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Cardiovascular and Neurophysiologic Changes during Graded Duration of Apnea in Piglets

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ABSTRACT. To examine the interrelationship between the duration of apnea and changes in oxygen saturation, blood pressure, electroencephalogram (EEG), and heart rate, reflex apnea of 10, 20, 40, and 60 s duration was induced by stimulating the superior laryngeal nerves. Piglets ($n = 11$, age 5–14 days) were chronically instrumented for continuous monitoring of SaO_2 and blood pressure and for sampling arterial blood. Ventilation was recorded using whole body plethysmography and EEG and electrocardiogram were measured by acutely placed subcutaneous electrodes. Central apnea produced an immediate rise in blood pressure and a decrease in SaO_2 by 20 s. By 30 s into the apnea, EEG amplitude had already decreased. Major cardiac slowing did not occur until 80 s after the start of apnea. Hyperoxia delayed the start of desaturation, hypertension, and EEG attenuation. These data suggest that during superior laryngeal nerve-induced apnea in young piglets: 1) desaturation can reach profound levels rapidly, 2) EEG amplitude decreases substantially and becomes nearly isoelectric within 1 min, and 3) bradycardia is a late manifestation when compared to changes in oxygen saturation, blood pressure, and EEG. (*Pediatr Res* 23:402–407, 1988)

Abbreviations

SLN, superior laryngeal nerves
EEG, electroencephalogram
SaO_2, arterial oxygen saturation
MAP, mean arterial blood pressure
EKG, electrocardiogram
IVH, intraventricular hemorrhage

Apnea is a common problem in neonatal intensive care units with an incidence of 80–90% in infants weighing less than 1000 g (1, 2). The importance of this phenomenon stems from the fact that apnea has been associated with cyanosis, bradycardia, altered neurologic state (3–7), and recently, with decreased cerebral blood flow (8).

Despite the importance of apnea as a potentially detrimental phenomenon (9), the time of onset and the sequence of physiologic changes associated with apnea are unclear. Some infants require intervention at 10–15 s into an apnea, whereas some observations suggest that hypotonia and other indications of cerebral dysfunction do not occur until 45 s (3, 10). Similarly, the latency of bradycardia and its relationship to oxygen saturation is variable. Bradycardia may occur early into an apnea, at a time before significant desaturation (3, 11, 12), but also can occur late in 40% of protracted apneas (13) or after the onset of EEG supression (14).

The purpose herein was to examine the sequence of neurologic and cardiovascular consequences of graded periods of apnea. Prolonged neonatal apnea can be of variable etiology such as central nervous system immaturity, infection, metabolic disturbances, IVH, airway obstruction, and vagal reflex. For our studies, we used laryngeal stimulation to induce a central apnea secondary to reflex effect. In this way, apnea duration could be controlled by the duration of stimulus presentation and the cause for central apnea was consistent among experimental animals. Experiments were conducted in piglets because they have a similar time course of brain development and cardiovascular control systems as infants. Inasmuch as unterminated respiratory pauses up to 80 s duration were examined, similar studies on human infants could not ethically be undertaken. We hypothesized that in healthy animals, significant desaturation and neurologic electroencephalographic alterations occur during the course of an apnea and that bradycardia may be a poor indicator of an apneic period.

MATERIALS AND METHODS

Eleven farm bred newborn piglets were used. The animals were bottle fed pig milk replacer every 4–5 h for the first five days of life and then allowed to feed *ad libitum* from a bowl. Environmental temperature was maintained between 30.5–32° C. Piglets were weighed daily and an increase in weight was noted in all.

Electrode and catheter placement. On day 4–13 of life, surgery was performed under sterile conditions using Halothane anesthesia. A no. 5 Oxymetrix oxygen saturation catheter was inserted into the carotid artery. This allowed us to make continuous recordings of O_2 saturation and blood pressure and to take intermittent samples for blood gas analysis. Both SLN were exposed and isolated along their path from larynx to nodose ganglia. The nerves were cut at the entrance to the larynx and placed in individual cuff electrodes that were sutured to the neighboring laryngeal muscles. These electrodes were constructed by sewing a pair of Teflon insulated steel wires (7 strands no. 44 wire, Medwire Corp., Mt. Vernon, NY) circumferentially within silastic tubes and separated by 2 mm. Because the fine wires allowed for a tight closure of the wound, the site of exteriorization could be kept free from infection. The piglets were then allowed to recover for 24 h.

