Reversal of Cardiopulmonary Failure During Active Sleep in Hypoxic Kittens: Implications for Sudden Infant Death

Abstract. *Experimentally induced hypoxia in kittens precipitated episodes of depressed respiration and irregular cardiac function during quiet sleep, waking, and transitional states. The onset of active sleep stimulated both breathing and heart rate and decreased abnormal variability in these functions. However, hypoxia markedly reduced the proportion of active sleep. These data suggest that active sleep protects against respiratory and cardiac abnormalities in infants. Chronic hypoxemia or other factors that reduce active sleep in infants, including the normal developmental decrement in this state, may increase the risk of cardiopulmonary failure and death.*

Postmortem histological findings in many victims of the sudden infant death syndrome (SIDS) indicate a history of chronic hypoxemia. These include pulmonary arteriole hypertrophy, retention of brown fat, prolonged extramedullary hematopoesis, hypertrophy of carotid bodies, and enlarged right ventricles (*1*). Most SIDS fatalities occur during sleep (*2*). Sleep apnea has been associated with SIDS (*3*), and sleep-related respiratory pauses in adults are known to produce hypoxemia, pulmonary hypertension, right-heart failure, and sudden death (*4*). However, neither the incidence of chronic hypoxemia in pre-SIDS infants nor consequent alteration of sleep-waking patterns and cardiopulmonary function have been adequately studied.

We sought to evaluate cardiopulmonary responses to hypoxemia during early development in relation to sleep states and to define criteria by which to recognize hypoxemic infants. Intermittent hypoxemia was produced in unanesthetized kittens at different developmental ages. The results indicate that infant mammals are susceptible to hypoxic cardiorespiratory failure, that they are protected from such failure during active sleep (AS), and that hypoxemia inhibits AS.

Ninety-three kittens were isolated from their mothers and littermates in Plexiglas chambers and exposed to 10 percent oxygen in nitrogen (hypoxic groups) or 21 percent oxygen (controls). Subjects spent 8 hours in the chambers daily (four 2-hour sessions interrupted by ½-hour nursing periods), for either 3 or 8 days. This "hypoxic conditioning" was scheduled such that on the last day of the experiment, kittens were 10 ± 1, 20 ± 1, or 40 ± 2 days of age. Physiological variables and a time code were recorded polygraphically and on magnetic tape during the last 3 days of hypoxic conditioning. One day before the first recording, electrodes were surgically implanted for long-term measurement of electroencephalogram (EEG), electrocardiogram (EKG), electrooculogram (EOG), and neck-muscle electromyogram (EMG); a thermister was permanently suspended in one naris to monitor nasal respiration (*5*). A separate group of nine 20-day-old kittens were, in addition, prepared with permanently implanted carotid catheters in order that arterial blood could be sampled during both control and hypoxic conditions. Within 10 minutes of the onset of each hypoxic conditioning, P_{a,O_2} decreased from 102.5 ± 11.7 to 36.7 ± 2.2 mm-Hg, and P_{a,CO_2} dropped from 27.7 ± 4.1 to 21.4 ± 2.3 mm-Hg. These low blood-gas levels were sustained for the duration of each 2-hour session.

Each minute of polygraphic data was classified for state as AS, quiet sleep (QS), waking (W), or transitional (T) according to established conventions (*5*). Data were subjected to a multivariable computer analysis, which yielded minute-by-minute values of heart rate, beat-to-beat variability, respiratory rate, and breath-to-breath variability (*6*). Apnea was defined as an end-expiratory pause in respiration that exceeded the duration of three respiratory cycles during QS.

When compared with controls, hypoxic kittens exhibited consistent differences in sleep patterns, apnea frequency, and respiratory rate (Table 1). During hypoxic conditioning, the amount of AS was uniformly depressed, and QS was increased. Epochs of AS were shorter and less frequent; QS epochs were both longer and more numerous. Waking was slightly increased, but the primary effect of hypoxia was clearly a redistribution of sleep states rather than suppression of sleep. Mean reduction of AS in hypoxic groups, compared with controls, was 35 to 49 percent. In some animals, AS was almost totally suppressed.

Apnea frequency was greatly diminished in hypoxic kittens at all ages (Table 1); 60 percent of the hypoxic kittens were completely free of apnea. Apneas exhibited by hypoxic animals were more often accompanied by extreme bradycardia, a transient drop of heart rate exceeding 80 beats per minute, than apneas in control kittens. (Of the apneas exhibited by 10-day-old hypoxic kittens, 24 percent were associated with extreme bradycardia; at 20 days, 14 percent; and at 40 days, 3 percent. Only 3 percent of apneas among 10-day-old controls and none of the apneas in 20- and 40-day-old subjects involved extreme bradycardia.) At all ages, most apneas (91 to 98 percent) occurred during sleep and T states. Mean respiratory rate was predictably elevated in most hypoxic kittens during both sleep states.

