

# Fetal Heart Rate Response to Maternal Hypocapnia and Hypercapnia in Late Gestation

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## Abstract

**Objective:** To examine the effects of acute maternal hypocapnia and hypercapnia on electronic fetal heart rate (FHR) patterns in late gestation.

**Methods:** Thirty-five women with healthy singleton pregnancies performed a modified carbon dioxide (CO<sub>2</sub>) rebreathing procedure between 34 and 38 weeks of pregnancy. Prior to rebreathing, subjects hyperventilated for five minutes to reduce end-tidal CO<sub>2</sub> tensions (PETco<sub>2</sub>) below 23 Torr (hypocapnia). During rebreathing, PETco<sub>2</sub> progressively increased from hypocapnia to hypercapnia (PETco<sub>2</sub> = 40–60 Torr) at a constant hyperoxic end-tidal O<sub>2</sub> tension of 150 Torr. FHR responses were classified using standardized guidelines over four periods: 20 minutes before rebreathing (pretest), during hypocapnia and hypercapnia, and 20 minutes after rebreathing (post-test).

**Results:** Mean baseline FHR measures (SD) over the four test periods were 138(8), 144(10), 132(11), and 137(9) beats per minute (bpm). All pairwise comparisons were statistically significant except the pretest versus post-test comparison ( $P < 0.05$ , Tukey-Kramer multiple comparisons test). A single tachycardia episode of 170 bpm was recorded in the post-test period. In 20 subjects FHR variability changed from moderate in the pretest period to minimal during hypocapnia and/or hypercapnia. All but two returned to moderate FHR variability in the post-test period. One other fetus with minimal post-test variability had moderate values in the three preceding test periods.

**Conclusion:** Electronic FHR parameters remained within normal limits for third-trimester fetuses with the exception of one fetus that experienced tachycardia. Acute maternal hypocapnia and hypercapnia over the range studied had no adverse effects on fetal well-being. These results support the safety of the modified CO<sub>2</sub> rebreathing procedure for research in healthy, low-risk pregnancy.

**Key Words:** Fetal heart rate, hypercapnia, hypocapnia, rebreathing, pregnancy

Competing Interests: None declared.

Received on August 10, 2007

Accepted on December 4, 2007

## Résumé

**Objectif :** Examiner les effets de l'hypocapnie et de l'hypercapnie maternelles aiguës sur les tracés électroniques du rythme cardiaque fœtal (RCF) au cours de la dernière partie de la gestation.

**Méthodes :** Trente-cinq femmes présentant une grossesse monofœtale en santé ont effectué une intervention modifiée de réinhalation du dioxyde de carbone (CO<sub>2</sub>) entre la 34<sup>e</sup> et la 38<sup>e</sup> semaine de grossesse. Avant la réinhalation, les sujets ont été soumis à une hyperventilation pendant cinq minutes en vue d'abaisser les tensions de CO<sub>2</sub> de fin d'expiration (PCO<sub>2</sub> de fin d'expiration) en deçà de 23 torr (hypocapnie). Au cours de la réinhalation, la PCO<sub>2</sub> de fin d'expiration est progressivement passée de l'hypocapnie à l'hypercapnie (PCO<sub>2</sub> de fin d'expiration = 40–60 torr) à une tension d'O<sub>2</sub> de fin d'expiration hyperoxique constante de 150 torr. Les réactions du RCF ont été classées au moyen de lignes directrices standardisées pendant quatre périodes : 20 minutes avant la réinhalation (prétest), au cours de l'hypocapnie, au cours de l'hypercapnie et 20 minutes à la suite de la réinhalation (post-test).

**Résultats :** Les mesures moyennes du RCF de base ( $\sigma$ ) pendant les quatre périodes d'essai étaient 138(8), 144(10), 132(11) et 137(9) battements par minute (bpm). Toutes les comparaisons par paire étaient significatives sur le plan statistique, sauf dans le cas de la comparaison prétest/post-test ( $P < 0,05$ , test de comparaisons multiples de Tukey-Kramer). Un seul épisode de tachycardie de 170 bpm a été enregistré au cours de la période post-test. Chez 20 sujets, la variabilité du RCF est passée de modérée au cours de la période prétest à minimale au cours de l'hypocapnie et/ou de l'hypercapnie. Tous ces sujets, sauf deux, ont connu un retour à une variabilité du RCF modérée au cours de la période post-test. Un autre fœtus connaissant une variabilité post-test minimale présentait des valeurs modérées au cours des trois périodes d'essai précédentes.

