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The effects of sleeping position, maternal smoking and substance misuse on the ventilatory response to hypoxia in the newborn period

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ABSTRACT

Background: Maternal smoking, substance misuse in pregnancy and prone sleeping increase the risk of sudden infant death syndrome (SIDS). We examined the effect of maternal smoking, substance misuse and sleeping position on the newborn response to hypoxia.

Methods: Infants born between 36 and 42 weeks of gestational age underwent respiratory monitoring in the prone and supine sleeping position before and during a hypoxic challenge. Minute ventilation (MV) and end tidal carbon dioxide ($ETCO_2$) levels were assessed.

Results: Sixty-three infants were studied: 22 controls, 23 whose mothers smoked and 18 whose mothers substance misused and smoked. In the supine position, baseline MV was higher and $ETCO_2$ levels were lower in infants of substance misusing mothers compared to controls ($p=0.015$; $p=0.017$ respectively). Infants of substance misusing mothers had in the prone position a lower baseline MV and higher $ETCO_2$. ($p=0.005$; $p=0.004$ respectively). When prone the rate of decline in minute ventilation in response to hypoxia was greater in infants whose mothers substance misused and smoked compared to controls ($p=0.002$) and infants of smoking mothers ($p=0.016$).

Conclusion: The altered response to hypoxia in the prone position of infants whose mothers substance misused and smoked in pregnancy may explain their increased vulnerability to SIDS.

INTRODUCTION

Despite the significant reduction in the number of cases of Sudden Infant Death Syndrome (SIDS) following the 'Back to Sleep' campaign in which parents were advised to avoid their infant prone sleeping, there were over two thousand SIDS cases in the USA in 2012 (1). Following the 'Back to sleep' campaign other risk factors such as maternal smoking and maternal substance misuse became more prominent (2).

A meta-analysis of 35 case-control studies estimated an approximately two-fold increase in the risk of SIDS in infants of mothers who smoked in pregnancy compared to controls (odds ratio (OR) = 2.25 95% confidence intervals (95% CI) = 2.03–2.50)) (3). Furthermore, the risk was dose dependent (3). Infants of substance misusing mothers (ISAMs) are also at increased risk of SIDS compared to controls. This risk has been reported to be from four to eight-fold (4, 5). The effect of a combination of risk factors may be more than additive, in particular non-supine sleeping and smoking in pregnancy (6).

In this study, we have tested the hypotheses that the ventilatory response to hypoxia would be dampened in infants of smoking and/or substance misusing mothers compared to infants not exposed to either insult (controls) and any dampening would be more marked in the prone compared to the supine position.

METHODS

Infants were eligible for inclusion in the study if they were born between 36 weeks and 42 weeks of gestation at King's College Hospital NHS Foundation Trust. Exclusion criteria were major congenital abnormalities, respiratory disease or sepsis. Approval for the study was obtained from the London – Bromley Research Ethics Committee. Parents gave informed written consent for their infant to participate.

Protocol

Infants were studied prior to maternity unit discharge in the first week after birth. After a feed, the infant was placed in either the prone or supine sleeping position, the other position being studied afterwards on the same day. The order in which the positions were studied was randomised between infants. Measurements were made once the infant was in quiet sleep. Sleep state was determined by observation of the behavioural state (7). If arousal occurred the measurement was abandoned and recommenced once the infant returned to quiet sleep.

Baseline ventilation was measured for five minutes with the infants breathing medical air from a cylinder (BOC Gases, UK). The inspired gas was then switched to a premixed gas containing 15% oxygen in nitrogen delivered from a cylinder (BOC Gases, UK). Exposure to the hypoxic gas was maintained for a further five minutes. The test was terminated if the transcutaneous oxygen saturation fell below 85%. The last minute of tidal breathing prior to switching to the hypoxic gas mix was used as a baseline value.

Equipment

The test gas was delivered using an open circuit system via a soft latex nasal mask (Neomask, Draeger, Germany) and pneumotachograph (Mercury F10L, G M Instruments, Kilwinning, Scotland) to measure respiratory flow. Pressure drop across the pneumotachograph was measured using a differential pressure transducer-amplifier system (Gould model 13-4615-70, Cleveland OH, USA). The pneumotachograph had a dead space of 0.8 ml and resistance of 0.86 $mmH_2O/l/min$ (manufacturer's data) and was connected to the nasal mask using a snugly fitting connector. A leak free seal over the infant's nose was achieved by gentle pressure and confirmed by the absence of any discrepancy between the inspired and expired tidal volumes on the real-time computer display. The distal end of the pneumotachograph was connected to the common port of a two-way, non-rebreathing valve which separated inspired from expired gas and ensured that the controlled mixture of gases was inspired by the infant. A constant flow of gas was delivered to the inspiratory port of the valve via wide bore (20 mm), low resistance tubing eliminating any dead space. A capnograph (CO_2SMO capnograph; (Respironics UK, Chichester, UK) sampled gas continuously from the nasal mask through a fine bore catheter at a rate of 180ml/minute. The carbon dioxide content of the sampled gas was determined by infrared spectroscopy. Respiratory flow and gas concentration were acquired and displayed in real time on a PC computer running Spectra software (Grove Medical, London, UK) with 100 Hz analogue to digital sampling (PCI-MIO-16XE-50, National Instruments, Austin TX, USA). Tidal volume was obtained by digital integration of the airflow signal by the acquisition software. Minute ventilation was calculated per breath from the tidal volume trace. Oxygen saturation

was measured using a pulse oximeter (Masimo rainbow SET Pulse Oximetry) attached to the foot of the infant.