Ten of 36 10- and 20-day-old hypoxic kittens were designated "noncompensators" because they occasionally exhibited extremely slow and irregular respiration during QS, W, and T (less than 60 percent of that during AS). During QS, respiration rate among 10-day-old noncompensators was so depressed that the overall hypoxic group mean was lower than the control value (Table 1); respiration rate during QS in these kittens was as low as 15 percent of that during AS. Depressed respiration in noncompensators consisted of extended sequences of gasp-like breathing (long postinspiratory pauses as opposed to end-expiratory apneas). These episodes of labored respiration were accompanied by bradycardia and high beat-to-beat variability in the EKG (Fig. 1A) of seven of ten noncompensating animals. Transition to brief or sustained W usually terminated these sequences, but in some cases this respiration pattern continued. By contrast, the onset of AS was invariably associated with an augmented respiration rate, irrespective of the severity of the ongoing hypoxemic failure. All noncompensating kittens that exhibited AS during periods of depressed respiration rate (three 10-day-old and four 20-day-old) showed dramatic recovery within seconds after each AS epoch began (Fig. 1B). At AS onset, respiration reverted to a stereotypically rapid, irregular, and shallow pattern, which varied little between epochs of AS. Following the increased respiration rate at AS onset, heart rate increased and its variability decreased (Fig. 1A). After termination of each AS epoch in a noncompensating kitten, respiration rate and heart rate again became depressed (Fig. 1C). The hypoxic kitten represented in Fig. 1C also had cardiac arrhythmia with ectopic beats during QS, W, and T, which disappeared during AS (Fig. 1D).

In view of the observed AS-related recovery from respiratory failure, the reorganization of sleep states induced by

hypoxemia is notable. For example, all four 10-day-old noncompensators that died in the course of this experiment displayed more pronounced suppression of AS (86 percent less than controls) during hypoxic conditioning than compensating hypoxic kittens (32 percent less than controls). Similarly, the only hypoxic 40-day-old kitten that died had less AS than any other 40-day-old kitten (AS was 6.5 percent of total time) (*7*).

Whereas low AS percentages may be correlated with increased risk of hypoxemic failure and death, high percentages of AS may be protective during hypoxia. A 20-day-old kitten that exhibited extreme respiratory depression during QS yet survived 8 days of hypoxia had a very low percentage of QS (14 percent of total time) and more AS (only 12 percent less than controls) than all other subjects in that group (76 percent less AS than controls).

Respiratory failure during QS and stimulation of respiration during AS has also been reported in human infants. Respiratory depression during sleep in two infants (Ondine's curse) was expressed only in QS; respiration reverted to normal patterns in AS and W (*8*). A survey of sleep apnea among premature infants and among those which had survived cyanotic episodes (SIDS "near-miss" infants) indicated that "obstructive" apneas during QS, compared with AS apneas, were longer in duration and associated with more extreme bradycardia (*9*). Similarly, infants with clinically severe apneas showed longest apneas in QS, bradycardia during apnea, and respiratory cessations secondary to hypoxemia and cerebral anoxia (*10*). Our findings indicate that apneic respiratory interruptions in chronically hypoxemic kittens are infrequent, but they are accompanied by more severe disruptions of cardiac function.

The differential influence of QS and AS on respiration during hypoxic stress may reflect the operation of intrinsically different regulatory mechanisms. Existing supportive evidence for this concept of state-dependent differences in cardiopulmonary function may be summarized as follows: (i) Heightened neuronal discharge in most brain areas and increased cerebral metabolism during AS (*11*) indicates elevated central nervous system

Table 1. The proportion of active sleep (AS) and quiet sleep (QS), apnea frequency, and respiration and mortality data in hypoxic and control kittens. Three- and 8-day treatment groups were combined. Data for individual subjects were derived from six to eight 2-hour conditioning sessions recorded on days 1 and 3 or 6 and 8. All epochs longer than 4 minutes were sampled to obtain respiration data. Apnea frequency is expressed as the mean number of apneas per animal per 100 minutes of sleep and transition. Significant differences between control and hypoxic groups were determined by one-way analyses of variance.

