Elevated body temperature enhances the laryngeal chemoreflex in decerebrate piglets


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Curran, A. K., L. Xia, J. C. Leiter, and D. Bartlett Jr. Elevated body temperature enhances the laryngeal chemoreflex in decerebrate piglets. J Appl Physiol 98: 780–786, 2005. First published November 12, 2004; doi:10.1152/japplphysiol.00906.2004.—Hyperthermia and reflex apnea may both contribute to sudden infant death syndrome (SIDS). Therefore, we investigated the effect of increased body temperature on the inhibition of breathing produced by water injected into the larynx, which elicits the laryngeal chemoreflex (LCR). We studied decerebrated, vagotomized, neonatal piglets aged 3–15 days. Blood pressure, end-tidal CO2, body temperature, and phrenic nerve activity were recorded. To elicit the LCR, we infused 0.1 ml of distilled water through a polyethylene tube passed through the nose and positioned just rostral to the larynx. Three to five LCR trials were performed with the piglet at normal body temperature. The animal’s core body temperature was raised by ~2°C, and three to five LCR trials were performed before the animal was cooled, and three to five LCR trials were repeated. The respiratory inhibition associated with the LCR was substantially prolonged when body temperature was elevated. Thus elevated body temperature may contribute to the pathogenesis of SIDS by increasing the inhibitory effects of the LCR.

EPIDEMIOLOGICAL STUDIES HAVE identified numerous biological, sociological and environmental risk factors for sudden infant death syndrome (SIDS). For example, environmental factors such as sleeping prone, maternal smoking, covering the baby’s head, and overheating all increase the risk of SIDS (6, 14, 25, 26). Among the biological factors, recent studies indicate that babies who die of SIDS may have significant neurotransmitter receptor defects. The number and distribution of muscarinic, kainate, and serotoninergic receptors in the brain stem were significantly reduced in babies who died of SIDS compared with babies who died as a result of chronic illnesses or accidents (24, 34, 35).

Identification of risk factors, some of which can be modified, led to recommendations that significantly reduced the occurrence of SIDS (22, 27, 36). Less progress has been made integrating the epidemiological and neuroanatomical findings into a coherent pathophysiological explanation of the exact mechanism whereby infants die in SIDS. It is our working hypothesis that the neurotransmitter defects interfere with protective homeostatic responses to potentially life threatening, but often-occurring events during infant sleep. Thus the epidemiologically defined risk factors identify either a potentially life-threatening event (e.g., sleeping prone presumably increases the risk of asphyxiation) or a factor that interferes with protective homeostatic responses (e.g., the neurotransmitter defects may interfere with cardiac, respiratory, or arousal responses to life-threatening events).

In previous studies in neonatal piglets, we investigated the effect of inhibiting neuronal activity in parts of the brain stem that were associated with reduced receptor binding in infants dying of SIDS. Inhibition of neurons within the rostral ventral medulla (RVM) reduced the response to stimuli that enhance ventilation; the ventilatory responses to hypercapnia (7) and hypoxia (19) were diminished by muscimol dialysis into the RVM. However, inhibition of neurons within the RVM enhanced the response to stimuli that diminish ventilation; baroreceptor-mediated inhibition of phrenic nerve activity was enhanced in decerebrate animals (9), and the laryngeal chemoreflex (LCR) was prolonged in sleeping neonatal piglets during muscimol dialysis into the RVM (42). The LCR can be elicited by infusing distilled water into the hypopharynx (4, 18), and the response consists of suppression of ventilation, apnea, coughing, and swallowing (42). Thus the physiological studies in neonatal piglets provided support for our working hypothesis that inhibition of those parts of the brain stem that are abnormal in babies dying of SIDS tends to reduce protective respiratory responses to a variety of respiratory stimuli.

