ABNORMAL HYPERCARBIC AND HYPOXIC SLEEP AROUSAL RESPONSES IN NEAR-MISS SIDS INFANTS

Carl E. Hunt, M.D.

From the Department of Pediatrics, Children's Memorial Hospital
and Northwestern University, Chicago, Illinois.

SUMMARY

Arousal responses (AR) to hypercarbia and to hypoxia were ascertained in 25 N-M SIDS infants and 21 control infants in whom ventilatory responses to hypercarbia and hypoxia were also measured. Although the frequency of a positive AR to hypercarbia was not significantly less in the N-M SIDS compared to control group, the overall pattern was a generally absent AR in the lowest hypercarbic ventilatory response slope group progressing to a generally positive AR in the highest hypercarbic response slope group. Among the 25 infants having a positive hypercarbic AR, the mean ($\pm$ SEM) PAO_2 at which arousal occurred was 48.5 ± 1.6 in N-M SIDS versus 42 ± 1.2 mmHg in control infants ($p < .001$). The overall pattern for hypoxic AR was also a generally absent AR in the lowest hypoxic ventilatory response slope group progressing to a generally positive AR in the highest response slope group. Although the PAO_2 level at which an AR occurred did not differ in the two groups, a positive hypoxic AR occurred in 76% of the control versus only 29% of the N-M SIDS group ($p < .01$). In summary, infants with a clinical N-M SIDS history and diminished ventilatory response slopes have as a group a concomitant abnormality in hypercarbic and/or hypoxic arousal.

SPECULATION

A deficient arousal response to hypercarbia and/or hypoxia may be a fundamental respiratory control abnormality in N-M SIDS infants and may contribute to an inability to respond appropriately to sleep-related asphyxia.

INTRODUCTION

A respiratory control deficit has been postulated for Sudden Infant Death Syndrome (SIDS). In infants who have survived an episode of symptomatic sleep apnea and who have thus been classified as Near-Miss (N-M) SIDS, one or more of the following deficits in respiratory control have been reported: prolonged sleep apnea (5), increased frequency of brief inspiratory pauses (18), increased periodic breathing (9), diminished hypercarbic (17) and hypoxic (8) ventilatory response slopes.

Arousal from sleep, although not previously assessed in N-M SIDS infants, is a potentially important component of the respiratory control system. Indeed, infants with central hypoventilation syndrome, in whom the ventilatory response slopes are negligible, tend not to arouse from sleep regardless of magnitude of the hypercarbic or hypoxic stimulus. Since N-M SIDS infants have a partial ventilatory response deficit (8,17), we have hypothesized that an arousal response (AR) deficit coexists in N-M SIDS. The following study in N-M SIDS infants and in control infants without sleep apnea was designed to determine whether abnormal AR to hypercarbia and/or hypoxia may be a fundamental abnormality in N-M SIDS and to assess the inter-relationship between AR and ventilatory response slopes.

MATERIALS AND METHODS

The study group consisted of 46 infants in whom hypercarbic and hypoxic ventilatory response slopes were also measured (8). Twenty-five infants were diagnosed clinically as N-M SIDS on the basis of at least one observed episode of sleep apnea associated with marked pallor or cyanosis and requiring at least minimal stimulation. The remaining 21 infants constituted a control group consisting of four asymptomatic infants and 17 infants referred for evaluation due to a history of awake apnea or intermittent cyanosis, feeding-related apnea or other awake symptoms suggestive of gastroesophageal reflux (GER); none had any sleep-related apnea. GER was documented in 44% of the control group, but none had any acute respiratory symptoms suggestive of aspiration and all had normal roentgenograms. Arousal response results did not differ in these two control groups and were therefore combined for analysis. Mean age ($\pm$ SEM) was 2.6 ± 0.3 months in the N-M SIDS group and 2.1 ± 0.4 in the control group, a difference which was not significant.

