Effects on breathing of carotid body denervation in neonatal piglets


Departments of Physiology and Pediatrics, Medical College of Wisconsin, Zablocki Veterans Affairs Medical Center, and Program in Physical Therapy, Marquette University, Milwaukee, Wisconsin 53226

Lowry, T. F., H. V. Forster, L. G. Pan, A. Serra, J. Wenninger, R. Nash, D. Sheridan, and R. A. Franciosi. Effects on breathing of carotid body denervation in neonatal piglets. J. Appl. Physiol. 87(6): 2128–2135, 1999.—The purpose of these studies was to test the hypothesis that carotid chemoreceptor activity is necessary for postnatal maturation of the ventilatory control system. By using a lateral surgical access, 17 piglets were carotid body denervated (CBD) and 14 were sham denervated at 3–25 days of age. After surgery, there was no irregular breathing in any group. There was no significant hyperventilation when CBD was performed at less than 5 days of age (n = 5) and only a mild (arterial $P_{\text{CO}_2}$ 5 Torr; $P < 0.05$) to moderate, transient (arterial $P_{\text{CO}_2}$ 8 Torr; $P < 0.5$) hyperventilation in piglets denervated at 10–15 (n = 6) and 20–25 (n = 6) days of age, respectively. Three weeks after surgery, both breathing of a hypoxic gas mixture and jugular venous NaCN injections elicited a hyperpnea in the CBD piglets that was attenuated compared with that in sham CBD piglets. In the CBD piglets, there was no response to injections of NaCN in the carotid arteries, but there was a response to NaCN injected into the proximal descending aorta, suggesting the residual peripheral chemosensitivity was of aortic origin. Carotid chemoreceptor-intact piglets had carotid and aortic NaCN chemosensitivity by 2 days of age. The carotid response persisted for the 40 days of the study, but the aortic reflex persisted only until ~8 days of age. We conclude that 1) the major effect of CBD per se in neonatal piglets is age-dependent hyperventilation and 2) there is a high degree of plasticity in peripheral chemosensitivity in neonates that may contribute to minimizing the changes in breathing after CBD.

control of breathing; carotid chemoreceptors; neonates

THE ACUTE EFFECT of carotid body denervation (CBD) in adult mammals includes hyperventilation; short-lasting hypertension; near total loss of responsiveness to hypoxia; and, in some species, irregular breathing (1, 2, 13–15). In addition, CBD in several neonatal mammals resulted in highly irregular breathing and/or a high rate of mortality when denervations were carried out within a certain period of postnatal life (3, 6, 8). These results in neonates led Donnelly and Haddad (6) to postulate that carotid chemoreceptor activity was necessary for the postnatal maturation of the ventilatory control system. A recent study by Cote et al. (4) did not find a high mortality rate but did find that high irregular breathing resulted when CBD was performed within a 9- to 15-day window of postnatal age. These latter findings led to speculation that at the youngest denervation age (4–5 days), fetal respiratory control mechanisms persisted and were able to compensate for the loss of carotid afferents (4). The location and nature of the mechanism were not specified.

In contrast to the above, our laboratory (12) recently found that CBD in 1- to 3-day-old goats produced only mild, transient irregular breathing. In addition, our laboratory (14) found no evidence to suggest that CBD in goats at 1–3 days of age caused long-lasting changes in breathing that differed from the effects of CBD in adult goats. Peripheral ventilatory chemosensitivity was normal or slightly attenuated days and weeks after CBD in both neonatal and adult goats. This residual responsiveness did not appear to originate as a result of regenerated carotid chemosensitivity. The data on neonates and adult goats suggest that goats have extensive plasticity in peripheral chemosensitivity, which, if greater than that in other species, may prevent the more severe respiratory abnormalities observed in other species after CBD in the neonatal period. Thus, in the present study, we used piglets to again test the hypothesis that carotid chemoreceptor activity is necessary for postnatal maturation of the ventilatory control system. In addition, to investigate a potential site for plasticity of peripheral chemoreception, the present study was also designed to gain insight into the aortic chemoreflex in neonatal piglets and to determine the effect of CBD on this aortic ventilatory chemoreflex.

