

The effects of sleeping position on ventilatory responses to carbon dioxide in premature infants

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ABSTRACT

Background The prone sleeping position, particularly in prematurely born infants, is associated with an increased risk of sudden infant death syndrome. A possible mechanism is an impaired ability to respond to respiratory compromise. The hypothesis that the ventilatory response to a carbon dioxide (CO₂) challenge in convalescent, prematurely born infants would be lower in the prone compared with the supine position was therefore tested.

Methods In each position, ventilatory responses to increasing levels of inspired CO₂ were assessed. The airway pressure change after the first 100 ms of an occluded inspiration (P_{0.1}) and the maximum inspiratory pressure with an occluded airway during crying (P_{imax}) were measured; the ratio of the P_{0.1} to the P_{imax} at each inspired CO₂ level and the slope of the P_{0.1}/P_{imax} response were calculated. Chest and abdominal wall asynchrony was assessed using inductance plethysmography and functional residual capacity (FRC) measured using a helium gas dilution technique.

Results Eighteen infants with a median postmenstrual age of 35 (range 35–37) weeks were studied. In the prone versus the supine position, the mean P_{0.1} (p=0.002), the mean P_{imax} (p=0.006), the increase in P_{0.1} with increasing CO₂ (p=0.007) and the P_{0.1}/P_{imax} response slope (p=0.007) were smaller.

Thoracoabdominal asynchrony was not significantly influenced by position or inspired CO₂. FRC was higher in the prone position (p=0.019).

Conclusions Convalescent, prematurely born infants have a reduced ventilatory response to CO₂ challenge in the prone position, suggesting they may have an impaired ability to respond to respiratory compromise in that position.

INTRODUCTION

In the developed world, sudden infant death syndrome (SIDS) is the leading cause of death in infants between 1 month and 1 year of age. The cause of SIDS remains to be identified; however, it is likely to be multifactorial. The triple risk model suggests that SIDS occurs when there is a combination of a vulnerable infant, a critical stage of development and an acute exogenous stress situation.¹ A possible contributory factor is a reduced responsiveness to carbon dioxide (CO₂). Post-mortem examination studies of chemosensitive brainstem tissue from infants who had died of SIDS have highlighted decreased neuromodulator receptor binding.² In addition, increased levels of mRNA encoding an Na⁺/H⁺ exchanger associated

with reduced CO₂ responsiveness have been found.³ Prematurely born infants compared with those born at term are at increased risk of SIDS. The ventilatory response to CO₂ has been demonstrated to be reduced in prematurely born infants, although it increased as the infants matured.^{4–6} Prone sleeping is particularly a risk factor for SIDS in prematurely born infants.⁷ In the Nordic epidemiological study,⁷ the OR for SIDS for term infants who slept prone rather than supine was 13.9, but 48.4 for prematurely born infants. A possible mechanism for the increased risk of SIDS for prematurely born infants sleeping prone could be an impaired ability to respond to respiratory compromise, for example a raised CO₂. Indeed, an impaired response to added dead space (tube breathing) in the prone compared with the supine position in convalescent prematurely born infants has been demonstrated⁸; the major stimulus during tube breathing is hypercapnia.⁹ In contrast, in an earlier study of convalescent prematurely born babies, a greater increase in ventilation, as assessed by respiratory inductance plethysmography (which assesses chest and abdominal wall movement) but not pneumotachography (which assesses airflow), was demonstrated in the prone compared with the supine position in response to carbon dioxide rebreathing.¹⁰ A possible explanation for the differences in the results of the two studies^{8 10} is the lower level of hypercapnic challenge during tube breathing.⁹ We, therefore, have compared the ventilatory response of convalescent prematurely born infants to a range of inspired CO₂ levels (hypercapnic challenge) in both the prone and supine positions.