Overheating has been identified in numerous epidemiological studies as a risk factor in SIDS. However, mechanisms whereby overheating might enhance life-threatening events or diminish protective reflexes have not been explored extensively. Haraguchi et al. (17) stimulated the superior laryngeal nerve electrically and demonstrated that the latency and threshold of thyroarytenoid muscle activation decreased as body temperature was changed from 34 to 41°C in anesthetized puppies and adult dogs. The reduction in threshold as body temperature increased was much greater in younger neonatal animals compared with adult dogs. The superior laryngeal nerve also mediates the LCR. Therefore, we tested the hypothesis that overheating would enhance the LCR. These studies were conducted in decerebrated neonatal piglets, and the results indicate that increased body temperature significantly prolongs the respiratory inhibition associated with the LCR.

METHODS

Successful experiments were performed on a total of 30 piglets, aged 3–16 days, with body weights ranging from 1.6 to 5.4 kg (average weight = 3.1 ± 0.2 kg). Piglets were housed with the sow in our animal care facility before they were studied. The Institutional Animal Care and Use Committee of Dartmouth College approved all protocols in these studies.
Surgery. Animals were anesthetized with 2% halothane (2-bromo-2-chloro-1,1,1-trifluoroethane; Halocarbon Laboratories) in O₂. A rectal probe was inserted, and body temperature was maintained at 37–38°C using a heating pad during the remaining preparations for the actual studies. Femoral arterial and venous catheters were inserted to measure blood pressure and administer drugs, respectively. Each animal was tracheostomized and artificially ventilated (dual-phase respirator, Harvard Apparatus, South Natick, MA) to maintain end-tidal CO₂ at ~5%. The carotid sinus regions were exposed bilaterally, and the internal and external carotid arteries were ligated to facilitate decerebration. The vagus nerves were sectioned bilaterally to prevent phrenic entrainment to the mechanical ventilator rhythm. The animal was placed prone, and the head was positioned in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA). The skull was opened, and the animal was decerebrated at the level of the superior colliculus. After decerebration, halothane anesthesia was discontinued, and the animal was paralyzed using pancuronium bromide (1 mg/kg iv; Elkins-Sinn, Cherry Hill, NJ). Supplemental doses of pancuronium were given as required, usually at a rate of 0.5 mg·kg⁻¹·h⁻¹. A phrenic nerve was exposed and sectioned, and the central cut end was placed on a bipolar recording electrode to monitor respiratory output. Phrenic activity was amplified (Gould Universal Amplifier, Cleveland, OH), and the moving-time average (“integrated activity”) was calculated electronically (100-ms time constant; CWE, Ardmore, PA). Peak integrated phrenic nerve activity, phrenic frequency, phrenic minute activity (= peak integrated phrenic nerve activity × phrenic frequency), body temperature, end-tidal CO₂ and O₂, and blood pressure were recorded on a computer (PowerLab, ADI, Castle Hill, Australia) for later analysis.

Eliciting the LCR. After decerebration, animals were allowed at least 30 min to stabilize before any further interventions. A small-diameter polyethylene tube was inserted into one nostril and placed with its tip at the caudal extent of the soft palate, just rostral to the larynx. The correct position of the tube was visually checked with a laryngoscope before the outer portion of the catheter was fixed to the nose. The LCR was produced by infusing 0.1 ml of distilled water into the larynx through the nasal tube during inspiration. The LCR is a complex mix of respiratory inhibition and activities that clear the airway, such as swallowing. In a previous study, the duration of the LCR provided a single measurement that captured the multiple events that may occur as part of the LCR (42). We defined the duration of the LCR as the period of respiratory instability from the beginning of the breath during which water was injected into the larynx to the onset of at least five regular breaths. These five breaths did not need to be the same frequency or amplitude as the control breaths; we simply required that they be regular. The LCR thus contained periods of both unstable respiratory activity and apneas. Examples of the LCR are shown in Fig. 1. The apneic periods during the LCRs were also measured and analyzed separately. Apnea was defined as a cessation of breathing greater than the duration of the two breaths preceding the breath during which the LCR was elicited. Animals were allowed to recover for a minimum of 10 min before the LCR trial was repeated. We elicited the LCR at least three times in each experimental condition and averaged responses within a treatment condition to obtain a measure of the LCR in each piglet in each treatment condition. We conducted preliminary studies in which the temperature of the distilled water used to elicit the LCR was either 34, 38, or 42°C. Between the LCR trials in these studies, the water was withdrawn to equilibrate with body temperature. To stimulate the LCR, a volume of water equal to the dead space of the laryngeal catheter plus 0.1 ml was injected. The order of testing the three water temperatures was randomized.