Data were averaged over 10 second periods. The averaged data points were used to quantify the initial increase in ventilation in response to hypoxia and the timing and magnitude of the subsequent decline in ventilation in response to sustained hypoxia.

The responses to the hypoxic challenge were determined by:

(i) the time from the start of hypoxic challenge to the peak ventilatory response

(ii) the magnitude of the increase in minute ventilation from baseline to the peak ventilatory response

(iii) the magnitude of decline in minute volume from the peak to the lowest minute volume

(iv) the rate of decline in minute volume, calculated as the peak minute volume-lowest minute volume divided by the time from peak to the lowest minute volume.

(v) the change in the oxygen saturation level from baseline to the lowest oxygen saturation level.

Exposure to smoking and substance misuse

Urine samples were obtained from all infants and mothers at the time of study for cotinine analysis and assessment of maternal substance misuse. Urine was tested for

cannabinoids, opiates, amphetamines, methadone, cocaine and benzodiazepines using cloned enzyme donor immunoassays (CEDIA).

Data collection

Data were gathered from the medical records: gestational age at birth, birth weight, mode of delivery, Apgar score, ethnicity, parity, maternal reported smoking and substance misuse during pregnancy. Individual birth weight centiles were calculated using data which took into account gestational age, sex and birth weight (8) via an online calculator (9).

Analysis

Recruited infants were divided into three groups:

1. Infants of mothers who neither smoked nor misused substances during pregnancy (controls)
2. Infants of mothers who smoked, but did not misuse substances during pregnancy
3. Infants of mothers who misused substances during pregnancy (see results, all mothers who substance misused smoked)

Statistical analyses

Differences in baseline characteristics between the three groups were assessed for statistical significance using the Kruskal-Wallis analysis of ranks test or the Chi-

square test as appropriate. Differences in the responses to the hypoxic challenge between groups were assessed using regression analysis. Data were transformed as necessary using a square root or logarithmic transformation to meet regression assumptions. Adjustment was made for baseline differences in birthweight, gestational age and postnatal age at study by fitting the variables as covariates. Results are presented as unadjusted and adjusted arithmetic means or geometric means. Adjusted means are marginal estimates set to the mean value of the covariates. Comparisons between prone and sleeping positions were made using the paired samples t-test.

Analyses were conducted using SPSS Version 22 (SPSS Inc., Chicago, IL, USA).

Sample size

Recruitment of twenty infants into each of the three groups allowed detection of a difference of one standard deviation in each outcome between the groups with 80% power at the 5% level. That magnitude of difference had been detected in the ventilatory response to added dead space between newborns of smoking and non-smoking mothers (10).

RESULTS

Ninety-one infants were recruited to the study. Twenty–eight infants did not complete the study protocol as the infants did not sleep (n=22) or were discharged before the study could be performed (n=6). There were no significant differences between those

who were and were not studied with respect to gestational age, birth weight, birth weight centile, or sex (Table 1).

Sixty-three infants were studied in the newborn period. There were no significant differences between the three groups with regard to gestational age, birth weight, birth weight centile, sex and age of study (Table 2).

(i) Urine results

The urine drug screen was positive for all mothers in the substance misusing group, and negative for all mothers and infants in the control and smoking group. All urine results for those mothers who substance misused showed they had smoked antenatally. Two infants in the substance misusing group had reported maternal use of amphetamines, benzodiazepines and 3,4-Methylenedioxymethamphetamine (ecstacy), but these were not detected on urine screen (Table 3). All control mothers' and infants' urines were negative for cotinine. All maternal urines in both the smoking group and substance misuse group were positive for cotinine. Urine from two infants in the smoking group and two in the substance misuse group were negative for cotinine.

Four infants from the substance misusing group subsequently required treatment for withdrawal with oral morphine, the assessments had been made prior to commencing treatment.

(ii) Results in the supine position

In the supine position, at baseline while breathing air, the tidal volume, respiratory rate and minute volume differed significantly between the three groups. Tidal volume was lower ($p=0.011$) and the respiratory rate and minute ventilation were higher in the substance misuse group compared to controls ($p<0.001$, $p=0.008$ respectively). Baseline tidal volume was also lower and respiratory rate higher in infants of substance misusing mothers compared to infants of smoking mothers ($p=0.002$, $p=0.017$ respectively). (Table 4) There were, however, no significant differences between the groups in any of the measures of the hypoxic ventilatory response. (Table 5).

(iii) Results in the prone position

There were no significant differences in baseline results of tidal volume, respiratory rate and minute volume between the three groups when studied in the prone position (Table 6). There were, however, statistically significant differences in the rate of decline in minute volume during hypoxia across the three groups ($p=0.002$) (Figure 1). A greater rate of decline was observed in the infants of substance misusing mothers compared to the controls ($p=0.002$) and infants of smoking mothers ($p=0.016$). Those differences remained significant after adjusting for gestation at birth, postnatal age and birth weight (Table 7).

