3. Bryce, D., Yeh, M., Funderburk, C., Todd, H., and Hertelendy, F.: Studies on growth hormone secretion. VII. Effects of somatostatin on plasma G. H., insulin, and glucagon in sheep. Diabetes, *24:* 842 (1975).
4. Cahill, G. F., Jr., Zottu, S., and Earle, A. S.: In vivo effects of glucagon on hepatic glycogen phosphorylase and glucose-6-phosphatase. Endocrinology, *60:* 265 (1957).
5. Char, V. C., and Creasy, R. K.: Lactate and pyruvate as fetal metabolic substrates. Pediat. Res., *10:* 231 (1976).
6. Cherrington, A. D., Chiasson, J. L., Liljenquist, J. E., Fennings, A. S., Keller, U., Lacy, W. W.: The role of insulin and glucagon in the regulation of basal glucose production in the postabsorptive dog. J. Clin. Invest., *58:* 1407 (1976).
7. Dobbs, R., Sakurai, H., Sasaki, H., Faloona, G., Valverde, I., Baetens, D., Orci, L., and Unger, R.: Glucagon: Role in the hyperglycemia of diabetes mellitus. Science, *187:* 544 (1975).
8. Exton, J. H.: Gluconeogenesis. Metabolism, *21:* 945 (1972).
9. Felig, P., Wahren, J., Sherwin, R., Hendler, R.: Insulin, glucagon and somatostatin in normal physiology and diabetes mellitus. Diabetes, *25:* 1091 (1976).
10. Fiser, R. H., Jr., Phelps, D. L., Williams, P. R., Sperling, M. A., Fisher, D. A. and Oh, W.: Insulin-glucagon substrate interrelationships in the neonatal sheep. Amer. J. Obstet Gynecol., *120:* 944 (1974).
11. Gerich, J. E., Lorenzi, M., Bier, D. M., Schneider, V., Tsalikian, E., Karam, J. H., and Forsham, P. H.: Prevention of human diabetic ketoacidosis by somatostatin. New Engl. J. Med., *292:* 985 (1975).
12. Gerich, J. E., Lorenzi, M., Hane, S., Gustafson, G., Guillemin, R., and Forsham, P. H.: Evidence for a physiologic role of pancreatic glucagon in human glucose homeostasis: Studies with somatostatin. Metabolism, *24:* 175 (1975).
13. Gerich, J. E., Lorenzi, M., Schneider, V., Forsham, P. H.: Effect of somatostatin on plasma glucose and insulin responses to glucagon and tolbutamide in man. J. Clin. Endocrinol. Metab., *39:* 1057 (1974).
14. Gerich, J. E., Lorenzi, M., Schneider, V., Karam, J. H., Rivier, J., Guillemin, R., and Forsham, P. H.: Effects of somatostatin on plasma glucose and glucagon levels in human diabetes mellitus. New Engl. J. Med., *291:* 544 (1974).
15. Gerich, J. E., Lorenzi, M., Schneider, V., Kwan, C. W., Karam, J. E., Guillemin, R., and Forsham, P. H.: Inhibition of pancreatic glucagon responses to arginine by somatostatin in normal man and in insulin-dependent diabetics. Diabetes, *23:* 876 (1974).
16. Girard, J. R., Cuendet, G. S., Marliss, E. B., Kervran, A., Rieutort, M. and Assan, R.: Fuels, hormones, and liver metabolism at term and during the early postnatal period in the rat. J. Clin. Invest., *52:* 3190 (1973).
17. Grajwer, L. A., Sperling, M. A., Sack, J. and Fisher, D. A.: Possible mechanisms and significance of the neonatal surge in glucagon secretion: Studies in newborn lambs. Pediat. Res., *11:* 833 (1977).
18. James, E. J., Rayen, J. R., Grasham, E. L., Makowski, H. L., Meschia, G., and Battaglia, F. C.: Fetal oxygen consumption, carbon dioxide production, and glucose uptake in a chronic sheep preparation. Pediatrics, *50:* 361 (1972).
19. Johnson, D. G., Ensinck, J. W., Koerker, D., Palmer, J., and Goodner, C. J.: Inhibition of glucagon and insulin secretion by somatostatin in the rat pancreas perfused in situ. Endocrinology, *96:* 370 (1975).
20. Koerker, D. J., Ruch, W., Chideckel, E., Palmer, J., Goodner, C. J., Ensinck, J., and Gale, C. C.: Somatostatin: Hypothalamic inhibitor of the endocrine pancreas. Science, *184:* 482 (1974).
21. McGarry, J. D., Wright, P. H., and Foster, D. W.: Hormonal control of ketogenesis. J. Clin. Invest., *55:* 1202 (1975).
22. Miller, L. L.: Some direct actions of insulin, glucagon and hydrocortisone on the isolated perfused rat liver. Recent Prog. Horm. Res., *17:* 539 (1961).
23. Morgan, C. R., and Lazarow, A.: Immunoassay of insulin: Two antibody system. Plasma insulin levels of normal, subdiabetic and diabetic rats. Diabetes, *12:* 115 (1963).
24. Parilla, R., Goodman, M. N., and Toews, C. J.: Effect of glucagon: Insulin ratios on hepatic metabolism. Diabetes, *23:* 725 (1974).
25. Samols, E., Marri, G., and Marks, V.: Promotion of insulin secretion by glucagon. Lancet, *ii:* 415 (1965).
26. Sherwin, R. S., Fisher, M., Hendler, R., and Felig, P: Hyperglucagonemia and blood glucose regulation in normal obese and diabetic subjects. New Engl. J. Med., *294:* 455 (1976).
27. Sperling, M. A., DeLamater, P. V., Fiser, R. H., Fisher, D. A. and Kazenelson, M.: Development and application of a radioimmunoassay for glucagon. Clin. Chem., *20:* 566 (1974).
28. Sperling, M. A., DeLamater, P. V., Phelps, D., Fiser, R. H., Oh, W. and Fisher, D. A.: Spontaneous and amino acid stimulated glucagon secretion in the immediate post-natal period; relation to glucose and insulin. J. Clin. Invest., *53:* 1159 (1974).
29. Tsoulos, N. G., Colwill, J. R., Battaglia, F. C., Makowski, E. L., and Meschia, G.: Comparison of glucose, fructose and O_2 uptakes by fetuses of fed and starved ewes. Amer. J. Physiol., *221:* 234 (1972).
30. Unger, R. H.: Alpha- and Beta-cell interrelationships in health and disease. Metabolism, *23:* 581 (1974).
31. Vale, W., Brazeau, P., Rivier, C., Brown, M., Boss, B., Rivier, J., Burgus, R., Ling, N., and Guillemin, R.: Somatostatin. Recent Prog. Horm. Res., *31:* 365 (1975).
32. Wahren, J., and Felig, P.: Influence of somatostatin on carbohydrate disposal and absorption in diabetes mellitus. Lancet, *ii:* 1213 (1976).
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Breathing
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Lack of Effects of Continuous Positive Airway Pressure on Vagal Control of Breathing in Term and Preterm Newborn Lambs

