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Effects of Carotid Body Maturation and Terbutaline on the Laryngeal Chemoreflex in Newborn Lambs

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ABSTRACT. The response to laryngeal chemoreflex (LCR) water stimulation was compared in unanesthetized awake 4- to 10-day-old preterm and 2- to 4-wk-old term lambs before and after infusion of a β-adrenergic agonist, terbutaline, given pre- and postcarotid body denervation (CBD). Ventilation decreased more in response to LCR stimulation post-CBD in the older lambs. CBD did not change the respiratory response to LCR stimulation in the younger lambs. LCR stimulation resulted in less bradycardia post-CBD in both groups. Terbutaline significantly attenuated the LCR response in the older lambs pre-CBD but not post-CBD. LCR respiratory response was not changed in the younger lambs when terbutaline was infused, pre- or post-CBD. Compared to wakefulness, the LCR response in preterm lambs was greater in sleep not associated with arousal. If arousal occurred, LCR response during sleep did not differ from that during wakefulness. The incidence of arousal decreased markedly after CBD, suggesting that arousal is modified by the carotid bodies. It is concluded that the carotid bodies modify the reflex response to LCR stimulation in 2- to 4-wk-old lambs. During the 1st postnatal wk, preterm lambs have a reduced carotid body function during wakefulness and, therefore, a decreased hypoxic ventilatory response and increased respiratory response to LCR stimulation. The attenuating effect of terbutaline on LCR response is partially related to mature carotid body function. (*Pediatr Res* 20: 724–729, 1986)

Abbreviations

CBD, carotid body denervation
LCR, laryngeal chemoreflex

Reflex apnea from stimulation of the LCR has previously been described in several animal species (1–3) and in human infants (4). The reflex is thought to be a protective mechanism through which animals and humans can preserve vital functions while they are not breathing. Laryngeal water stimulation elicits apnea, swallowing, hypertension, bradycardia, and blood flow redistribution in the "diving seal" pattern (2, 5). The respiratory response is associated with a decrease in arterial oxygen tension which should stimulate arterial chemoreceptors. In a previous study (2), we demonstrated a decrease in the cardiovascular response to LCR stimulation during hyperoxia and proposed that part of the cardiovascular response to laryngeal water administration in newborn lambs might be due to stimulation of arterial chemoreceptors. Postnatal age appears to be an important factor in the LCR response. The respiratory response to LCR stimulation is markedly diminished in the adult animal compared to the newborn of the same species (3). A postnatal maturation effect has been demonstrated on the carotid body mediated hypoxic ventilatory response during the first 10 days after birth in newborn lambs (6, 7). We, therefore, hypothesized that the age-dependent magnitude of the LCR response is due to carotid body maturation.

We have previously described an attenuating effect from terbutaline, a β adrenergic agonist, on the apnea reflex response in term lambs (5). This effect was age dependent, since terbutaline was more effective in lambs older than 9 days. The stimulating effect of β-adrenergic agonists on ventilation is mediated by the carotid bodies (8–10). We, therefore, postulated that the terbutaline effect on the LCR response also is mediated by the carotid bodies and that their postnatal maturation is required for a full effect.

This study was performed in order to: 1) study the modifying role of the carotid bodies on the LCR response; 2) examine if the carotid bodies mediate the terbutaline effect on the LCR response; 3) evaluate possible maturational effects on the LCR response.

In order to study the maturational effect, we compared a group of 4- to 10-day-old preterm lambs (in the following referred to as the younger lambs) with a group of 2- to 4-wk-old term lambs (later referred to as the older lambs). The younger lambs were first studied at a postnatal age of 4 to 5 days, when the carotid bodies in lambs are said not to be mature, and when their postnatal oxygen sensitivity has yet to be adjusted (6, 7). The older lambs were studied at a postnatal age of 2 wk when the carotid bodies are said to be mature and the postnatal reset of oxygen sensitivity has occurred (11). Although a gestational age effect cannot be excluded, we consider that the difference in results between the two groups of lambs is mainly due to a difference in postnatal age.