To assess the ventilatory response to a hypercapnic challenge, we measured the P_{0.1}/P_{imax} ratio. P_{0.1} is the airway pressure change after the first 100 ms of an occluded inspiration and P_{imax} is the maximum inspiratory pressure generated against a maintained airway occlusion (5–7 breaths) during crying. P_{0.1} has been used as an indicator of respiratory output.¹¹ P_{0.1}, however, is affected by respiratory muscle strength, hence we controlled for this by relating the P_{0.1} to the P_{imax} results at each inspired CO₂ level. Use of this normalised measure has been shown in ventilated adult patients to be a better indicator of respiratory drive and predictor of successful weaning than absolute P_{0.1} values.¹²

Our aim was to test the hypothesis that their ventilatory response to a CO₂ challenge would be lower in the prone compared with the supine position. In addition, we assessed thoracoabdominal asynchrony and lung volume (functional residual

capacity (FRC)) in both positions to determine if differences in the response to the CO₂ challenge were associated with postural-related differences in thoracoabdominal synchrony and/or lung volume.

METHODS

Inclusion and exclusion criteria

Infants born prior to 33 weeks of gestation without congenital abnormalities were eligible for recruitment into the study. Parents were approached once their infants were at least 35 weeks postmenstrual age and had achieved 3 hourly feeding. Exclusion criteria were that the infant was receiving supplementary oxygen or methylxanthines. Infants were studied only when well. Infants whose parents gave informed written consent were recruited. The study was approved by the King's College Hospital Research Ethics Committee.

Protocol

For each study session, the position (prone or supine) in which infants were first studied was randomised. Measurements in the two positions were performed consecutively on the same day ~3 h apart. Measurements were commenced in each position after the infants had been fed and had been in quiet sleep for at least 20 min. The infants were only assessed when in a quiet sleep state. Sleep state was behaviourally assessed and measurements undertaken when the infants were in a quiet sleep state as indicated by the infant's eyes being closed, a regular respiratory pattern and minimal spontaneous movements. If the infant aroused from sleep (other than during the P_{imax} measurement) the assessment was discontinued and only restarted if the infant returned to quiet sleep. In each position, the hypercapnic challenge was undertaken first and then FRC was measured. Thoracoabdominal synchrony was assessed during the hypercapnic challenges. Oxygen saturation was continuously monitored using a pulse oximeter (Ohmeda Biox 3740; BOC Health Care, Louisville, Colorado, USA).

Hypercapnic challenge

The hypercapnic challenge was delivered via a facemask and pneumotachograph through an open circuit system with individually adjustable flows of CO₂ and air. The pneumotachograph was inserted into a facemask, which was fitted snugly over the infant's nose and mouth. The distal end of the pneumotachograph was attached to a two-way, non-rebreathing bag. Flow was measured using the pneumotachograph (GM Engineering, Kilwinning, UK), which was attached to a differential pressure transducer (MP45; Validyne, Northridge, California, USA). Flow was digitally integrated to give tidal volume. Minute volume was calculated from the respiratory rate and tidal volume. Airway pressure was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45; Validyne). Flow and pressure signals were amplified (Validyne CD 280; Validyne). A constant flow of medical air from a cylinder was delivered to the inspiratory port of the valve via a length of wide bore (20 mm), low resistance tubing. This inspiratory line could be clamped to produce the occlusions necessary for P_{0.1} and P_{imax} measurements. The inspired air could be enriched with a variable concentration of CO₂ from a cylinder, the flow being controlled by a rotameter. Inspired and expired gases were sampled continuously using a small cannula inserted through the wall of the facemask and positioned close to the infant's mouth, and measured using a capnograph (CO₂SMO capnograph; (Respironics UK, Chichester, UK). The

capnograph was calibrated with certified calibration gas (5% CO₂/95% air, BOC Gases, UK) prior to each measurement. Inspired CO₂ and end-tidal CO₂ (ETCO₂) levels were derived from the continuous capnogram recording which was displayed throughout the study.

