The divergent ventilatory and heart rate response to moderate hypercapnia in infants with apnoea of infancy

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Abstract

Background—Inspired CO₂ is a potent ventilatory stimulant exhibiting a paradoxical inhibitory effect on breathing at high concentrations. Severe respiratory depression as a result of CO₂ rebreathing during sleep has been implicated as a possible trigger factor in sudden infant death syndrome (SIDS).

Objective—To investigate the ventilatory and heart rate (HR) responses to inhaled CO₂ in infants with apnoea of infancy, a group believed to be at increased risk of SIDS.

Study design—Thirty one infants with severe sleep related apnoea, 31 infants with mild recurrent apnoea, and 31 age and sex matched controls for the infants with severe sleep related apnoea were studied. HR was computed from digitised RR intervals, "ventilation" was recorded by inductance plethysmography, and Pco₂ and Po₂ were monitored by transcutaneous electrodes. The ventilatory and HR responses to CO₂ were expressed as percentage increase in ventilation and change in HR/unit change in transcutaneous Pco₂.

Results—The mean increase in transcutaneous Pco₂ during CO₂ challenge (0.45 kPa = 3.4 mm Hg) resulted in a mean increase in ventilation of 291%/1 kPa (7.3 mm Hg) increase in transcutaneous Pco₂, with no difference between the groups. A significant difference between infants with severe sleep related apnoea and mild recurrent apnoea versus controls ($p < 0.02$, $p < 0.01$, respectively) was found in their HR response to CO₂ challenge: HR decreased in 12 severe sleep related apnoea infants and 10 infants with mild recurrent apnoea, but only in two controls.

Conclusion—Infants with apnoea of infancy frequently show a paradoxical decrease in HR during CO₂ challenge, possibly because of an insufficient ability to mobilise cardiovascular defence mechanisms when challenged with hypercapnia.

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governed by feedback mechanisms based on information from peripheral and intracranial chemoreceptors.¹ A prerequisite for rhythmic and efficient respiration is the adequate functioning of afferent inputs from the chemoreceptive structures that sense pH values and CO₂ and O₂ concentrations in plasma and cerebrospinal fluid.

Inspired fractional CO₂ concentrations in the range of 1-8% have potent stimulatory effects on ventilation. Thus, the ventilatory response to inhalation of CO₂ enriched gas has long been used as a standard test of the function of the central chemoreceptor structures. However, excessive concentrations of CO₂ (> 8%) do produce a paradoxical inhibition of respiration.²

Thus, CO₂ has dual effects on respiratory control, it is a potent ventilatory stimulant in moderate concentrations and acts as a ventilatory inhibitor at high concentrations. The depressive effects of CO₂ rebreathing might elicit central ventilatory depression, leading to hypercarbia and hypoxaemia. This scenario has been proposed as a mechanism for the increased risk of sudden infant death syndrome (SIDS) when sleeping in the prone position.^{3,4}

One might speculate that a deterioration in the ability to increase ventilation in response to CO₂ might be paralleled with a propensity to CO₂ induced depression of respiration. This has been shown in preterm babies who have an attenuated ventilatory response to CO₂⁵ and a lower threshold for inhibition of ventilation when subjected to hypercapnia.⁶ However, an association between CO₂ response and increased sensitivity to CO₂ induced depression has not been shown in term infants who have experienced severe apnoea as a result of an apparent life threatening event.⁷

Thus, an attenuation of other physiological responses might be a more sensitive indicator of increased vulnerability to the depressive effects of CO₂.

An increase in heart rate (HR) is nearly always part of the physiological response to exogenous stress, and infants who are likely to experience hypercapnic episodes—infants with apnoea of infancy—in spite of a normal ventilatory response to CO₂, might have a reduced ability to activate cardiac responses when subjected to CO₂ accumulation.