Treatment	*N*	AS (% total time)	QS (% total time)	AS (% total sleep)	Apnea frequency	Respiration rate		Respiratory rate variability		Noncompensators (*N*)	Deaths (*N*)
						QS	AS	QS	AS		
					10-day-old						
Control	15	42.5	20.0	72.5	6.9	50.2	50.3	8.7	14.1	0	0
Hypoxic	20	23.1†	31.2*	45.5†	0.2†	47.3	56.0	8.2	14.6	6	4
					20-day-old						
Control	13	43.7	30.3	64.7	9.2	39.1	44.9	3.7	12.7	0	0
Hypoxic	16	18.0†	45.8†	31.9†	0.5†	52.6†	60.7†	7.0†	14.3	4	0
					40-day-old						
Control	13	29.9	46.0	42.0	5.2	32.5	39.9	2.7	10.0	0	0
Hypoxic	16	15.5†	58.0†	22.2†	0.8†	42.9†	49.8†	3.2	9.3	0	1

*$P < .05$. †$P < .01$

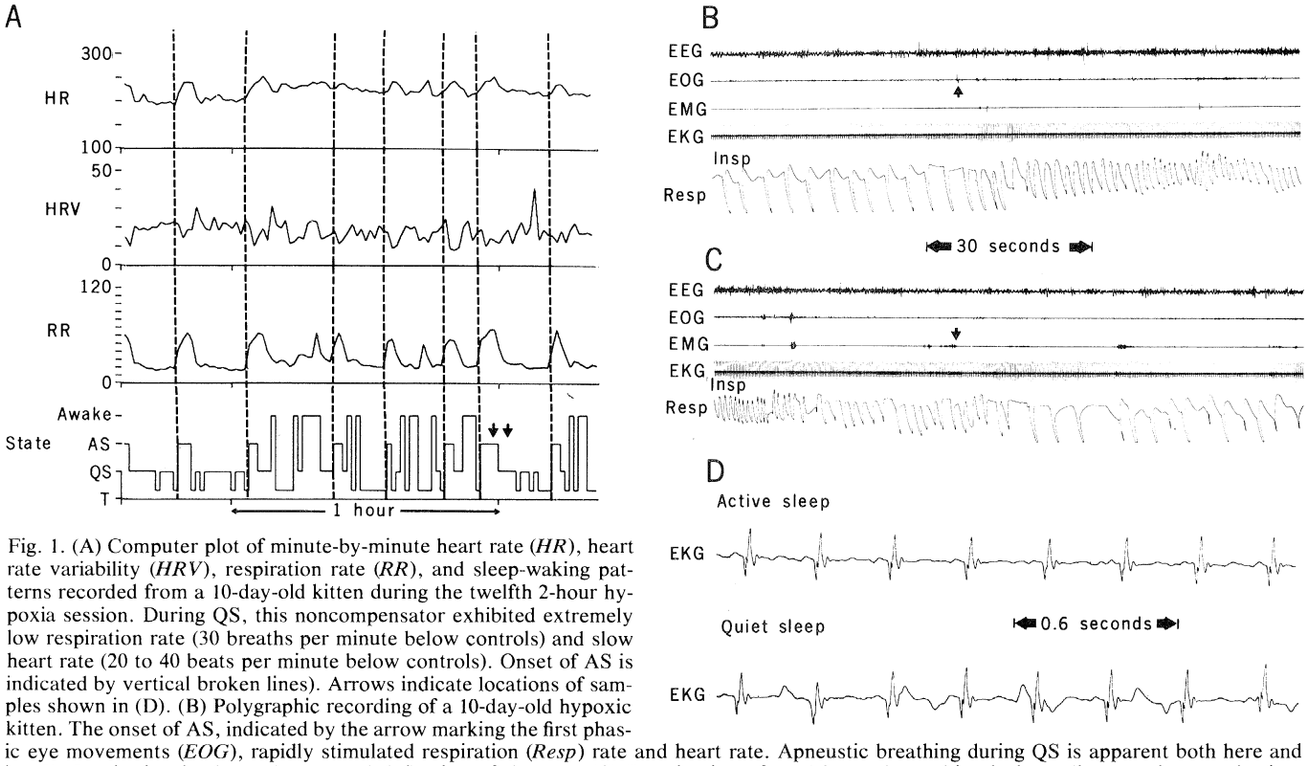

Fig. 1. (A) Computer plot of minute-by-minute heart rate (*HR*), heart rate variability (*HRV*), respiration rate (*RR*), and sleep-waking patterns recorded from a 10-day-old kitten during the twelfth 2-hour hypoxia session. During QS, this noncompensator exhibited extremely low respiration rate (30 breaths per minute below controls) and slow heart rate (20 to 40 beats per minute below controls). Onset of AS is indicated by vertical broken lines). Arrows indicate locations of samples shown in (D). (B) Polygraphic recording of a 10-day-old hypoxic kitten. The onset of AS, indicated by the arrow marking the first phasic eye movements (*EOG*), rapidly stimulated respiration (*Resp*) rate and heart rate. Apneustic breathing during QS is apparent both here and in (C). Inspiration is shown by upward deflection of the pen. (C) Termination of an AS epoch resulting in immediate respiratory slowing, bradycardia, and increased beat-to-beat irregularity in the EKG. The arrow marks the last phasic neck muscle activity associated with AS. (D) Samples of EKG taken from adjacent periods of AS and QS during the hypoxic conditioning session represented in (A) show cardiac arrythmias with ectopic beats during QS that are absent during AS.