In each sleeping position, assessments were made at three levels of CO₂ (0% (baseline), 2% and 4%) These levels were chosen to provide increases in ventilation without generating significant behavioural arousal and were in keeping with previous studies.^{6 13} A biased flow was passed through the open circuit, eliminating any dead space, and the facemask placed over the infant's nose and mouth. Each mixture of CO₂ was titrated and a stable inspiratory CO₂ concentration was achieved within the delivery tubing as assessed by the capnograph readout, before the infant was connected to the breathing circuit. The infant breathed the air/CO₂ mixture for at least 5 min to allow ventilation and ETCO₂ to reach steady state as assessed from the real-time display using the Spectra software (Grove Medical, London, UK). The P_{0.1} and P_{imax} were assessed at baseline and at the end of each period of hypercapnia. Five sets of airway occlusions at end expiration were performed and the mean P_{0.1} calculated. During the fifth occlusion, the line remained occluded for 5–7 breaths once the infant cried. From those occluded breaths, P_{imax} was determined. Once the series of occlusions at a CO₂ level had been made, the infant was only studied at the next CO₂ level once they had returned to quiet sleep. The measurements were repeated at each inspired CO₂ concentration and in both positions. P_{0.1}/P_{imax} ratios were plotted for each inspired CO₂ level and the CO₂ response slope derived for each position. For each position, the subject's respiratory rate, tidal volume and minute ventilation were calculated for each CO₂ level.

Thoracoabdominal synchrony

Thoracoabdominal synchrony was assessed using uncalibrated respiratory inductance plethysmography (Respirace model 10.9230; Ambulatory Monitoring, New York, USA) in AC-coupled mode. Inductance coils embedded in two elastic bandages were placed around the rib cage (at the level of the axilla) and mid-abdomen to measure changes in rib cage and abdominal circumference during breathing. Thoracoabdominal asynchrony in individuals was determined in each position from five breaths after stabilisation of ETCO₂. For each breath, the chest and abdominal wall movements were derived from the recording software. A Lissajous figure was plotted and the phase angle determined according to the method described by Allen and colleagues.¹² For each position, the mean phase angle from the five breaths was used for analysis. Flow, airway pressure, capnogram and Respirace signals were acquired using a personal computer (Dell Computers, Texas, USA) with analogue-to-digital sampling at 100 Hz (PCI MIO 16XE 50; National Instruments; Austin, Texas, USA). The signals were acquired and displayed in real time using Spectra software (Grove Medical). Airway pressure measurements were acquired and displayed in real time using a custom-written software application (LabView 5.1, National Instruments, Austin, Texas, USA).

Functional residual capacity

FRC was assessed using a helium gas dilution technique as previously described.¹⁴ A facemask (Rendell Baker, Laerdal, Norway) was held snugly over the infant's nose and mouth; silicone putty was used around the mask to achieve a tight seal. The facemask was connected to a rebreathing bag via a three-way valve. The FRC system contained a helium analyser (Series

7700, Equilibrated Biosystems, Smithtown, New York, USA) with a digital display. During the measurement, if there was no change in the helium concentration over a 15 s period, equilibration was deemed to have occurred. The initial and equilibration helium concentrations were used in the calculation of FRC, which was corrected for oxygen consumption (assumed to be 7 ml/kg/min)¹⁵ and to body temperature, pressure and water vapour-saturated conditions. FRC was measured twice in each position and the results of the paired measurements were averaged and related to body weight. The mean intrasubject coefficient of variation of the measurement of FRC was 5.8%.

Analysis

The data were tested using the Kolgorov–Smirnov test and found to be normally distributed, except the thoracoabdominal asynchrony and FRC data. The thoracoabdominal asynchrony data were rank-transformed prior to analysis. Three by two (0, 2 and 4% inspired CO₂ levels—prone/supine position) multivariate repeated measures analysis of variance (ANOVA) were used. Degrees of freedom were corrected using the Greenhouse–Geisser procedure. A paired t test was used to compare the hypercapnia response slopes in the prone and supine positions. Additionally, where repeated measures of ANOVA revealed significant main effects, posthoc paired t tests were undertaken, and corrected for multiple comparisons where appropriate by the Bonferroni method. Differences in the FRC results were assessed for statistical significance using the Wilcoxon signed rank test.

Sample size

Recruitment of 18 infants allowed us to detect, with at least 80% power at the 5% level, a difference of 50% in the response to the CO₂ challenge between positions; such a difference was found when using inductance plethysmography to assess the difference between positions in the response to hypercapnia.¹⁰ In addition, recruitment of 18 infants allowed us to detect, with 80% power at the 5% level, differences in the results between positions equivalent to 1 SD of the measurements.

RESULTS

Patients

Eighteen infants (10 male) were studied at a postmenstrual age of 35 (range 35–37 weeks) (table 1). None of the infants was receiving medications at the time of study and none had received caffeine for a minimum of 72 h prior to study. Two mothers had smoked during pregnancy.