METHODS

Before initiation of any studies, all aspects of procedures and protocols for this study were reviewed and approved by the Medical College of Wisconsin Animal Care Committee. Pregnant Yorkshire sows were obtained, brought to our animal care facility, and allowed to naturally deliver piglets. Heat lamps were placed in the pen to provide warm rest areas. Except for periods of study, the piglets were kept with the sow throughout the study and were allowed to nurse ad libitum. When litter size was large or sow milk production was questionable, milk replacer was made available to the piglets. When piglets began to show interest in the sow’s food, additional feed was made available to the piglets.

Eight litters of piglets were studied. Five litters were studied before and after bilateral CBD (n = 17) or sham CBD (n = 14). Three litters (n = 26) were not operated on and studied to gain insight into the temporal pattern of peripheral chemosensitivity over the first 27 days of life. Finally, three piglets were studied before and after unilateral CBD.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Surgery. Piglets were anesthetized for CBD surgery and for catheterization of blood vessels with 1–2% isoflurane-balance O2 delivered via face mask before catheterization and CBD or sham surgeries. Telazol (1–3 mg/kg) was given as a premedication if piglets showed aversion to the face mask.

In preliminary studies (unpublished observations), we followed the surgical procedure for CBD used by Cote et al. (4) and Donnelly and Haddad (6). The carotid bifurcations were accessed by using a midline approach, which required retraction of the larynx and dissection through tissue surrounding the airway. On recovery, most of the CBD piglets had severe upper airway dysfunction, irregular breathing, and marked hypoventilation, and some died within a few days. Therefore, for all piglets included in the CBD and sham CBD data sets in this paper, we switched to a lateral surgical approach to minimize trauma to the airway and its innervation. A 3-cm incision was made parallel to and 1 cm caudal to the caudal edge of the mandible, ~2–3 cm inferior to the attachment of the earlobe. Dissection proceeded medially, superior to the external jugular and caudal to the parotid gland. The carotid sinus region was identified as the first major bifurcation of the carotid artery and was stripped for 1–1.5 cm, ensuring sectioning the carotid sinus nerve. For sham animals the carotid sinus region was exposed, but all innervation was left intact. Because previous studies (4, 6) found the effects of CBD were dependent on the age of denervation, bilateral CBD was performed on piglets 5–5 days old (CBD-5), 10–15 days old (CBD-15), and 20–25 days old (CBD-25) (n = 5, 6, and 6, respectively). Sham CBD was also performed at all three age ranges (Sham-5, Sham-15; and Sham-25, respectively) (n = 5, 6, and 3 respectively). Three other piglets in the 10- to 15-day-old age group were unilaterally denervated.

Surgery for catheterizations. In piglets to be studied as CBD or sham CBD at ~5 days of age, a catheter was placed in the umbilical artery within 24 h of birth. The catheter was inserted after a small incision (~1 cm) was made in the side of the umbilicus. The catheter was tunneled to an exit site on the dorsal, posterior surface of the rib cage and was protected with a custom-fitted elastic jacket. Femoral artery catheters were inserted 3–4 days before CBD or sham CBD in the other groups and were similarly tunneled and protected. Catheters were flushed daily and filled with heparin (1,000 U/ml) to maintain patency.

Catheters were also placed in the jugular vein of all piglets when they were 25–40 days of age for bolus injections of NaCN. Such injections are a standard means of assessing peripheral ventilatory chemosensitivity even though NaCN has effects in addition to stimulation of peripheral chemoreceptors. For piglets at this age, we also catheterized each carotid artery for NaCN injections that specifically assessed carotid chemosensitivity. Finally, in four CBD piglets and three sham CBD piglets, a catheter was inserted into the left brachial artery and advanced into the distal descending aorta (verified radiologically). All catheters were secured to the skin with suture and tape.