Experiments were performed 1–2 days after surgery at which time piglets were sedated with penobarbital (20 mg/kg, intraarterially). Pentobarbital was used to suppress periodic breathing that is observed during SLN stimulation in awake, unanesthetized animals (15). Throughout the experimental period the animal was maintained under a light level of anesthesia as assessed by withdrawal from nocioceptive stimuli.

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Physiologic measurements. Respiration was measured using barometric plethysmography (16, 17). In brief, the animal is placed in a closed chamber and tidal volume is calculated from pressure changes due to humidification and heating of inspired air. The chamber air is circulated through a scrubbing system to remove expired CO_2 and control for humidity. The total volume of the chamber and scrubbing system is 51 liters. Oxygen was added periodically to maintain an FiO_2 between 0.19 and 0.22.

Oxygen saturation and blood pressure were measured continuously through a carotid artery catheter. Heart rate was monitored by inserting pins subcutaneously and attaching these to electrode wires (17). Similarly, pins were inserted subcutaneously over the temporoparietal cortex to measure the electroencephalogram. A hot water bottle was used to maintain the temperature in the box at 32° C. After the animal was placed in the chamber, which was carefully sealed to avoid any leakage of air, baseline recordings were obtained. The SLN were briefly stimulated (BAK Electronics, Rockville, MD BPG-1/BSI-2 constant current source, 1 ms duration, 10 Hz) at increasing current until central apnea was produced at which time the stimulus was removed and the current intensity noted.

Each study was divided into a control, stimulus, and poststimulus period. After control recordings (three consecutive 10-s intervals immediately before each stimulus period), the SLN were stimulated for 10, 20, 40, and 60 s. Data were analyzed for an additional 20 s into the poststimulus period. Piglets were allowed to recover spontaneously between stimuli, *i.e.* all physiologic parameters that were being measured returned to baseline before the next stimulus was applied. At the end of the study rectal temperature was measured.

In six piglets, after SLN stimulation in normoxia, the FiO_2 was raised to 50–70% in order to increase O_2 stores and delay the arterial oxygen desaturation associated with apnea. Again the SLN were stimulated to induce central apnea for 10, 20, 40, and 60 s.

Data acquisition and statistical analysis. All signals were acquired on a PDP 11/03 computer and transferred to a Prime minicomputer for analysis. The respiratory waveform was graphically displayed for accurate marking of the start and end of inspiration. Tidal volume and respiratory frequency were calculated as previously described (16, 17).

The EEG was quantified in one of two ways: 1) in six studies the EEG was bandpass filtered at 0.5–25 Hz and digitized at 50 Hz. The variance of EEG voltage was computed before and during the apnea and was used as an index of EEG amplitude. 2) In the remaining five studies where EEG tape recording was not available, quantification of EEG amplitude was measured by peak-peak polygraph excursion.

Mean and SE of absolute values as well as percent changes from baseline were computed for all variables. To determine whether significant changes occurred at discrete time points in the stimulus period, stimulus values were compared to those in baseline using Student's paired t test with Bonferroni correction for multiple samples (18). Population differences were considered significant if p was less than 0.05.

RESULTS

Bilateral electrical stimulation of the SLN induced alterations in respiratory, cardiovascular, and neurophysiologic functions in lightly anesthetized piglets. Data obtained at 10, 20, and 40 s of the 60-s stimulus period were identical to those values for 10-, 20-, and 40-s stimulus trains. Therefore, only the 60-s stimulus periods were analyzed in detail and are presented herein.