The mean (\pm SD) P_{0.1} was lower in the prone (3.4 \pm 0.96 cm H₂O) compared with the supine position (4.72 \pm 1.45 cm H₂O)

Table 1 Patient demographics

n	18
Gestational age (weeks)	31 (28–32)
Birth weight (g) (centile)	1469 (860–2298) (9th–91st)
Antenatal steroids	10
Duration (days) of:	
Mechanical ventilation	1 (0–8)
CPAP	1 (8–23)
Supplementary oxygen	1 (0–59)
Oxygen dependency at:	
28 days	1
36 weeks PMA	0

Data are displayed as n or median (range).

CPAP, continuous positive airway pressure; PMA, postmenopausal age.

(p=0.002). The increase in P_{0.1} with increasing CO₂ levels was smaller in the prone compared with the supine position (p=0.007) (table 2). The mean P_{imax} was lower in the prone (48.7 \pm 8.5 cm H₂O) compared with the supine (53.6 \pm 11.0 cm H₂O) position (mean difference 4.9, 95% CI 1.6 to 8.3) (p=0.006), but there were no significant differences in the mean P_{imax} at the different inspired CO₂ levels in either position (table 2) (figure 1).

Posthoc paired t tests (p values reported for two-tailed tests and adjusted for multiple comparisons, overall α =0.05) demonstrated no significant differences in P_{0.1}/P_{imax} results between positions at 0% and 2% inspired CO₂ levels. At the 4% inspired CO₂ level, however, respiratory drive normalised to inspiratory muscle strength, the P_{0.1}/P_{imax} was significantly smaller in the prone compared with the supine position (mean difference 0.037, 95% CI 0.04 to 0.006, p=0.006). The P_{0.1}/P_{imax} ratio increased as the inspired CO₂ was increased in both positions (prone p=0.005; supine p=0.001). Analysis using a paired t test demonstrated that the mean (\pm SD) P_{0.1}/P_{imax} response slope (expressed as the percentage increase in P_{0.1}/P_{imax} per percentage increase in CO₂) was significantly lower in the prone (6.67 \pm 6.86%) compared with the supine (18.91 \pm 16.67%) position (mean difference 12.25%, 95% CI 3.89% to 20.61%, p=0.007) (figure 2). Respiratory rate (p=0.003), tidal volume (p<0.001) and minute volume (p<0.001) increased in both positions with increasing CO₂ levels but were not significantly influenced by sleeping position (table 2).

Thoracoabdominal asynchrony was not significantly influenced by position or inspired CO₂ concentration (table 2). FRC was higher in the prone (median 28.4, range 26.8–39.3 ml/kg) compared with the supine (median 27.7, range 22.9–31.7 ml/kg) position (p=0.019) (figure 3).

Table 2 Ventilatory responses according to sleeping position and inspired CO₂ (iCO₂) level

Inspired CO ₂ (%)	0		2		4		ANOVA effects and interactions		
	Prone	Supine	Prone	Supine	Prone	Supine	iCO ₂ p Value	Position p Value	Position \times iCO ₂ p Value
P _{0.1} (cm H ₂ O)	3.07 \pm 0.81	3.38 \pm 0.88	3.55 \pm 0.92	4.33 \pm 0.92	3.99 \pm 1.42	6.41 \pm 3.25	0.001	0.002	0.007*
P _{imax} (cm H ₂ O)	47.6 \pm 10.4	50.7 \pm 12.5	48.5 \pm 9.5	53.5 \pm 11.3	50.0 \pm 10.8	56.7 \pm 14.0	0.057	0.003	0.512
P _{0.1} /P _{imax}	0.066 \pm 0.028	0.067 \pm 0.021	0.075 \pm 0.030	0.083 \pm 0.030	0.081 \pm 0.035	0.119 \pm 0.061	<0.001	0.003	0.008*
Respiratory rate (bpm)	59.2 \pm 11.4	61.4 \pm 13.0	60.8 \pm 11.5	68.5 \pm 15.7	65.4 \pm 14.5	72.4 \pm 17.7	0.003	0.310	0.275
Tidal volume (ml/kg)	7.32 \pm 1.38	7.05 \pm 1.01	9.75 \pm 2.02	9.9 \pm 1.74	12.5 \pm 2.70	12.5 \pm 2.49	<0.001	0.797	0.996
Minute ventilation (ml/kg/min)	418 \pm 94	418 \pm 93	542 \pm 143	644 \pm 215	702 \pm 271	785 \pm 158	<0.001	0.159	0.494
Phase angle (°)	20.3 \pm 15.9	15.5 \pm 15.2	22.8 \pm 22.1	15.2 \pm 16.1	18.1 \pm 16.3	16.0 \pm 10.6	0.833	0.444	0.981

Data are given as mean (\pm SD).