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Summary

The relationships between tidal volume (V_T), ventilation ($\dot{V}_E$), inspiratory duration (Ti), and total breath duration (T_{tot}) during hyperventilation induced by 4% CO_2 exposure were studied in five term and four preterm lambs to evaluate the effect of continuous positive airway pressure (CPAP) on control of breathing. At barometric pressure $\dot{V}_E$ was 308 ± 44 ml/kg and V_T was 41.5 ± 10.3 ml (mean ± SD) in term lambs; in preterm animals, $\dot{V}_E$ was 511 ± 133 ml/kg and V_T was 32.6 ± 0.6 ml. Application of CPAP (+5 cm H_2O) produced an increase in thoracic gas volume of 9.6 ± 3.4 ml/kg in term lambs and 9.6 ± 3.5 ml/kg in preterm lambs. $\dot{V}_E$, V_T, and the slope of the $\dot{V}_E$-V_T relationship were not significantly affected by CPAP. At baro-

metric pressure, all animals showed inverse curvilinear relationships between V_T and Ti and between V_T and T_{tot}. When CPAP was applied, Ti and the relationship of V_T to Ti did not change; the curvilinear relationship between V_T and T_{tot} was unchanged in shape, but was shifted to the right due to a significant increase in expiratory time (Te) in response to the increase in end expiratory lung volume. The increase in Te was 0.10 ± 0.05 sec in term lambs (mean ± SD, $P < 0.01$) and 0.11 ± 0.04 sec in preterm lambs ($P < 0.01$). Vagotomy abolished the curvilinear relationship between V_T and T_{tot} and decreased the slope of the $\dot{V}_E$-V_T relationship. The data indicate that vagal feedback control of breathing is similar in term and preterm lambs. The mechanism responsible for breath-to-breath regulation of Ti and T_{tot} is unchanged when CPAP is applied and is dependent on phasic lung volume changes above end expiratory volume.