In addition to these CBD and sham CBD piglets, catheters were also placed in a separate group of 26 intact piglets to determine whether ventilatory responses to NaCN changed in piglets over the first 27 days after birth. In six piglets, a femoral vein was catheterized 1–2 days after birth. This catheter remained in place for 27 days, and no other vessel was catheterized. In the remaining 20 piglets of this group, the femoral or jugular vein, the carotid arteries, and/or the descending aorta was catheterized at 2–25 days of age. These catheters remained in place for 2 days. Piglets were maintained on antibiotics (cefetilfer sodium; 2 mg·kg−1·day−1) prophylactically if catheterized or before removal of sutures from surgical wounds.

Experimental design. All piglets were studied while in a 100-liter plethysmograph, daily for 2–3 days before and at least 10 days after CBD. For measurement of breathing, a Validyne differential pressure transducer was used to monitor pressure changes in the plethysmograph, with the other side of the transducer connected to a stable pressure reservoir. The relative humidity and temperature within the plethysmograph (measured by a monitor) ranged between 50 and 80% and between 24 and 27°C, respectively. Each day before and after CBD, arterial blood was withdrawn for Pco2 (PaCo2), Po2 (PaO2), and pH (pHa) determination on a Ciba-Corning blood-gas analyzer (model 278). Rectal temperature was measured after blood sampling.

Studies were also completed 2–3 wk post-CBD to test the response to elevated inspired CO2. CBD-5 and Sham-5 animals were studied between 20 and 26 days of age. CBD-15 and Sham-15 animals were studied between 28 and 33 days of age. CBD-25 and Sham-25 animals were studied between 35 and 42 days of age. Each animal was studied twice at inspired CO2 fraction (FICO2) levels of 3.5, 5.0, and 6.0%. Ventilation was monitored, arterial blood was sampled under control conditions, and then ~3.5, 5, or 6 liters of 100% CO2 were added to the plethysmograph to elevate FICO2. The Pco2 in the chamber stabilized within 10 s after the addition of 100% CO2. Ventilation was monitored, and arterial blood was sampled after 5–6 min at elevated FICO2. Rectal temperatures were taken before and after each experiment. For individual animals, experiments were separated by at least 3 h, and only two experiments were conducted each day.

For hypoxia studies, arterial blood was sampled while the piglets were resting quietly in the prone position breathing normal room air. About 40 liters of 100% N2 were then pumped into the plethysmograph over 20 s. A mixing pump facilitated reaching a stable inspired O2 fraction (FIo2) of 0.125 within 30 s. Arterial blood samples were obtained 5 min after the induction of hypoxia. Rectal temperature was obtained before and after completion of the study.

All NaCN studies were completed (after CO2 and hypoxic responsiveness were tested) while the piglet was in the 100-liter plethysmograph, breathing room air; thus, as shown in Table 1 and Fig. 1, PaO2, ranged between 95 and 117 Torr for all groups. The injection catheter was connected to a pressure transducer via a T connector so that pressure in the injection catheter and vessel could be observed. Pressure data (recorded with a transducer) were used to verify catheter position and patency and also to indicate the beginning and end of the injection. Bolus injections of NaCN were made into the jugular catheter (0.05 mg/kg), the carotid catheters (0.005 mg/kg), or the aortic catheter (0.05 mg/kg). Volume of the injection was 0.1–0.3 ml and required 3–5 s. Jugular venous and carotid artery injections were made once 3–6 h and a second time 24 h after catheterization. Aortic NaCN responsiveness was assessed in only four CBD and three sham CBD piglets, and these measurements were completed 25 h after catheterization.

In six carotid-intact piglets, jugular venous NaCN injections were made beginning 2 days after birth and then repeated every third day until ~27 days of age. In 16 other carotid-intact piglets, jugular venous and aortic NaCN injections were made on only 2 days, at 24 and 48 h after catheterization. In three of this latter group, we were also able to inject NaCN directly into the carotid arteries.