(iv) Comparison of the results in the supine and prone positions

In the controls, sleeping position had no effect on baseline ventilatory variables. The rate of decline in minute volume during hypoxia, however, was greater in the supine

compared to the prone position (p=0.02) (Table 8). In the smoking group, at baseline, the respiratory rate was significantly lower in the prone compared to the supine position, (Figure 2), but sleeping position had no significant effect on the ventilatory response to hypoxia (Table 9). In the substance misuse group prone sleeping was associated with a lower respiratory rate (p=0.001) (Figure 2) and minute volume (Figure 3) (p= 0.005) and a trend towards a higher end-tidal CO_2 compared to the supine position (Table 10). There were no significant differences in the response to hypoxia between sleeping position.

DISCUSSION

We have demonstrated a significantly greater rate of decline in minute ventilation during the hypoxic challenge in the prone position in infants of mothers who had misused substances and smoked during pregnancy compared to those whose mothers had smoked or whose mothers neither substance misused nor smoked

Maternal cocaine use in pregnancy can alter placental blood flow inducing intermittent hypoxia (11). Furthermore, maternal opiate use can cause intermittent hypoxia via direct effects on maternal respiratory control (12). Fourteen adult methadone users were studied while breathing air and during hypoxic and hypercarbic challenges. The ventilatory responses to both challenges were damped, even when the adults were breathing air, frequent oxygen desaturations occurred following methadone administration (12). Martin et al demonstrated that chronic intermittent hypoxia in piglets increased the magnitude of this hypoxic decline (13). The decline in ventilation in response to prolonged hypoxia is centrally mediated (14). Our

results, then suggest that maternal substance misuse had a central effect on respiratory control. However, the effect of maternal substance misuse on the rate of hypoxic ventilatory decline was not seen in the supine position. In the supine position respiratory drive may be maintained during hypoxia, whereas prone positioning may dampen respiratory control such that hypoxia has a significant effect on the response to hypoxia. This would be supported by our findings of differing baseline ventilation in the prone and supine position in infants of smoking and substance misusing mothers.

We have demonstrated significant differences in baseline ventilation compared to controls in infants exposed to smoking and substance misuse during pregnancy and between the prone and supine sleeping position. Infants exposed to substance misuse in pregnancy had a significantly higher respiratory rate and lower tidal volumes in the supine position. A possible explanation for those findings is that the infants were withdrawing from substance exposure. The end tidal CO_2 was significantly lower in infants of substance misusing mothers, suggesting that the increased minute volume and respiratory rate was not driven solely by increased metabolic demands and increased CO_2 production. The findings of differences in baseline ventilation between groups is consistent with other studies evaluating respiratory control in infants exposed to substances in-utero. Glass et al. measured the respiratory rate and blood gases of 22 infants born to heroin addicted mothers and compared them to unexposed controls matched by gestational age and birth weight. The heroin exposed infants had significantly higher respiratory rates and a higher pH compared to controls (15). No measurements of tidal volume, however, were included. Ali et al. reported significantly higher minute volumes and respiratory rates in infants of substance

misusing infants (16). In contrast, Wingkun et al. found no difference in baseline respiratory characteristics between 12 term infants born to substance misusing mothers and 12 controls (17). The infants, however, were mostly studied within the first twenty-four hours after birth and, therefore, may not have exhibited evidence of withdrawal at the time of measurement (17). Prone sleeping was associated with significantly lower respiratory rates and minute volumes and higher end-tidal CO_2 levels when compared to sleeping supine in infants exposed to substance misuse in-utero. The infants were studied supine and prone within the same protocol and hence their baseline results in the two positions were obtained usually less than 60 minutes apart. Hence, we feel it is appropriate to compare the results to determine if there was an effect of position on tidal and minute volume. Prone compared to supine sleeping has been shown to result in a greater functional residual capacity with improved oxygenation in convalescent preterm infants (18). In eighteen prematurely born infants (median gestational age 30 weeks) a stronger Hering-Breuer inflation reflex was demonstrated in the prone compared to supine position. The strength of the reflex, which is mediated by pulmonary stretch receptors, correlated strongly with the higher FRC in the prone position (19). In the prone position we therefore hypothesise that it may, exert a greater inhibitory effect on respiratory drive, hence a lower respiratory rate and minute volume in the prone position in the infants of substance misusing mother.

Smith et al. found no significant differences in minute volume, tidal volume or respiratory rate between the prone and supine sleeping positions in eighteen convalescent preterm infants that had not been exposed to substance misuse in-utero (20). This is in keeping with the results from our control infants. Ali et al reported a

significantly greater initial ventilatory increase in response to hypoxia in the supine position in infants of substance misusing mothers compared to controls and infants of smoking mothers studied (16). No such significant differences were found this study. It is possible that the infants we assessed had less exposure to either maternal smoking or substance misuse as in the previous study (16) there was a significant difference in birth weight and gestation between the infants of substance misusing, smoking and control parents which was not seen in this cohort. A comparison of urinary cotinine levels highlighted higher cotinine levels in the previous study (median 145 (range 11-8760) ng/ml versus 130 (range 0-3240) ng/ml ($p=0.036$). Furthermore, 9 of 21 infants of substance misusing mothers in the previous study subsequently required treatment for neonatal abstinence syndrome compared to only 4 of 17 infants in the present study.