Respiratory pattern and function. Immediately after the start of SLN stimulation the piglet became apneic (Fig. 1). Apnea lasted the duration of the stimulus period but with longer stimulation (40 and 60 s) it continued after stimulus cessation (Fig. 1). In general, the longer the stimulus period, the longer the time to resumption of spontaneous and regular breathing. The range of the poststimulus apneic period after 60 s of stimulation was 10–110 s. Almost simultaneously with the onset of apnea, O_2 saturation began to decrease; by 30 s into the apnea, SaO_2 was down to 50%, and by 60 s it had dropped to 25% (Table 1). The fall in O_2 saturation was significant at 20 s and continued to be so throughout the entire stimulus and poststimulus period. The mean PaO_2 measured at the end of the 60-s period of stimulation was 25 mm Hg and $PaCO_2$ increased from 37 to 50 mm Hg. The SaO_2 was fit to an exponential and estimated as $SaO_2 = 90\exp(-0.021t)$; $r = 0.99$.

Cardiovascular function. Blood Pressure. The MAP during baseline recordings was 82 mm Hg (Table 1). MAP began to rise approximately 10 s after the onset of apnea and almost simultaneously with oxygen desaturation (Fig. 2). The piglets became considerably hypertensive. By 30 s MAP was 110 mm Hg and by 60 s reached a peak of 125 mm Hg, an increase of 55%. After the start of apnea, all MAP values were significantly elevated above control. Blood pressure gradually fell in the poststimulus period.

Heart Rate. The mean heart rate during the control period was 198 beats/min (Table 1). Ten seconds after the start of stimulation the mean heart rate had decreased to 193 and by 20 s it was significantly down to 185. During the rest of the period, although the average heart rate remained below the baseline value, the differences were insignificant. At no time during the 60 s of apnea was the mean heart rate less than 170 beats/min. It was not until 80 s after the start of apnea or 20 s into the poststimulus period that the heart rate decreased to less than 75% of control (150 beats/min).

Neurophysiologic Function. There was a substantial effect on

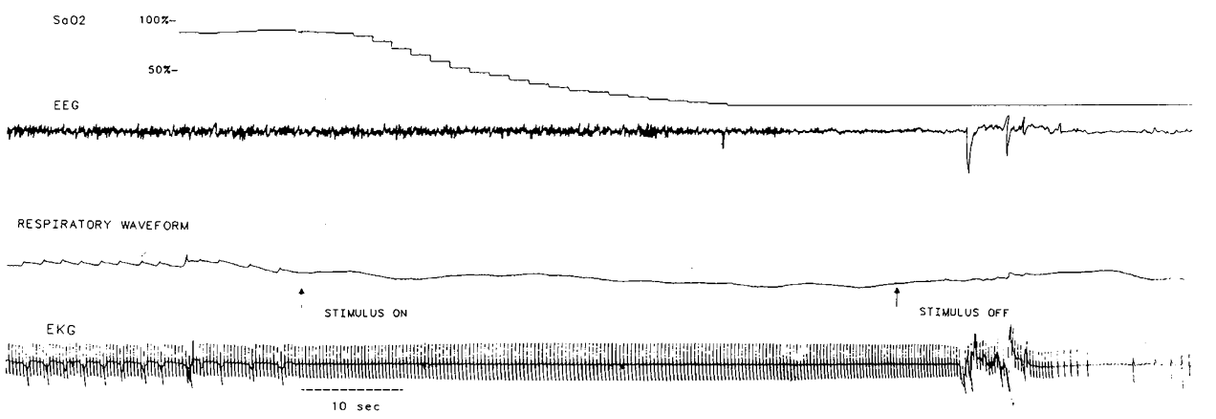

Fig. 1. Original polygraph tracing before (*left*) and through a 60-s stimulus period in room air. Signals recorded were arterial oxygen saturation (*top*), EEG, respiration, and EKG. Note rapid desaturation and a gradual decline of EEG amplitude; bradycardia occurred late in the apnea.

