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Influence of Carotid Denervation on the Arousal and Cardiopulmonary Response to Rapidly Developing Hypoxemia in Lambs

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ABSTRACT. Experiments were done on five lambs to determine if carotid denervation influences the arousal and cardiopulmonary responses to rapidly developing hypoxemia during sleep. Each lamb was anesthetized and instrumented for recordings of electrocorticogram, electrooculogram, nuchal and diaphragm electromyograms, and measurements of arterial blood pressure and arterial hemoglobin oxygen saturation. The carotid chemoreceptors and baroreceptors were denervated, a tracheostomy was done, and a fenestrated tracheostomy tube was placed in the trachea so that the inspired oxygen mixture could be changed quickly. No sooner than 3 d after surgery, measurements were made in quiet sleep and active sleep during control periods when the animal was breathing 21% oxygen and during experimental periods of rapidly developing hypoxemia when the animal was breathing 5% oxygen. Rapidly developing hypoxemia was terminated during each epoch by changing the inspired gas mixture back to 21% oxygen once the animal aroused from sleep or once the arterial Hb oxygen saturation decreased to 30%. Arousal occurred during only 4 of 11 epochs in quiet sleep and during only 3 of 14 epochs in active sleep before the arterial Hb oxygen saturation decreased to 30%. These data provide evidence that the carotid chemoreceptors and/or carotid baroreceptors play a major role in causing arousal from sleep during rapidly developing hypoxemia in lambs. (*Pediatr Res* 25: 473–477, 1989)

The arousal response is an important protective response that may prevent severe hypoxemia and death during sleep (1). Hypoxemia may occur during sleep in individuals with chronic lung disease (*e.g.* cystic fibrosis [2], bronchopulmonary dysplasia [3], asthma [4]) and/or during central or obstructive apnea. The usual respiratory response to hypoxemia is an increase in ventilation, which tends to increase the alveolar and arterial oxygen tension. However, as the ventilatory response to hypoxemia is decreased during active sleep compared to quiet sleep in lambs (5) and calves (6) (*i.e.* species that develop rib-cage paradox during active sleep) and the resumption of tidal ventilation during obstructive apnea is usually preceded by arousal (7–10), the arousal response may be the most important response to hypoxemia during sleep.

Previous experiments on young lambs (5, 11–13) and calves (6) have demonstrated that arousal occurs from both quiet sleep and active sleep in response to alveolar hypoxia, but the mechanism remains unclear. The purpose of the present experiments was to investigate the effect of carotid-denervation on the arousal response from sleep to rapidly developing hypoxemia in young lambs.

MATERIALS AND METHODS

Five lambs ranging in age from 11 to 24 d were studied. Each lamb was separated from its ewe 3 to 7 d after birth and was housed in our laboratory in a Plexiglas cage with continuous access to milk (Lamb Milk Replacer, Land O'Lakes, Inc., Fort Dodge, IA). The lambs were among other lambs, fed and slept *ad libitum*, and soon became accustomed to the surroundings and laboratory personnel.

Surgical preparation. Each lamb underwent one operation before the study. For surgery, each lamb was given atropine sulfate (0.2 mg/kg subcutaneously); anesthesia was induced by having the lamb breath 3 to 4% halothane in oxygen via a mask. The trachea was then intubated with a cuffed endotracheal tube; anesthesia was maintained by ventilating the lamb's lungs with 0.5–1.0% halothane in oxygen. An ECG, end-tidal carbon dioxide levels, and rectal temperature were monitored during surgery; body temperature was kept near 39°C with a heating pad, and end-tidal carbon dioxide levels were kept near 5% with a volume-cycled ventilator.

The operation was done when the lambs were between 7 and 21 d of age. A double-lumen fiberoptic catheter oximeter (Model U440 Opticath, Oximetrix, Inc., Mountain View, CA; 90% response to a step change in SaO_2 within 5 s) was inserted to the thoracic aorta via a femoral artery for continuous measurement of arterial Hb oxygen saturation and blood pressure. Electrodes for the following recordings were also implanted: electrocorticogram (recorded from electrodes placed through burr holes to lie over the parietal cortex), electro-oculogram (recorded from electrodes placed at the inner and outer canthus of the right eye), nuchal electromyogram (recorded from electrodes placed in the dorsal cervical musculature) and diaphragm electromyogram (recorded from electrodes placed transabdominally into muscle fibers adjacent to the lateral margin of the central tendon of the right hemidiaphragm). A reference wire was sutured into the subcutaneous tissue of the scalp. The electrodes were made in our laboratory and were paired, Teflon-coated, multistranded stainless steel wires (AS 633, Cooner Wire Co., Chatsworth, CA); approximately 3 mm of the tip of each was bared and implanted.