This study had strengths and some limitations. To our knowledge this is the first study to evaluate the combined effect of sleeping position with the antenatal risk factors for SIDS: that is, maternal smoking and substance misuse. As we were able to assess the infants prior to maternity/neonatal unit discharge, we were able to assess the affect of only antenatal exposure. The assessment of the hypoxic response quantified both the initial hypoxic ventilatory response and the later decline in ventilation. The latter component has frequently been ignored in the assessment of hypoxic responses (21-23), despite persisting at the high risk age for SIDS (24). We did not rely on maternal reporting of smoking and substance misuse but assessed the results of maternal and infant urine screens. A further limitation is that we could not assess the specific effects of other drug misuse as polydrug course.

In conclusion, infants of substance misusing mothers which studied in the prone position had a significantly faster decline in ventilation in response to hypoxia than infants exposed only to smoking in utero or controls. This altered ventilatory response to hypoxia may impair an infant's ability to respond effectively to an exogenous stressor and increase vulnerability to SIDS.

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FIGURE LEGENDS

Figure 1: Box and whisker plot showing hypoxic rate of decline in the prone sleeping position. The box represents the interquartile range. Whiskers extend two standard deviations from the mean.

Figure 2: Box and whisker plot showing the change in baseline respiratory rate between the supine and prone position. The box represents the interquartile range. Whiskers extend two standard deviations from the mean.

Figure 3: Box and whisker plot showing the change in minute volume between the supine and prone position. The box represents the interquartile range. Whiskers extend two standard deviations from the mean.

Table 1: Demographics of infants recruited to the study comparing those that completed the protocol to those that did not.

The data are demonstrated as median (range)

	Recruited and completed protocol	**Recruited and did not complete protocol**	**p-value**
Number	63	28	
Birthweight (gms)	2890 (1950-4960)	3190 (2340-3850)	0.158
Gestational age (weeks)	39 (36-42)	40 (36-41)	0.102
Birth weight centile	13 (1-99)	28 (1-99)	0.18
Male (n)	31	18	0.25

Table 2: Demographics of infants undergoing the hypoxic challenge.

The data are demonstrated as median (range)

	Controls	**Smoking**	**Substance misuse**	**p-value**
Number recruited	36	35	20	
Number studied	22	23	18	
Birthweight (gms)	2950 (1980-4960)	3060 (1950-3720)	2880 (2010-4450)	0.89
Gestational age (weeks)	39 (36-42)	39 (36-42)	39 (36-42)	0.87
Birth weight centile	18 (1-99)	12 (1-68)	12 (1-93)	0.56
Male (n)	7	13	11	0.28
Age at study (days)	3 (0-10)	2 (1-7)	3 (1-9)	0.35

Table 3: Positive urine drug screens for mothers, some mothers were positive for several substances

Substance	Number of mothers testing positive after delivery
Opiates	14
Methadone	9
Morphine	11
Codeine	7
Cannabis	17
Coccaine metabolites	4

Table 4: Baseline cardiorespiratory characteristics while supine

Unadjusted results are expressed as arithmetic mean (standard deviation; range). Results adjusted for birth weight, gestational age and postnatal age expressed as arithmetic mean and 95% confidence interval.

		Control	**Smoking**	**Substance misuse**	**p-value**
Tidal Volume (ml/kg)	Mean (SD; Range) Unadjusted	7.9 (2.0; 5.5-15.2)	7.6 (1.7; 4.8-10.8)	6.4 (1.2; 4.5-8.7)	0.023
	Mean (95% CI), adjusted	7.9 (7.3-8.5)	7.6 (7.0-8.3)	6.3 (5.7-7.0)	0.002
Respiratory rate (breaths/min)	Mean (SD; Range) Unadjusted	46 (12; 21-75)	52 (13; 34-77)	69 (20; 39-110)	<0.001
	Mean (95% CI), adjusted	46 (40-53)	52 (46-59)	69 (62-76)	<0.001
Minute volume (ml/kg/min)	Mean (SD; Range) Unadjusted	336 (80; 232-501)	373 (92; 220-600)	434 (136; 220-782)	0.017
	Mean (95% CI), adjusted	335 (291-379)	376 (333-419)	432 (385-478)	0.015
Mean inspiratory flow (ml/kg/s)	Mean (SD; Range) Unadjusted	12.7(2.6; 8.5-16.5)	14.0 (3.2; 9.6-20.9)	14.7 (4.5; 8.8-28.3)	0.182
	Mean (95% CI), adjusted	12.6 (11.2-14.0)	14.1 (12.7-15.5)	14.6 (13.1-16.1)	0.140

Heart rate (bpm)	Mean (SD; Range) Unadjusted	129 (10; 110-148)	130 (16; 102-161)	130 (17; 86-156)	0.961
	Mean (95% CI), adjusted	128 (122-133)	131 (125-137)	131 (124-137)	0.702

Table 5: Results of hypoxic challenge in the supine position according to group.