MATERIALS AND METHODS

Healthy, normally grown lambs of Dorset or Suffolk mixed breed were used. All lambs were chronically instrumented with tracheostomy and arterial and venous catheters. The tracheostomy was plugged, allowing the lambs to breathe through the nose except for the time of the study according to a previously described method (2). Electrodes for electrooculogram and EEG were implanted (12) and the lambs were allowed to recover for 48 h before they were studied.

Two groups of lambs were used. A group of seven term lambs were instrumented on the 10th–12th day after birth and were

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studied between the 14th–28th day after birth. A second group of six premature lambs were born at 135 days of gestation following 3 days of maternal steroid therapy (13) to induce premature parturition. The prematurely born lambs were instrumented on the 2nd day after birth. They were first studied on the 4th–5th postnatal day and again after CBD, on the 8th–10th postnatal day. During the studies, ventilation was monitored by using a Fleisch pneumotachograph connected to a respiratory integrator (2). A Baby Bird respirator was used to supply humidity and a continuous positive airway pressure (+2 to +3 cm H_2O) to compensate for a reduced upper airway tone due to the tracheostomy. A biluminal balloon catheter (Fr. 8 Foley) was directed upward in the tracheostomy with the tip placed below the larynx, and the balloon was inflated. Thus, water could be flushed retrograde through the larynx without compromising normal ventilation. The status of the lambs was monitored during the experimental period with frequent blood gas analysis. They were only studied if their rectal temperature was normal (39.3 ± 0.2° C) and the ambient temperature was 24 to 25° C. Blood sugar ranged 90–175 mg/100 ml during the studies. The lambs were studied unanesthetized standing upright in a sling (Alice King Chatham, Medical Arts, Los Angeles, CA), which restricted the movements but allowed them to fall asleep. The term lambs weight ranged from 5.7 to 9.7 kg, and the premature lambs weight ranged from 4.0 to 7.9 kg.

Experimental protocol. The response to laryngeal water stimulation was tested in a standardized manner with distilled water at body temperature. Each LCR test consisted of a baseline period of 30 s followed by retrograde injection of 1 ml of water into the larynx during a 5-s period. A series of four stimulations were made in each activity state.

LCR response was tested with laryngeal water stimulation during a 1- to 3-h period before terbutaline was given. Terbutaline was given as an infusion of 2 to 4 μg/kg/min over a 1- to 2-h period. The infusion rate was adjusted in order to maintain heart rate, at a level 50 to 60 beats per minute higher than baseline throughout the terbutaline study. The mean total dose of terbutaline was 216 ± 39 μg/kg (range 166–264 μg/kg) in the term lambs and 208 ± 35 μg/kg (range 165–260 μg/kg) in the premature lambs. CBD was performed in five term lambs and five premature lambs. Two term lambs and one preterm lamb were sham-operated. CBD included bilateral cutting of the sinus nerve and stripping of the vascular walls down to the layer of adventitia at the junctions of the carotid, lingual, and occipital arteries.

The efficacy of CBD was confirmed by the absence of a change in respiratory rate and tidal volume after an injection of 0.1 mg/kg potassium cyanide into the brachiocephalic trunk, as well as a 15-min period of hypoxia (F_{IO_2} = 0.13). The activity states of the lambs were continuously recorded throughout the studies, determined by direct observation as well as by electrooculogram and EEG criteria as previously described by Marchal *et al.* (12). All studies in the term lamb group were done in an awake state, while the preterm lambs were studied awake and during quiet and rapid eye movement sleep. During sleep, occurrence of arousal resulting from LCR stimulation was recognized as definite change in behavior of the lamb: eye opening and gross motor movements or standing up usually associated with a forced inspiration.