Speculation

Recent studies in human infants have shown that application of continuous positive airway pressure results in the prolongation of inspiratory time and the slowing of respiratory rate implicating either a vagal response (20) or the generation of intercostal afferent impulses related to a stabilization of the rib cage (10). Although our data in lambs cannot be extrapolated to the human infant, our results suggest that the beneficial effect of continuous positive airway pressure on apnea of prematurity is probably independent of the vagal control mechanism, and that the reflex phenomenon is probably derived from the intercostal afferent impulses.

During the last few years there has been an increasing interest in the problem of apnea of prematurity (7, 24, 28). The etiology of this disorder is still unclear and different hypotheses have been proposed, including: neurologic immatuity (13), altered pattern of sleep state (11, 25), periodic breathing associated with relative hypoxia (22, 23), patent ductus arteriosus with pulmonary edema (16), mechanical characteristics of the chest lung system in the premature infant, and altered sensitivity of the pulmonary stretch receptors (2, 3, 15, 21). More recently, it has been shown that the frequency of apnea of prematurity is reduced when CPAP is applied (4, 14, 26). This clinical observation has been attributed to the improvement of oxygenation by increasing lung volume (27) and to the stabilization of the rib cage (10). It could also be theorized that CPAP modifies vagal control of breathing to account for the reduction of apneic spells. The purpose of this study was to determine whether or not the vagal control of breathing is affected when CPAP is applied. Term and preterm lambs were used as experimental subjects to evaluate the role of maturity in the control of breathing.

MATERIALS AND METHODS

Seven experiments were performed on five spontaneously delivered full term lambs ranging in weight from 4.8 kg–7.2 kg, within the first 5 days of life, and four studies were done on four preterm lambs delivered spontaneously at 125–130 days of gestation weighing between 2.3 and 3.4 kg. Premature delivery was achieved by fetal intramuscular injection of betamethasone to induce labor and fetal lung maturation (1, 5, 17–19). The preterm lambs were free of respiratory distress. The anesthetized full term lambs (chloralose, 25 mg/kg of body weight) and unanesthetized preterm lambs were intubated with an endotracheal cuffed tube of appropriate size and studied while breathing spontaneously. The spirogram was obtained following electronic integration of the instantaneous flow by a Fleisch pneumotachograph (no. 00) connected to the endotracheal tube. Both signals, instantaneous flow, and tracheal pressure were fed through two carrier preamplifiers (Hewlett-Packard). Arterial blood pressure was constantly monitored through one carotid artery with a Hewlett-Packard (Sanborn) 267 BC transducer. Arterial samples were obtained for blood gas determinations. Body temperatures were monitored using a rectal probe. All studies were performed with the animal lying in the side position.

Tidal volume, inspiratory duration, total breath duration, and ventilation were calculated during control periods and following hyperventilation induced by exposure to 4% CO_2 in atmospheric pressure. Similar measurements were obtained following 10 min application of CPAP (5 cm water). The tracings were those of a stable respiratory pattern corresponding to a new ventilatory steady state. The CPAP was given by a constant flow (12 liters/min) and monitored continuously with a water manometer adapted on the expiratory side of the circuit. The CO_2 was delivered with a blender to avoid any drop in CPAP at the moment of change. The tracings were recorded 20 sec before and continuously during the first 2 min following CO_2 administration, then for a period of five breaths every 30 sec over the next 3 min.

Bilateral vagotomy was performed in one term and four preterm lambs, and after a new steady state was reached the same study protocol was followed.

