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FOREWORD

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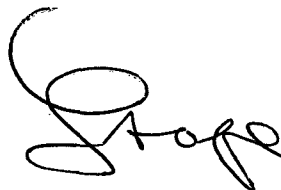
N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

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TABLE OF CONTENTS

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FOREWORD

TABLE OF CONTENTS

I.	INTRODUCTION	6
II.	BODY OF REPORT	
	STUDY #1 - CARDIAC AUTONOMIC FUNCTION	7
	• Objectives	7
	• Methods	7
	• Results	7
	• Practical Implications	7
	STUDY #2 - RESPIRATORY GAS EXCHANGE KINETICS.....	8
	• Objectives	8
	• Methods	8
	• Progress to Date	9
	• Factors That Move Impeded Progress	9
	STUDY #3 - ACID-BASE PHYSIOLOGY.....	9
	• Objectives	9
	• Methods.....	10
	• Results.....	10
	• Practical Implications	11
	• Parallel Studies	11
	STUDY #1, #3 - MATERNAL RESPONSES TO MAXIMAL EXERCISE TESTING	12
	STUDY #1, #3 - FETAL RESPONSES TO MAXIMAL EXERCISE TESTING	13
III	KEY RESEARCH ACCOMPLISHMENTS.....	13

IV	REPORTABLE OUTCOMES.....	15
•	M.Sc. Theses and Ph.D. Dissertations	15
•	Review Article.	15
•	Chapters in Books	15
•	Journal Publications.....	15
•	Abstracts.....	16
•	List of Personnel who Received Pay from This Research	17
V	CONCLUSIONS	18
VI	REFERENCES	19
VII	APPENDICES	20
Appendix A	Manuscript from Study #1 entitled "Effects of Human Pregnancy on Cardiac Autonomic Functions Above and Below the Ventilatory Anaerobic Threshold" (in review, <i>Journal of Applied Physiology</i>).	
Appendix B	Review article that provides rationale for Study #3 entitled "Acid-base Regulation and Control of Ventilation in Human Pregnancy" (<i>Can. J. Physiol. Pharm.</i> 76:815-827, 1998).	
Appendix C	Manuscript from Study #3 entitled "Plasma Acid Base Regulation Above and Below the Ventilatory Threshold in Late Gestation" (<i>Journal of Applied Physiology</i> , Vol 86(1): (in press), 2000).	
Appendix D	Manuscript from Study #3 entitled "Control of Ventilation in Healthy Women : Effects of Plasma Osmolality [SID] and Circulating Hormones" (in review, <i>American Journal of Physiology</i>).	
Appendix E	Manuscript from Studies #1 and #3 entitled "Maximal Exercise Testing in Late Gestation: Maternal Response" (in review, <i>American Journal of Obstetrics and Gynecology</i>).	
Appendix F	Manuscript from Studies #1 and #3 entitled "Maximal Exercise Testing in Late Gestation : Fetal Responses" (in review, <i>Obstetrics and Gynecology</i>).	
Appendix G	Copies of published abstracts from this contract.	

I. INTRODUCTION

Traditional medical advice has been for pregnant women to rest throughout gestation. However, during the past decade there has been increasing participation of women in sports and fitness activities (Mottola and Wolfe, 1994), as well as employment of women in nontraditional occupations (e.g., military services, police work, fire fighting) that involve strenuous physical activities (Fox *et al.*, 1977; Ramirez *et al.*, 1990). When such women become pregnant, it is important to know the modalities, intensities and durations of physical activity that help to promote maternal fetal health. It is also important to know the effects of pregnancy on maternal exercise capacities to maintain a safe and productive working environment.

With specific reference to military service, a firm scientific basis is needed to formulate specific policies for the duration of pregnancy leave, assignment of tasks involving strenuous exertion and formulation of guidelines to maintain physical fitness during the childbearing year. This is particularly important, since active duty military pregnancy has been identified as a high risk category. Risks associated with this population have included a much higher than average risk of preterm labour, toxemia/pre-eclampsia (Fox *et al.*, 1990).