Interpretation of response and data analysis. LCR response was expressed as percent change from baseline values for ventilation, heart rate, and blood pressure. The effect of LCR stimulation on respiration was assessed in two ways: 1) respiratory response (percent change in ventilation volume) was measured with the pneumotachograph as the volume of gas inspired during the 30-s period after onset of LCR stimulation compared to the 30-s baseline period immediately preceeding stimulation. 2) Post-stimulus apnea following LCR stimulation (recovery time) was defined as the time in seconds elapsed from the onset of stimulation to the onset of regular breathing for 10 consecutive s. If the lambs were still not breathing 100 s after onset of stimulation, their lungs were mechanically inflated five times by the respirator every 20 s until regular breathing was resumed. Blood pressure and heart rate were measured 20 s after the onset of laryngeal stimulation. All data were expressed as means ± SEM. Data analysis was performed using the INDAS statistical package (S & H Computer Systems, Nashville, TN). Unpaired two-tailed *t* tests were used on group means of measured data values. Kruskal-Wallis nonparametric one-way analysis of variance and the Wilcoxon-Mann–Whitney two sample test were applied to those variables representing percent changes from baseline values. $p < 0.05$ was accepted as a significant difference.

RESULTS

Baseline variables. Table 1 presents the effects of CBD and terbutaline infusion on baseline ventilation, blood pressure, and heart rate measured immediately before LCR stimulation. A significant decrease in ventilation was seen after CBD in the older lambs. Arterial P_{AO_2} decreased and $PaCO_2$ increased after CBD. In the younger lambs ventilation decreased slightly but not significantly after CBD. Blood pressure, heart rate, and $PaCO_2$

Table 1. *Effect of CBD and terbutaline on baseline variables in five 4- to 10-day-old preterm lambs and five 14- to 28-day-old term lambs during wakefulness**

	4- to 10-day-old preterm lambs				14- to 28-day-old term lambs			
	Pre-CBD		Post-CBD		Pre-CBD		Post-CBD	
	Pre-T	Post-T	Pre-T	Post-T	Pre-T	Post-T	Pre-T	Post-T
$\dot{V}$	234 ± 16†	262 ± 13	204 ± 11	233 ± 16	176 ± 4‡	208 ± 9§	149 ± 5‖	155 ± 8
$\bar{X}$ BP	71 ± 1	73 ± 2	89 ± 1‖	86 ± 2§	86 ± 1	83 ± 1	93 ± 1	84 ± 1
HR	226 ± 3	286 ± 4§	261 ± 4‖	277 ± 4	219 ± 3	279 ± 4§	215 ± 3	264 ± 2§
pH¶	7.37 ± 0.2	7.22 ± 0.04§	7.29 ± 0.06	7.23 ± 0.005	7.40 ± 0.02	7.29 ± 0.04§	7.32 ± 0.03	7.30 ± 0.04
PaO_2	76 ± 5	88 ± 8	66 ± 3	83 ± 13	93 ± 9	95 ± 7	69 ± 6‖	92 ± 12
$PaCO_2$	40 ± 3	47 ± 4	57 ± 5‖	55 ± 4	40 ± 3	41 ± 7	58 ± 4‖	53 ± 6
$\Delta\dot{V}$ 1 min hypoxia	42 ± 8		−9.3 ± 10‖		92 ± 21**		0 ± 3‖	

* Pre-T, preterbutaline; post-T, postterbutaline; $\dot{V}$, ventilation ml/kg/30 s; $\bar{x}$ BP, mean blood pressure (torr); HR, heart rate (bpm); $\Delta\dot{V}$, % change in ventilation.

† Mean ± SEM, n = 40–50 measurements.

‡ Mean ± SEM, n = 89 before and 101 after CBD.

§ $p < 0.05$ for comparison before and after terbutaline.

‖ $p < 0.05$ before and after CBD.

** $p < 0.05$ for comparison preterm and term lambs.

¶ Hydrogen ion concentrations were used for statistics.

increased significantly post-CBD in the younger lambs. Before CBD, the ventilatory response to 1 min of hypoxia ($F_{IO_2} = 0.13$) was significantly greater in the older lambs than in the younger lambs (Table 1). After CBD the hypoxic ventilatory response was abolished in both groups of lambs.

When terbutaline was infused pre-CBD in the older lambs a significant increase in ventilation and heart rate was seen. After CBD, only the increase in heart rate was significant following terbutaline. The younger lambs showed an insignificant increase in ventilation after terbutaline both pre- and post-CBD, while the heart rate increased significantly only pre-CBD. After CBD, terbutaline resulted in a decreased blood pressure only in the younger lambs. Terbutaline infusion caused an increase in PaO_2 but this was not significant in either group of lambs. pH decreased significantly during terbutaline infusion in both the younger and the older lambs pre-CBD. Post-CBD, the decrease in pH was insignificant.