We tested this hypothesis by comparing the ventilatory and HR responses to mild hypercapnia (4% in room air) in infants who had suffered severe sleep related apnoea with age and sex matched controls. In addition, these

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During physiological rest, such as quiet sleep, the homeostatic regulation of "ventilation" is

Table 1 Background data of infants with severe sleep related apnoea (SSRA), mild recurrent apnoea (MRA), and controls

	SSRA	MRA	Controls	p value
Birth weight (g)	3565 (118)	3107 (192)	3478 (131)	0.06
Gestational age at birth (weeks)	39 (0.4)	38 (0.8)	39 (0.3)	0.03*
Study weight (g)	6160 (308)	5529 (364)	5837 (370)	0.51
Study age (months)	3.7 (0.5)	2.8 (0.2)	3.5 (0.3)	0.19

Values are mean (SD).

*MRI ≠ controls and SSRA.

two groups were compared with infants who had experienced recurrent apnoeic episodes that did not necessarily occur during sleep and had not required resuscitation.

Methods

SUBJECTS

The study population consisted of infants with apnoea of infancy who were subdivided into two groups based on clinical features: 31 infants with severe sleep related apnoea, and 31 infants with mild recurrent apnoea. The third group consisted of age and sex matched controls for infants with severe sleep related apnoea.

Infants with severe sleep related apnoea

Severe sleep related apnoea was defined as a sleep related episode where the infant was found apparently lifeless, limp, pale, or cyanotic, and where vigorous stimulation or cardiopulmonary resuscitation was required. One infant had a previous sibling who died of SIDS. The diagnosis was based on case history as given by the parents and, in some cases, confirmed by other witnesses and/or the ambulance personnel. This group fulfilled the criteria of apparent life threatening events.

Infants with mild recurrent apnoea

Mild recurrent apnoea was defined as two or more episodes of apnoea associated with pallor

or colour change. Resuscitation or vigorous stimulation was not a requirement for diagnosis and the episode might have occurred either during rest or sleep. Thus, the clinical severity of the episodes of mild recurrent apnoea was substantially milder than in severe sleep related apnoea.

Controls

One age and sex matched control was recruited for each infant with severe sleep related apnoea. When an infant with severe sleep related apnoea was referred for investigation, a letter explaining the purpose of the study was sent to one randomly selected infant born in our nursery who was of the same sex and at the same age as the corresponding patient with severe sleep related apnoea. When written parental consent was obtained, the control infants were admitted for investigation within one to two weeks. These infants were born at term after an uneventful pregnancy and delivery. None of them had a family history of SIDS or apnoea.

Additional background data for the study group are presented in table 1.

EXPERIMENTAL MONITORING PROCEDURES

Infants in both apnoea groups (severe sleep related apnoea and mild recurrent apnoea) were referred to us for investigation after a three day hospitalisation, during which other possible causes of apnoea such as infection, congenital heart disease, or seizure disorder had been ruled out.

All infants were admitted to the laboratory at around 20:00 and put to sleep supine and lightly dressed. The room temperature was kept at 23–25°C and lights were dimmed. A computerised polysomnography unit (CARDAS, Maternal and Infant Telemonitoring Centre, Oxford, UK) that allowed digital storage of eight analogue channels, real time replay of the stored data, and data exchange with commercial statistical packages was used. The CARDAS utilises inductance plethysmography (respirace) with thoracic and abdominal respiration bands for non-invasive measurements of tidal volumes and calculation of a sum value that is proportional to tidal volume. A three lead electrocardiogram (ECG) was used for measurements of beat to beat RR intervals and a finger pulse oximeter probe for measurements of pulse amplitude and SaO_2 . In addition, skin surface Po_2 (transcutaneous Po_2) and Pco_2 (transcutaneous Pco_2) tensions were monitored with a combined transcutaneous electrode (Radiometer TCM3, Copenhagen, Denmark). A calf movement sensor was used for monitoring body position and movements. All the analogue signals of thoracic and abdominal excursions and their sum, oxygen saturation, transcutaneous Po_2 and Pco_2 , and RR intervals were sampled at 10, 20, and 100 Hz, respectively, converted in a built in 12 bit AD converter, and stored on the disk of a 486, IBM compatible personal computer. Sleep states (active or quiet sleep) were scored by behavioural criteria⁸ by a single trained observer and compared with a classification of

Figure 1 Tracing of the polysomnographic recording including saturation (Satur.), transcutaneous (Tc) Po_2 and Pco_2 , heart rate (HR, beats/min), pulse rate (PR), and respiratory movements of chest (chst) and abdomen (abdo).