**Conclusion :** Les paramètres électroniques du RCF sont demeurés dans les limites normales pour ce qui est des fœtus du troisième trimestre, exception faite de ceux d'un fœtus ayant connu une tachycardie. L'hypocapnie et l'hypercapnie maternelles aiguës se situant dans la gamme de valeurs étudiée n'ont pas entraîné d'effets indésirables sur le bien-être fœtal. Ces résultats soutiennent l'innocuité de l'intervention modifiée de réinhalation du CO<sub>2</sub> à des fins de recherche dans le cas de grossesses en santé et n'étant exposées qu'à de faibles risques.

J Obstet Gynaecol Can 2008;30(4):312–316

## INTRODUCTION

Previous studies have examined the effects of maternal hypocapnia and hypercapnia on fetal breathing movements, fetal gross body movements, and uterine, placental, or cerebral blood flow in laboratory animals.<sup>1-3</sup> However, there is limited information, particularly in humans, regarding the effects of experimentally widening or narrowing the maternal-fetal CO<sub>2</sub> gradient on electronic FHR patterns. Acute changes in fetal Pco<sub>2</sub> may be expected to influence electronic FHR patterns by altering fetal central and peripheral chemoreceptor activity. Central and peripheral chemoreceptors are active in the fetus. Changes in FHR patterns are mediated, at least in part, by sympathetic and parasympathetic pathways in response to chemoreceptor stimulation.

Studies in our laboratory have employed a modified CO<sub>2</sub> rebreathing procedure to examine the effects of human pregnancy on ventilatory control.<sup>4</sup> During this procedure, pregnant women are exposed to acute periods of systemic hypocapnia and hypercapnia lasting from five to 10 minutes, which may affect fetal well-being through changes in the maternal-fetal gradient for CO<sub>2</sub> and perhaps also fetal PCO<sub>2</sub>. Although other laboratories have employed similar CO<sub>2</sub> rebreathing procedures for studies of ventilatory control throughout human pregnancy,<sup>5-8</sup> none have described their effects on electronic FHR patterns.

The purpose of the present study was to conduct a detailed analysis of the effects of the modified CO<sub>2</sub> rebreathing procedure on fetal cardiac parameters. We hypothesized that brief periods of maternal hypocapnia and hypercapnia would have transient effects on electronic FHR patterns (baseline FHR, FHR variability) but that these changes would remain within normal limits based on the guidelines developed by the NICHHD.<sup>9</sup>

## METHODS

Prospective subjects were recruited via media advertisements, posted announcements, and contact with obstetricians and midwives for participation in an ongoing study in our laboratory designed to investigate the effects of human pregnancy on ventilatory control and acid-base regulation.

Inclusion criteria were the following: age 20 to 40 years, gestational age 34 to 38 weeks, singleton pregnancy, non-smoker, regularly active (= 30 minutes of walking three times per week), parity < 3, and not taking medications other than prenatal vitamin supplements. All subjects were screened for medical contraindications to study participation (cardiorespiratory disease, anemia, placenta previa, toxemia or preeclampsia, gestational diabetes) by the physician or midwife monitoring their pregnancies. A general medical-health questionnaire and the Physical Activity Readiness Medical Examination for Pregnancy<sup>10</sup> were used for this purpose. During the week before laboratory testing, subjects underwent a routine fetal ultrasound examination and biophysical profile to demonstrate normal fetal growth and behaviour, and amniotic fluid volume. All women who enrolled completed the study and none were excluded because of obstetric complications. The study protocol and consent form were approved by the Research Ethics Board, Faculty of Health Sciences at Queen's University. Each subject provided written consent before study participation.