RESULTS

After the application of CPAP, a period of transient hypoventilation was observed, with compensation within 5 min. Ventilation was 308 ± 44 (mean ± SD) ml/kg during the control period in term lambs and 313 ± 53 ml/kg at the end of 5 min of CPAP application. The preterm lambs had a similar ventilatory response to CPAP: 511 ± 133 ml/kg vs. 547 ± 121 ml/kg, respectively. Tidal volume was not significantly affected by CPAP: 41.5 ± 10.3 ml vs. 42.3 ± 10.8 ml in term animals and 32.6 ± 0.6 ml vs. 32.9 ± 1.8 ml in preterms during control periods and at the end of 5 min of CPAP, respectively. The spirogram was constantly shifted upwards when CPAP was applied, showing an increase in thoracic gas volume (TGV). The average increase in TGV measured at the end of expiration was 9.6 ± 3.4 ml/kg and 9.6 ± 3.5 ml/kg for term and preterm lambs, respectively.

Figure 1 shows the correlation between $\dot{V}_E$ and V_T at barometric pressure, during the application of CPAP, and following bilateral vagotomy in a preterm lamb (P_3) during hyperventilation induced by exposure to 4% CO_2. A linear correlation between $\dot{V}_E$ and V_T was observed with and without CPAP, with no difference in the slopes obtained under the two experimental conditions. The individual values of the slope (a), the intercept (b), and the regression coefficient (r) for all study subjects are shown on Table 1. The correlation between $\dot{V}_E$ and V_T was always high ($r > 0.945$ for term lambs and $r > 0.854$ for preterm lambs). There was a slight reduction in the slope of the correlation in both term and preterm lambs following the application of CPAP, but the change was not statistically significant (a = 55.4 ± 10.7 during control and 49.1 ± 8.7 during CPAP in term lambs, and 72.1 ± 24 vs. 64.5 ± 15 in preterm lambs, respectively). When bilateral vagotomy was performed (Fig. 1), the linear correlation persisted but the slope of the linear regression was significantly less steep than in nonvagotomized lambs at the same experimental conditions (a = 24.2 ± 10 vs. 72.1 ± 24 for the preterm lambs, $P < 0.025$). Since only one term lamb was vagotomized, statistical analysis cannot be done, but the slope of the regression line is considerably less steep than the nonvagotomized value (23.0 vs. 59.7, respectively).

An inverse curvilinear relationship was observed when V_T was plotted against Ti during 4% CO_2 exposure in both term and preterm lambs, and no difference in the curvilinear slope was observed when CPAP was applied. A representative graph for a preterm lamb (*P1*) is shown in Figure 2.

When plotting V_T against T_{tot}, there was also a curvilinear inverse relationship. Figure 3 shows the representative graph from lamb *T4II*. This curvilinear relationship was similar between term and preterm lambs and was not significantly modi-

Table 1. *Slope (a), intercept (b), and regression coefficient (r) of correlation between ventilation and tidal volume in term and preterm lamb following application of continuous positive airway pressure (CPAP) and bilateral vagotomy during 4% CO_2*

			a			b			r		
			P_B[1]			P_B			P_B		
Animal no.	Birth wt, kg	Age at study, days	[2]	[3]	CPAP[2]	[2]	[3]	CPAP[2]	[2]	[3]	CPAP[2]
Term											
T1	5.2	2	32		31.9	265		−140	0.904		0.990
T2	5.4	4	66.4		55.6	−716		−95	0.992		0.945
T3I	5.2	2	59.3		48.9	619		−746	0.971		0.990
T3II	4.8	4	59.7	23.3	50.1	−1567	623	35	0.975	0.668	0.981
T4I	6.6	3	48.5		45.2	−334		−396	0.992		0.996
T4II	7.2	5	61.9		50.3	−817		958	0.997		0.996
T5	6	1	60.3		62.3	−401		−436	0.994		0.990
Mean ± SD	5.7		55.4		49.1	−674		−300			
	±0.8		±10.7		±8.7	±443		±360			
Preterm											
P1	3.4	1	40.9	22.7	51.2	−99	331	−616	0.924	0.779	0.983
P2	2.9	1	69	20.6	58.5	−459	211	−346	0.927	0.706	0.935
P3	2.3	1	68.8	39.8	57.3	1311	−553	−709	0.854	0.910	0.966
P4	3.3	1	110	14	91.7	−976	21	−489	0.894	0.482	0.881
Mean ± SD	2.9		72.1	24.2	64.5	−711	−173	−539			
	±0.5		±24	±10	±15	±537	±336	±156			

[1] Barometric pressure.
[2] Novagotomized lambs.
[3] Bilateral vagotomy.

