0.69	44
9	0.52	0.79	52	0.34	0.68	100
10	0.33	0.62	88	0.43	0.62	44
11	0.39	0.73	87	0.39	0.95	144
12	0.28	0.29	4	0.40	0.39	−3
13	0.36	0.54	50	0.27	0.51	89
14	0.39	0.61	56	0.51	0.83	63
Mean	0.37	0.47	26.2	0.38	0.59	55.8
±S.E.	±0.02	±0.05	±10.6	±0.02	±0.06	±12.5
$P <$				NS	0.02	0.01

Table 3. *Maximal occlusion pressure (P_{mo}), tidal volume before occlusion (VT) and effective elastance of the respiratory system (E'rs) before and during animophylline treatment*

	Before aminophylline			During aminophylline		
	P_{mo} (cmH_2O)	VT (ml)	E'rs (cmH_2O/ml)	P_{mo} (cmH_2O)	VT (ml)	E'rs (cmH_2O/ml)
1	3.2	4.8	0.65	7.4	4.8	1.53
2	6.1	5.5	1.10	6.1	5.5	1.10
3	7.3	8.1	0.89	10.3	9.0	1.14
4	8.1	6.0	1.34	10.3	9.9	1.04
5	5.1	3.8	1.32	4.3	3.6	1.19
6	6.0	5.6	1.06	5.3	5.8	0.91
7	7.9	6.9	1.15	10.1	7.3	1.38
8	2.9	5.2	0.56	6.9	7.2	0.98
9	8.4	6.8	1.22	9.7	6.6	1.47
10	8.5	5.7	1.50	12.9	6.4	2.02
11	10.9	4.4	2.49	15.4	5.7	2.68
12	3.4	5.3	0.63	4.4	5.7	0.77
13	5.1	5.0	1.02	13.9	7.9	1.76
14	3.2	5.1	0.62	6.5	9.2	0.70
Mean	6.1	5.6	1.09	8.8	6.8	1.33
±S.E.	±0.7	±0.3	±0.14	±1.0	±0.5	±0.14
$P <$				0.001	0.01	0.02

DISCUSSION

During aminophylline therapy this group of premature infants with apnea showed the following changes: (1) a significant increase in respiratory center output reflected by the rise in P100 and Pmo; (2) a significant increase in the strength of the Hering Breuer reflex indicated by the increase in % prolongation of the occluded inspiration; and (3) an increased capacity for load compensation as shown by a gain in effective elastance.

How each of these changes contribute to the decreased incidence of apnea in aminophylline-treated infants is not clear, but there are several possible mechanisms.

Apnea of prematurity seems to be related to an immaturity of the central respiratory control mechanisms. Histologically this immaturity is reflected by a lack of dendritic arborization and a decreased number of synaptic connections in the central nervous system (29). This can lead to a decreased number of afferent impulses, and a decreased state of excitation in the reticular formation and respiratory center (29). This view is supported by the observation that various stimuli can increase respiratory drive and reduce the incidence of apnea in preterm infants (16).

Functionally this immaturity is reflected by an abnormal ventilatory response to hypoxia, (5, 25) and a decreased sensitivity to CO_2 (8, 26). Infants with periodic breathing and apnea have evidence of central hypoventilation, hypercapnea, and a shift of the CO_2 response curve to the right (24). Likewise there is immaturity of some of the respiratory reflexes. The Hering Breuer inflation reflex is poorly developed in infants of 28–32 wk gestation and reaches its maximal strength around term (1, 9). This reflects a decrease in phasic vagal afferent impulses normally occuring with each breath and may deprive the preterm infant of the alternating excitation and inhibition, which contributes to the establishment and maintenance of regular breathing (29).

The effects of aminophylline on some of these abnormalities in control of breathing have been recently described. In the preterm infant, aminophylline increases minute ventilation and decreases arterial CO_2 tension (7, 11) with no significant effects on lung function (10). The CO_2 response curve is shifted to the left (11) whereas its slope may be increased (7). This increased activity of the respiratory center leads to a significant decrease in the number of apneic episodes (30, 34). All these effects of aminophylline have been well documented, but no work has been done to define the effects of this drug on respiratory reflexes in preterm infants with apnea.

Some investigators have suggested that neonatal apnea may be related to a deficiency of central neurotransmitters, especially catecholamines, which play an important role in the regulation of sleep state, perfusion of the brain, and regulation of breathing (15). The mechanism of action of aminophylline is most likely through the inhibition of phosphodiesterase and increased levels of cyclic AMP (12, 34). This cyclic nucleotide plays an important role in the action of a variety of neurotransmitter agents (27). Through this mechanism aminophylline potentiates the effects of catecholamines, which also increase cyclic AMP levels via stimulation of adenyl cyclase (12). The use of aminophylline in preterm infants with apnea may, therefore, compensate for the deficiencies in catecholamines found in these infants. (15)

The prolongation of inspiration during airway occlusion is believed to be secondary to the elimination of stretch receptor activity due to the absence of lung volume changes (13, 35). The prolongation of the occluded breath reflects therefore the phasic stretch receptor influence on inspiratory timing or the activity of the Hering Breuer reflex. (22, 32).

The increase in the strength of the Hering Breuer reflex in infants treated with aminophylline indicates that phasic vagal afferent impulses from the pulmonary stretch receptors increased. Likewise it may be expected that afferent impulses from the peripheral chemoreceptors and sensory skin receptors may also increase with aminophylline therapy. This increase in afferent traffic to the brainstem will contribute to the sustained tonic activity of the reticular formation, which is essential for stable rhythmic respiratory center output (29). It is not clear whether the increased afferent information is secondary to increased sensitivity of peripheral receptors or a facilitation of afferent signals or both.

In small premature infants, the airway occlusion may produce distortion of the chest wall, which may then terminate the inspiratory activity through the intercostal phrenic inhibitory reflex (18). This reflex, which occurs mainly during the first wk of life, can reduce the duration of inspiration during airway occlusion (32). This may explain the variability among results obtained in the smaller infants in this study.

The functional implication of a prolonged inspiration during airway occlusion is that the sustained contraction of inspiratory muscles results in a lower intrapleural pressure than during normal breathing (3). This helps maintain a normal VT in the face of transient mechanical loads (3, 21). A measure of this load compensatory activity is the effective elastance of the respiratory system (19, 21, 23), which increased during aminophylline therapy.

An increase in % prolongation or E'rs may be beneficial in overcoming airway obstruction, a possible cause of apnea of prematurity (31, 33). Although this may contribute to a decrease in the incidence of apnea, it is not the only mechanism of action of aminophylline. In fact there were some patients who did not show a change in reflex activity and still had a decrease in the incidence of apnea.

It has been reported that during REM sleep there is a tonic inhibition of the intercostal muscles that can impair respiratory load compensation (17); however, this finding has recently been questioned (6). Sleep state was not monitored in the present study because definition of sleep state is difficult in infants of less than 36 wk gestation and impossible in infants of less than 28 wk gestation (28). All of our infants were studied during periods of regular respiration with stable tidal volume and rate and this type of breathing is usually associated with quiet sleep (2, 14). It is therefore unlikely that the differences in sleep state were responsible for the changes seen during aminophylline therapy.

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