## Modified CO<sub>2</sub> Rebreathing Procedure

Subjects abstained from aerobic and muscular conditioning exercise as well as caffeine on the day of testing. A modified CO<sub>2</sub> rebreathing procedure that included five minutes of prior hyperventilation and maintenance of a constant (or iso-oxic) end-tidal O<sub>2</sub> tension (PETO<sub>2</sub>) was used to evaluate the effects of human pregnancy on ventilatory control, as previously described.<sup>4</sup> Briefly, subjects voluntarily hyperventilated room air for five minutes, using a deep and deliberate breathing pattern to lower end-tidal PCO<sub>2</sub> (PETCO<sub>2</sub>) between 19 and 23 Torr. PETCO<sub>2</sub> stability was achieved after approximately one minute of voluntary hyperventilation. Subjects were then switched from room air to a rebreathing bag containing a hyperoxic-hypercapnic gas mixture (6% CO<sub>2</sub>-24% O<sub>2</sub>-N<sub>2</sub> balanced). Rebreathing began with three to five deep breaths causing rapid equilibration of the PCO<sub>2</sub> in the bag, lungs, and arterial blood to that of the mixed-venous blood, thereby minimizing the arteriovenous PCO<sub>2</sub> difference.<sup>11</sup> This ensures that changes in PETCO<sub>2</sub> accurately reflect changes in arterial, pulmonary and venous PCO<sub>2</sub>. Upon equilibration, subjects were asked to relax and breathe as they felt the need.

During rebreathing, PETCO<sub>2</sub> increased progressively from hypocapnia to hypercapnia at a rate determined by the metabolic production of CO<sub>2</sub>, and iso-oxia was maintained, under computer control, at a hyperoxic PETO<sub>2</sub> of 150 mmHg by providing a flow of 100% O<sub>2</sub> to the rebreathing bag. Maternal arterial blood O<sub>2</sub> saturation and heart rate were monitored continuously throughout each test using an ear oximeter (OXI; Radiometer Copenhagen,

## ABBREVIATIONS

FHR	fetal heart rate
NICHHD	National Institute of Child Health and Human Development
PCO <sub>2</sub>	partial pressure of carbon dioxide
PETCO <sub>2</sub>	partial pressure of end-tidal carbon dioxide

**Table 1. Fetal heart rate parameters (n = 35)**

Measure	Test period			
	Pretest	Hypocapnia	Hypercapnia	Post-test
Baseline FHR, beats/minute*				
mean (SD)	138 (8)	144 (10)	132 (11)	137 (9)
range	125 to 150	125 to 160	110 to 150	120 to 170
FHR variability, n (%)†				
minimal	0 (0)	14 (40.0)	13 (37.1)	3 (8.6)
moderate	34 (97.1)	21 (60.0)	22 (62.9)	32 (91.4)
marked	1 (2.9)	0 (0)	0 (0)	0 (0)

\* $P < 0.001$  (repeated measures analysis of variance). All pairwise comparisons were statistically significant ( $P < 0.05$ , Tukey-Kramer multiple comparisons test), except the pretest versus post-test comparison.

† $P < 0.001$  (Pearson chi-square test), pooling moderate and marked categories.

Copenhagen, Denmark). Rebreathing was terminated at a PETCO<sub>2</sub> of 60 Torr and/or subject discomfort.

### Fetal Monitoring and Analyses

FHR responses were monitored and recorded in the sitting position for 20 minutes immediately before (pretest), during, and 20 minutes immediately after (post-test) rebreathing experiments by an experienced obstetric nurse using a Doppler ultrasound cardiocotometer (8041-A; Hewlett Packard, Avondale, PA). Electronic FHR patterns were analyzed by a single interpreter (DF) experienced in the interpretation of FHR tracings in both clinical and research situations using guidelines developed by the NICHD.<sup>9</sup> These guidelines include criteria for valid and unambiguous interpretation of FHR tracings, as well as standard definitions of fetal tachycardia, bradycardia, accelerations, decelerations, and variability. Any electronic FHR patterns that fell outside of the NICHD<sup>9</sup> guidelines were reviewed by the senior investigator (GALD). This occurred in one subject, as described below.