The diving reflex. The diving reflex consists of bradycardia and apnea, and the reflex is usually elicited by cold, wet stimuli applied in the sensory distribution of the fifth cranial nerve around the nose (10). Therefore, we determined whether elevating body temperature altered the respiratory inhibition associated with the diving reflex. We used two methods to try to elicit the diving reflex. First, we applied a 5-cm × 5-cm surgical sponge soaked in ice-cold water on the dorsal surface of the nose for 30–60 s. We also tried dipping the snout and mouth directly into a bowl of ice-cold water for 30–60 s.

Baroreflex stimulation. Elevating the blood pressure inhibits phrenic nerve activity in decerebrated neonatal piglets (9). Therefore, we determined whether elevating body temperature changed the phrenic response to elevating blood pressure. Care was taken to maintain the carotid bodies intact in these experiments. We confirmed that the sinus nerve was intact by injecting sodium cyanide into the femoral vein. In all animals tested, short-lasting respiratory stimulation followed the injection of sodium cyanide. Blood pressure was increased by injecting 200–300 μg of phenylephrine into the femoral vein. This stimulation was repeated at least three times at each body temperature, and we waited 10 min between baroreflex stimulations to allow phrenic nerve activity to return to baseline.

The control state was defined by averaging the mean arterial pressure and minute phrenic activity of the three breaths preceding the phenylephrine infusion. The baroreceptor stimulus was defined by the peak of this average mean arterial pressure obtained within each breath, and the response was defined by the single breath with the
lowest minute phrenic activity occurring within 20 breaths of the phenylephrine infusion. Thus the peak mean arterial pressure and the minimum minute phrenic response were not necessarily coincident in time; the minimum minute phrenic activity lagged the peak mean arterial pressure by approximately four to six breaths. This is similar to the measurement system we used in the past (9).

**Elevating aerial CO2.** Elevated upper aerial CO2 inhibits respiration in adult cats (2), and this reflex is mediated by receptors in the superior laryngeal nerve (1). We determined whether elevating body temperature altered the respiratory inhibition associated with increased upper aerial CO2. We tested this reflex response in three neonatal piglets by comparing phrenic nerve activity while room air (nominally free of CO2) passed through the isolated upper aerial with phrenic activity obtained while gas containing 9% CO2 passed through the upper aerial for 3–4 min. Airflow was unidirectional and passed from the trachea upward through the larynx and out the nose at a flow rate of 1.8 l/min. All gasses were heated (35°C) and humidified. The effect of elevating upper aerial CO2 on phrenic activity was evaluated before and after elevation of each animal’s body temperature by 2–2.5°C.

**Heating and cooling the animal.** Each animal was wrapped in a heating pad that was used to increase core temperature by 2–2.5°C when the heating pad was on. The heating pad was in place during all stages of most studies, but the heat was on only when each animal’s temperature was elevated. The retained heat in the pad and the insulation of the pad reduced heat loss, and once the body temperature was elevated, it remained stable for >90 min without further heating. We cooled each animal by bathing it with 70% isopropyl alcohol. It took ~20–30 min to raise the temperature of each animal by 2–2.5°C and a similar time to cool the animal. We conducted preliminary studies in which we compared the LCR with the heating pad in place or removed, and we detected no effect of the heating pad itself on the characteristics of the LCR.

**Experimental protocol.** Studies began with a control period during which the reflex being studied was elicited three times. After this control period, each animal’s body temperature was increased by 2–2.5°C, and at least three more tests of the reflex were performed. In most animals, the body temperature was reduced subsequently by cooling the animal with isopropyl alcohol to return body temperature to control temperature before a second set of control tests of the reflex were performed. The baseline peak integrated phrenic nerve activity, phrenic frequency, and minute phrenic activity (peak integrated phrenic activity multiplied by phrenic frequency) and the magnitude of the reflex responses were compared before, during, and after the elevation of body temperature.