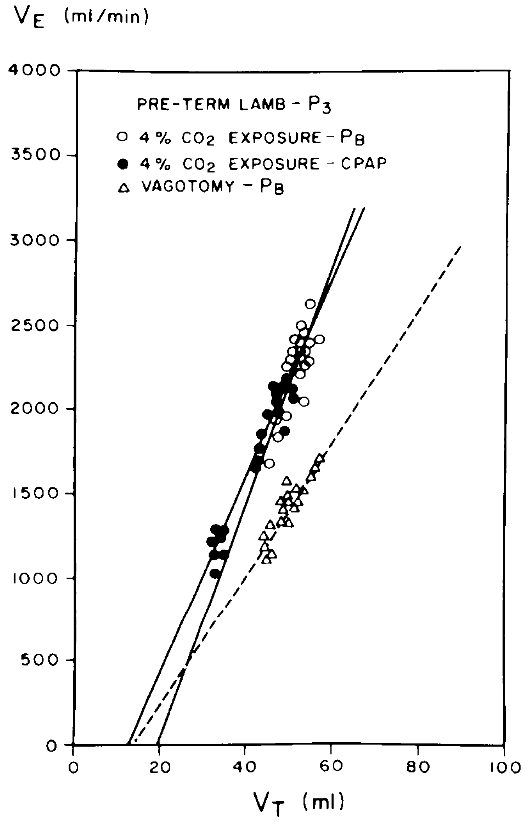

Fig. 1. Linear correlation between ventilation ($\dot{V}_E$, milliliters per min) and tidal volume (V_T, milliliters) in premature lamb *P3* during 4% CO_2 exposure in barometric pressure (○); continuous positive airway pressure (*CPAP*) (●), and after bilateral vagotomy in barometric pressure (P_B) (△). Each point is a mean value of five consecutive breaths.

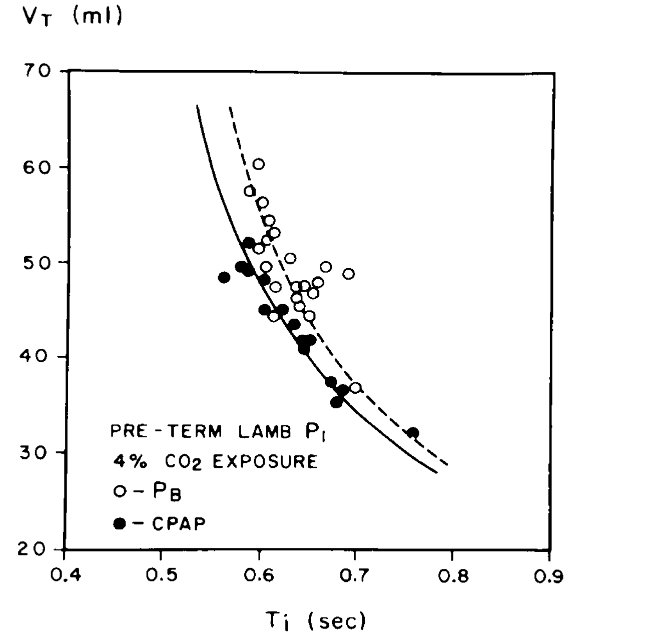

Fig. 2. Curvilinear relationship between V_T (milliliters) and Ti (seconds) in preterm lamb *P1* during 4% CO_2. Continuous positive airway pressure (*CPAP*) has no significant effect on the shape and on the position of the curve (Same symbols as in Figure 1). P_B: barometric pressure.

fied in its shape when CPAP was applied. However, there was a significant shift of this curve to the right when CPAP was applied.

These two curvilinear relationships (V_T-Ti and V_T-T_{tot}) represent the vagal feedback mechanism regulating breath to breath inspiratory duration and total breath duration. Bilateral vagotomy abolished these curvilinear relations when hyperventilation was induced. The frequency remained constant and the increase in $\dot{V}_E$ was mainly dependent on the increase in V_T (Fig. 1).

