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Continuous distending airway pressure
Hering-Breuer reflex
inspiratory and expiratory duration
lung volume
vagal activity

Prolonged Expiratory Duration with Elevated Lung Volume in Newborn Infants

ANN R. STARK (17) AND IVAN D. FRANTZ, III

Department of Pediatrics, Harvard Medical School, Boston Hospital for Women and Children's Hospital Medical Center, Boston, Massachusetts, USA

Summary

End-expiratory lung volume increased 17.5 ± 5.4 ml (mean ± SD) in full term infants and 7.7 ± 2.1 ml in premature infants when 5–7 cm H_2O continuous negative pressure (CNEG) was applied around the thorax. In the full term infants, respiratory rate decreased from 52–43 min^{-1} ($P < 0.001$), mean inspiratory duration (t_i) was unchanged, and mean duration of expiration (t_e) increased from 0.62 ± 0.14 (SE)-0.84 ± 0.22 sec ($P < 0.001$) after application of CNEG. T_e of occluded efforts on CNEG was also prolonged ($P < 0.005$), although less than t_e of spontaneous breaths on CNEG ($P < 0.005$). T_e increased in four of eight premature infants when CNEG was applied. We conclude that phasic vagal feedback regulates T_i and t_e is controlled by tonic vagal activity.

Speculation

Premature infants may have an optimum functional residual capacity (FRC) which can be achieved with continuous distending pressure, resulting in regularization of respiration.

Clark and von Euler (3), studying the relationship between the depth of a breath and its duration in rebreathing studies on conscious men and anesthetized cats, found that the shortening of inspiration that occurs with increasing tidal volume (V_T) depends on intact vagal feedback. They further showed that the t_e depends on the preceding t_i, although the timing within each breath is independent of the preceding breath. The relationship of tidal volume and respiratory frequency in newborn infants subjected to inspiratory elastic loads and CO_2 breathing was examined by Taeusch *et al.* (11) and Thach *et al.* (12). The infants showed little decrease in inspiratory time or breath duration when tidal volume increased with CO_2 breathing; however, t_i increased when tidal volume was diminished by inspiratory loading. In these studies, tidal volume varied, presumably affecting phasic vagal activity, but FRC and, thus, tonic vagal activity, remained relatively constant.

Studies of the effect of elevated resting lung volume (FRC) on respiratory frequency have yielded conflicting results. In anesthetized cats, Grunstein *et al.* (7) showed that the relationship of V_T and t_i was independent of end-expiratory lung volume, although t_e, and, thus, total breath duration (t_{tot}), was affected by changes in FRC. Similarly, in paralyzed dogs on closed-chest cardiopulmonary bypass, Bartoli *et al.* (2) showed that an increase in lung volume produced an increase in duration of t_e, but had little effect on t_i, as measured from the phrenic electroneurogram. In contrast, D'Angelo and Agostoni (4) reported that increasing lung volume with continuous positive pressure breathing affected both the V_T-t_i relationship and t_e in anesthetized rabbits, cats, and dogs. In human, premature infants with hyaline membrane disease, increasing lung volume with continuous distending pressure produced a decrease in respiratory frequency (1), although this change was not seen in healthy premature infants (10). In neither study was the effect on t_i and t_e specifically examined. The purpose of the present study was to quantify the effects of static lung volume changes on respiratory rate and inspiratory and expiratory duration, both with and without the influence of phasic vagal activity, in a group of normal, full term and premature infants.

MATERIALS AND METHODS

Fifteen normal, full term infants (birth weight, 3.40 ± 0.35 kg, mean ± SD) and eight healthy, premature infants of 32–34 wk gestation (birth weight, 1.67 ± 0.21 kg) were studied during the first 2–4 days of life, with the exception of one premature infant studied on day 9. Informed consent for the study was obtained from the parents and pediatrician of each infant. Measurements were made while the infants were sleeping quietly in the supine position, enclosed below the neck in a negative pressure box. This box was a plastic enclosure with an inflatable latex neck seal and side portholes for access to the infant. Negative pressure was applied to the box by a vacuum cleaner motor attached by a three-way valve. In the premature infants, skin temperature was maintained at 36.5° with a servocontrolled radiant warmer.

All measurements were obtained for each infant before and after application of 5–7 cm H_2O CNEG to the box. Air flow was measured with a heated Fleisch pneumotachograph (no. 00) and Statham PM 15E pressure transducer while the infant breathed through a face mask, and flow was integrated electronically to give volume. Mask pressure was measured with a Hewlett-Packard 270 transducer. The dead space of the system was approximately 6 ml. All signals were recorded on a Beckman polygraph.