Table 2 Saturation, transcutaneous PO_2 and PCO_2 , and heart rate during reference conditions preceding inhalation of CO_2 enriched gas mixture

	SSRA	MRA	Controls	p value
Saturation O_2 (%)	97 (2)	96 (3)	96 (2)	0.23
Transcutaneous PO_2 (kPa)	10 (2)	11 (2)	11 (1)	0.66
Transcutaneous PCO_2 (kPa)	5.3 (0.4)	5.5 (0.5)	5.4 (0.3)	0.38
Heart rate (beats/min)	115 (14)	113 (19)	118 (16)	0.43
SD_{HR} (beats/min)	8.6 (11.4)	5.2 (2.5)	6.1 (3.8)	0.15

Values are mean (SD).

SD_{HR} , standard deviation of heart rate; SSRA, infants with severe sleep related apnoea; MRA, infants with mild recurrent apnoea.

Table 3 "Ventilatory" and heart rate responses to changes in transcutaneous (Tc) PCO_2

	SSRA	MRA	Controls	p value
Ventilatory increase/1 kPa $TcPCO_2$	247 (135)	268 (163)	307 (167)	0.33
ΔHR change/1 kPa $TcPCO_2$	1.0 (8.7)	-1.4 (13.4)	5.7 (11.8)	0.02

Values are mean (SD).

SSRA, infants with severe sleep related apnoea; MRA, infants with mild recurrent apnoea.

infant sleep state based on HR variability scoring.⁹ All infants were monitored during a six to eight hour nocturnal period using the polygraphic procedure as above. During the first quiet sleep period, as defined by behavioural criteria, a CO_2 challenge test was performed. A 10 litre polycarbonate head box was placed gently over the head. After a three minute control period in room air using a gas flow through the box of 10 l/min, the gas flow was switched to a 10 l/min flow of 4% CO_2 in room air. The CO_2 inhalation was continued for nine minutes or until the infant moved or changed body position, in which case tidal volumes could no longer be estimated from the excursions of the respibands. The minimum duration of tests accepted for analysis was six minutes. If an infant aroused, had a startle, or changed body position before six minutes had elapsed, the CO_2 test was repeated during the following sequence of quiet sleep. As a consequence, a total of five tests had to be repeated.

DATA ANALYSIS

Reference values

The mean HR, transcutaneous PCO_2 , transcutaneous PO_2 , and SpO_2 during one minute of air breathing preceding the CO_2 challenge were used as resting reference values. Because the induction plethysmography device was not calibrated for volume, both tidal volume and minute ventilation are written in quotes.

Changes in "ventilation" were calculated from the respiratory rate multiplied by sum signal of chest and abdominal excursion. The latter corresponded to changes in "tidal volumes".

The mean value of breath by breath "ventilation" ("tidal volume" $\times$ respiratory rate) during one minute immediately preceding the CO_2 challenge was used as the reference period "ventilation".