The aortic catheter was inserted several centimeters caudally into the abdominal aorta. NaCN injections in this catheter were made at ~5-min intervals, and, after all
Table 1. Body weight, rectal temperature, and \( \text{Pa}_2 \), \( \text{Pa}_4 \), and \( \text{pH}_a \) obtained while piglets were breathing room air (control) and blood gases and \( \text{pH}_a \) 6 min after inspired oxygen had been reduced to 12.5% (hypoxia)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Body Wt, kg</th>
<th>Rectal Temperature, °C</th>
<th>Control</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \text{pH}_a )</td>
<td>( \text{Pa}_2 ), Torr</td>
</tr>
<tr>
<td>Sham-5</td>
<td>5</td>
<td>8.2 ± 0.9</td>
<td>39.9 ± 0.2</td>
<td>7.445 ± 0.005</td>
<td>37.5 ± 1.0</td>
</tr>
<tr>
<td>CBD-5</td>
<td>5</td>
<td>7.0 ± 1.0</td>
<td>40.1 ± 0.2</td>
<td>7.433 ± 0.011</td>
<td>38.8 ± 0.3</td>
</tr>
<tr>
<td>Sham-15</td>
<td>6</td>
<td>8.4 ± 0.5</td>
<td>39.7 ± 0.2</td>
<td>7.441 ± 0.005</td>
<td>36.6 ± 0.9</td>
</tr>
<tr>
<td>CBD-15</td>
<td>6</td>
<td>9.1 ± 1.3</td>
<td>39.6 ± 0.1</td>
<td>7.439 ± 0.008</td>
<td>38.9 ± 1.5</td>
</tr>
<tr>
<td>Sham-25</td>
<td>3</td>
<td>10.8 ± 1.3</td>
<td>39.6 ± 0.1</td>
<td>7.438 ± 0.008</td>
<td>36.2 ± 1.3</td>
</tr>
<tr>
<td>CBD-25</td>
<td>6</td>
<td>10.4 ± 0.4</td>
<td>39.8 ± 0.1</td>
<td>7.429 ± 0.009</td>
<td>38.8 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of piglets. Data were obtained in piglets 2–3 wk after carotid body denervation (CBD) or sham CBD at 2–5 (CBD-5 and Sham-5), 10–15 (CBD-15 and Sham-15), or 20–25 days of age (CBD-25 and Sham-25). \( \text{pH}_a \), arterial pH; \( \text{Pa}_2 \), arterial \( \text{PCO}_2 \); \( \text{Pa}_4 \), arterial \( \text{PO}_2 \). All groups, including CBD, hyperventilated during hypoxia (\( P < 0.05 \)), but the hyperventilation was less (\( P < 0.05 \)) in CBD-15 and CBD-25 piglets than in sham piglets.

injections that did not elicit a response, the catheter was withdrawn 1 cm. This process was continued until a response occurred or until the catheter was totally withdrawn. If an injection elicited a hyperpnea, then the position of the catheter was verified radiologically with the piglet under anesthesia. The piglet then either recovered from anesthesia for a second day of \( \text{NaCN} \) testing or was euthanized for dissection to visually identify the catheter location. If no response occurred to any aortic \( \text{NaCN} \) injection, then a final jugular venous injection was made to ensure that overall peripheral chemosensitivity was intact.

The NaCN responses were quantified in the following manner. The first breath of the response was visually identified, and the 10 breaths preceding this breath were regarded as control. If no response could be visually identified, the first breath after the injection was designated as the first breath. The response ratio was calculated as “average ventilation of the first five breaths of the response” divided by “average control ventilation.” This method was determined to be reliable and repeatable. Trial determinations in which no injections (or sham NaCN injections, i.e., saline alone) were made showed that “normal variability” of breathing could result in ratios that ranged from 0.8 to 1.2. Analysis of data from responses showed that varying the designated “first breath” by one breath altered the calculated ratio by 0.2–0.3.

The NaCN responses were considered significant. The NaCN responses were considered significant.