Table 1. *Mean ± SEM of arterial oxygen saturation, arterial blood pressure, EEG amplitude, and heart rate for control, 60-s stimulus, and 20-s poststimulus period*

	Control period (s)	Stimulus period (s)						Poststimulus period (s)	
		10	20	30	40	50	60	10	20
SaO_2 (%) ($n = 11$)	85 ± 3	79 ± 4	63 ± 5*	48 ± 6*	36 ± 6*	30 ± 5*	24 ± 4*	21 ± 3*	18 ± 2*
BP (mm Hg) ($n = 12$)	82 ± 3	86 ± 4*	97 ± 5*	110 ± 5*	120 ± 5*	124 ± 4*	125 ± 4*	119 ± 5*	112 ± 5*
EEG (×10 UV) ($n = 16$)	11 ± 1	11 ± 1	10 ± 1	8 ± 1*	7 ± 1*	7 ± 1*	5 ± 1*	2 ± 1*	1 ± 0*
HR (bpm) ($n = 16$)	198 ± 12	193 ± 12	185 ± 10*	183 ± 11	181 ± 9	181 ± 9	185 ± 7	173 ± 8	136 ± 12*

* $p < 0.05$ *versus* control.

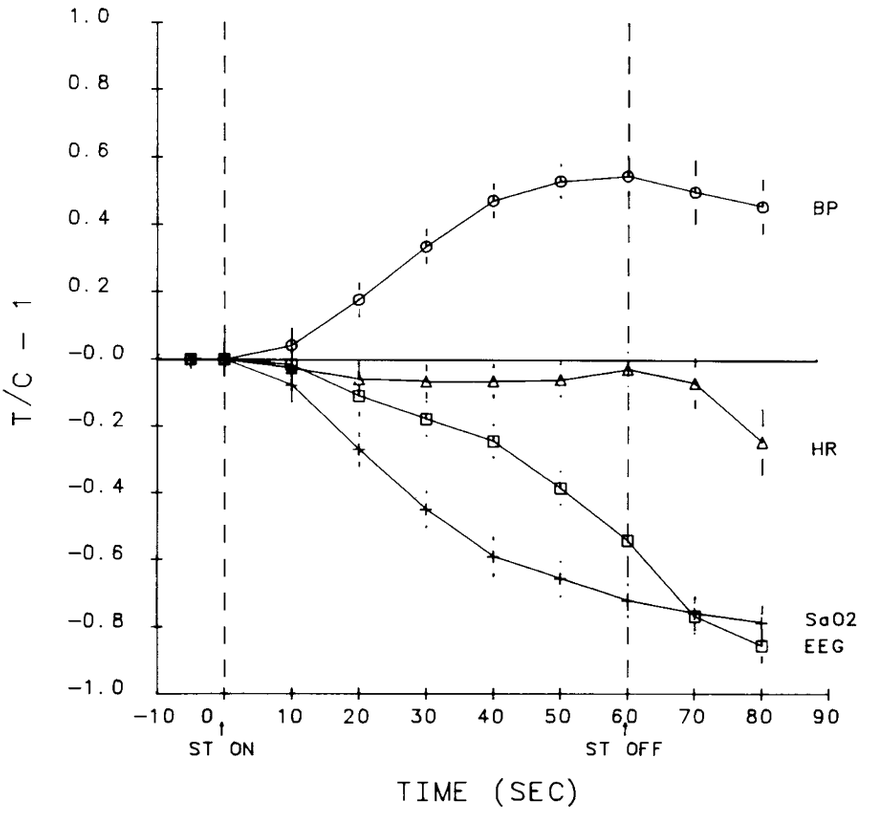

Fig. 2. Percent change from control value (mean + SEM) of systemic blood pressure (*circle*), heart rate (*triangle*), EEG (*square*), and arterial oxygen saturation (*cross*) during 60 s of SLN-induced apnea and 20 s of the poststimulus period in room air.