Ventilatory response to CO_2

A representative original tracing of the CO_2 test is shown in fig 1. The entire six to nine minute challenge period, from the beginning of CO_2 inhalation until the termination of the test, was used to calculate the ventilatory response to CO_2 . The changes in "ventilation" during CO_2

Figure 2 Scatter diagram of the slopes of heart rate response to CO_2 inhalation in three infant groups. Each symbol represents the slope of an individual infant. Shaded symbols depict negative slopes. SSRA, severe sleep related apnoea; MRS, mild recurrent apnoea.

breathing were expressed as percentage change from the reference period (assigned 100%). For example, a doubling of "ventilation" was expressed as 200%. Each change from resting "ventilation" was plotted against the corresponding change in transcutaneous PCO_2 in a coordinate system, with changes in "ventilation" on the Y axis and changes in transcutaneous PCO_2 on the X axis. Regression analysis was then used to calculate the above relation. The slope of the regression line describing a percentage change in "ventilation"/unit change in transcutaneous PCO_2 ($\Delta \text{vent}/\Delta \text{transcutaneous } PCO_2$) was used as an index of the ventilatory response to CO_2 . The slope of this regression line (the regression coefficient) was tested for significance. A positive slope indicated a significant rise in "ventilation", a negative slope a significant decrease in "ventilation", and a zero slope a non-significant change in "ventilation" during the test.

Heart rate response to CO_2

Similarly to the calculations of ventilatory response, the HR response to CO_2 was expressed by plotting instantaneous HR on the Y axis against the corresponding transcutaneous PCO_2 values on the X axis. The slope of the regression line ($\Delta HR/\Delta \text{transcutaneous } PCO_2$) describes the HR response to CO_2 . As above, the slope of the regression line (the regression coefficient) was tested for significance and $p < 0.05$ was considered to be significant.

Statistical methods

Numerical data of breath by breath SaO_2 , transcutaneous PO_2 and transcutaneous PCO_2 , the sum of chest and abdominal excursions and RR intervals were exported from the polygraphic recording as Lotus WKS files and analysed using a commercial statistical package (Statgraphics 6.0).

The differences between severe sleep related apnoea, mild recurrent apnoea, and the control infant groups were tested by Kruskal-Wallis analysis of variance by ranks and, thereafter, by the Mann-Whitney U test. A level of $p < 0.05$ was considered to be significant.

Results

AIR BREATHING

The mean (SD) HR before CO_2 challenge for all infants was 115.2 (16.4) beats/min. No significant differences in HR and HR variability, expressed as standard deviation of HR between the three groups of infants, were found. SaO_2 , transcutaneous PO_2 , and transcutaneous PCO_2 levels were also comparable (table 2).

CO_2 STIMULUS

The inhalation of 4% CO_2 in air resulted in a mean increase in transcutaneous PCO_2 by 0.45 kPa (3.4 mm Hg), range 0.2–0.8 kPa (1.5–6.0 mm Hg). The individual transcutaneous PCO_2 values at the beginning of CO_2 inhalation varied greatly among individual infants,

but the maximal transcutaneous PCO_2 values were similar in all three groups.

VENTILATION DURING CO_2 BREATHING

“Ventilation” increased significantly and to a similar extent in all subject groups (infants with severe sleep related apnoea, infants with mild recurrent apnoea, and controls; table 3). On average, “ventilation” increased by 291%/1 kPa (7.3 mm Hg) increase in transcutaneous PCO_2 .

HEART RATE DURING CO_2 BREATHING

In control infants, the slope of HR changes during CO_2 breathing ($\Delta \text{HR}/\Delta$ transcutaneous PCO_2) was significantly higher ($p = 0.02$) than in infants with either severe sleep related apnoea or mild recurrent apnoea (5.7, 1.0, and -1.4, respectively). Figure 2 shows that 12 of the infants with severe sleep related apnoea and 10 of the infants with mild recurrent apnoea reacted with a decrease in HR as transcutaneous PCO_2 increased, whereas only two of the control infants showed this response pattern. Thus, despite the differences in the clinical severity of an apnoeic episode, the infants with severe sleep related apnoea and mild recurrent apnoea showed a similar HR reaction pattern. The infants in whom the HR decreased in response to CO_2 could not be distinguished from the other infants by clinical criteria.