Means were obtained for each animal, by specified age and denervation status. SPSS was used to perform analysis of variance. Duncan post hoc tests were used after one-way analysis of variance. Duncan post hoc tests were used after one-way analysis of variance. Scheffe’s post hoc tests were performed after two-way analysis of variance. Results for which \( P < 0.05 \) were considered significant.

RESULTS

The average weight at birth of the Yorkshire piglets used in this study was 1.8 ± 0.05 kg. Healthy piglets grew at an average weight gain of ~0.2 kg/day. Rectal temperature over the first 2–3 days of life was 39.1 ± 0.1°C with a significant (\( P < 0.05 \)) increase by 15 days of age to 39.8 ± 0.1°C. In carotid chemoreceptor-intact piglets, \( \text{Pa}_4 \) increased significantly with age from 31.9 ± 1.2 Torr at 2 days of age to 36.0 ± 0.6 Torr at 25 days of age (Fig. 1). Similarly, \( \text{Pa}_2 \) increased significantly (\( P < 0.05 \)) from 96 ± 3.8 Torr at 2 days to 116.7 ±
2.1 Torr at 25 days of age. pH did not change significantly (P > 0.10) over the first 25 days of life.

Effects of CBD. There were no signs of upper airway dysfunction in any of the CBD or sham CBD piglets. All CBD and sham CBD piglets gained weight normally and appeared healthy throughout the study, and there were no fatalities. There were also no indications that prolonged apneas or highly irregular breathing was characteristic of either intact or CBD piglets. The coefficients of variation for both inspiratory (Ti) time and expiratory (Te) time did not differ between CBD and sham CBD piglets. In both sham and CBD piglets, Ti and Te decreased (P < 0.05) during the first 10 days of postnatal life and then increased (P < 0.05) with age. There was an age-dependent decrease in heart rate and increase in mean arterial blood pressure in both sham and CBD piglets, and these age-dependent changes did not differ between the two groups.

There was a small, nonsignificant (P > 0.10) increase in PaCO2 after denervation in the CBD-5 group when compared with the Sham-5 age group (Fig. 2). In those piglets denervated at 10–15 and 20–25 days of age, there was a transient, significant (P < 0.05) hypoventilation with PaCO2 increasing 5 and 8 Torr in the two age groups, respectively (Fig. 2). Unilateral CBD at 12–15 days of age did not result in hypoventilation.

Two to three weeks after bilateral CBD and sham CBD at <5, 10–15, and 20–25 days of age, there were no significant differences between CBD and sham CBD piglets in PaCO2, PaO2, pH, arterial temperature, and body weight (Table 1).

All animals exhibited a brisk response to elevated F1CO2, and there were no significant (P < 0.05) differences among the denervation or age groups. In the sham CBD and CBD piglets, respectively, expired pulmonary ventilation increased 158 ± 40 and 124 ± 30 ml/min for each Torr increase in PaCO2 above eupneic PaCO2.

Overall, there was a significantly (P < 0.05) greater hyperventilation during hypoxia in intact vs. CBD piglets (Table 1). The difference was significant (P < 0.05) in the 10- to 15-day and 20- to 25-day CBD age groups.

Venous NaCN responses. A consistent response to bolus injections of 0.05 mg/kg NaCN in the jugular vein [intravenous (iv) NaCN] was found in all carotid-intact and -denervated animals, at all ages. An example of an

---

Fig. 2. In awake piglets breathing room air, change in PaCO2 (ΔPaCO2) from presurgery over days after carotid body denervation (CBD) or sham CBD. Values are means ± SE for piglets that had CBD (●) or sham CBD (♦) at <5 (A), 10–15 (B), or 20–25 (C) days of age. No. of piglets in each group is presented in Table 1. *Days past surgery where sham and CBD piglets differed significantly, P < 0.05. Note: 1) no significant (P > 0.01) differences in PaCO2 between sham and CBD piglets when surgery was at <5 days of age and 2) a significant (P < 0.05) transient difference in PaCO2 between sham and CBD piglets when surgery was at 10–15 and 20–25 days of age.
individual carotid-intact piglet NaCN response indicates that there was a distinct delay between the injection and the response (Fig. 3). The delay in the response and the time course of the response did not significantly change with age or CBD. In some preliminary studies, the dose was increased to 0.10 mg/kg, and a “behavioral” (head shaking, body movement) component of the response became evident. The higher dose was discontinued because it clearly disturbed the piglets. There was no ventilatory response when only saline rather than NaCN was injected (sham NaCN; Fig. 3).