*Interactions identifying significant effects of position on hypercapnic responses.

ANOVA, analysis of variance; P_{0.1}, airway pressure change after the first 100 ms of an occluded inspiration; P_{imax}, maximum inspiratory pressure with an occluded airway during crying.

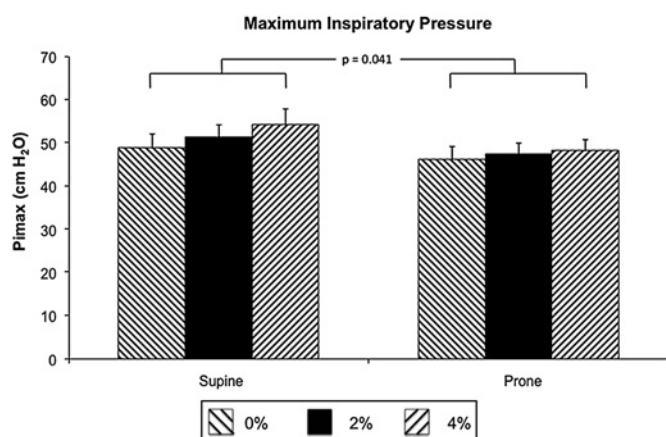


Figure 1 Maximum inspiratory pressure by position and inspired CO₂ level.

DISCUSSION

We have demonstrated a poorer response to the CO₂ challenges in the prone compared with the supine position as evidenced by smaller increases in the $P_{0.1}/P_{imax}$ ratio in response to increasing inspired CO₂ levels. The increase in $P_{0.1}$, but not P_{imax} , in response to the CO₂ challenge was smaller in the prone compared with the supine position. We did not find P_{imax} to be significantly greater in the prone compared with the supine position at any inspired CO₂ level. Our results then do not suggest a mechanical advantage of the prone position in the infants we studied. We did not demonstrate a significant difference in minute ventilation between the two positions. Unlike the corrected measure ($P_{0.1}/P_{imax}$) of respiratory drive, minute ventilation is affected by both drive and mechanical factors; this may lead to the effects of position being less clear cut.

Our findings of a lower response to a CO₂ challenge in the prone compared with the supine position agree with our results of a reduced response to tube breathing in the prone position,⁸ but not with those of Martin *et al*,¹⁰ who found a greater response to a CO₂ challenge in that position. We had speculated⁸ that the difference in the results of the previous studies^{8 10} was due to the levels of CO₂ used. In this study, however, we examined the response to two inspired CO₂ levels and found a greater response to both in the supine position. The CO₂ challenge we employed differed from that of Martin *et al*,¹⁰ in that we used at least 5 min of CO₂ exposure under normoxic

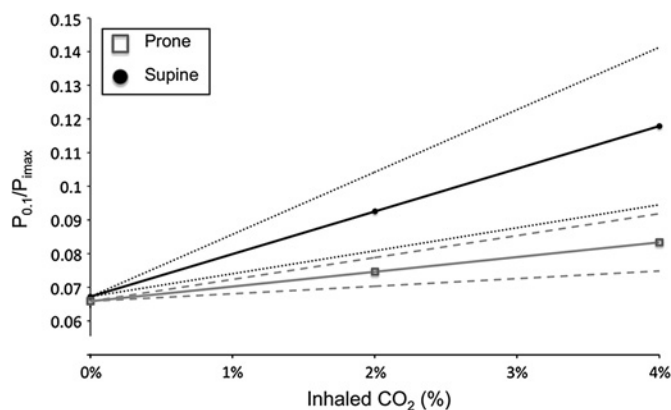


Figure 2 Response to hypercapnia in the prone and supine positions. The data are demonstrated as the mean response slopes (solid lines) and 95% CIs (dotted lines).