Respiratory response to LCR stimulation during wakefulness. Figure 1 shows that the respiratory response (percent decrease in ventilation volume) to LCR stimulation before CBD was significantly less in the older lambs compared to the younger lambs. A significantly increased respiratory response was seen after CBD in the older but not in the younger lambs. Terbutaline infusion given before CBD to the 4- to 5-day-old preterm lambs resulted in an insignificant decrease in the respiratory response to LCR stimulation, while a significantly decreased response was seen in the older lambs. Terbutaline given after CBD did not significantly alter the respiratory response to LCR stimulation in either group of lambs.

Recovery time during wakefulness. The average time elapsed after onset of LCR stimulation until onset of regular breathing is plotted in Figure 2. Pre-CBD, recovery time was similar in both groups of lambs. Recovery time was not altered by CBD in the younger lambs but was significantly prolonged in the older lambs post-CBD. Terbutaline resulted in a significantly shortened recovery time only in the older lambs, whether given before or after CBD.

Cardiovascular response to LCR stimulation during wakefulness. Blood pressure (hypertension) and heart rate (bradycardia) response to LCR stimulation was significantly reduced following CBD in the younger lambs (Table 2). In the older lambs, heart rate response decreased significantly following CBD, but blood pressure response did not change. Terbutaline did not change the cardiovascular response to LCR stimulation in either group, before or after CBD.

Response to LCR stimulation in sham-operated lambs. The respiratory response to LCR stimulation in the two sham-operated older lambs decreased from 45 ± 3 to 17 ± 4% when terbutaline was given before surgery. After the shamoperation, terbutaline still caused a decrease from 39 ± 3 to 22 ± 22%.

The sham-operated younger lamb did not respond to terbutaline before surgery (71 *versus* 75%), but terbutaline had an attenuating effect on the respiratory response after surgery (72 *versus* 40%).

Effect of CBD and terbutaline on respiratory response to LCR stimulation in the younger lambs during sleep. A sufficient

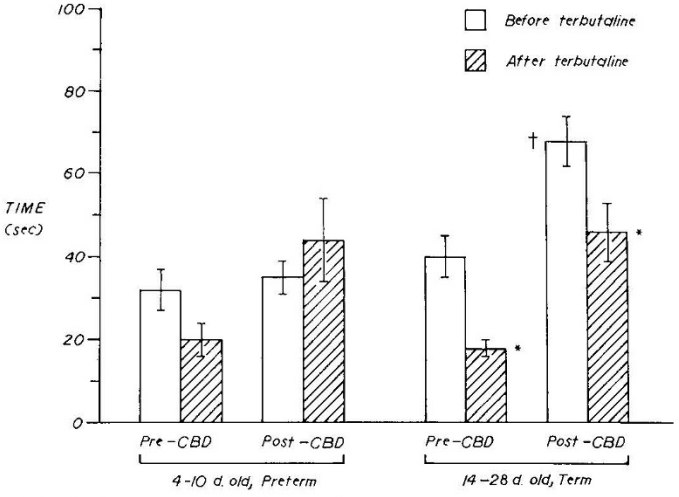

Fig. 2. Recovery time (time until regular breathing) following LCR stimulation during wakefulness in five 4- to 10-day-old preterm lambs and five 14- to 28-day-old term lambs performed before and after an intravenous terbutaline infusion given both pre- and post-CBD. Mean ± SE, n = 18–23 stimulations. * Indicates significant difference between recovery times obtained before and after terbutaline. † Indicates significant difference between recovery times obtained pre- and post-CBD.