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The proximal end of each wire was bared and soldered to the appropriate pin of an 18-pin electrical plug, which was interfaced with four differential high-impedance probes (7HIP5G, Grass Medical Instruments, Quincy, MA) during a study.

Carotid denervation was performed as follows: The carotid body and carotid sinus was approached as described by Appleton and Waites (14) and denervated as described by Bureau *et al.* (15). Briefly, the denervation procedure consisted of *1*) cutting the sinus nerve, *2*) stripping the adventitia from the wall of the carotid artery from the origin of the lingual artery to 0.5 cm below the origin of the occipital artery , *3*) removing all fibroadipose nodular tissue from around the occipital-carotid artery junction, *4*) sectioning all minute vessels arising in the area of the carotid and occipital artery bifurcation, *5*) stripping the adventitia from the wall of the occipital artery for 1 cm from its origin from the carotid artery, and *6*) painting the walls of the stripped vessels with 7% phenol.

A tracheotomy was also performed, and a fenestrated tracheostomy tube (Shiley, Inc., Irvine, CA) was placed in the trachea. This tracheostomy tube allows one to select whether an animal breathes entirely through the opening of the tracheostomy tube (cuff inflated, inner cannula in place) or breathes entirely through its upper airway (cuff inflated, decannulation cannula in place). After surgery, the decannulation cannula was inserted into the tracheostomy tube so that airflow during tidal respiration would be through the upper airway. The lambs were allowed to recover from surgery in a Shor-Line intensive care unit for small animals (Schroer Manufacturing Company, Kansas City, MO) and were then placed back in their Plexiglas study cage in our sleep laboratory but were not studied before the 3rd postoperative day. The lambs received antibiotics daily, (penicillin G and dihydrostreptomycin) beginning on the day of surgery.

Conditions of observations. Our sleep laboratory consists of a large room containing two sound-attenuating chambers. Temperature, sound, and lighting can be precisely controlled in each chamber. The lambs in this series of experiments were raised in an environmental temperature of 25 ± 1°C. Each chamber also has a 1-way viewing mirror as well as a closed circuit video system to observe the lambs. Before a study, a partition is placed in the cage to prevent the lamb from turning around once the catheter, electrode, and breathing circuit are connected. However, the lamb can still lie down, stand up, and feed *ad libitum.*

For a study, the vascular catheter is connected to a strain gauge manometer (Gould P23ID, Gould, Inc., Oxnard, CA) using rigid pressure monitoring tubing, and the optical connector is connected to the optical module of the oximeter processor; the strain gauge manometer is placed at the approximate level of the heart when the animal is lying down. *In vivo* calibration of the fiberoptic catheter oximeter was done after the oxygen saturation of a sample of arterial blood was determined using a co-oximeter (Instrumentation Laboratories 282). The inner cannula is placed into the tracheostomy tube and a breathing circuit (Neonatal Ventilator Circuit, model 5302, Intec Medical Inc., Blue Springs, MO) attached so that 10 liters/min of a known gas (*i.e.* 21% or 5% O_2) can be passed by the tracheostomy tube. The 18-pin electrical plug is connected to the differential high impedance probes; a heavy duty cable connects the differential high impedance probes to AC preamplifiers (model 7P5 Wide Band AC EEG Preamplifier, Grass Medical Instruments, Quincy, MA) in the adjacent room. The amplified activity from the electrocorticogram is full-wave rectified and then integrated (model 7P10 Polygraph Integrator, Grass Medical Instruments) to give a running record of the total accumulated area under the electrocortical waves (11). The tracing writes out a ramp function, the slope of which is directly proportional to the ongoing input activity.

The following electrophysiologic criteria were used to define behavioral state once the animal was lying down (11). During quiet wakefulness, the electrocorticogram shows a fast-wave, low-voltage pattern; there are occasional eye movements, and there is tonic activity on the nuchal electromyogram. During quiet sleep, the electrocorticogram shows a slow-wave, high-voltage pattern; there are no eye movements and there is tonic activity on the nuchal electromyogram. During active sleep, the electrocorticogram shows a fast-wave, low-voltage pattern; there are rapid eye movements on the electro-oculogram; there is no activity on the nuchal electromyogram, and there are occasional fast ear, facial, and limb twitches. Each lamb was allowed to cycle through at least one epoch of quiet sleep before the experiment actually began so that we could determine the amplitude of the integrated electrocortical activity and set strict criteria for defining quiet sleep.