FHR tracings were separated into four segments: pretest, hypocapnia, hypercapnia, and post-test. Hypocapnia was taken as the last four minutes of the five-minute hyperventilatory period corresponding to a steady-state PETCO<sub>2</sub> of approximately 20 Torr (range: 19 to 23 Torr). The mean duration of hypercapnia (defined as a maternal PETCO<sub>2</sub> = 40 mm Hg) was 3.9 minutes with a range of one to seven minutes. For each segment, FHR variability was described as being absent, minimal, moderate or marked according to the NICHD criteria.<sup>9</sup> FHR accelerations and decelerations were not determined during the hypocapnia or hypercapnia periods due to their relatively short durations.

### Statistical analyses

Baseline FHR measures were analyzed over four test periods (pretest, hypocapnia, hypercapnia and post-test) with a repeated measures analysis of variance followed by the Tukey-Kramer multiple comparisons test using GraphPad InStat 3.06. All other descriptive and comparative statistics were computed using SPSS 14.0 (SPSS Inc., Chicago IL). FHR accelerations and decelerations (post-test minus pretest values) were analyzed using paired *t* tests. FHR variability was analyzed using a Pearson chi-square test after pooling moderate and marked categories. A two-sided  $P < 0.05$  indicated statistical significance.

### RESULTS

Thirty-five women with healthy singleton pregnancies completed the study. The mean age (SD) was 30.8(4.0) years with a range of 22 to 38 years. The mean body mass index (SD) at the time of testing was 28.4(3.4) kg/m<sup>2</sup> with a range of 24.6 to 36.8. Twenty-four women were nulliparous, eight were para 1 and three were para 2. The mean gestational age (SD) at the time of testing was 36.2(1.1) weeks with a range of 34.1 to 38.6 weeks. Maternal heart rate (SD) increased slightly by an average of 5 beats per minute (bpm) from the first 30 seconds to the last 30 seconds of rebreathing (93[10] vs. 98[9] bpm,  $P < 0.001$ , paired *t* test). Maternal arterial blood O<sub>2</sub> saturation was kept between 97% and 99% throughout rebreathing.

Fetal heart rate responses are shown in Table 1. A repeated measures analysis of variance showed that the variation among means was significantly greater than expected by chance ( $P < 0.001$ ). Compared with the pretest period, mean FHR increased by 6 bpm during hypocapnia and decreased by 6 bpm during hypercapnia, before returning to within 1 bpm of baseline during the post-test period. All

**Table 2. Fetal heart rate accelerations and decelerations (n = 35)**

Measure	Test Period		Difference (Post-test minus pretest)	95% CI* P†
	Pretest	Post-test		
Accelerations, mean (SD)	4.8 (3.1)	6.3 (3.1)	1.4 (3.6)	0.18 to 2.7
Range	0 to 14	0 to 12	-6 to 10	0.026
Decelerations, mean (SD)	0.03 (0.17)	0.06 (0.24)	0.03 (0.30)	-0.07 to 0.13
Range	0 to 1	0 to 1	-1 to 1	0.571

\*95% Confidence interval (CI) for mean difference.  
†Paired *t* test.

mean FHR pairwise comparisons were statistically significant ( $P < 0.05$ , Tukey-Kramer multiple comparisons test), except the pretest versus post-test comparison. There was no evidence of fetal bradycardia (FHR  $< 110$  bpm). A mild fetal tachycardia (FHR  $> 160$  bpm) of 170 bpm was observed in one subject during the post-test period; however, there were no other worrisome features noted on FHR monitoring in this fetus; it showed moderate variability throughout testing and no decelerations.

There was a statistically significant association between FHR variability and test period ( $P < 0.001$ , Pearson chi-square test) (Table 1). All but one fetus with marked FHR variability had moderate FHR variability in the pretest period. In 20 subjects, FHR variability changed from moderate in the pretest period to minimal during hypocapnia or hypercapnia. All but two returned to moderate FHR variability in the post-test period. One other fetus with minimal post-test FHR variability had moderate FHR variability in the three preceding test periods.