The measurements were made during quiet, regular breathing. The increment in lung volume that occurred with application of CNEG was measured from the integrated flow signal as the difference between the volume at end-expiration during control breathing and that at the increased volume. Usually the new resting lung volume was achieved within 2–3 breaths after CNEG was applied. Ten single breath occlusions of the airway were done at end-expiration in each infant before and after application of CNEG, allowing a 30–60 sec recovery period between occlusions. Tidal volume and breath duration were measured from breaths preceding each occlusion. T_i and t_{tot} were measured between points of zero flow. T_e was then obtained by subtraction. Percent t_e was calculated as $t_e/t_{tot} \times 100\%$. For the occluded breaths, t_i was measured on the pressure tracing from the start of the occlusion to the point of peak inspiratory effort, and t_e was measured from the end of t_i to the start of the next inspiratory effort. Results were tested for statistical significance using the paired *t* test.

RESULTS

FULL TERM INFANTS

When 5–7 cm H_2O negative pressure was applied around the thorax, end-expiratory lung volume increased 17.5 ± 5.4 ml (mean ± SD), a value consistent with reported compliance measurements. Tidal volume did not change significantly. Respiratory rate decreased from 52–43 min^{-1} ($P < 0.001$). Schematic representations of average breaths on and off CNEG are shown in Figure 1 and individual values are contained in Table 1. Mean t_i was unchanged after application of CNEG. Mean t_e increased from 0.62 ± 0.14 (SE)–0.84 ± 0.22 sec ($P < 0.001$). Percent t_e ($t_e/t_{tot} \times 100$) also increased in 14 of the 15 infants. The effect of CNEG on breath duration was immediate, and there was no change in the effect during the approximately 20 min period of CNEG. Timing immediately returned to control values when CNEG was discontinued (Fig. 2). End-expiratory occlusion of the airway resulted in significant prolongation of the inspiratory effort, as has been described previously (9, 11). The occluded t_i was similar before and after application of CNEG. Occlusion did not affect expiratory duration. T_e of occluded efforts on CNEG was shorter than t_e of spontaneous breaths on CNEG ($P < 0.005$), but still longer than t_e of spontaneous breaths off CNEG ($P < 0.005$).

PREMATURE INFANTS

Resting lung volume increased 7.7 ± 2.1 ml when CNEG was applied to the premature infants, also consistent with reported compliance values. As in the full term infants, tidal volume was not affected. The effects on timing were less consistent in the premature than in the full term group (Table 2). Mean respiratory rate, 58 min^{-1}, was not changed. Inspiratory duration was affected little in six of the eight infants. In four of the infants, t_e increased when CNEG was applied, while it was essentially unchanged in the other four infants. The effect on t_e was not associated with the magnitude of lung volume increase, nor with the initial respiratory rate. Airway occlusion in the premature infants resulted in prolongation of t_i, both on and off CNEG. As in full term infants, t_e was not affected by occlusion.

DISCUSSION

We have shown in newborn infants that an increase in resting lung volume of nearly 20% of estimated FRC, or approximately equivalent to tidal volume, results in significant prolongation of t_e, with little effect on t_i or V_T. Elimination of phasic lung volume change by airway occlusion results in lengthening of t_i, as previously shown (9, 11), but this effect is not influenced by static lung volume changes. Our findings support the hypothesis that t_e is influenced by changes in FRC, while t_i is affected by phasic lung volume changes. We conclude from our data that phasic lung

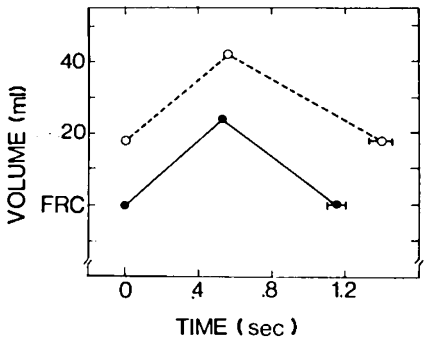

Fig. 1. Representation of breaths off (*solid line*) and on (*broken line*) CNEG. The confidence limits indicated are ± 1 SE. Note that while CNEG increases FRC an amount almost equivalent to tidal volume, t_i is not shortened. There is however, a prolongation of t_e on CNEG.