As summarized in a separate report (8), hypercarbic ventilatory responses were performed with steady-state normoxic breathing of 5% CO_2 and the hypoxic ventilatory responses were obtained as the FIO_2 was progressively decreased to 0.15. All infants were evaluated during non-REM sleep as determined by standard behavioral criteria and a stable respiratory pattern. No attempt was made to maintain eupnea during the hypoxic responses. A nasal pneumotachograph was utilized for volume measurement and a mass spectrometer for measurement of end-tidal (A) PCO_2 and PO_2 . The ventilatory responses to hypercarbia and hypoxia were linear and were therefore expressed as the slope increase in inspiratory minute volume ($\dot{V}_I/\text{kg/min}$) per mmHg change in PAO_2 and PAO_2 , respectively. No $\dot{V}_I$ measurements obtained during or just prior to an AR were utilized for calculation of the response slope. All infants having an hypercarbic response slope < 30 met the clinical criteria for N-M SIDS whereas none of the infants with hypercarbic slopes > 40 fulfilled the criteria. Eleven (92%) of infants with an hypoxic response slope < 7.0 were N-M SIDS infants whereas only five (22%) of the infants with a slope ≥ 12.0 met the clinical criteria for N-M SIDS.

The presence or absence of an AR was determined during the same sleep interval in which the hypercarbic and hypoxic ventilatory response slopes were measured, and while the nasal pneumotachograph was still in place. A positive AR was defined as agitation, eye opening, or crying which related to the PAO_2 or PAO_2 achieved and which reversed upon return to air breathing. Although no attempt was made to achieve a specific maximum PAO_2 or minimum PAO_2 , a $\text{PAO}_2 \geq 50$ or $\text{PAO}_2 \leq 80$ mmHg was generally achieved. If an AR occurred the specific PAO_2 or PAO_2 at which arousal occurred was noted. If no AR occurred, the maximum PAO_2 or minimum PAO_2 achieved was noted.

Chloral Hydrate (50 mg/kg) was necessary to facilitate sleep in 15 (60%) of the N-M SIDS and 14 (67%) of the control infants. However, the chloral hydrate and natural sleep infants did not differ in the frequency of a positive AR to either hypercarbia or hypoxia (chi-square analysis). Also, in those having a positive AR, the mean PAO_2 or PAO_2 level at which arousal occurred was not different in the N-M SIDS compared to control infants (t test). The AR to hypoxia and to hypercarbia also did not differ in chloral hydrate-induced versus natural sleep in two infants assessed under both sleep conditions. Within the N-M SIDS and control groups, therefore, the chloral hydrate-induced and natural sleep results were combined for analysis.

The arousal responses were analyzed qualitatively (chi-square analysis) according to whether or not arousal occurred. In those having a positive AR, the results were also analyzed according to the actual (quantitative) PAO_2 or PAO_2 level at which arousal occurred (Student t test). The qualitative AR results were analyzed in relation to the clinical diagnosis and to the hypercarbic and hypoxic ventilatory response slope obtained. The frequencies of absent and of positive AR in the infants with the lowest hypercarbic (< 30) and the lowest hypoxic (< 7) response slopes were compared by chi-square analysis to the frequencies obtained in the infants with the highest hypercarbic (≥ 50) and hypoxic (≥ 12) slopes. Statistical significance was defined as $p < .05$.

RESULTS

A positive AR to hypercarbia was observed in 56% of the 45 infants assessed, 11 N-M SIDS and 14 control infants. Although the frequency of a positive hypercarbic AR was not significantly different in the two groups ($.05 < p < .10$), the overall tendency (Fig. 1A) was one of absent AR in the lowest hypercarbic ventilatory response slope group despite higher achieved maximum PAO_2 levels, progressing to a pattern in the highest hypercarbic response slope group of usually positive AR despite lower maximum PAO_2 levels. Among the 25 infants with a positive hypercarbic AR, the mean ($\pm$ SEM) PAO_2 at which arousal occurred was 48.5 ± 1.6 in the N-M SIDS versus 42 ± 1.2 mmHg in control infants ($p < .001$).

A positive AR to hypoxia was observed in 50% of the 40 infants assessed. Although the PAO_2 at which arousal occurred in those having a positive AR was not significantly different in the N-M SIDS versus control infants (83 and 85 mmHg, respectively), a positive AR occurred in only 29% of N-M SIDS compared to 76% of control infants ($p < .01$). The overall tendency (Fig. 1B) was one of absent AR in the lowest hypoxic ventilatory response slope group (< 7.0), progressing to a pattern in the highest hypoxic response slope group of usually positive AR despite a smaller decrease in PAO_2 .