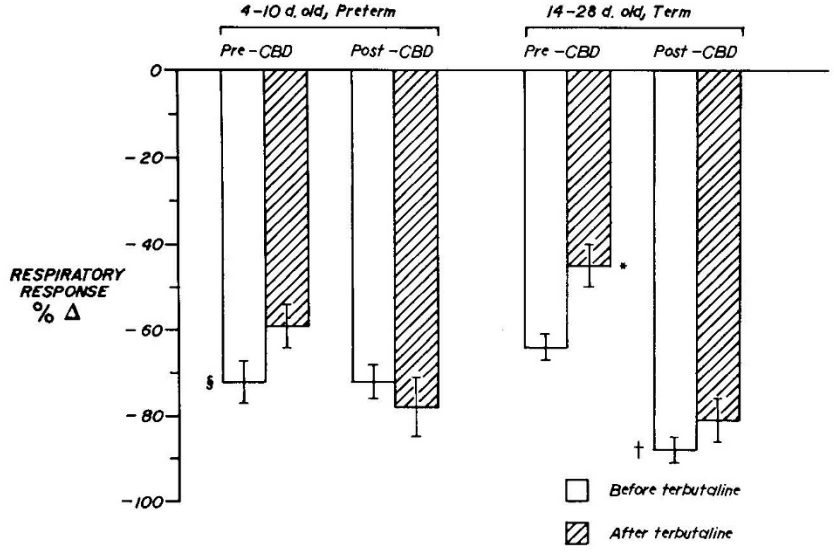

Fig. 1. Respiratory response (percent change in ventilation volume) to laryngeal chemoreflex stimulation during wakefulness in five 4- to 10-day-old preterm lambs and five 14- to 28-day-old term lambs performed before and after an intravenous terbutaline infusion given both pre- and post-CBD. Mean ± SE, n = 18–23 stimulations. * Indicates significant difference between responses obtained before and after terbutaline. † Indicates significant difference between responses obtained pre- and post-CBD. § Indicates significant difference between responses obtained in preterm and term lambs.

Table 2. *Effect of CBD and terbutaline on cardiovascular response to laryngeal stimulation in 4- to 10-day-old preterm lambs and 14- to 28-day-old term lambs during wakefulness expressed as percent change from baseline**

	4- to 10-day-old preterm lambs				14- to 28-day-old term lambs			
	Pre-CBD		Post-CBD		Pre-CBD		Post-CBD	
	Pre-T	Post-T	Pre-T	Post-T	Pre-T	Post-T	Pre-T	Post-T
Mean blood pressure	25 ± 2†	23 ± 2	16 ± 1‡	22 ± 3	27 ± 2	26 ± 1	26 ± 2	26 ± 3
Heart rate	−42 ± 2	−40 ± 2	−27 ± 1‡	−27 ± 1	−38 ± 2	−34 ± 2§	−31 ± 1‡	−26 ± 2

† Mean ± SE, n = 18–23 measurements.

‡ Significant difference between responses obtained before and after CBD ($p < 0.05$).

§ Significant difference between preterm and term lambs ($p < 0.05$).

* Pre-T, preterbutaline; post-T, postterbutaline.

number of studies during sleep were only obtained in the younger lambs. Baseline ventilation did not change significantly after CBD in any of the sleep states. When respiratory response and recovery time to laryngeal water stimulation were compared during rapid eye movement and quiet sleep, no significant differences were found. The results from the two sleep states were, therefore, combined. The respiratory response to LCR stimulation performed before CBD, during sleep, was not different from the LCR response in the awake state if the response was associated with arousal (Fig. 3). The respiratory response during sleep was significantly increased compared to wakefulness if arousal did not occur. After CBD, the respiratory response to laryngeal water stimulation was significantly increased during sleep ($p < 0.05$) compared to the response before CBD, if arousal did not occur. Before CBD, arousal from sleep occurred in 18 of 55 tests (32%). After CBD, the incidence of arousal was significantly decreased ($p < 0.01$) and was found in two of 23 tests (9%) in four lambs. In one lamb, we did not obtain tests during sleep states after CBD.

The respiratory response to LCR stimulation during sleep was not altered by terbutaline whether given pre- or post-CBD.