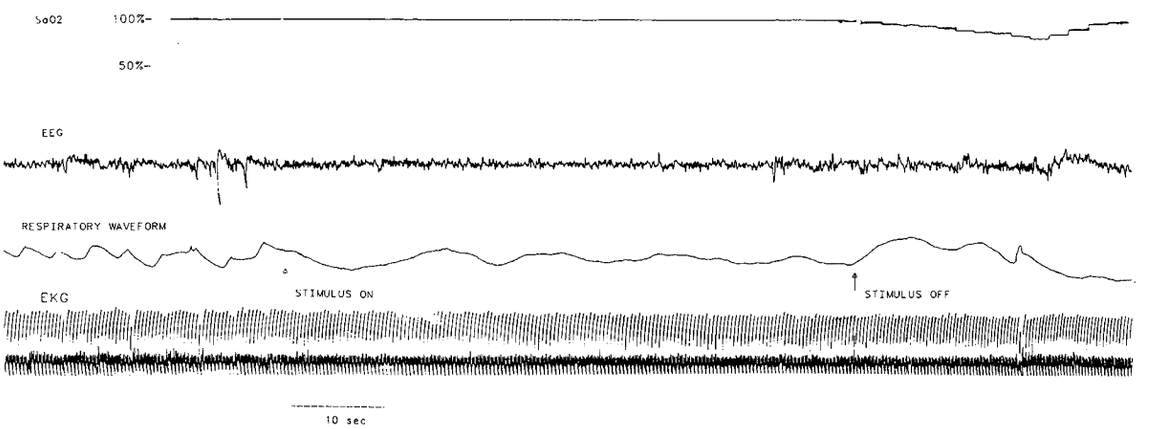

Fig. 3. Original polygraphy tracing before (*left*) and through a 60-s stimulus period with $FiO_2 = 0.6$. Signals recorded were arterial oxygen saturation (*top*), EEG, respiration, and EKG. Note delayed desaturation and no EEG attenuation or bradycardia.

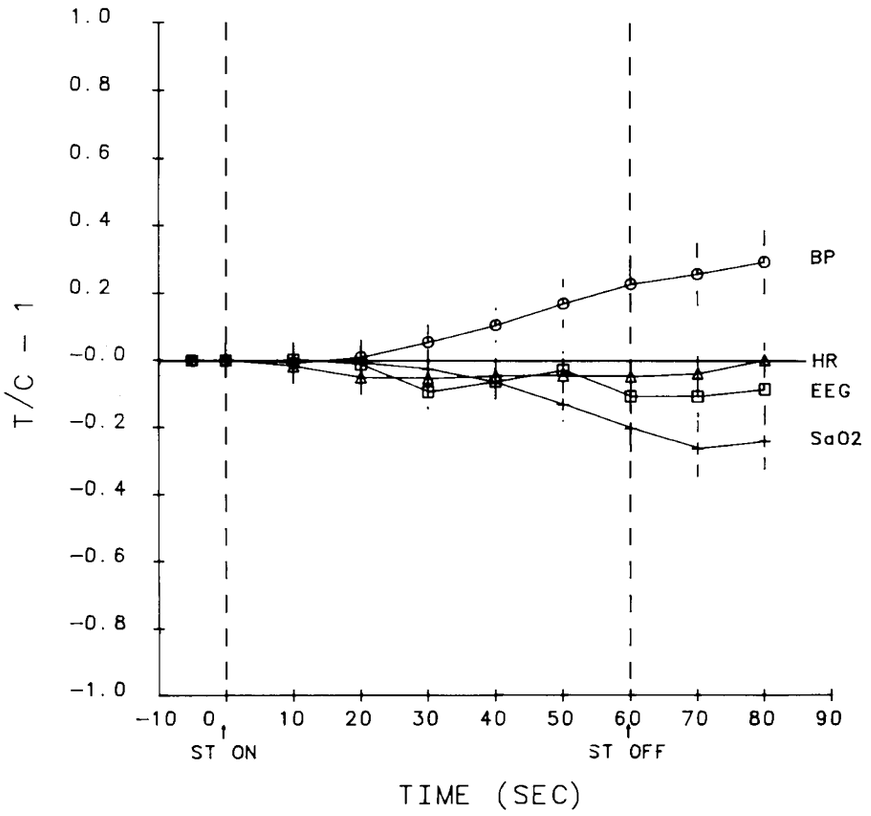

Fig. 4. Percent change from control value (mean + SEM) of systemic blood pressure (*circle*), heart rate (*triangle*), EEG (*square*), and arterial oxygen saturation (*cross*) during 60 s of SLN-induced apnea and 20 s into the poststimulus period in a hyperoxic environment (FiO^2 = 0.5–0.7). Note that hyperoxia delayed the start of desaturation and EEG attenuation, bradycardia did not occur.