We performed a series of time control studies for the LCR in which the same sequence of “temperature changes” was made (control temperature, test temperature, and return to the control temperature), but the heating pad was not turned on. The timing of these studies was identical to the actual heating studies. These studies were used to control for any temporal changes in the LCR over the course of each experiment.

**Data analysis and statistics.** In general, we analyzed each experiment by using a one-way, repeated-measures ANOVA in which body temperature was a within-subjects factor with three levels (control, test, and a follow-up control). Preliminary analysis of the LCR duration and the length of apnea indicated that the variances were not homogeneous among treatment groups. Therefore, the LCR data were transformed using a logarithmic function. The statistical analysis of the LCR was conducted on the log-transformed data (in which the variances were homogeneous and the values were normally distributed). It was not necessary to transform any other variables examined. Specific preplanned comparisons were made using P values adjusted by the Bonferroni method when the ANOVA indicated that significant differences existed among treatment groups. Data are presented as means ± SE.

**RESULTS**

**Effect of body temperature on the LCR.** In intact animals, the LCR consists of respiratory inhibition that may include apnea, coughing, swallowing, and an extended period of irregular breathing. In decerebrate animals, the reflex tends to consist of apnea and a period in which respiratory frequency is prolonged and integrated phrenic activity is reduced, but the irregularity of breathing and the coughing and swallowing are less prominent in decerebrated vagotomized animals. Examples of the LCR in a decerebrate piglet are shown in Fig. 1. In the top panel, the body temperature of the animal was 36.7°C in the control condition, and in the middle panel, the body temperature was 38.6°C after heating. The duration of the apnea and the duration of the LCR were both prolonged by elevating body temperature. The duration of the LCR returned to the control value when body temperature was returned to the control value (36.3°C; bottom panel).

The average duration of the LCR, the length of the longest apnea, and body temperature for the time control animals and heated animals are shown in Fig. 2. In the treatment group, the duration of the LCR and the longest apnea time both increased significantly (P < 0.05). In contrast, these variables were unchanged in the time control group. When body temperature was restored to the control level in the third treatment condition, the duration of the LCR and the longest apnea time both returned to control values. Thus elevating body temperature, and not time alone, was associated with marked prolongation of the LCR.

When body temperature was held constant, but the temperature of the distilled water used to stimulate the LCR was varied among 34, 38, or 42°C, we saw no temperature-dependent changes in the duration of the LCR (n = 3 piglets).

**Effect of body temperature on the diving response.** We wanted to determine whether the effect of elevated body temperature on the LCR was unique or whether elevated body temperature also enhanced the respiratory depression associated with other inhibitory respiratory reflexes. Therefore, we tested a variety of reflexes before and after elevating body temperature. The diving response is elicited by cold and wet stimuli applied in the distribution of the trigeminal nerve. The cardinal features of the response are apnea, bradycardia, and systemic vasoconstriction (3, 10). We applied ice water-soaked gauze sponges directly on the nose and ice-cold water in the nose, and we dipped the entire nose and snout into ice water. We also dissected the branches of the trigeminal nerve and stimulated individual fibers electrically. We studied three piglets aged 3, 8, and 16 days. None of these stimuli consistently elicited a diving response in any of the animals. Occasionally, the piglet responded to one of these stimuli, but the responses were inconsistent within each piglet and among piglets. Even when we saw a response, the respiratory inhibition was modest.

**Effect of body temperature on the baroreceptor-mediated inhibition of phrenic activity.** Baroreceptor stimulation is associated with inhibition of phrenic activity in decerebrated piglets (9). The phrenic inhibition consists of respiratory slowing or frank apnea and diminished peak integrated phrenic amplitude. The baroreceptors are stimulated when arterial blood pressure is elevated, and we elevated blood pressure by infusing small doses of phenylephrine. We determined whether elevated body temperature altered the response of the phenyl-
Effect of body temperature on the response to elevated airway CO₂. Elevated upper airway CO₂ inhibits breathing and phrenic nerve activity (2, 5). The effect is mediated by inhibition of laryngeal receptors (1). Therefore, we examined the effect of elevating body temperature on the response to upper airway CO₂ in neonatal piglets. As was the case with the diving response, we were unable to detect any inhibitory effect of elevated CO₂ (inspired CO₂ fraction = 9%) on phrenic activity in three piglets. Moreover, elevating the body temperature did not unmask any inhibitory effect of elevated upper airway CO₂; there was no identifiable inhibition of phrenic activity in any of the piglets at either body temperature.