Table 2 shows that following CPAP in term lambs total breath duration was significantly elevated (mean increase = 0.10 ± 0.10 sec, ($P < 0.01$) in term lamb, by paired *t*-test) as a result of a longer expiratory duration, ΔTe = 0.10 ± 0.05. The inspiratory duration was not significantly affected. Preterm lambs had changes similar to those in term animals.

DISCUSSION

The linear relation between tidal volume and ventilation during hyperventilation as a result of CO_2 exposure is consistent with the results obtained by Hey *et al.* (12) in man. The slope of this $\dot{V}_E$-V_T relationship has the dimension of a frequency; it is independent of wide variation of alveolar CO_2 and pH but is influenced by body temperature (6, 29). In our experiments, body temperature did not change significantly to account for the decrease in slope seen in most animals (Table 1). The decrease in slope is related to an increase in T_{tot} with CPAP (Table 2) through a vagal influence regulating Te, dependent on TGV. The increase in T_{tot} seen after bilateral vagotomy is shown by the significant decrease in slope of the $\dot{V}_E$-V_T relationship, as shown in Figure 1.

The curvilinear relationship between V_T and Ti is similar to those described in man and in the adult cat by Clark and Von Euler (6). The similarity in the curvilinear relationship in term and preterm lambs suggests that the vagal feedback mechanism regulating Ti is well organized in lambs of different level of maturity during the first few days of life. The lack of effect of CPAP on the curvilinear relationship between V_T and Ti indicates that distending airway pressure does not alter the pulmonary stretch receptors' activity. This observation is consistent with a previous work of Grunstein *et al.* (8, 9) in cats following expiratory threshold loading. The pulmonary stretch receptors underwent an adaptation process to the increase in TGV and acted only in response to the phasic changes in lung volume above the end expiratory volume. The V_T-T_{tot} relationship is not affected in its shape for the same reason, and the vagal control of T_{tot} from breath to breath remains unchanged when CPAP is applied. The shift to the right of the V_T-T_{tot} relationship is accounted for by an increase in Te as a vagal effect of increase in absolute thoracic gas volume in response to CPAP (Table 2).

In conclusion, this study shows that in term and preterm lambs, CPAP (*1*) does not alter the vagal feedback mechanism regulating Ti related to phasic changes in lung volume, and (*2*) increases Te, probably through a vagal pathway dependent on absolute end expiratory lung volume. These findings cannot be extrapolated to the human infant, but the absence of an effect of CPAP on the vagal mechanism regulating Ti and T_{tot} from breath to breath suggests that the beneficial action of CPAP in apnea of prematurity is independent of this vagal control mechanism.

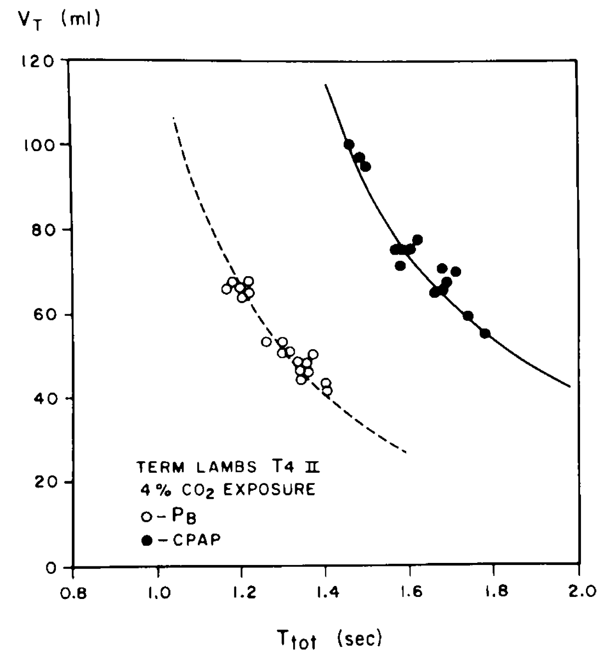

Fig. 3. Curvilinear relationship between V_T (milliliters) and T_{tot} (seconds) in term lamb *T4II* during 4% CO_2 exposure. When continuous positive airway pressure (*CPAP*) is applied the curve is shifted to the right but not modified in its shape. (Same symbols as in Figure 1). P_B: barometric pressure.