Table 2. *Mean ± SEM of arterial oxygen saturation, arterial blood pressure, EEG amplitude, and heart rate for control, 60-s stimulus, and 20-s poststimulus period during hyperoxia*

	Control period (s)	Stimulus period (s)						Poststimulus period (s)	
		10	20	30	40	50	60	10	20
SaO_2 % (n = 11)	96 ± 1	97 ± 1	96 ± 1	94 ± 2	90 ± 3	84 ± 5	78 ± 7*	72 ± 8*	74 ± 8*
BP (mm Hg) (n = 6)	82 ± 2	82 ± 2	83 ± 2	87 ± 3	91 ± 4	96 ± 7	101 ± 8	104 ± 9	107 ± 9*
EEG (×10 UV) (n = 11)	11 ± 1	11 ± 1	11 ± 1	10 ± 1	10 ± 1	10 ± 1	10 ± 1*	9 ± 1	9 ± 1
HR (bpm) (n = 11)	187 ± 11	184 ± 10*	178 ± 10*	177 ± 10*	178 ± 9	178 ± 9	177 ± 8	176 ± 9	185 ± 7

* $p < 0.05$ *versus* control.

the EEG as measured by a decrease in amplitude. As seen in Table 1, the EEG amplitude decreased early in the stimulus period, and this decrease was statistically significant by 30 s. At approximately 55 s, the EEG was down to 50% of baseline and between 60 and 70 s there was complete flattening in 80% of the trials (Fig. 2). The EEG amplitude was fit to a single exponential and estimated as EEG(%control) = 100exp(−0.027t); r = 0.89.

Hyperoxia. The effect of inducing a similar central apnea in a hyperoxic environment is shown in Figure 3. The increased O_2 stores delayed the start of desaturation and hypertension; EEG attenuation was mild (10% of baseline at 60 s) (Fig. 4). Mild cardiac slowing only occurred during the first 30 s of stimulation (Table 2). Average baseline PaO_2 was 217 mm Hg and at 60 s into the stimulus period it was 110 mm Hg. Mean $PaCO_2$ increased from 35 to 55 mm Hg after 60 s of stimulation.

DISCUSSION

Respiration in immature infants is characterized by a wide spectrum of breathing patterns ranging from regular breathing, to periodic breathing, to apnea. Apnea can be life-threatening and is usually considered dangerous if longer than 20 s, or if associated with cyanosis, pallor, bradycardia, or hypotonia (19).

In general, there are two ways of monitoring the severity of an apnea: 1) by the duration of the apnea itself, the rationale being that the longer the apneic episode, the more severe the sequelae and 2) by the advent of bradycardia. Both methods have inherent difficulties. Most ICU respiratory transducers are based on thoracic impedance changes. This method is sensitive to chest wall movements and thus insensitive to obstructive or mixed apneas. Criteria for critical apnea durations based on this device may therefore be misleading. Heart rate monitoring may also be used for indicating an apneic event. However, bradycardia of less than 100 beats/min is variably associated with apnea, occurring in only 56% of apneas lasting between 20–40 s duration (13).

Developing criteria for critical apneic times is further complicated by the variable etiology of neonatal apnea. Whereas apnea may be related to immaturity of the central nervous system (4, 20), it may be also caused by a number of conditions including

infection, metabolic disturbances, IVH, and vagal stimulation. Furthermore, variability among infants in lung function and resting PaO_2 values may alter a critical value in apneic duration among infants.

The purpose herein was to examine the cardiovascular and neurophysiologic changes that occur during graded apneic periods under controlled conditions. Apneas were produced in healthy, young piglets using reflex stimulation, and thus the etiologies for the apneas were the same in all subjects.

Apnea and oxygen desaturation. Herein we have demonstrated that in lightly anesthetized newborn piglets, central apnea led to rapid, progressive desaturation that continued as long as the piglet remained apneic. Oxygen saturation was significantly lower than control by the first 10 s of apnea. Similar results have been found in preterm infants monitored for both central and obstructive apnea, in whom the mean time to onset of desaturation was 6.9 s (21). This rapid fall in oxygen saturation can be explained on the basis of a high metabolic oxygen consumption in relation to their lung oxygen stores in young infants. In addition, newborn infants may start at a lower O_2 saturation than older infants or adults and thus be on the steep part of the oxyhemoglobin dissociation curve (22).