DISCUSSION

There are two main findings in this study. First, elevating body temperature enhanced the respiratory inhibition associated with the LCR, a reflex mediated by upper airway water receptors that communicate with the central nervous system through the superior laryngeal nerve. Second, elevating body temperature did not similarly affect other reflexes that inhibit respiration (the diving reflex, the baroreflex, and upper airway CO₂), even though one of these responses (upper airway CO₂) is also mediated through laryngeal receptors and the superior laryngeal nerve.

Effect of temperature on the LCR. The LCR is mediated by “water” receptors in the larynx. The receptors are activated by liquids with low chloride concentrations (4), and stimulation of the receptors elicits a complex reflex response. Facets of the response clear the airway (e.g., coughing and swallowing), and other facets prevent inhalation of foreign substances and conserve oxygen delivery to vital organs (e.g., apnea, bradycardia, and changes in peripheral resistance) (3, 10). Enhancing the bradycardia and redistribution of blood flow associated with the LCR might prove beneficial in younger animals when body temperature and metabolic rate are elevated. However, these aspects of the LCR are not well represented in the decerebrate vagotomized preparation and were not measured. Furthermore, those parts of the central nervous system involved in the integration of thermoregulation and metabolism (e.g., the hypothalamus) were actually missing from our experimental preparation. Thus we know of no a priori reason that the LCR should be enhanced by elevating body temperature.

The thermal amplification of the LCR may have been mediated by peripheral or central modifications of the reflex. A central effect of temperature seems most likely to us. First, Haraguchi et al. (17) used electrical stimulation of the superior laryngeal nerve to elicit respiratory inhibition, and they found that elevating the body temperature of puppies reduced the stimulation threshold necessary to elicit the LCR. This finding is more consistent with a central mechanism because the

Fig. 2. Average duration of the LCR, duration of the longest apnea, and rectal temperature. Values are means ± SE. •, Results from animals in which body temperature was elevated during the test period (n = 12); ○, results from the control animals when the same comparisons were made (ns, not significant). cntrl-2. Second control period.
peripheral levels of stimulation were fixed by the investigators. Moreover, we found no evidence that the response of individual laryngeal receptors to water instilled in the larynx is enhanced by elevating the body temperature (L. Xia, J. C. Leiter, and D. Bartlett, Jr., preliminary observations). Finally, increasing the temperature of the water instilled into the larynx did not enhance the LCR when body temperature was held constant at the control value. Thus the body temperature effect on the LCR is probably a central effect of temperature on the processes within the brain stem that define the LCR.

Limitations of the methods. The average body temperature of intact neonatal piglets of similar age (3–15 days) studied in a plethysmograph (ambient temperature −26°C) is 38.2°C \((n = 20)\) in our laboratory (L. van der Velde, unpublished observations). The decerebrate animals in the present study had an average body temperature of 37.3 ± 0.2°C (range 35.8–38.1°C), which is less than the temperature of normal piglets. However, we doubt that the reduced temperature of the decerebrated animals misrepresented the effect of elevating body temperature on the LCR. First, in some animals, body temperature in the control condition was >38.0°C and the temperature was elevated to >41°C. In these animals, the LCR was prolonged just as much as it had been in animals starting at temperatures of 37°C.

The decerebrate animal provides a stable preparation in which to study brain stem reflexes, but much of the interesting part of the central nervous system of the animal has been removed. This is a major limitation of our method, and the nature of the preparation may misrepresent the importance of thermal effects on the LCR. First, descending influences from the midbrain and cortex may provide an excitatory drive that sustains and regularizes respiration; for example, the “waking stimulus” seems to have this effect. Therefore, the respiratory disruption of the LCR may be more apparent in the decerebrate preparation, and the duration of the LCR and the duration of apneas within the LCR are substantially longer in the decerebrate animal compared with intact animals, even when studied during rapid eye movement and non-rapid eye movement sleep (42). Furthermore, the thermoregulatory responses to the thermal stress that we applied might be expected to blunt the actual increase in brain temperature that we observed and perhaps also modify respiratory drive in ways that would limit the respiratory inhibition associated with the LCR.