There was a ventilatory response to iv NaCN injection in 2-day-old carotid chemoreceptor-intact piglets, and this response did not change significantly ($P > 0.01$) over the next 27 days (Fig. 4). In 30- to 40-day-old piglets, the ventilatory response to iv NaCN was significantly ($P < 0.05$) lower in piglets that had undergone CBD at 10–15 and 20–25 days of age than in piglets that had sham CBD at those ages (Fig. 5). There also was a large average difference between piglets that had CBD or sham CBD at <5 days of age, but the group difference did not quite reach statistical significance ($P = 0.07$).

Intracarotid NaCN responses. Intracarotid NaCN injections resulted in vigorous ventilatory responses in three carotid-intact piglets studied at 2, 4, and 6 days of age (response ratios of 1.7, 2.1, and 1.6, respectively). Similarly, in all eight piglets studied ~3 wk after sham CBD, intracarotid NaCN injection increased breathing (mean response ratio $= 1.75 \pm 0.4$). This response was immediate, beginning before the NaCN injection was complete (Fig. 6). No response, either immediate or delayed (Fig. 6), was seen in 17 bilateral CBD piglets with a mean carotid NaCN ventilatory ratio of 1.02 $\pm 0.02$. The three unilateral CBD piglets, responded to carotid NaCN only in the side not denervated. These piglets had a normal response to jugular venous NaCN injections.

Aortic NaCN responsiveness. In all three sham CBD piglets with aortic catheters, there was no ventilatory response to NaCN injection at any aortic site (Fig. 7). In four CBD piglets, there was no response at most aortic sites, but a hyperpnea was elicited when NaCN was injected just distal to the origin of the left subclavian artery (Fig. 7).

Aortic NaCN tests were also completed in several carotid chemoreceptor-intact piglets not operated on. Piglets aged $\leq 6$ days exhibited brisk responses to NaCN injections when the tip of the catheter was just...
found that CBD resulted in a highly irregular breathing, high levels of mortality, decreased weight gain, and elevated resting PaCO₂ (3, 4, 6, 8). In addition, several aspects of these studies suggested upper airway dysfunction after CBD but not sham CBD. Findings in our preliminary studies in piglets in which denervation was carried out with a midline approach were similar to those of past studies. However, we did not find such severe effects when midline access CBD was performed in 1- to 3-day-old goats (12). The midline access is much easier in goats than in piglets because of differences in anatomy between the two species. We found no evidence of airway damage in the goats. In any event, the cause of the severe effects with midline access CBD in most past studies and our preliminary studies remains largely obscure.

Lateral access for CBD in piglets. When the lateral approach CBD technique was implemented to avoid compromising the function of the upper airway, piglets did not display highly irregular breathing and there were no deaths. Piglets denervated in this manner at <5 days of age did not hypoventilate, but piglets denervated at 15 days and, to an even greater extent, at 25 days did hypoventilate (Fig. 2). Such age-dependent hypoventilation was also observed by Cote et al. (4).

Why does age of CBD in neonates influence the degree of subsequent hypoventilation? One possible explanation is that at <5 days of age, immature carotid chemoreceptor mechanisms may contribute relatively little excitatory drive to eupneic breathing; thus denervating these chemoreceptors has minimal effect on breathing. Inconsistent with this explanation are our present findings that there was a marked hypopnea at 2 days of age when NaCN was injected into the jugular vein or a carotid artery and that there was no significant change in these responses for 3 wk thereafter.