Apnea and hypertension. Hypertension developed in synchrony with O_2 desaturation. The effect of hyperoxia was to delay the start of desaturation and hypertension. At 60 s, mean blood pressure during normoxia and hyperoxia increased by 55 and 23%, respectively (Figs. 2 and 4). Therefore, the hypertensive response seen during SLN-induced central apnea (without periodic breathing) appears secondary to hypoxemia and, to a lesser degree, to the activation of the laryngeal reflex.

Apnea and heart rate. Overall, only mild changes in heart rate occurred during SLN-induced apnea. In the beginning of the respiratory pause, there was a slight but significant decrease in heart rate. This early fall in heart rate has been previously reported during spontaneous respiratory pauses in infants and is believed to be secondary to the absence of lung inflation (23). A drop in heart rate was also seen in newborn lambs in which apnea was elicited by laryngeal water stimulation (24). However, the magnitude of heart rate slowing that we observed is less than that seen in the above, tracheostomized lambs. Although this difference may be due to the use of pentobarbital in our studies (25), we believe it is more likely due to differences in the experimental preparations. In our piglets the upper airway remained intact and thus they could regulate expiratory lung volume. Increases in lung volume are known to dramatically attenuate the bradycardia associated with laryngeal reflex activation (25).

Pentobarbital may have affected the cardiovascular function in our studies. However, existing evidence suggests that its effect on blood pressure and heart rate is small or negligible at the doses used (26). Also, this anesthetic dosage maintains baroreceptor and peripheral vascular constrictor responses (27). From our data, a comparison of the control heart rates and blood pressure against a population of unaesthetized piglets (28) of the same age showed a slight difference in blood pressure (80 versus 82 mm Hg) and a resting heart rate about 15% higher (170 *versus* 198 bpm).

Whether the SLN stimulation per se contributed to the cardiovascular changes cannot be determined with certainty. However, evidence from this laboratory as well as other laboratories suggest that the stimulation did not play a major role. Approximately 80% of the cardiovascular changes are secondary to the induced apnea, loss of lung inflation reflexes, and blood gas changes (25), *i.e.* reflexes evoked regardless of the cause of the apnea. Furthermore, we have previously shown that SLN stimulation in unanesthetized piglets resulted in no significant change in heart rate or blood pressure (28). Similarly, herein SLN stimulation in the presence of hyperoxia had a negligible effect on heart rate or blood pressure (Table 2).

Apnea and EEG. Of particular interest was the observation

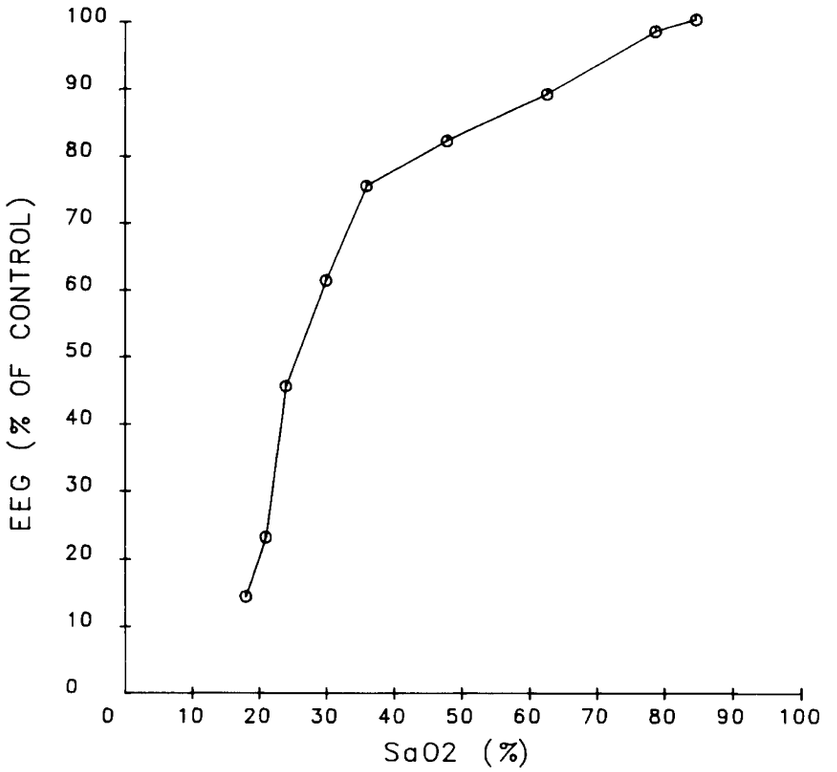

Fig. 5. EEG (percent change from control) *versus* oxygen saturation. Note rapid decline of EEG amplitude with saturation when the latter falls below 50%.