FHR accelerations and decelerations are shown in Table 2. There were, on average, 1.4 more accelerations recorded in the post-test period than in the pretest period. No decelerations were recorded for 32 subjects during either the pretest or post-test periods. In one subject a single deceleration was recorded in the pretest period followed by none in the post-test period. In two subjects no decelerations were recorded in the pretest period followed by one deceleration in the post-test period.

Mean gestational age (SD) at birth was 40.1 (0.9) weeks with a range of 38.3 to 41.9 weeks. Mean birth weight (SD) was 3744 (493) g with a range of 2855 to 4880 g. Eight of the thirty-five neonates (22.9%) had Apgar scores at one minute of  $< 7$ . All neonates had Apgar scores at five minutes of  $\geq 7$ . One neonate had a cord artery pH of 6.92; this was a healthy boy weighing 3780 g who delivered at 40.7 weeks to

a 26-year-old primiparous woman. Cord artery pH values were unavailable for four subjects.

## DISCUSSION

This study examined the effects of experimentally manipulating maternal-fetal  $\text{PCO}_2$  gradients on electronic FHR patterns. The observed changes in response to increasing and decreasing maternal  $\text{PCO}_2$  were unlikely to be of any clinical significance, as baseline FHR remained within the normal limits of the guidelines developed by the NICHHD.<sup>9</sup>

The effects on FHR of manipulating maternal  $\text{PCO}_2$  have been examined in several animal studies.<sup>1-3,12-14</sup> The collective results of these studies suggest that increasing or decreasing maternal  $\text{PCO}_2$  has little or no demonstrable effect on baseline FHR,<sup>15</sup> despite significant changes in other indices of fetal well-being, including fetal breathing movements and placental and fetal cerebral blood flow.

Ritchie and Lakhani<sup>13</sup> studied the effects of 15 minutes of maternal inhalation of 5%  $\text{CO}_2$  on fetal breathing movements and baseline FHR in a group of 49 healthy women with uncomplicated singleton pregnancies between weeks 32 and 39 of pregnancy. In that study, steady-state maternal hypercapnia had no significant effect on baseline FHR, despite a threefold increase in fetal breathing movements. More recently, Connors et al.<sup>16</sup> examined the effects of maternal hypocapnia and hypercapnia on fetal cardiac parameters in a group of 12 healthy women with uncomplicated singleton pregnancies between 36 and 40 weeks' gestation. In keeping with the results of the present study, they observed a decrease in baseline FHR of approximately 6 bpm during hypercapnia. Unlike the present study, however, Connors et al.<sup>16</sup> found that changes in maternal  $\text{PCO}_2$  had no significant effect on FHR variability or the number of FHR accelerations. We observed a decrease in FHR variability from moderate to minimal during acute periods of

maternal hypocapnia and hypercapnia in over half the subjects. These changes may be explained by sleep state, as circadian influences and fetal behavioural state prior to testing were not controlled for in the present study. Nevertheless, it is reasonable to suggest that the observed changes in FHR variability were not clinically significant because the hypocapnia and hypercapnia periods were of short duration, FHR variability returned to moderate during the post-test period in the majority of subjects, and absent FHR variability was not seen.

## CONCLUSION

Brief periods of maternal hypocapnia and hypercapnia had transient effects on electronic fetal heart rate patterns, an index of fetal well-being. However, with minor exceptions, these changes remained within normal limits according to the guidelines developed by the NICHD. This study supports the safety of the modified CO<sub>2</sub> rebreathing procedure for use in research studies of ventilatory control and acid-base balance in healthy, low-risk pregnancy.

## ACKNOWLEDGEMENTS

This study was supported by the Ontario Thoracic Society Grant-in Aid, Ontario Thoracic Society Block Term Grant, and the William M. Spear Endowment Fund for Pulmonary Research at Queen's University. Dennis Jensen was supported by an Ontario Graduate Scholarship. We wish to acknowledge the assistance of Christine Brown, Diana Lindsay, Penny Lowe, and Sarah McLennan of Queen's University.

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