Infants in the lowest hypercarbic response slope group (< 30) had a significantly reduced frequency of both hypercarbic and hypoxic AR (Table 1) compared to infants with hypercarbic response slopes ≥ 50 ($p < .01$). In addition, only 11% of infants in the lowest hypercarbic response slope group had an hypoxic ventilatory response ≥ 12 whereas 85% of those in the highest hypercarbic response slope had an hypoxic response slope ≥ 12 ($p < .001$).

Infants in the lowest hypoxic response slope group (< 7.0) had a significantly reduced frequency of both hypoxic and hypercarbic AR (Table 2) compared to infants in the highest (≥ 12) hypoxic response slope group, $p < .05$ and $p < .02$, respectively. In addition, only 8% of infants in the lowest hypoxic response group had an hypercarbic response slope ≥ 50 compared to 48% among infants in the highest hypoxic response slope group ($p < .02$).

The close inter-relationship of hypercarbic and hypoxic AR to the corresponding response slopes is illustrated in Fig. 2. That is, when infants are classified according to presence or absence of the hypercarbic or hypoxic AR, the corresponding response slope is significantly more abnormal when the respective AR is absent than when present. Among all infants with an absent hypercarbic AR, for example, the mean hypercarbic response slope was 30 ± 4.7 (SEM) compared to 44 ± 4.1 in those having a positive hypercarbic AR ($p < .02$). Similarly, in infants with an absent hypoxic AR, the mean slope was only -9.8 ± 1.8 compared to -18.1 ± 3.1 in those having a positive hypoxic AR ($p = .01$).

DISCUSSION

Our study results demonstrate that N-M SIDS infants as a group have a significantly lower frequency of positive hypoxic AR compared to infants without symptomatic sleep apnea. Although not previously assessed in N-M SIDS infants, an AR abnormality can be inferred from studies which have considered SIDS from a behavioral rather than respiratory control perspective. Based on the tactile-adaptive subscale of the Rosenblith modification of the Graham scale, Anderson and Rosenblith (1) assessed response to nasal occlusion and combined nasal and oral occlusion, and observed lower scores in nine subsequent SIDS victims compared to 793 normal infants. The significance of sleep state in this response to airway occlusion was specifically considered in a later study (19) in which 5-10% of sleeping newborn infants demonstrated delayed initiation of mouth breathing after nasal occlusion during REM sleep, with a greater proportion of delayed responses at age six weeks. Although no apnea was observed, they postulated that such a delayed response to airway obstruction could cause hypoxia or trigger a reflex resulting in fatal apnea.

These behavioral studies have led to the hypothesis that infants at risk for SIDS may not have a strong built-in response to respiratory threats, and may not have yet learned appropriate voluntary behavior (11). It is tempting to speculate that the impaired defensive rage response thus postulated by Lipsitt (11) and the abnormal behavioral response to airway occlusion previously reported (1,19) are in fact both related to a deficiency in asphyxic arousal which is equivalent to the impaired AR to hypercarbia and/or hypoxia which we have observed in N-M SIDS infants.

SIDS has often been associated clinically with nasopharyngitis. Similar to our hypothesis that the normal behavioral response to airway occlusion during sleep is an AR phenomenon, the reduction in apnea observed in normal infants during clinical nasopharyngitis (4) may also be a consequence of normal AR. The ability of normal infants to respond to nasopharyngitis with a reduction in sleep apnea whereas infants at increased risk of SIDS may have increased apnea may thus be explained by the presence of normal AR in the former and impaired AR in the latter.

Quantitative assessments of hypercarbic and hypoxic AR have been reported in adult dogs. Defining arousal on the basis of behavioral and EEG criteria for awakening, Phillipson et al have reported arousal from eupneic hypoxia at arterial saturations of 87% and 70% in quiet sleep and REM, respectively, and arousal from hyperoxic hypercapnea at PAO_2 levels of 54 and 60 mmHg, respectively (13,14). There may be some species differences in the inter-relationship of sleep state, ventilatory response slope and AR in that whereas REM sleep in newborn lambs was associated with inspiratory ribcage deflation and diminished ventilatory and arousal responses to hypoxia, in puppies both ribcage movement and hypoxic ventilatory and arousal responses were similar in REM and quiet sleep (7).