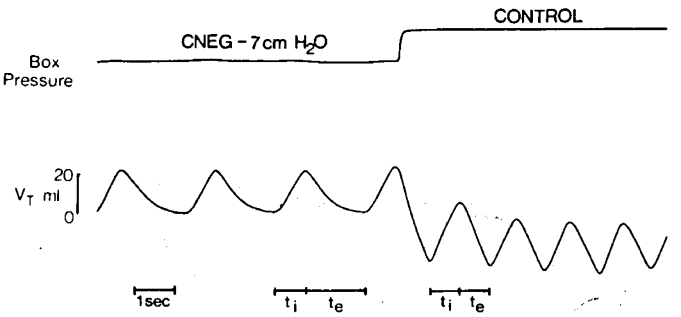

Fig. 2. Sample tracing from an infant as box pressure is changed from −7 cm H_2O to atmospheric. Note the change in end-expiratory lung volume and shortening of t_e which occur simultaneously with the change in box pressure.

Table 1. *Effect of CNEG and occlusion on respiratory timing in full term infants*

	Inspiratory time (sec × 10^{-2})				Expiratory time (sec × 10^{-2})				Percent t_e	
Infants	Control	CNEG	Control occluded	CNEG occluded	Control	CNEG	Control occluded	CNEG occluded	Control	CNEG
1	38	45	53	75	51	83	54	70	57	65
2	44	47	117	75	52	63	55	49	51	57
3	43	35	81	54	58	59	39	45	57	63
4	64	66	120	126	54	73	62	65	46	53
5	64	57	80	68	66	96	56	60	51	63
6	48	48	62	63	54	61	51	58	53	56
7	60	56	109	103	81	84	57	82	57	60
8	53	52	70	68	60	71	51		53	58
9	63	59	96	96	80	99	47	70	56	63
10	55	55	115	113	51	67	65	60	48	55
11	56	57	84	77	54	114	68	81	49	67
12	68	76	58	84	92	111	70	103	58	59
13	46	45	49	72	51	62	56	69	53	58
14	56	78	63	88	78	130	77	105	58	63
15	44	58	47	73	50	74	57	75	53	56
Mean ± SE	54 ± 2	56 ± 3	80 ± 5	82 ± 5	62 ± 4	84 ± 6	58 ± 2	71 ± 5	53 ± 1	60 ± 1

Table 2. *Effect of CNEG and occlusion on respiratory timing in premature infants*

	Inspiratory time (sec × 10^{-2})				Expiratory time (sec × 10^{-2})				Percent t_e	
Infants	Control	CNEG	Control occluded	CNEG occluded	Control	CNEG	Control occluded	CNEG occluded	Control	CNEG
16	65	62	54	51	77	98	79	83	54	61
17	33	29	82	60	35	38	46	39	51	57
18	46	40	55	68	55	52	74	58	54	57
19	54	50	61	69	83	81	81	104	61	62
20	42	43	73	66	49	52	66	74	54	55
21	46	61	77	83	59	80	56	75	56	57
22	43	47	64	70	51	58	69	55	54	55
23	38	30	33	24	59	65	41	30	61	68
Mean ± SE	45 ± 3	45 ± 4	62 ± 6	61 ± 6	59 ± 5	66 ± 7	64 ± 5	65 ± 9	56 ± 1	59 ± 2

feedback regulates t_i and that t_e is controlled by tonic vagal activity.

This condition is illustrated schematically in Figure 3. In Figure 3 (*left panel*) the *open circle* represents t_i in the absence of phasic vagal activity (*i.e.*, after airway occlusion at FRC). When the infant takes a normal breath, t_i is shortened (*closed circle*). When a new elevated FRC is achieved with CNEG, t_i in the absence of phasic vagal activity (*open triangle*) is unchanged from that at the control lung volume. When a breath is taken (*closed triangle*) t_i is shortened to the same extent as before CNEG was applied. The difference in t_i before and after occlusion (*open vs. closed* symbols) represents the effect of phasic vagal activity on t_i. On the other hand, changing FRC by an amount approximately equal to tidal volume has no effect on t_i, indicating an absence of influence on tonic vagal effect on t_i.

Figure 3 (*right panel*) is a similar representation for t_e. In this case, phasic vagal activity has little effect; that is, there is little change in t_e from the occluded to the unoccluded state. However, increasing tonic activity by increasing lung volume (moving from circles to triangles) results in a prolongation of t_e. The occluded t_e on CNEG, although prolonged, is significantly shorter than unoccluded t_e on CNEG. This may be secondary to blood gas changes occurring during occlusion. Evidence to support this comes from the studies of Frantz and Milic-Emili (5) and Younes *et al.* (14) who have observed that when airway occlusion at FRC is maintained for multiple inspiratory efforts, a progressive increase in pressure is generated. This pressure increase can be attributed to blood gas changes and is apparent by the second occluded effort, which occurs 1.5–2 sec after occlusion. Blood gas changes may likewise affect t_e to cause premature shortening.