Effect of CBD and terbutaline on recovery time following LCR stimulation in the younger lambs during sleep. During sleep, the recovery time follows the same pattern as the respiratory response to LCR stimulation (Fig. 4). CBD significantly prolonged the recovery time following LCR stimulation during sleep, when the response was not associated with arousal (21/23 tests). The recovery time after LCR stimulation was not significantly changed by terbutaline.

DISCUSSION

This study shows that laryngeal chemoreflex inhibition of ventilation and heart rate are enhanced after carotid body denervation in 2- to 4-wk-old term lambs, indicating that the reflex response is modulated by the carotid bodies. We have demonstrated in lambs of comparable age a decrease in oxygen tension during the apnea response to LCR stimulation (2). This decrease in oxygen tension should, at that age, result in a carotid body-mediated stimulation of ventilation with resumption of regular breathing. After CBD, the lambs in the present study were unable to increase ventilation rapidly in response to acute hypoxemia, and they had prolonged apnea following LCR stimulation. A hypoxemic stimulus of the carotid chemoreceptors is, however, less effective in increasing ventilation during simultaneous LCR stimulation than during hypoxia alone as demonstrated in seals (14) and in monkeys (15). Prolongation of LCR–induced apnea after CBD, can be explained by the absence of carotid chemoreceptor mediated excitation of the reticular activating system (16).

Compared to the older lambs, the younger lambs showed a significantly weaker carotid body-mediated hypoxic ventilatory response. While the older lambs nearly doubled the minute ventilation during the 1st min of hypoxia, the younger lambs only increased ventilation by 40%. These results correlate with those of other investigators (6, 7, 11), demonstrating a maturation effect on the carotid body-mediated hypoxic ventilatory response during the first 10 days after birth. In contrast to the older lambs, CBD in the younger lambs did not significantly alter the respiratory response to laryngeal water stimulation. This could be due to incomplete maturity of the carotid bodies. A similar decrease in PaO_2 during LCR stimulation would, therefore, give a weaker carotid body response and subsequently less modulation of the respiratory response in the younger lambs. A weaker carotid body modulation of the LCR respiratory response would lead to an increased and prolonged respiratory response. Consequently, CBD in these lambs would not necessarily give an increase in the LCR respiratory response since they already have an inferior carotid body function.

The decreased bradycardia response to laryngeal water stimulation, after CBD, is consistent with the results of our previous cardiovascular study in carotid body innervated lambs, where a comparison was made between the response to LCR stimulation performed in room air and hyperoxia (2). The previous study indicated that 20–25% of the bradycardia and hypertension elicited during laryngeal water stimulation was due to secondary stimulation of arterial chemoreceptors. Absence of a significant effect of CBD on LCR blood pressure response in the older lambs might be attributed to a modulating effect of aortic chemoreceptors on blood pressure response during LCR stimulation (17).

Carotid chemoreceptor-mediated respiratory stimulation is probably not the only mechanism responsible for resumption of ventilation following LCR stimulation as seen in this study, since all the lambs started to breathe spontaneously during wakefulness. During LCR stimulation in sleep, however, mechanical ventilation was required in more than 50% of the LCR stimulations, post-CBD, when arousal did not occur.

Other investigators have found, in piglets, that laryngeal reflex apnea was independent of carotid body activity (18, 19). Differences in species, mode of reflex stimulation, and evaluation of reflex response may account for the differences in the results.

Our results, indicating that the effect of terbutaline on baseline ventilation is mainly mediated through the carotid bodies are consistent with reports concerning other β-adrenergic agonists (8–10). In a previous study we demonstrated an attenuating effect of terbutaline on the LCR response and we postulated that the terbutaline effect was mediated by the carotid bodies (5). This hypothesis is supported by the present results showing a markedly reduced terbutaline effect on the LCR response after CBD in the older lambs. An additional central effect of terbutaline is possible and is supported by the demonstration of shortened recovery time after LCR-induced apnea. The decrease in pH seen during terbutaline infusion may influence pH in the area of the medulla. Lowering of the cerebral spinal fluid pH in the medulla area is known to increase ventilation (20). A possible direct effect on the respiratory center was also suggested in our previous report (5).