The recent reports of decreased AR following periods of induced sleep fragmentation (2,15) indicate that an AR deficit can be acquired. Since the AR deficit which we have documented has been observed as early as 7-10 days of age as well as in clinically asymptomatic siblings of SIDS victims, we assume that this AR deficit is congenital in origin. Confirmation of the congenital origin

of this AR deficit might be obtained by documenting a quantitative AR deficit in either SIDS parents or siblings, two groups in which a respiratory control deficit has already been reported (10,16).

The physiologic mechanism by which arousal responses to respiratory chemostimuli occur during sleep has not yet been elucidated. A recent study in adult cats indicates that neither the carotid bodies nor the ventilatory response appear to be involved in arousal from sleep by hypoxia (12). In adult dogs, however, the carotid chemoreceptors appear to have a critical role in mediating the arousal response to hypoxia (3).

Our study was not designed to identify the origin of the deficient chemostimuli response and the AR abnormality in N-M SIDS infants. The concordance between diminished hypercarbic and hypoxic response slopes (8) and the concordance documented in this study between diminished ventilatory response slopes and significantly decreased frequency of positive AR, however, suggest that both deficits are related to a common pathologic lesion within the central nervous system.

Additional studies are necessary to better define the characteristics of infant AR and to obtain quantitative hypercarbic and hypoxic AR data in normal infants and in infants at risk for life-threatening sleep apnea. It is possible that at least some of the positive AR which we observed at relatively low P_{ACO_2} or high P_{AO_2} levels in N-M SIDS infants (Fig. 1) might have been related to nasal stimulation from the pneumotachograph rather than the chemostimulus. It is also possible that at least some of the absent AR in infants with normal slope responses may have been related to failure to achieve a sufficient hypercarbic or hypoxic stimulus. Although neither the ventilatory response slopes (6) nor the qualitative arousal responses appear to be affected by chloral hydrate, the effect of chloral hydrate on the quantitative hypercarbic and hypoxic AR has not yet been evaluated. Finally, although all of our qualitative AR were performed during periods of non-REM sleep as determined by behavioral criteria and a stable respiratory pattern, sleep state EEG monitoring may be useful in assessing quantitative arousal responses since a greater chemostimulus may be necessary to achieve arousal from REM than from quiet sleep (7,12-15).

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The authors thank Paul Gora, B. S., for his assistance in the performance and analysis of the ventilatory response slopes and AR assessments, and to Susan Seidler and Judy Carbone for their assistance in preparation of this manuscript.

Presented in part at American Thoracic Society, Washington, D.C., May, 1980.

Address for Reprints: Children's Memorial Hospital
2300 Children's Plaza
Chicago, IL 60614

Supported in part by Otho S. Sprague Foundation and NIH Grant PR-05475-14.

Figure 1

Relationship of ventilatory response slopes to the presence or absence of an AR. The end-tidal values indicated represent the level at which AR occurred (if positive) or the most abnormal value achieved (if absent).
A. Relationship of hypercarbic response slopes and hypercarbic AR. The hypercarbic slope responses have arbitrarily been divided into five groups.
B. Relationship of hypoxic response slopes and hypoxic AR. The hypoxic slope responses have arbitrarily been divided into three groups.

TABLE 1
AROUSAL RESPONSES IN RELATION TO HYPERCARBIC SENSITIVITY

Hypercarbic Ventilatory Response Slope (ml/kg/min/mmHg P_{ACO_2})	N	% With Positive Arousal Response		% With Hypoxic Ventilatory Response ≥ 12.0 (ml/kg/min/mmHg P_{AO_2})
		Hypercarbic	Hypoxic	
< 30	18	28	17	11
≥ 50	14	79	71	85
		$p < .01$		$p < .001$

Figure 2 Relationship of hypercarbic AR to mean hypercarbic ventilatory response slope and of hypoxic AR to mean hypoxic ventilatory response slope.

TABLE 2
AROUSAL RESPONSES IN RELATION TO HYPOXIC SENSITIVITY

Hypoxic Ventilatory Response Slope (ml/kg/min/mmHg PAO ₂)	N	% With Positive Arousal Responses		% With Hypercarbic Ventilatory Response ≥ 50 (ml/kg/min/mmHg PACO ₂)
		Hypoxic	Hypercarbic	
< - 7.0	12	25	25	8
≥ -12.0	23	61	70	48
		p < .05	p < .02	p < .02