Table 2. *Mean increment in total breath (T_{tot}), inspiratory duration (Ti), and expiratory duration (Te) following application of continuous positive airway pressure (CPAP) in term and preterm lambs*

Animal no.	P_B,[1] sec T_{tot}	Ti	Te	CPAP, sec ΔT_{tot}	ΔTi	ΔTe
Term						
T2	1.26	0.56	0.70	0.03	−0.08	0.11
T31	1.71	0.58	1.13	0.00	−0.05	0.05
T3II	1.35	0.42	0.93	0.05	+0.01	0.04
T4I	1.45	0.57	0.88	0.27	+0.07	0.20
T4II	1.45	0.58	0.87	0.13	0.00	0.13
T5	1.17	0.51	0.66	0.08	−0.02	0.10
Mean ± SD				0.10 ± .10	−0.01 ± 0.05	0.10 ± 0.05
P value[2]				<0.01	NS	<0.01
Preterm						
P1	1.76	0.69	1.07	0.15	+0.03	0.12
P2	1.09	0.44	0.65	0.16	−0.01	0.17
P3	1.80	0.67	1.13	0.12	+0.02	0.10
P4	1.04	0.44	0.60	0.02	−0.03	0.05
Mean ± SD				0.11 ± 0.06	0.00 ± 0.02	0.11 ± 0.04
P value				<0.01	NS	<0.01

[1] Barometric pressure.

[2] All *P* values are calculated by paired *t*-test.

CONCLUSION

Vagal control of breathing with and without CPAP was studied in five term and four preterm lambs during hyperventilation induced by 4% CO_2 exposure. CPAP produced an increase in end- expiratory lung volume and a significant lengthening of expiration time (Te) in both term and preterm animals. Ventilation ($\dot{V}_E$), tidal volume (V_T), duration of inspiration (Ti), and $\dot{V}_E$-V_T and V_T-Ti relationships were not significantly affected by CPAP. Bilateral vagotomy abolished the curvilinear relationships between V_T and Ti and between V_T and T_{tot} and lowered the slope of the $\dot{V}_E$-V_T relationship. The vagal feedback mechanism regulating Ti appears well developed in term and preterm lambs during the first few days of life, and constant distending airway pressure (CPAP) does not appear to alter the vagal control of respiration.