The following electrophysiologic criteria were used to define arousal from sleep. During quiet sleep, the point of arousal was determined by a change in the electrocorticogram from a high-voltage, slow-wave pattern to a low-voltage, fast-wave pattern with continued activity on the nuchal electromyogram (11). During active sleep, the point of arousal was determined by a return of tonic activity on the nuchal electromyogram with continued low-voltage, fast-wave activity on the electrocorticogram.

Experimental protocol. During a study, systemic arterial blood pressure, arterial Hb oxygen saturation, and the electrophysiologic signals were recorded on a Grass model 7 polygraph, and the lambs were monitored on a closed-circuit video system. Measurements were made during 30-s control periods when the lambs were breathing 21% oxygen and during experimental periods of rapidly developing hypoxemia when the lambs were breathing 5% oxygen. Hypoxemia was terminated during an experimental period by changing the inspired oxygen concentration to 21% once the animal aroused from sleep. If an animal did not arouse before the arterial Hb oxygen saturation decreased to 30%, the inspired oxygen concentration was changed back to 21%. Because the mean epoch lengths of quiet sleep and active sleep of chronically instrumented lambs during this age range are 6 to 7 min and 3 to 4 min, respectively (Johnson P, unpublished work), control measurements were made approximately 2 to 3 min after the lamb entered quiet sleep and approximately 30 s after the lamb entered active sleep. Experiments began between 0800 and 1000 and continued until sufficient data were collected.

Statistical analysis. For every animal, we determined an average value for each variable during the control period and during the experimental period immediately preceding arousal from quiet sleep and active sleep. If an animal did not arouse before the arterial Hb oxygen saturation decreased to 30%, the values obtained immediately preceding the development of an arterial oxygen Hb saturation of 30% were used. To analyze the data statistically, we performed a 2-factor ANOVA for repeated measures of the same variable to determine if state (quiet sleep *versus* active sleep) or period (control *versus* experimental) affected arterial Hb oxygen saturation, heart rate, systolic blood pressure, diastolic blood pressure, or respiratory frequency (16). If there was a significant difference, a Duncan's multiple comparison test was performed to determine which means were statistically different (34).

In addition, as arousal was delayed after carotid denervation, we determined an average value for each variable at 10–13 s into the experimental period for quiet sleep and at 41–44 s into the experimental period for active sleep; 13 ± 8 s and 44 ± 15 s are the times (mean ± SD) to arousal from quiet sleep and active sleep, respectively, during exposure to 5% oxygen in carotid-intact young lambs (11). Data from these time periods allows us to compare the cardiorespiratory responses to alveolar hypoxia obtained from carotid-denervated lambs (present study) to those obtained from carotid-intact young lambs (previous study, Ref 11). We performed a 3-factor ANOVA for repeated measures of the same variable to determine if group (carotid-denervated *versus* carotid-intact), period (control *versus* experimental) or state (quiet sleep *versus* active sleep) affected heart rate, systolic blood pressure, diastolic blood pressure, or respiratory frequency

(16). If there was a significant difference, a Duncan's multiple comparison test was performed to determine which means were statistically different (34).

RESULTS

Carotid denervation significantly influenced the arousal and cardiopulmonary responses to rapidly developing hypoxemia (Table 1, Fig. 1). Arousal occurred during only four of 11 epochs in quiet sleep and during only three of 14 epochs in active sleep before the arterial Hb oxygen saturation decreased to 30%. This is in contrast to the response we have previously observed in carotid-intact lambs (11) where arousal occurred during 25 of 25 epochs in quiet sleep (SaO_2 80 ± 5% at arousal, mean ± 1 SD) and during 20 of 23 epochs in active sleep (SaO_2 55 ± 11% at arousal, mean ± 1 SD) before electrocortical signs of cerebral hypoxia developed.

Carotid denervation affected baseline cardiorespiratory variables. Systolic and diastolic blood pressure were increased in carotid-denervated lambs compared to carotid-intact lambs (Ref 11, Table 2) in both quiet sleep and active sleep. However, heart rate was increased only during quiet sleep in carotid-denervated lambs compared to carotid-intact lambs. Arterial blood gases and pH during quiet wakefulness were as follows: pH, 7.37 ± 0.02; Pa_{O_2}, 67 ± 10 torr; and Pa_{CO_2}, 54 ± 2 torr.