		Controls	**Smoking**	**Substance misuse**	**p-value between groups**
Hypoxic increase in minute ventilation (ml/kg/min)	Mean (SD†; Range) Unadjusted	69 (65; 0-197)	82 (84; 0-290)	71 (67; 0-186)	0.95
	Mean (95% CI), adjusted‡	43 (18-79)	59 (30-98)	47 (20-86)	0.77
Time to peak minute ventilation during hypoxic challenge (s)	Mean (SD†; Range) Unadjusted	109 (55; 26-214)	97 (62; 10-218)	153 (108; 16-380)	0.08
	Mean (95% CI), adjusted‡	108 (73-143)	100 (66-134)	151 (114-188)	0.10
Hypoxic rate of decline in ventilation (ml/kg/min/s)*	Mean (SD†; Range) Unadjusted	3.9 (6.9; 0-23)	3.6 (6.7; 0-27)	4.2 (10.9; 0-36)	0.93
	Mean (95% CI), adjusted‡	3.5 (1.9-6.0)	3.9 (2.3-6.4)	4.1 (2.3-7.0)	0.92
Magnitude of decline (ml/kg/min)	Mean (SD†; Range) Unadjusted	130 (84; -40-270)	148 (156; -50-540)	155 (117; 10-380)	0.84
	Mean (95% CI), adjusted‡	123 (65-182)	153 (100-206)	155 (97-214)	0.69

Minimum saturations (%)	Mean (SD†; Range) Unadjusted	90 (5; 84-98)	89 (5; 81-98)	89(5; 81-97)	0.63
	Mean (95% CI), adjusted‡	90 (88-92)	89 (87-91)	89 (87-91)	0.56

*denotes that all means are geometric means due to skewness of the distribution.

†sd on natural scale.

‡denotes marginal means adjusted for birthweight, gestational age, and postnatal age (set to mean values).

Table 6: Baseline cardiorespiratory characteristics while prone.

Unadjusted results are expressed as arithmetic mean (standard deviation; range). Results adjusted for birth weight, gestational age and postnatal age expressed as arithmetic mean and 95% confidence interval.

		Control	**Smoking**	**Substance misuse**	**p-value**
Tidal Volume (ml/kg)	Mean (SD; Range) Unadjusted	7.7(1.3; 5.6-11.1)	7.8 (2.0; 4.1-11.9)	6.9 (1.5; 4.5-9.8)	0.133
	Mean (95% CI), adjusted	7.8(7.1-8.5)	7.8 (7.2-8.5)	6.8 (6.1-7.5)	0.056
Respiratory rate (breaths/min)	Mean (SD; Range) Unadjusted	45 (11; 26-69)	47 (15; 29-72)	54 (13; 30-81)	0.101
	Mean (95% CI), adjusted	45 (39-51)	48 (42-53)	54 (48-60)	0.112
Minute volume (ml/kg/min)	Mean (SD; Range) Unadjusted	342 (81; 211-486)	360 (94; 228-537)	348 (92; 219-593)	0.820
	Mean (95% CI), adjusted	342 (303-381)	361 (323-400)	347 (308-386)	0.769

Mean inspiratory flow (ml/kg/s)	Mean (SD; Range) Unadjusted	12.9 (3.3; 7.8-19.4)	13.8 (3.0; 8.1-19.5)	12.9 (2.8; 8.5- 18.2)	0.605
	Mean (95% CI), adjusted	12.8 (11.5-14.2)	13.9 (12.5-15.3)	12.9 (11.5-14.2)	0.481
Heart rate (bpm)	Mean (SD; Range) Unadjusted	132 (10; 115-159)	130 (12; 108-155)	130 (14; 100-155)	0.766
	Mean (95% CI), adjusted	130 (126-135)	132 (127-137)	130 (125-136)	0.909

Table 7: Results of hypoxic challenge in the prone position according to group.

		Controls	**Smoking**	**Substance misuse**	**p-value between groups**
Hypoxic increase in minute ventilation (ml/kg/min)	Mean (SD†; Range) Unadjusted	94 (86; 0-260)	62 (63; 0-240)	68 (58; 0-170)	0.32
	Mean (95% CI), adjusted‡	75 (43-114)	42 (20-72)	49 (25-82)	0.31
Time to peak minute ventilation during hypoxic	Mean (SD†; Range) Unadjusted	137 (91; 4-330)	103 (85; 6-348)	137 (94; 4-270)	0.41
	Mean (95% CI), adjusted‡	133 (90-177)	106 (64-149)	136 (93-180)	0.55
Hypoxic rate of decline in ventilation	Mean (SD†; Range) Unadjusted	1.5 (2.0; 0-7)	2.1 (3.2; 0-10)	5.6 (14.5; 1-57)	0.002
	Mean (95% CI), adjusted‡	1.5 (0.7-3.6)	2.1 (1.2-4.5)	6.4 (4.4-9.5)	0.002
Magnitude of decline (ml/kg/min)	Mean (SD†; Range) Unadjusted	121 (115; -30-360)	184 (86; 40-320)	189 (111; 40-430)	0.13
	Mean (95% CI), adjusted‡	121 (70-172)	185 (134-236)	186 (133-240)	0.14

Minimum saturations (%)	Mean (SD†; Range) Unadjusted	89 (5; 81-98)	89 (5; 78-97)	91 (5; 82-99)	0.52
	Mean (95% CI), adjusted‡	89 (87-91)	89 (86-91)	91 (88-94)	0.51

*denotes that all means are geometric means due to skewness of the distribution.

†sd on natural scale.

‡denotes marginal means adjusted for birthweight, gestational age, and postnatal age (set to mean values).

Table 8: Baseline measurements and hypoxic challenge results in prone and supine position, control group.