In contrast to the older lambs, terbutaline, whether given before or after CBD to the younger lambs, did not significantly affect the LCR respiratory response, recovery time, or the incidence of arousal from sleep. Baseline ventilation was also not altered by terbutaline in the younger lambs. Yet, the terbutaline

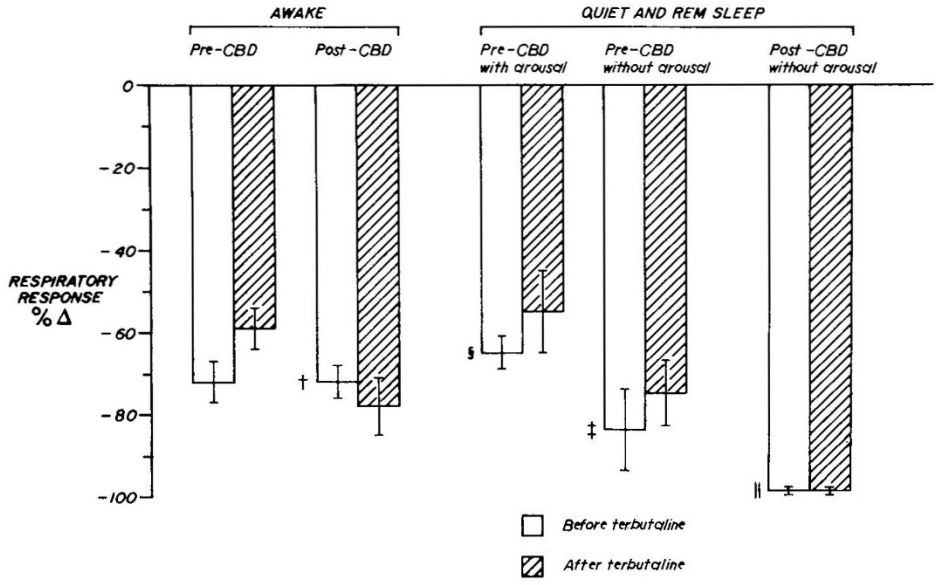

Fig. 3. Respiratory response (percent change in ventilation volume) to laryngeal chemoreflex stimulation during wakefulness and sleep in five 4- to 10-day-old preterm lambs performed before and after an intravenous terbutaline infusion given both pre- and post-CBD. Results during quiet and rapid eye movement sleep were not different and were, therefore, combined. Mean ± SE, n = 18–23 during wakefulness and 13–19 during sleep. ‡ Indicates significant difference between responses obtained during sleep and wakefulness pre-CBD. ‖ Significant difference between responses obtained pre- and post-CBD during sleep without arousal. § Indicates significant difference between responses obtained pre- and post-CBD during sleep. † Indicates significant difference between reponses obtained post-CBD during wakefulness and sleep without arousal.