Two other aspects of the preparation may have enhanced the LCR. First, the trachea of each animal was obstructed by an endotracheal tube. Thus the actual clearance mechanisms elicited by the LCR are relatively ineffective at removing the stimulus in the larynx. Therefore, the stimulus may have remained in the larynx longer and prolonged the LCR in a way that would not occur in an intact animal breathing normally. Second, vagotomy enhances the respiratory inhibitory effect of upper airway CO2 in cats (2), and vagotomy may also enhance the manifestations of the LCR.

Vagotomized, intubated, and decerebrate neonatal animals may posses an unusually robust LCR response for the reasons outlined above, and one should, therefore, be circumspect in extending these findings to intact animals. On the other hand, the apnea associated with the LCR was also enhanced in intact lambs given a respiratory syncytial virus infection at 2 wk of age (28). The authors attributed the enhanced LCR duration to a direct effect of the viral infection on the mucosal receptors in the larynx. However, body temperature was also elevated by 0.5°C in the virus-treated group compared with control animals. Thus the enhanced LCR in these intact animals may have arisen from a central effect of elevated body temperature on the LCR similar to the results of the present study in a reduced neonatal preparation.

Thermal effects on other inhibitory respiratory responses. We tried to test the hypothesis that other respiratory inhibitory responses would also be enhanced by elevating body temperature. We were partially frustrated in testing this hypothesis because we were unable to elicit either a diving response or an inhibitory effect of elevated upper airway CO2. The strength of the diving reflex is variable among species and wanes as terrestrial animals mature (3, 10). It may be that the snout of the piglet has been adapted for uses in which a diving reflex would be a handicap (rooting in mud for truffles comes to mind as such an activity), and as a consequence, the diving response may be attenuated in pigs. Alternatively, piglets are relatively precocious at birth; for example, they walk soon after birth and have no apparent visual limitations. Thus the power of the diving response may have diminished in piglets by the time of birth. Similarly, the response to upper airway CO2 is variable among species. Increased CO2 in the isolated upper airway of young guinea pigs actually stimulated ventilation (8), but increased upper airway CO2 had no effect on ventilation in adult guinea pigs (A. K. Curran, unpublished observations). Furthermore, upper airway CO2 had little or no inhibitory effect on geniohyoid or diaphragmatic electromyograph in anesthetized adult rats (33), and no inhibitory effect on ventilation (32). Thus differences among species with respect to the strength and maturation of both the diving response and responses to upper airway CO2 seem to be substantial and may have limited our ability to elicit responses to cold stimulation of the nose and to upper airway CO2 in piglets.

We were able to assess the effect of increased body temperature on baroreflex-mediated inhibition of ventilation. Elevating the blood pressure inhibited respiratory activity, but increasing the body temperature did not modify the baroreflex-mediated inhibition of phrenic activity. We know of no reason that the central mechanisms governing the LCR should differ in thermal sensitivity from those controlling the interactions between baroreceptor stimulation and respiratory control. Our test of thermal sensitivity of the baroreceptor response was, however, incomplete. The baroreceptor response in intact animals consists of changes in heart rate and blood flow distribution in addition to the effects on respiration. The decerebrated and vagotomized piglet has no heart rate response to baroreceptor stimulation, and we did not study the distribution of blood flow. Even though the respiratory response to baroreceptor stimulation was not modified by elevating body temperature, other aspects of the baroreceptor response, which we did not study, may have been affected by increased body temperature. Nonetheless, the thermal enhancement of respiratory inhibition was uniquely associated with the LCR in so far as we were able to study it.