The HR slope was not related to the resting HR ($p = 0.28$), but was significantly inversely

Figure 3 The shape of “ventilatory” and HR responses to CO_2 in three infants illustrating the response modes observed: (A) increase in ventilation and simultaneous decrease in HR; (B) increase in ventilation and no HR response; (C) increase in ventilation with a concomitant increase in HR. Tc, transcutaneous.

related to the initial transcutaneous PCO_2 ($p = 0.002$), as well as the maximum transcutaneous PCO_2 in each individual infant ($p = 0.005$).

In all infants studied, the HR response correlated significantly with the ventilatory slope ($p = 0.045$; correlation coefficient $r = 0.21$), meaning that the lower the ventilatory response, the lower the probability that the HR would increase during CO_2 challenge. The standard deviation of HR was the same in all infants ($p = 0.12$). Regression analysis showed a strong correlation between standard deviation of HR in air and in CO_2 ($r = 0.86$; $p = 0.0001$). The range of transcutaneous PCO_2 had no influence on the standard deviation of HR.

Figure 3 shows the three modes of response to the increased concentration of CO_2 : (1) a significant increase in "ventilation" with the concomitant decrease in HR was seen in 24 infants, 12 infants with severe sleep related apnoea, 10 with mild recurrent apnoea, and two controls (fig 3A); (2) a significant increase in "ventilation" with no change in HR was seen in 41 infants, 11 infants with severe sleep related apnoea, 15 infants with mild recurrent apnoea, and 15 controls (fig 3B); and (3) a significant increase in "ventilation" with a concomitant increase in HR was seen in 28 infants, eight infants with severe sleep related apnoea, six infants with mild recurrent apnoea, and 14 controls (fig 3C).

Discussion

The main finding of this study was that infants with severe sleep related apnoea and infants with mild recurrent apnoea exhibited a divergent HR response to mild hypercapnia. While most control infants responded with an increase in "ventilation" and an increased or unchanged HR, a decrease in HR was seen in a significant number of infants with severe sleep related apnoea and infants with mild recurrent apnoea. The lack of increase in HR during CO_2 breathing was associated with higher resting CO_2 values and lower ventilatory slopes—less steep and "right-shifted" ventilatory response curves. Thus, changes in HR during CO_2 challenge appear to reflect subtle differences in CO_2 sensitivity.

Prone position during sleep together with a slight hypoventilation might result in a CO_2 accumulation around the face of as much as 10%.⁴ Although such excessive CO_2 provocation was not part of the study protocol, one could speculate on the basis of the present results that a combination of hypoventilation and bradycardia could occur under such circumstances and put the infant at risk of asphyxia.

CO_2 is unique as a physiological stimulus in that it acts as a potent ventilatory stimulant at low concentrations but can inhibit breathing at high concentrations. The threshold values for producing ventilatory depression vary among individuals. The inhibitory effects can be seen at lower CO_2 concentrations in preterm babies than in term infants.⁵ The mechanisms of CO_2 induced inhibition have not been elucidated in

detail, but are believed by some authors to be a result of a sensory inhibitory reflex located in the upper airway.¹⁰ Our results suggest the presence of a central inhibitory mechanism operational at physiological alveolar CO_2 concentrations that primarily affects the HR response to exogenous stimuli.

Although some infants with severe sleep related apnoea or mild recurrent apnoea do have blunted ventilatory and arousal responsiveness to CO_2 ,^{11,12} there are conflicting opinions about whether apnoeic infants as a group have a normal or attenuated ventilatory sensitivity to inhaled CO_2 .⁷ This controversy might result in part from the different methodologies used in different studies.¹³ A prime concern in our investigation was to use non-invasive monitoring techniques that would not require sedation or interfere with normal sleep. Induction plethysmography was chosen to monitor changes in ventilation^{14–16} and is widely used.