Data presented as arithmetic mean (standard deviation; range)

	Supine	**Prone**	**p-value**
Tidal Volume (ml/kg)	7.9 (2.0; 5.5-15.2)	7.7(1.3; 5.6-11.1)	0.615
Respiratory rate (breaths/min)	46 (12; 21-75)	45 (11; 26-69)	0.688
Baseline minute volume (ml/kg/min)	336 (80; 232-501)	342 (81; 211-486)	0.906
Baseline Mean inspiratory flow (ml/kg/s)	12.7(2.6; 8.5-16.5)	12.9 (3.3; 7.8-19.4)	0.973
End tidal CO_2 (%)	4.7(0.5; 4.3-5.9)	4.8 (0.5; 4.1-6.3)	0.436
Hypoxic increase in minute ventilation (ml/kg/min)	69 (65; 0-197)	94 (86; 0-260)	0.18
Time to peak minute ventilation during hypoxic challenge (s)	109 (55; 26-214)	137 (91; 4-330)	0.29
Hypoxic rate of decline in ventilation (ml/kg/min/s)*	3.9 (6.9; 0-23)	1.5 (2.0; 0-7)	0.02

Magnitude of decline (ml/kg/min)	130 (84; -40-270)	121 (115; -30-360)	0.77
Minimum saturations (%)	90 (5; 84-98)	89 (5; 81-98)	0.50

Table 8: Baseline measurements and hypoxic challenge results in prone and supine position, smoking group.

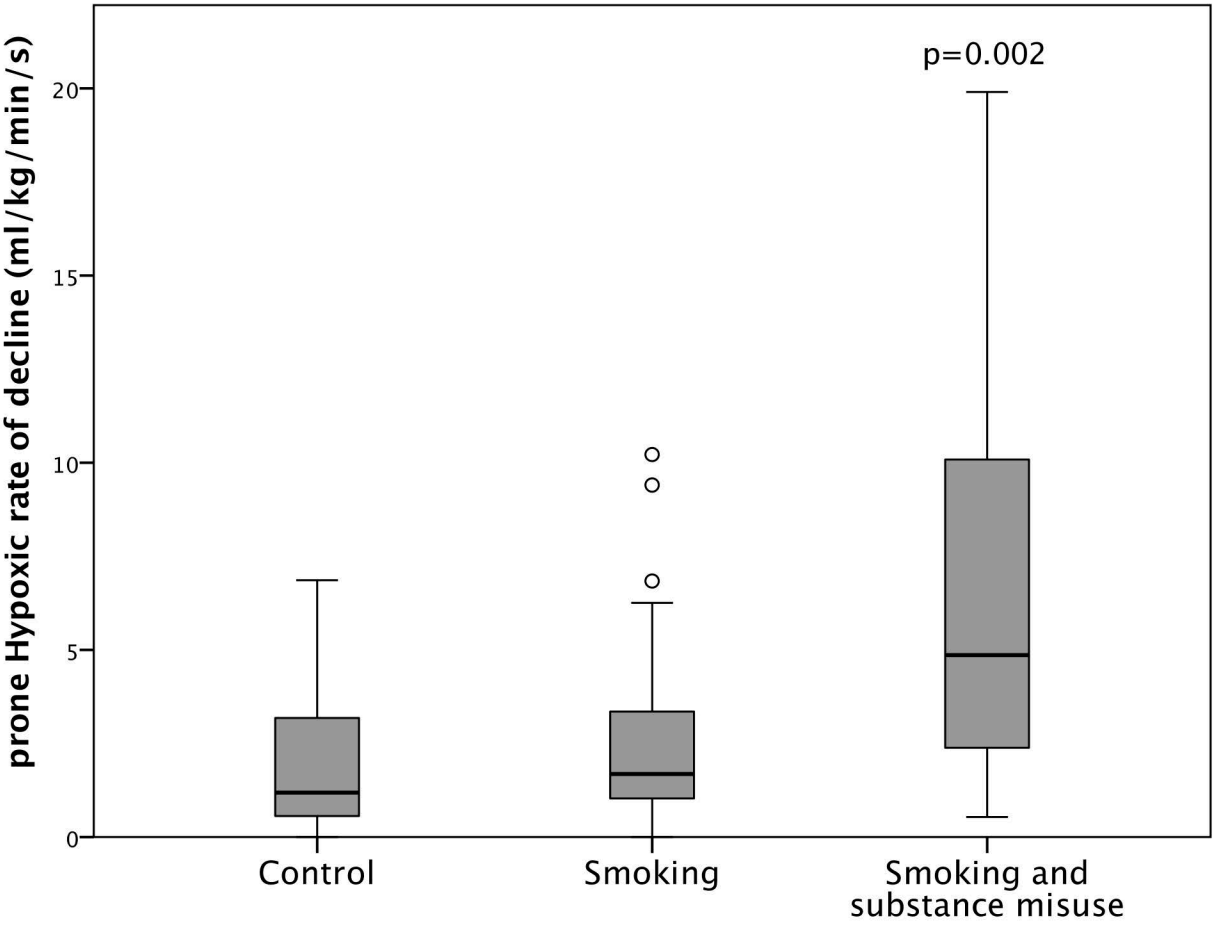
Data presented as arithmetic mean (standard deviation; range)