A second possible explanation was suggested by Cote et al. (4), who found that after CBD in <5-day-old piglets, there was no ventilatory response to hypoxia, which the authors concluded meant that aortic chemoreceptors were not active. Therefore, they hypothesized that “fetal mechanisms persisted in the absence of carotid chemoreceptors and were adequate to prevent hypoventilation.” However, the protocol used in their studies was not designed to detect the acute hypoxic response. Animals were instrumented with a catheter to measure oxygen saturation, and the chamber FIO₂ was gradually lowered over 15–20 min until PaO₂ was between 45 and 50 Torr. With this protocol, the central depressant effects of hypoxia may have prevented any aortic chemoreceptor stimulation from increasing breathing. In contrast, in the present study, PaO₂ was abruptly (<30 s) lowered, and the effect of the hypoxia was assessed by the hyperventilation 5 min later before hypoxic brain depression could potentially mask peripheral chemoreceptor stimulation. All of our CBD piglets hyperventilated during hypoxia. Moreover, in piglets <5 days of age, there was a definite ventilatory response to NaCN localized to the aortic area; therefore, in contrast to the conclusion of Cote et al., we conclude that an aortic chemoreflex exists in <5-day-old piglets.
This conclusion is consistent with documented aortic chemoreceptor activity in fetal and neonatal lambs (5, 11).

We believe the data from our study support the hypothesis of relatively enhanced plasticity of the peripheral chemoreflex in younger piglets, which may explain why the age of CBD in neonates is a determinant of how much they hypoventilate. “Plasticity” is generally used to describe situations where neurally mediated behavior is lost because of the nerve section but is regained over time after surgery. Redundancy in a control system provides plasticity; redundancy might reflect a system where two or more mechanisms are capable of mediating a function (such as arterial chemosensitivity), but normally one mechanism is dominant and the second only becomes functional in the absence of the dominant mechanism. Our postulate of enhanced plasticity in <5-day-old piglets is based on the finding that, in carotid chemoreceptor-intact piglets, an aortic chemoreflex is evident only in piglets <6–8 days old. However, in 40-day-old piglets that had undergone CBD at 10–15 or 20–25 days of age and therefore had no carotid chemoreflex (Fig. 6), there was a residual overall peripheral chemosensitivity (Fig. 5), which we documented was associated with an aortic ventilatory chemoreflex (Fig. 7). It appears then that during the first few days of life chemosensitivity is present in both the carotid and aortic areas (i.e., redundancy in chemosensitivity). We hypothesize that when the carotid chemoreceptors are removed bilaterally at <5 days of age, the aortic chemoreceptors immediately provide enough stimulation of breathing to prevent hypoventilation. However, with intact carotid receptors, the aortic chemoreceptors eventually become nonfunctional, but if both carotids are subsequently removed, the aortic chemoreceptors eventually regain chemosensitivity and become important in the control of eupneic breathing to minimize the hypoventilation because of loss of carotid chemoreceptor stimulation.

Plasticity in ventilatory control after CBD has been observed in other neonatal and adult mammals (1, 12, 14, 15). We found that by 3 mo of age (earliest measurement period) goats carotid denervated at 1–3 days of age did not differ from sham-operated neonates in eupneic breathing or ventilatory responses to NaCN, hypoxia, CO₂, and exercise (12). Moreover, in adult goats, bilateral CBD causes transient marked hypoventilation and reduced CO₂ sensitivity, but 2 wk later, these functions return to near normal (14); unilateral CBD results in less hypoventilation and attenuation of CO₂ sensitivity than does bilateral CBD. Last, adult cats (15), ponies (1), and rats (13) demonstrate similar plasticity after CBD, but recovery is not as rapid as in goats. It has been postulated that aortic chemoreceptors are the mechanisms of plasticity of peripheral chemosensitivity after CBD in adult cats and ponies (1, 15), but in rats (13) it appears the aortic chemoreceptors are not the site of peripheral chemosensitivity after CBD. Plasticity appears greater in neonates than in adults as indicated by findings that unilateral CBD in adult but not neonatal goats resulted in hypoventilation.