Carotid denervation also affected the cardiorespiratory response to rapidly developing hypoxemia (Table 2). Systolic and diastolic blood pressure and heart rate increased much more during active sleep in carotid-denervated lambs than in carotid-intact lambs. In addition, carotid denervation eliminated the early respiratory frequency response to rapidly developing hypoxemia as compared to carotid-intact animals (Table 2).

DISCUSSION

Our study provides new information about the mechanism of arousal from sleep in response to cardiorespiratory stimuli in lambs. The data provide evidence that the carotid body and/or the carotid sinus plays a major role in causing arousal from sleep during rapidly developing hypoxemia. Furthermore, carotid denervation significantly affected baseline cardiorespiratory control as well as the cardiorespiratory response to rapidly developing hypoxemia.

Carotid denervation significantly affected the arousal response to rapidly developing hypoxemia. Arousal occurred during only four of 11 epochs in quiet sleep and during only three of 14 epochs in active sleep before the arterial Hb oxygen saturation decreased to 30%. This is in marked contrast to what we have previously observed in carotid-intact lambs (11–13). Although our data provide evidence that the carotid sinus and/or carotid body play a major role in causing arousal from sleep during rapidly developing hypoxemia, they do not provide definitive information about the factor(s) that actually initiate the response. There are several possibilities.

The first possibility is that arterial hypoxemia stimulates the carotid bodies which stimulate the recticular activating system (17) and cause arousal. The second possibility is that arterial hypoxemia stimulates the carotid bodies that produce an increase in ventilation and sensory input to the recticular activating system from the lungs and chest wall and cause arousal. In support of this, Bowes *et al.* have reported that bilateral vagal blockade delays the arousal response to rapidly developing hypoxemia in adult dogs (18). The third possibility is that arterial hypoxemia stimulates the carotid bodies, which produces an increase in heart rate and blood pressure and stimulates the carotid sinus baroreceptors, which causes arousal. We have previously reported that acute increases in blood pressure cause arousal from sleep in lambs, (19) and Horne *et al.* (20) recently reported that the arousal response to an acute increase in blood pressure is abolished by sinoaortic denervation in lambs.

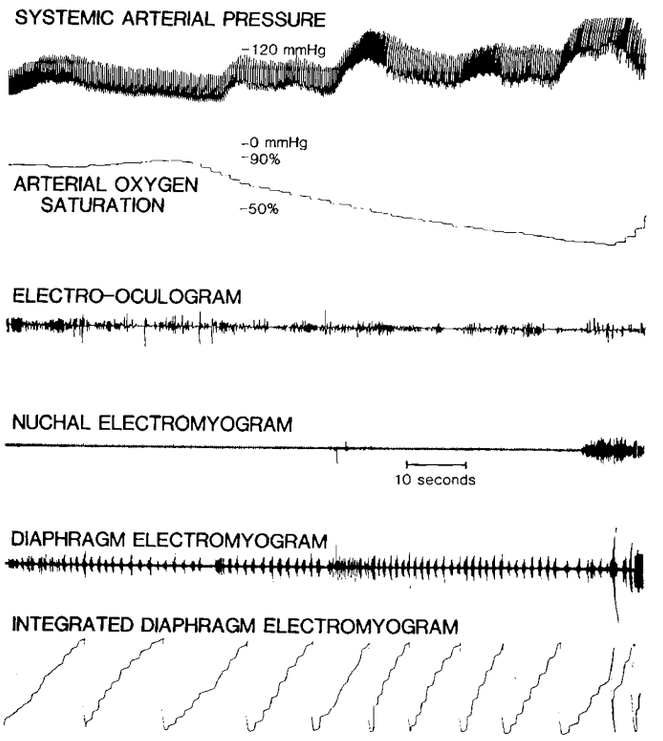

Fig. 1. Tracing showing variables during control period and during experimental period in one epoch of active sleep where animal did arouse in response to rapidly developing hypoxemia.