REFERENCES AND NOTES

1. Avery, M. E.: Pharmacological approaches to the acceleration of fetal lung maturation. Brit. Med. Bull., *31:* 13, (1975).
2. Bödegard, G., Schwierler, G., Skoglund, S., and Zetterstrom, R.: Control of respiration in newborn babies. I. The development of the Hering-Breuer inflation reflex. Acta Paediat., *58:* 567, (1969).
3. Bödegard, G., and Schwieler, G. H.: Control of respiration in newborn babies: The development of the thoracic reflex response to an added respiratory load. Acta Paediat. Scand., *60:* 181, (1971).
4. Boros, J. S., and Reynolds, J. W.: Prolonged apnea of prematurity: Treatment with continuous airway distending pressure delivered by nasopharyngeal tube. Clin. Pediat., *15:* 123, (1976).
5. Challis, J. R. G., and Thorburn, G. D.: Prenatal endocrine function and the initiation of parturition. Brit. Med. Bull., *31:* 57 (1975).
6. Clark, F. J., and Von Euler, C.: On the regulation of depth and rate of breathing. J. Physiol., *222:* 267 (1972).
7. Dubrow, I. W., Chen, J. W., and Kong, P. W. K.: Bradycardia preceding apneic attacks in low-birthweight infants. Clin. Pediat. *15:* 119 (1976).
8. Grünstein, M. M., Wyszogroski, I., and Milic-Emili, J.: Regulation of frequency and depth of breathing during expiratory threshold loading in cats. J. Appl. Physiol., *38:* 869 (1975).
9. Grünstein, M. M., Younes, M., and Milic-Emili, J.: Control of tidal volume and respiratory frequency in anesthetized cats. J. Appl. Physiol., *35:* 463 (1973).
10. Hagan, R., Bryan, A. C., Bryan, M. H., and Gulston, G.: The effects of stabilization of the rib cage on respiration in preterm infants. [Abstr.] Pediat. Res., *10:* 461 (1976).
11. Hathorn, M. K. S.: Analysis of the rhythm of infantile breathing. Brit. Med. Bull., *31:* 8 (1975).
12. Hey, E. N., Lloyd, B. B., Cunningham, D. J. C., Jukes, M. G. M., and Bolton, D. P. G.: Effects of various respiratory stimuli on the depth and frequency of breathing in man. Resp. Physiol., *1:* 193 (1966).
13. Kattwinkel, J., Mars, H., Fanaroff, A. A., and Klaus, M. H.: Urinary biogenic amines in idiopathic apnea of prematurity. J. Pediat. *88:* 1003 (1976).
14. Kattwinkel, J., Nearman, H., Fanaroff, A. A., Katona, P. G., and Klaus, M.: Apnea of prematurity: Comparative therapeutic effects of cutaneous stimulation and nasal continuous positive ariway pressure. J. Pediat., *86:* 588 (1975).
15. Kirkpatrick, S. M. L., Olinsky, A., Bryan, M. H., and Bryan, A. C.: Effect of premature delivery on the maturation of the Hering Breuer inspiratory inhibitory reflex in human infants. J. Pediat., *88:* 1010 (1976).
16. Kitterman, J. A., Edmunds, L. H., Jr., Gregory, G. A., Heyman, M. A., Tooley, W. H., and Rudolph, A. M.: Patent ductus arteriosus in premature infants: Incidence, relation to pulmonary disease, and management. N. Engl. J. Med., *287:* 473 (1972).
17. Liggins, G. C.: Premature delivery of fetal lambs infused with glucocorticoids. J. Endocrinol. Metab., *45:* 515 (1969).
18. Liggins, G. C.: Parturition in the sheep and the human. Basic Life Sci., *4 PT_B:* 423 (1974).
19. Liggins, G. C., Fairclough, R. J., Grieves, S. A., Kendall, J. Z., and Knox, B. S.: The mechanism of initiation of parturition in the ewe. Recent Prog. Horm. Res., *29:* 111 (1973).
20. Martin, R. J., Nearman, H., Katona, P., and Klaus, M.: A deflation Hering-Breuer reflex in the pre-term infant – A mechanism by which a low continuous positive airway pressure (CPAP) decreases apnea? [Abstr.] Pediat. Res., *10:* 428 (1976).
21. Olinsky, A., Bryan, M. H., and Bryan, A. C.: Influence of lung inflation on respiratory control in neonates. J. Appl. Physiol., *36:* 426 (1974).
22. Rigatto, H., and Brady, J. P.: Periodic breathing and apnea in preterm infants: Evidence of hypoventilation possibly due to central respiratory depression. Pediatrics, *50:* 202 (1972).
23. Rigatto, H., and Brady, J. P.: Periodic breathing and apnea in preterm infants: Hypoxia as a primary event. Pediatrics, *50:* 219 (1972).
24. Shannon, D. C., Gotay, F., Stein, I. M., Rogers, M. C., Todres, I. D., and Moylan, F. M. B.: Prevention of apnea and bradycardia in low-birthweight infants. Pediatrics, *55:* 589 (1975).
25. Shannon, D. C., Marsland, D. W., Gould J. B., Callaghan, B., Todres, I. D., and Dennis, J.: Central hypoventilation during quiet sleep in two infants. Pediatrics, *57:* 342 (1976).
26. Speidel, B. D., and Dunn, P. M.: Effect of continuous positive airway pressure on breathing pattern of infants with respiratory distress syndrome. Lancet, *7901:* 302 (1975).
27. Stark, A. R., Brown, E. R., and Frantz, I. D.: The adequacy of respiratory compensation to increase lung volume in the infant. [Abstr.] Pediat. Res., *10:* 461 (1976).
28. Vauy, R., Shapiro, D. L., Smith, B., and Warshaw, J.: Treatment of severe apnea in prematures with orally administered theophylline. Pediatrics, *55:* 594 (1975).
29. Von Euler, C., Herrero, F., and Wexler, I.: Control mechanism determining rate and depth of respiratory movements. Resp. Physiol., *10:* 93 (1970).

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