(CNS) arousal that may stimulate respiratory drive in a nonspecific manner. (ii) Respiration during AS is totally a function of diaphragmatic movements, whereas intercostal muscles are additionally involved in QS and W (*12*). (iii) In some adults, compared with QS, AS is characterized by a lower CO_2 threshold and a more sensitive CO_2 response curve (*13*). (iv) Coupling between respiration and heart rate (sinus arrhythmia) is more evident during QS than during AS in infants (*14*), and cat vagal nerves show less spontaneous activity during AS than during QS (*15*). Primitive intrauterine respiratory movements (fetal breathing) are observed regularly only during AS in the fetal lamb (*16*).

The predominant state in both newborn kittens and human infants is AS. Since AS is ontogenetically older than QS or W, neural modulation of the cardiorespiratory function in AS may be correspondingly more mature and stable early in life. During maturation, epochs of QS become longer, more frequent, and more stable: a process termed "coalescence" of the QS state (*17*). Comparison of 10- and 40-day-old control kittens in our study indicated much more developmental change in respiration rate and variability in QS than in AS (Table 1). Mechanisms controlling breathing during QS may mature in parallel with the emergence of that state, and immature respiratory control mechanisms may be more susceptible to hypoxic failure.

On the basis of the infant cat model of chronic hypoxemia, we hypothesize that AS "protects" human infants from SIDS. The predominance and tenacity of the AS state in the newborn period may account for the paradoxical immunity to SIDS in the first month of life. The peak risk period for SIDS coincides with the rapid decrease of AS time between 2 and 3 months of age. By 6 months of age, cardiopulmonary compensatory mechanisms in QS and W are more mature and effectual, and the risk of hypoxemic failure and death is reduced. Experimentally produced hypoxemia in kittens inhibits AS, perhaps by some nonspecific stress effect or by direct interference with metabolic conditions essential for CNS generation of AS. In a complementary manner, QS, W, and T states are prematurely augmented by hypoxia, which often results in abnormally extended intervals of labile cardiopulmonary control. Subsequent siblings of infants that die as a result of SIDS, a population with a higher risk of SIDS, showed less sleep apnea and higher respiration rate than a matched control group (*18*). These similarities to hypoxic kittens may constitute evidence of subclinical hypoxemia in infants with a high risk of SIDS. If AS is suppressed in hypoxemic infants, hypoxemia may progressively worsen, further inhibit AS, and terminate in the irreversible vicious circle of cardiopulmonary failure syndrome.

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Blind Man Living in Normal Society Has Circadian Rhythms of 24.9 Hours

Abstract. *A psychologically normal blind man, living and working in normal society, suffered from a severe cyclic sleep-wake disorder. Investigations showed that he had circadian rhythms of body temperature, alertness, performance, cortisol secretion, and urinary electrolyte excretion which were desynchronized from the 24-hour societal schedule. These rhythms all had periods which were longer than 24 hours and indistinguishable from the period of the lunar day.*

J.X., aged 28, who had been without light perception from birth owing to retrolental fibroplasia, was an otherwise healthy and active postgraduate student in biostatistics at a major university. For several years he had noticed that for 2 to 3 weeks at a time, insomnia and excessive daytime sleepiness severely interfered with his work and leisure activities. His strenuous but ineffective attempts to adjust to normal society included the cyclic administration of hypnotic and stimulant drugs. A sleep and activities diary suggested that he had a "free-running" circadian rhythm and that he was strongly and symptomatically entrained to a period slightly longer than 24 hours. His Minnesota Multi-phasic Personality Inventory (MMPI) was within normal limits.

After being without medication for 3 weeks, J.X. entered a hospital for a 26-day study in which he was allowed normal contact with society and access to all time cues except light perception. Facilities were provided so that he was able and encouraged to work, eat, sleep, and interact with others as he felt necessary or inclined. While awake, consecutive 90-minute urine samples were collected, and on five different occasions integrated 6-minute plasma samples were obtained by 24-hour continuous blood withdrawal through an antithrombogenic catheter.