Table 1. *Arousal and cardiorespiratory response to rapidly developing hypoxemia in carotid-denervated young lambs during quiet sleep and active sleep**

Variable	Quiet sleep			Active sleep		
	Control period		Experimental period	Control period		Experimental period
SaO_2 (%)	81 ± 9	†	37 ± 3	82 ± 6	†	32 ± 4
Heart rate (beats/min)	‡189 ± 26	‡	193 ± 39	147 ± 27	†	179 ± 29
Systolic blood pressure (mm Hg)	111 ± 13	†	149 ± 15	98 ± 8	†	142 ± 15
Diastolic blood pressure (mm Hg)	70 ± 7	†	104 ± 21	53 ± 13	†	92 ± 15
Respiratory frequency (breaths/min)	30 ± 11	†	41 ± 13	37 ± 15		43 ± 18

* Values are means ± 1 SD for $n = 5$. Measurements were made during the experimental period immediately preceding arousal; if arousal did not occur before a SaO_2 of 30%, measurements were made immediately preceding development of a SaO_2 of 30%. A value of 30% was used for SaO_2 during the experimental period if arousal did not occur.

† $p < 0.05$ for control period *vs.* experimental period.

‡ $p < 0.05$ for quiet sleep *vs.* active sleep for a given period as determined by MANOVA and Duncan's multiple comparison test.

Table 2. *Comparison of cardiovascular and respiratory responses to rapidly developing hypoxemia in carotid-intact (I) and carotid-denervated (D) young lambs during quiet sleep and active sleep.**

Variable	Group	Quiet sleep			Active sleep		
		Control period		10–13 s	Control period		41–43 s
Heart rate (beats/min)	I	162 ± 22 ‡	†	174 ± 28 ‡	153 ± 25		146 ± 23 ‡
	D	189 ± 26	†	202 ± 30	147 ± 27	†	188 ± 42
Systolic blood pressure (mmHg)	I	82 ± 9 ‡		86 ± 11 ‡	73 ± 12 ‡	†	83 ± 9 ‡
	D	111 ± 13		117 ± 14	98 ± 8	†	128 ± 27
Diastolic blood pressure (mmHg)	I	57 ± 5 ‡		60 ± 7 ‡	48 ± 14		52 ± 7 ‡
	D	70 ± 7		78 ± 10	53 ± 13	†	80 ± 30
Respiratory frequency (breaths/min)	I	25 ± 5	†	39 ± 11	39 ± 10	†	56 ± 10 ‡
	D	30 ± 11		32 ± 11	37 ± 15		38 ± 18

* Values are means ± 1 SD. $n = 8$ for carotid-intact animals (Ref. 11) and $n = 5$ for carotid-denervated animals. Experimental measurements were made at 10–13 s in quiet sleep and 41–43 s in active sleep.

† $p < 0.05$ for control period *vs.* experimental period.

‡ $p < 0.05$ for carotid-intact *vs.* carotid-denervated as determined by MANOVA and Duncan's multiple comparison test.

It is important to point out that our carotid denervation procedure, as well as the carotid denervation procedure of previous investigators (18, 21), not only eliminated afferents from the carotid chemoreceptors but also eliminated afferents from the carotid baroreceptors. The effectiveness of our carotid denervation procedure is provided by at least three lines of evidence. First, hypoventilation and hypoxemia were observed during resting conditions compared to intact animals (22). Second, the early respiratory frequency response to rapidly developing hypoxemia was eliminated as compared to intact animals (Table 2); the late respiratory frequency response to hypoxemia in carotid-denervated animals (Table 1) may have resulted from stimulation of the aortic chemoreceptors or from central stimulation as have previously been reported in adult cats (23). Third, systemic arterial hypertension was observed during resting conditions (Table 2).

Our experiments were done on lambs during the 2nd or 3rd wk of postnatal life. It is likely that the carotid chemoreceptors play a more important role in initiating the arousal response to rapidly developing hypoxemia during this period than during the immediate postnatal period, as Blanco *et al.* (24) have shown that carotid chemoreceptor activity—spontaneous or in response to a low Pa_{O_2}—is minimal during the 1st d or two of postnatal life. However, this requires further investigation.