that after approximately 30 s of apnea, EEG amplitude began to decrease and continued to do so until complete electrical inactivity. When piglets were made hyperoxic, desaturation was delayed and there was minimal EEG attenuation (Fig. 4). Thus, EEG activity appears to correlate well with the change in SaO_2 (Fig. 5). Although anesthesia may have influenced the sensitivity of the EEG to SaO_2 changes, we believe that the anesthetic effect is relatively minor compared to the major changes seen in our animals. Piglets were only lightly anesthetized and low dose barbiturates cause activation rather than attenuation of the EEG (29, 30; Sanocka UM, Donnelly DF, Haddad GG, unpublished observations).

EEG changes have been observed in newborn infants during apneic attacks. In 1969, Roberton (31) noted that during attempts at weaning preterm infants from the respirator they frequently became apneic, hypoxic, and EEG activity decreased and, in some cases, became virtually flat. More recently, Southall *et al.* (32) described a form of "prolonged expiratory apnea" in infants during which desaturation occurred and EEG amplitude decreased 25–30 s after the onset of apnea. This latency period was similar to that which we observed experimentally.

Clinical implications. Our data herein demonstrate that under certain circumstances, there is a consistent pattern of cardiovascular and neurophysiologic response that we believe is mostly due to the induced apnea and its consequences. Although these observations are made in anesthetized piglets, we suggest that this patterned response may not be very different from that in the newborn suffering from some forms of apneic spells.

The most striking and clinically relevant finding is that the heart rate remained relatively stable despite marked hypoxia and EEG attenuation. Heart rate was more than 120 beats/min when SaO_2 was very low (less than 40%), and at this time the EEG was nearly isoelectric. Southall *et al.* (32) previously reported that major bradycardia did not develop in some infants with prolonged expiratory apnea despite desaturation and EEG changes. From our clinical experience, we have seen two infants who developed a flat EEG during apnea. In one of these infants, EEG flattening was noted before the onset of major bradycardia. After stimulation and resumption of spontaneous breathing, the EEG remained flat for 1.5 min despite a return of the heart rate to 150 beats/min. Subsequently, EEG returned to normal.

What remains to be established is how frequently EEG flattening occurs in association with apneic spells and the exact relationship of this change to the degree of hypoxia, bradycardia, and type of apnea. In addition, little is known of the neurologic sequelae of apnea, not confounded by a variety of other perinatal insults to which the infant is subjected. For instance, in follow-up studies of low birth weight infants (less than 1500 g) without intraventricular hemorrhage, 10% were found to have major neurodevelopmental handicaps and 40% had minor handicaps (33). Perhaps repeated episodes of clinically undetected hypoxemia, severe enough to lead to EEG changes, contributed to this handicap.

In conclusion, we have shown that in newborn piglets SLN-induced central apnea results in rapid desaturation and hypertension followed by EEG flattening. A modest decrease in heart rate occurs late, after the EEG has become nearly flat. Although these observations were made in anesthetized and instrumented piglets, they may have important implications in the care of newborn infants. Our clinical experience together with data presented by Southall *et al.* (32) have suggested that the same sequence of events may occur in some types of infantile apneas. Inasmuch as bradycardia can be a late manifestation of hypoxemia, it may not be appropriate to rely solely on standard apnea and heart rate monitors. Our experimental data suggest that infants should have continuous $tcPO_2$ or arterial pulse oximetry recorded for proper assessment of cardiopulmonary function. This will allow for earlier intervention by health care personnel and may prevent potentially deleterious effect of hypoxemia on the central nervous system.

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