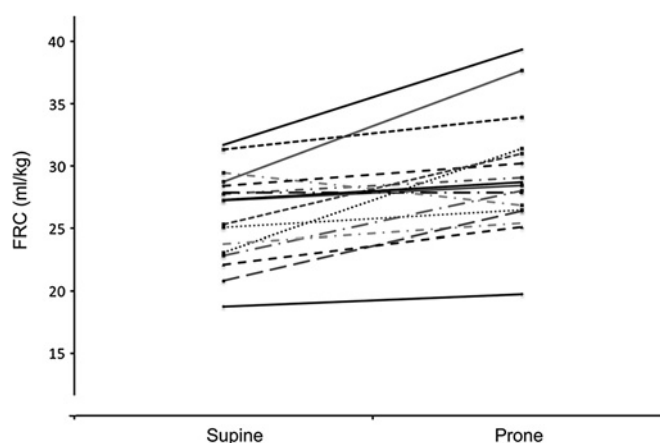


Figure 3 Functional residual capacity results by position. Individual data are demonstrated by linked data points.

conditions, whereas Martin used a shorter challenge (at least 30 s) with rebreathing of a 40% O₂/5% CO₂ mixture. The hyperoxic, hypercapnic challenge employed by Martin *et al*¹⁰ would have been predominantly mediated by the central chemoreceptors, as inspired oxygen concentrations >35% have been shown to significantly reduce peripheral chemoreceptor output.¹⁶ This could have resulted in a slower, dampened ventilatory response, which may not have fully developed over the 30 s exposure period. In the current study, the normoxic, hypercapnic challenge would have been mediated via both the peripheral and central chemoreceptors, resulting in a more immediate response. In addition, the longer duration of exposure would have allowed the response to develop fully. The prone position confers a mechanical advantage to the chest wall by stabilising the compliant rib cage,¹⁷ and synchrony of the rib cage and abdominal movement increases when preterm infants are moved from the supine to the prone position.^{17 18} In Martin's study¹⁰ significantly more asynchrony of the rib cage and abdominal motion was found in the supine compared with the prone position regardless of CO₂ level or sleep state. They therefore speculated that persistent asynchrony of the rib cage and abdominal movement was the major mechanism underlying the attenuated hypercapnic response in the supine infants.¹⁰ In this study, the phase angle (reflecting thoracoabdominal asynchrony) was neither significantly higher in the supine compared with the prone position nor significantly influenced by increasing inspired CO₂ concentration. We suggest that our thoracoabdominal asynchrony results reflect the longer CO₂ challenge which over-ride any mechanical advantage in the prone position.

We speculate that the reduced ventilatory response to the CO₂ challenge in the prone position resulted from altered peripheral feedback to the respiratory controller. As previously reported,¹⁴ we found that the FRC was significantly higher in the prone compared with the supine position. This may result in a greater level of inhibitory feedback from pulmonary stretch receptors in the prone position. The Hering–Breuer inflation reflex, which is stretch receptor mediated and terminates inspiration and prolongs expiration in response to lung inflation,¹⁵ has been demonstrated to be stronger in the prone compared with the supine position.^{19 20} Differences in the strength of the reflex between positions correlate significantly with differences in lung volume.²⁰ It may then be that prone positioning is associated with increased inhibitory feedback from pulmonary stretch receptors which reduces the response to the CO₂ challenge.

In conclusion, we have demonstrated that convalescent, prematurely born infants have a reduced ventilatory response to hypercapnia in the prone compared with the supine position. The results support the hypothesis that prematurely born infants may have an impaired ability to respond to respiratory compromise in the prone position. To our knowledge, this is the first use of $P_{0.1}/P_{i\max}$ to assess the ventilatory response to a hypercapnic challenge in prematurely born infants and it would be important to use other measures to confirm or refute our results. Further studies of prematurely born infants at the high risk age for SIDS are required to determine whether a reduced ability to respond to a CO_2 challenge could contribute to their increased vulnerability to SIDS in the prone position.

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Competing interests None.

Ethics approval This study was conducted with the approval of the King's College Hospital Research Ethics Committee

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