Our results on the arousal response are in agreement with those of Bowes *et al.* (18), who found that carotid denervation had a profound effect on the arousal response to rapidly developing hypoxemia with arousal failing to occur despite arterial Hb oxygen saturations below 50% in adult dogs. Arousal occurred at arterial Hb oxygen saturations of 83 ± 5% (mean ± 1 SE) and 71 ± 2% in quiet sleep and active sleep, respectively, in carotid-intact dogs. However, our results do not agree with those of Neubauer *et al.* (21), who found that rapidly developing hypoxemia produced arousal in 46 s and at an arterial Hb oxygen saturation of 47 ± 2% (mean ± SE) in carotid-intact adult cats and in 42 s and at an arterial Hb oxygen saturation of 50 ± 2% in carotid-denervated cats during quiet sleep. However, one might speculate that the apparent discrepancy is related to the fact that Neubauer *et al.* performed experiments on sleep-deprived adult cats, and previous experiments by Bowes *et al.* (5) have provided evidence that short-term sleep fragmentation delays the arousal response to alveolar hypoxia in adult dogs.

The arousal response from sleep has been suggested to be an important protective response that may prevent severe hypoxemia and death during an apneic episode (1). Although apnea occurs to some extent in almost all preterm (26) and term infants (27), little is known about the mechanism that terminates an apneic episode. Read and Henderson-Smart (26) have observed that prolonged apnea (*i.e.* apnea of 20 s or more) occurs in the majority of babies under 30 wk of gestation, in about 50% of babies at 30–32 wk of gestation, and in about 7% of babies at 34–35 wk of gestation. Furthermore, Southall *et al.* (28) have presented data showing that 34 of 50 (*i.e.* 68%) randomly selected, healthy term infants studied between 1 and 15 d postnatally had apneic episodes of 10 s or greater and that the 95th percentile extended up to 18 s. Guntheroth (28) has suggested that these infants do not die because of an intact arousal response and has hypothesized that the crucial area of abnormal physiology in the sudden infant death syndrome is arousal after apnea. The importance of the arousal response is at least 2-fold. First, wakefulness *per se* is a potent stimulus to breathing. Second, arousal permits the limitation of behavioral and a ventilatory response to the stimulus; arousal is generally thought to precede resumption of tidal ventilation during apnea (7–10).

Two recent studies have provided evidence of an abnormal arousal response to hypoxemia in infants who have had an apparent life-threatening event (30, 31). McCulloch *et al.* (29) found that only one of 11 infants with an apparent life-threatening event aroused in response to progressive alveolar hypoxia (F_{IO_2} 0.15) compared to 14 of 22 normal infants. After this study, it was suggested that the lack of an arousal response in 30% of the control infants was due to lack of maximal chemoreceptor stimulation (31). Subsequently, van der Hal (30) found that nine of nine control infants aroused in response to more pronounced alveolar hypoxia (F_{IO_2} 0.11), compared to only 19 of 50 infants who had experienced an apparent life-threatening event. Although these data might support the hypothesis that an abnormal arousal response to hypoxemia plays a role in the final pathway to the sudden infant death syndrome, one also has to implicate failure of other "backup" mechanism(s) (*e.g.* gasping or circulatory failure), as these infants did not die (31). Recent evidence has been provided that the arousal response to alveolar hypoxia in some infants with bronchopulmonary dysplasia is delayed to the extent that some of the infants required vigorous stimulation and supplemental oxygen after the initial arousal response (32).

The results of our studies may have implications for the sudden infant death syndrome. If the final event is apnea, as has been hypothesized (28, 33), data from our previous studies would

allow one to speculate that *1*) if the rate of change of arterial oxygen is great enough during apnea in active sleep, arousal may fail to occur before electrocortical signs of cerebral hypoxia and primary apnea occur (11); and that *2*) if an infant is repeatedly exposed to hypoxemia—either as a result of multiple apneic episodes or hypoxemia during sleep as a result of gas exchange abnormalities—that the arousal response to apnea might be impaired (12). Furthermore, data from our present study would allow one to speculate that if carotid chemoreceptor and/or carotid baroreceptor function is impaired, arousal may fail to occur before hypoxic cerebral depression occurs. If, in addition, there is a deficit in the gasping mechanism or if the circulation fails before the onset of gasping, death could quickly ensue.

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Erratum

The article by Hirokazu Tsukahara et al. entitled "Insulin resistance in a boy with congenital generalized lipodystrophy" (Pediatr Res 24:668–672, 1988) contained an error in an author's name. The correct spelling is **Kazunori Yamada.** The correct affiliation for authors H. Tsukahara, K. Kikuchi, H. Kuzuya, A. Kosaki, T. Kakehi, H. Nishimura, K. Yamada, Y. Yoshimasa, H. Imura, and H. Mikawa is **Kyoto University School of Medicine.** The printer regrets these errors.