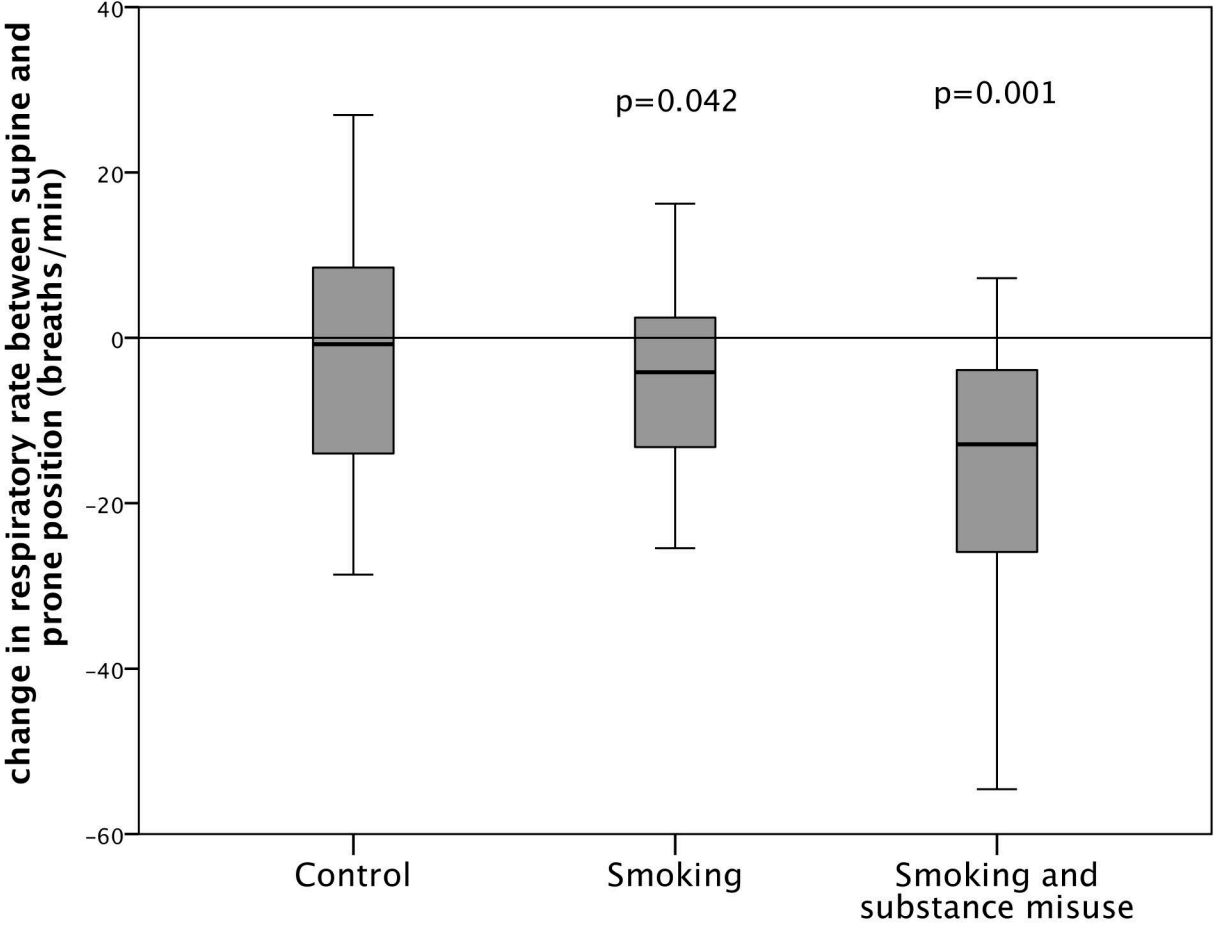
	Supine	**Prone**	**p-value**
Tidal Volume (ml/kg)	7.6 (1.7; 4.8-10.8)	7.8 (2.0; 4.1-11.9)	0.209
Respiratory rate (breaths/min)	52 (13; 34-77)	47 (15; 29-72)	0.042
Baseline minute volume (ml/kg/min)	373 (92; 220-600)	360 (94; 228-537)	0.388
Baseline Mean inspiratory flow (ml/kg/s)	14.0 (3.2; 9.6-20.9)	13.8 (3.0; 8.1-19.5)	0.764
End tidal CO_2 (%)	4.6 (0.5; 3.8-5.5)	4.6 (0.5; 3.9-5.5)	0.268
Hypoxic increase in minute ventilation (ml/kg/min)	82 (84; 0-290)	62 (63; 0-240)	0.49
Time to peak minute ventilation during hypoxic challenge (s)	97 (62; 10-218)	103 (85; 6-348)	0.74
Hypoxic rate of decline in ventilation (ml/kg/min/s)*	3.6 (6.7; 0-27)	2.1 (3.2; 0-10)	0.40
Magnitude of decline (ml/kg/min)	148 (156; -50-540)	184 (86; 40-320)	0.13
Minimum saturations (%)	89 (5; 81-98)	89 (5; 78-97)	0.94