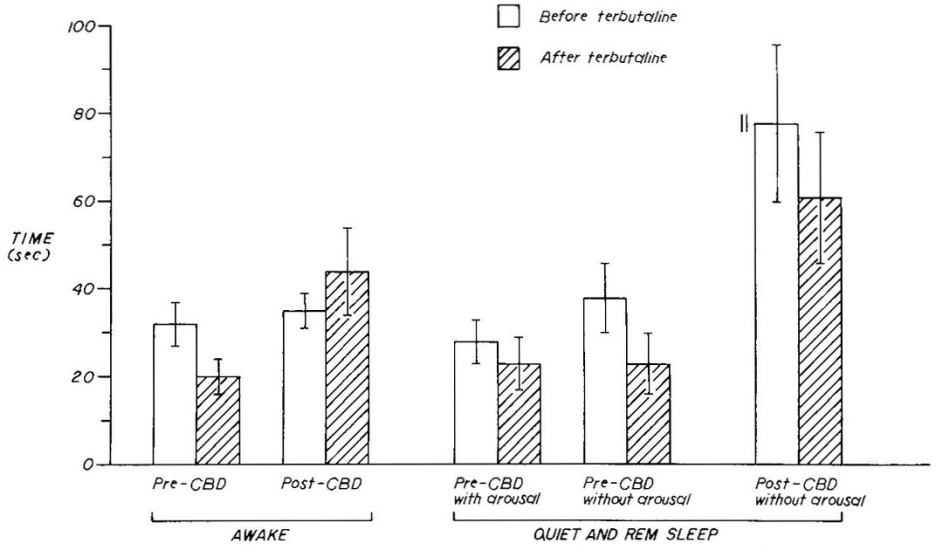

Fig. 4. Recovery time (time until regular breathing) following laryngeal chemoreflex stimulation during wakefulness and sleep in five 4- to 10-day-old preterm lambs performed before and after an intravenous terbutaline infusion given both pre- and post-CBD. Results during quiet and rapid eye movement sleep were not different and were, therefore, combined. Mean ± SE, n = 18–23 during wakefulness and 13–19 during sleep. ‖ Indicates significant difference between responses obtained pre- and post-CBD.

dose was comparable on a per kilo weight basis, and a pharmacologic drug effect was demonstrated by the same increase in heart rate in both groups of lambs. The lack of terbutaline effect in the younger lambs is possibly due to immaturity or intrinsic inhibition of the carotid bodies during the 1st wk of life. Thus, before CBD they behaved like the denervated older lambs. The absent terbutaline effect in the younger lambs supports our previous assumption that the carotid bodies are the primary mediator of the terbutaline effect on respiration.

A lack of maturity of β two receptors is probably not an adequate explanation for the omitted terbutaline effect, since the young lambs increased their heart rate during terbutaline infusion. One explanation for the postnatal maturation process of the carotid bodies is that there is a progressive increase in sensitivity of the chemoreceptor element of the carotid body itself (6, 7). Dopamine, adrenaline, and noradrenaline have been found in high concentrations in the carotid bodies (21), and a gradual reduction in biogenic amine content of the carotid bodies occurs during the first 16 days of life in newborn rats. Although no clear physiologic role for these carotid body monoamines has been established, recent studies have demonstrated that dopamine may act as an inhibitor of carotid bodies chemosensitivity (22–24). Exogenous catecholamines can change the sensitivity of chemoreceptors to hypoxia and hypercapnia (25), which might be due to an action on excitatory and inhibitory dopaminergic receptors (26). One might speculate that the absence of a terbutaline effect on the respiratory response to LCR stimulation in the younger lambs shortly after birth is related to the presence of

already high catecholamine concentrations in their carotid bodies.

During the 1st postnatal wk the younger lambs showed an increased respiratory response to LCR stimulation during sleep compared to wakefulness, if arousal was not associated with the response, which is consistent with previous results in our laboratory (12). In the current study, the incidence of arousal associated with the LCR response was significantly reduced after CBD. After CBD, the respiratory response to laryngeal stimulation during sleep was more severe, and the recovery time was significantly prolonged. The LCR respiratory response was potentially lethal after CBD, since in more than 50% of the sleep tests without arousal mechanical ventilation was thought to be required when the duration of apnea exceeded 100 s. Bowes *et al.* (27) have demonstrated the role of the carotid bodies for creating the arousal response to hypoxia. It is, therefore, likely that the carotid bodies mediate the arousal response to hypoxemia elicited from the LCR apnea response in sleeping lambs. This study would also indicate that, in contrast to wakefulness, the carotid bodies in preterm newborn lambs are able to shorten the LCR respiratory response during sleep through arousal.

In conclusion, this study has shown that the carotid bodies modify the respiratory and heart rate response to LCR stimulation in 2- to 4-wk-old lambs. The attenuating effect of terbutaline on the apnea reflex response in these lambs is partially mediated through the carotid bodies. Postnatal maturation of the carotid bodies is required for these effects, since the reduced hypoxic ventilatory response seen in the 1st postnatal wk was associated with an increased apnea reflex response to laryngeal water stimulation during wakefulness, which was not altered by carotid body denervation. The attenuating effect of terbutaline on the LCR response also appeared to be related to mature carotid body function. Compared to wakefulness, LCR response was greater in sleep not associated with arousal. The incidence of arousal decreased after CBD, suggesting that arousal in lambs is modified by the carotid bodies even during the 1st wk after birth.

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