Thermal stresses in SIDS. We have been pursuing the hypothesis that SIDS occurs in infants when an underlying vulnerability is revealed by an exogenous stressor during a critical period of homeostatic control (12). We believe that elevated body temperature may act as an additional exogenous stressor. The Back to Sleep campaign has been the single most
effective risk reduction strategy in SIDS (29), but the mechanism(s) whereby prone sleeping increases the risk of SIDS remains a subject of debate. Recently, the view that prone sleeping enhances rebreathing has been ascendant, but historically, epidemiological and physiological evidence is at least as strongly in favor of the hypothesis that prone sleeping impairs thermoregulation (16).

Thermal stress has been identified as a risk factor for SIDS in a number of studies. Infants who died of SIDS often had a preceding upper respiratory tract infection and may have had a fever (39). Furthermore, otherwise healthy babies may become overheated when they are covered or swaddled excessively or when they sleep prone, although excess covering and prone sleeping also increase rebreathing and may also increase the risk of SIDS in that way (38). Heavy wrapping and excessive room heating independently increased the risk of SIDS, especially in infants greater than 70 days of age (14). Thus more of the infants who died of SIDS were found with covers over their heads than control infants (13, 26). Hyperthermia seemed to require an interaction among multiple risk factors: for example, Ponsoby et al. (37) found an increased risk of SIDS when prone sleeping position was combined with swaddling, recent illness, or room heating. Babies lose much of their heat through the head and face, particularly when the rest of the body is covered (31). Therefore, prone sleeping may increase the risk of rebreathing, but it also dramatically reduces the capacity for heat loss (41). The elevated risk of SIDS when prone sleeping and swaddling, recent illness, or elevated room temperature were also present suggests an interaction between prone sleeping and the risk of overheating in the pathogenesis of SIDS. In this context, it is worth pointing out that rebreathing during prone sleep may increase the risk of hypercapnia and asphyxia (23), but rebreathing water-saturated air at body temperature also impairs heat loss just as inhaling gas with an elevated CO2 concentration impairs removal of CO2. The thermal effects of rebreathing are not mentioned often, but prone sleeping both reduces the effective surface for heat loss in infants and causes rebreathing, which impairs respiratory heat loss.

The results of the present study indicate that overheating may amplify the respiratory inhibition associated with the LCR. Furthermore, prone sleeping appears to modify the LCR independent of any temperature effects. When the LCR was investigated in term infants during active sleep, the prone sleeping position was associated with reduced swallowing and breathing compared with the supine sleeping position (20). Arousal responses during tilt testing were reduced in full-term infants when they were tested while sleeping prone compared with sleeping supine (15). Thus the prone sleeping position may alter the manifestations of the LCR, may alter arousal responses after the elicitation of the LCR, and may adversely affect thermoregulation. Elevated body temperature and the prone sleeping position may provide a particularly potent combination of factors that amplify the respiratory inhibition associated with the LCR. It seems plausible, therefore, that the epidemiologically identified risk factors of prone sleeping and overheating may operate in concert with the LCR to produce profound respiratory inhibition (11, 20, 30, 40).

The foregoing analysis suggests that hyperthermia may increase the likelihood of respiratory depression when the LCR is elicited. A recent study in mice indicates that hyperthermia may also impair autoregulatory processes that terminate periods of hypoxic apnea (21). Autoregulation was much less effective when hyperthermia was combined with hypoxic apnea. Thus hyperthermia may increase the severity of respiratory depression associated with the LCR, but it may also limit the capacity for recovery from episodes of respiratory depression.

In summary, the LCR was prolonged when the body temperature was elevated in vagotomized decerebrated piglets. Similar enhancement of respiratory inhibition by elevated body temperature was not found when baroreceptor-mediated inhibition of respiration was studied. We were unable to eliciting a diving response in neonatal piglets and unable to detect any inhibition of respiration when upper airway CO2 was elevated. We conclude that, among the responses we studied, the LCR is peculiarly susceptible to amplification by elevating body temperature. This probably reflects an effect of hyperthermia on the central neural mechanisms controlling the LCR within the brain stem. These findings may be relevant to SIDS. If elevated temperature also enhances the LCR in intact infants, then increased body temperature may amplify the disruption of regular respiratory activity when the LCR occurs and in so doing foster apnea, respiratory instability, and death.

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REFERENCES

Increased body temperature prolongs the LCR