The purpose for two functional peripheral chemoreceptor sites in the neonatal period is unclear. Such development-related changes in sites of chemosensitivity or other functions of ventilatory control may not be unique to peripheral chemoreception. Torgerson et al. (17) found that intracranial chemosensitivity in tadpoles shifts with development from the caudal to the rostral ventrolateral medulla. Conceivably, redundant systems exist in early development for many physiological functions, but a part of maturation is “economy,” that is, a downregulation of some components that are then capable of reactivation if the primary system becomes nonfunctional. Accordingly, this redundant system contributes to plasticity.

Analogy with visual cortex. Donnelly and Haddad (6) hypothesized that carotid and/or aortic nerve activity was necessary for the development of normal medullary function. This hypothesis was suggested by studies of the visual cortex (9, 10, 18), which showed that if nerve activity in an eye is silenced, normal patterns of activity do not develop. However, there are distinct differences in the anatomy of the visual system and the respiratory control system. In the visual system as well as other areas of the sensory cortex, the organization is described as “parallel” (10). Specific retinal areas map to specific areas of the visual cortex. In contrast, the respiratory control system consists of several brain stem nuclei which are highly interconnected (16). If a portion of the retina is silenced, a specific portion of the visual cortex will become silent. Removal of only a proportion of the input to respiratory nuclei will probably not exert similar profound effects. This seems even more probable if other chemoreceptors (the aortic chemoreceptors) are still active. In other words, the residual peripheral chemosensitivity, regardless of its origin, may provide the input to central medullary neurons that is needed for maturation and/or stability. It appears that the respiratory system is a redundant system or has more redundancy and therefore plasticity than the visual system.

Clinical relevance. The data of this study may be pertinent to the “triple-risk model” of sudden infant death (7). In this model, there is not a “single factor” that causes potentially fatal apneic events but rather a series of factors that interact to produce such effects. A “vulnerable infant” (a CBD piglet) within a “critical period” (during the period in which aortic receptors have become silent or nearly silent) experiences life-threatening apnea when subjected to an “exogenous stressor.” One potential stressor might be obstructive apnea, which would normally be reflexively resolved but is not when upper airway function is compromised or when there is insufficient respiratory drive.

Cote et al. (4) noted a “window of postnatal age” during which CBD resulted in severe respiratory irregularity. Despite the fact that we found no respiratory irregularity and therefore no evidence of a “window of vulnerability,” the data do suggest how a window of vulnerability might arise. If CBD occurs before the age...
at which the aortic chemoreceptors become silent, the aortic chemoreceptors remain active and maintain adequate respiratory drive to prevent apnea and, indeed, maintain eupneic $P_{a\text{CO}_2}$ close to the normal range. If CBD occurs after the time that the aortic chemoreceptors become silent, then there might be a period before aortic chemosensitivity (and therefore respiratory drive) redevelops to prevent sustained apnea. The potential for respiratory disturbance would be greatest during this period if airway function has been compromised or there are increased inhibitory effects on breathing from airway receptors.

Summary. CBD per se, as shown in the lateral access CBD studies, does not lead to highly irregular breathing, and basic respiratory timing parameters ($T_i$ and $T_e$) appear unaffected. However, there is an age-dependent hypoventilation after CBD. During the first week after birth, both aortic and carotid chemoreceptors are functional; thus we postulate that CBD during this period does not cause hypoventilation because of persisting aortic stimulation. In carotid-intact piglets, the aortic chemoreceptors become nonfunctional after 10 days of age, but, if CBD is performed after 8–10 days of age, the aortic chemoreceptors again become functional to minimize the hypoventilation caused by loss of carotid afferents. We did not obtain any data to support the hypothesis that carotid afferents are required for maturation of ventilatory control.

This study was supported by the Sudden Infant Death Research Fund of Wisconsin; National Heart, Lung, and Blood Institute Grant HL-25739; and the Department of Veterans Affairs.

Address for reprint requests and other correspondence: H. V. Forster, Dept. of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226 (E-mail: BForster@mcw.edu).

Received 19 November 1998; accepted in final form 21 July 1999.

REFERENCES