The von Euler (3) concept of the respiratory control system states that t_i is decreased at increased lung volume, and that t_e is dependent on t_i. Our results appear to be in conflict with this concept. That t_i was not shortened by the application of CNEG can be explained in three ways. First, the increase in volume may have been insufficient to get the infant out of von Euler's range 1 (t_i independent of V_T) into a range where significant shortening of t_i would occur. Second, vagal stretch receptors may already be maximally stimulated at resting tidal volume so that a further increase in lung volume would evoke no additional response. Third, there may be a resetting of tonic vagal activity when FRC is increased, thus moving the entire V_T-t_i relationship upward. Rebreathing and elastic loading data (6, 9, 10) imply that either of the first two possibilities could be correct. That is, increasing tidal volume by 2–3 fold by CO_2 rebreathing did not, on the average, result in a decrease in t_i. Decreasing tidal volume with elastic loads did, however, cause prolongation of t_i, implying that infants are maximally stimulated at resting tidal volumes. Since t_i after occlusion in our study was the same before and after CNEG was applied, we conclude that the third possibility is correct. That is, increasing FRC as opposed to tidal volume, results in a resetting of tonic stretch receptors and shifts the V_T-t_i relationship upward.

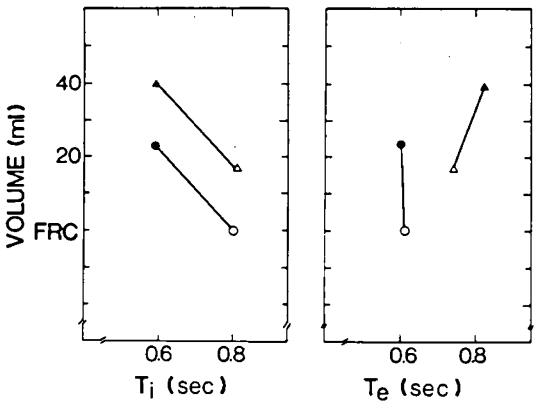

Fig. 3. Comparison of t_i and t_e on (*triangles*) and off (*circles*) CNEG with (*open symbols*) and without (*closed symbols*) airway occlusion. Note from the left panel that occlusion results in a marked prolongation of t_i, but that CNEG has little effect. In the right panel, note the minimal effect on t_e of occlusion, and the pronounced prolongation resulting from CNEG.

Furthermore, inasmuch as t_e was prolonged on CNEG while t_i was unaffected, it is apparent that t_e is not necessarily dependent on t_i. Tonic stretch receptor stimulation must act to prolong t_e independent of effects on t_i.

The variability seen in the results obtained in premature infants may be part of the inherent variability of respiration in these infants. Sleep state, not controlled in this study, may also be a factor. Another possibility is that there is an optimum FRC for appropriate respiratory timing in premature infants, and that these infants have lung volumes that vary in relationship to the optimum. Those infants who demonstrated a prolongation of t_e and a decrease in minute ventilation may have been brought to optimum FRC when CNEG was applied. Other infants who did not respond may have been at or near optimum FRC before CNEG was applied or may have been too far below it for the amount of CNEG administered to have been effective. Bartoli *et al.* (2) have shown in dogs that vagotomy can have variable effects on the lung volume-expiratory time relationship, depending on the FRC before vagotomy was done. They postulate that there is a neutral point for FRC and different results can be obtained if vagotomy is done at lung volumes on either side of the neutral point. This neutral point may be similar to the optimum FRC we have postulated for the preterm infants in our study.

Increasing FRC in preterm infants has been shown to decrease irregularity of respiration. FRC is lower in premature than term infants and has been shown to decrease over the 1st wk of life (13), a time when respiratory irregularity (apnea and periodic breathing) is at a maximum. Infants whose FRC is brought to optimum may have the most prominent decrease in apneic spells

when continuous distending pressure is used to regularize respiration.

We conclude from our studies that phasic vagal influence on inspiration in the neonate is at a maximum in the normal tidal volume range, and that increasing resting lung volume results in a resetting of tonic stretch receptors so that t_i does not change. T_e can be influenced by changes in tonic vagal activity in the absence of effects on t_i, indicating that t_i and t_e are not necessarily coupled. Infants may have an optimum FRC which can be achieved with continuous distending pressure, resulting in a decrease in minute ventilation and regularization of respiration.

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17. Requests for reprints should be addressed to: Dr. Ann R. Stark, Joint Program in Neonatology, 221 Longwood Avenue, Boston, MA 02115 (USA).

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