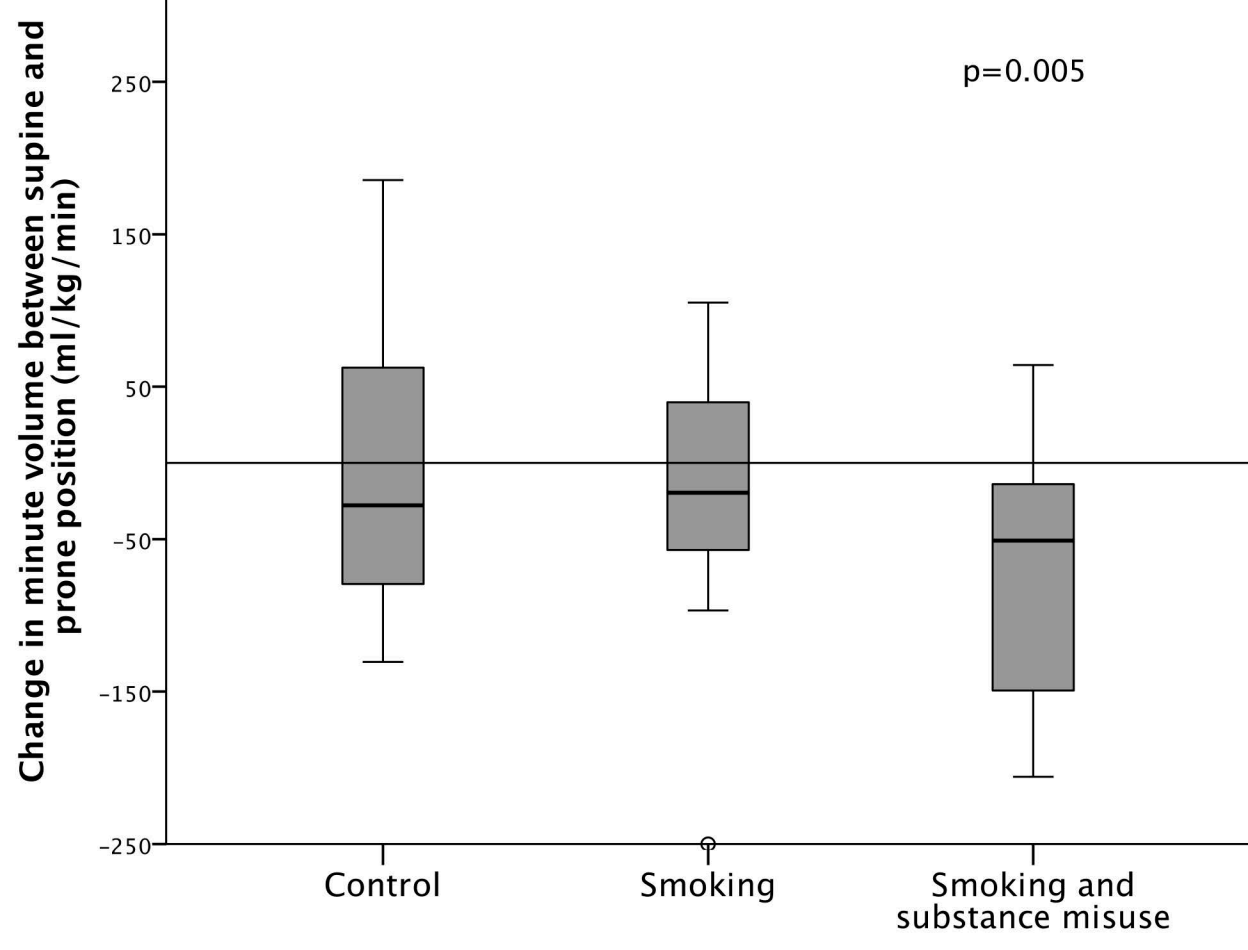
Table 9: Baseline measurements and hypoxic challenge results in prone and supine position, substance misuse group.

Data presented as arithmetic mean (standard deviation; range)

	Supine	**Prone**	**p-value**
Tidal Volume (ml/kg)	6.4 (1.2; 4.5-8.7)	6.9 (1.5; 4.5-9.8)	0.063
Respiratory rate (breaths/min)	69 (20; 39-110)	54 (13; 30-81)	0.001
Baseline minute volume (ml/kg/min)	434 (136; 220-782)	348 (92; 219-593)	0.005
Baseline Mean inspiratory flow (ml/kg/s)	14.7 (4.5; 8.8-28.3)	12.9 (2.8; 8.5- 18.2)	0.08
End tidal CO_2 (%)	4.2 (0.6; 3.1-5.1)	4.5 (0.5; 3.3-5.6)	0.006
Hypoxic increase in minute ventilation (ml/kg/min)	71 (67; 0-186)	68 (58; 0-170)	0.86
Time to peak minute ventilation during hypoxic challenge (s)	153 (108; 16-380)	137 (94; 4-270)	0.67
Hypoxic rate of decline in ventilation (ml/kg/min/s)*	4.2 (10.9; 0-36)	5.6 (14.5; 1-57)	0.39
Magnitude of decline (ml/kg/min)	155 (117; 10-380)	189 (111; 40-430)	0.67
Minimum saturations (%)	89(5; 81-97)	91 (5; 82-99)	0.42


p=0.002
prone Hypoxic rate of decline (ml/kg/min/s)
20
15
10
5
0
Control
Smoking
Smoking and substance misuse


change in respiratory rate between supine and prone position (breaths/min)
40
20
0
-20
-40
-60
p=0.042
p=0.001
Control
Smoking
Smoking and substance misuse


Change in minute volume between supine and prone position (ml/kg/min)
250
150
50
-50
-150
-250
p=0.005
Control
Smoking
Smoking and substance misuse