The ventilatory changes estimated by inductance plethysmography were correlated to changes in transcutaneous CO_2 and not end tidal PCO_2 to avoid irritation of the nasal orifice by a sampling tube. A similar method has been described previously by Hazinski *et al* and Schafer *et al*.^{17,18} However, this meant that only relative changes in ventilation (percentage change from control) could be assessed. Another limitation of our method was that a low concentration of CO_2 was used and an equilibrium between inhaled, alveolar, and central CO_2 values might not have occurred; consequently, the response slopes obtained might not accurately reflect central chemoreceptor activity. These disadvantages were considered and balanced against the need to perform the test during physiological conditions without causing sympathetic activation as a result of tactile or other stimuli. Given the limitations of our technique, the results of the CO_2 challenge tests do support previous reports suggesting that the magnitude of the CO_2 ventilatory response of apnoeic infants is within the range of controls.

The observed differences between controls and infants with severe sleep related apnoea or mild recurrent apnoea were confined to the HR response to inhaled CO_2 .

Traditional physiological theory postulates that HR is determined mainly by a dynamic balance between sympathetic stimulation and vagal inhibition.¹⁹ Sympathetic withdrawal or vagal stimulation produce a decrease in mean HR, whereas sympathetic activation or a decrease in vagal tone generate the opposite effect. These changes in autonomic balance usually act synergistically, although the activity of the right "chronotropic" vagal trunk is believed to be a major determinant of HR.²⁰

Physiological stress such as the inhalation of CO_2 can be assumed to produce a sympathetic stimulation and a concomitant vagal inhibition leading to a rise in mean HR.²¹ However, if the CO_2 sensing structures have a lower dynamic sensitivity, either because of a low efferent discharge "response slope" or a high sensitivity threshold to inhaled CO_2 , the likely consequence would be a low sympathetic stimula-

tion. This might result in an absent or delayed arousal and lack of a concomitant rise in HR in response to the excess of CO₂.²¹ Whether the lack of sympathetic activation is a consequence of a central inhibitory effect of CO₂ cannot be deduced from our study. However, it should be noted that brain areas that are considered to be relay stations for the integration of blood pressure and HR control mechanisms (such as the arcuate nucleus²²) are located close to the chemosensory area at the ventral medullary surface. Our observation that a failure to increase HR during CO₂ breathing is related to a lower ventilatory response illustrates the close relations between CO₂ sensitivity and cardiac control mechanisms. Notably, patients with central congenital hypoventilation syndrome who lack CO₂ drive have an abnormal HR variability.²³

In addition to these putative central mechanisms regulating the ventilatory and HR response to CO₂, two peripheral mechanisms are also likely to modulate the characteristics of the response.

The epithelial lining of the upper airway and tracheobronchial tree contains liquid, H⁺, and CO₂ sensitive receptors.²⁴ Stimulation of any of these receptor pools induces a slowing of respiration, bradycardia, and a rise in blood pressure. This response is more accentuated in infants and neonates.²⁵ Infants with apnoea appear to have a particularly strong response to laryngeal stimulation with liquid and severe bradycardia, sometimes progressing to cardiac arrest, has been described.²⁶ A hyperactive chemoreflex resulting in a marked slowing of respiration and cardiac rhythm in response to stimulation of airway CO₂ receptors could explain the concomitant decrease in HR and the trend towards higher post-challenge transcutaneous CO₂ values in apnoeic infants.²⁶

A finding not entirely explained by a hyperactive chemoreflex of the airway receptor is the time course of the altered CO₂ response. Airway receptor stimulation is known to produce a relatively long lasting inhibition of breathing but a relatively short lasting vagally mediated bradycardia.²⁷ The sustained decrease in HR during CO₂ challenge appears different from this reflexly induced vagal bradycardia,²¹ and such reactive long lasting bradycardia has to our knowledge not been described previously. This type of response seems to be typical of apnoeic infants because siblings of infants who died of SIDS do not show this type of reaction.²⁸

In summary, our study has shown that a significant proportion of apnoeic infants do not have the expected increase in HR during moderate CO₂ challenge. We suggest that this is caused by a lack of sympathetic stimulation as a result of a hyperactive chemoreflex inhibition of respiration and HR rate or an altered CO₂ sensitivity threshold.

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