Research over the past decade has established that regular moderate physical activity is both safe and beneficial to women experiencing normal pregnancies. However, basic information is still needed on responses of active pregnant women and their fetuses to strenuous physical activity. The present proposal focuses on cardiovascular control, respiratory gas exchange kinetics, acid-base regulation, and specific hormonal responses to strenuous exercise above the ventilatory anaerobic threshold. Fetal responses to maximal exercise testing in late gestation will also be studied.

The body of this report is organized to provide summaries of accomplishments for each of the three studies that this contract entails:

Study #1	Cardiac Autonomic Function
Study #2	Respiratory Gas Exchange Kinetics
Study #3	Acid-Base Physiology

Study #1 and #3 combined results of Maternal-Fetal Responses to maximal exercise testing in late gestation.

A series of four original research papers have been published or submitted for publication in peer-reviewed biomedical journals and are included in Appendices A, B, C, D, E and F, respectively. Copies of published abstracts appear in Appendix G.

II. BODY OF REPORT

STUDY #1 - CARDIAC AUTONOMIC FUNCTION

Objectives

This study employed modern computer-based noninvasive methods to examine cardiac autonomic function and spontaneous baroreflex sensitivity in healthy, physically active pregnant women (n=14) in late gestation. Results were compared to those of a matched group of 14 healthy nonpregnant female subjects. It was hypothesized that parasympathetic nervous system (PNS) modulation would be reduced in the resting state and that sympathetic nervous system (SNS) modulation would be reduced during heavy exercise.

Methods

Subjects in both groups were studied in the resting state and during exercise at 60% and 110% of the measured ventilatory anaerobic threshold (T_{VENT}). Heart rate variability (HRV) total power, high frequency power/total power and spontaneous baroreflex (SBR) sensitivity were employed as indexes of cardiac PNS modulation. HRV low frequency power/high frequency power and plasma catecholamines (epinephrine, norepinephrine) were used as indicators of cardiac SNS modulation.

Results

This study has been successfully completed. The results have been presented at scientific meetings and the full manuscript is currently in review in the *Journal of Applied Physiology* (Appendix A). The findings were very clear and provided strong support for our original hypothesis that PNS modulation is reduced in the resting state and that SNS modulation is reduced during heavy exercise. This explains from a mechanistic viewpoint why resting heart rate is higher at rest and why heart rate responses to strenuous exercise are also attenuated.

Practical Implications

This study has important practical implications for the use of heart rate to monitor and prescribe aerobic exercise intensity in fitness programs for healthy pregnant women. This study validates our recommendation that conventional heart rate target zones for healthy adults need to be modified for exercising pregnant women (Wolfe and Mottola, 1993). Since maximal heart rate reserve (difference between maximal heart rate and resting) is reduced in pregnancy, we have suggested that the target zone be reduced from approximately 20 beats/min to 15 beats/min. Since maximal heart rate is reduced, this can be best accomplished by reducing the upper end of the conventional target zone by approximately 5 beats/min (Table 1).

TABLE 1.
REVISED HEART RATE TARGET ZONES FOR PRENATAL EXERCISE
(CSEP, 1996, 1999).

AGE (yr)	Conventional Range (beats/min)	Revised Range for Pregnant Women (beats/min)
<20	140 to 160	140 to 155
20 - 29	135 to 155	135 to 150
30 - 39	130 to 150	130 to 145
40<	125 to 145	125 to 140

STUDY #2 - RESPIRATORY GAS EXCHANGE KINETICS

Objectives

This study is examining the effects of pregnancy on oxygen uptake kinetics (and related respiratory parameters) in response to a step increase in work rate to a level below T_{VENT} (Phase II kinetics) and to a step increase in work to an intensity just above T_{VENT} (Phase III kinetics). It was hypothesized that Phase II kinetics would be faster in pregnancy because of the "hyperkinetic" circulation and increased respiratory sensitivity to carbon dioxide observed in pregnant women. It was also hypothesized that Phase III kinetics would be attenuated in association with lower blood lactate levels that are observed during strenuous exercise in late gestation.

Methods

Responses of a group of 12 healthy physically active pregnant women are being compared to those of a matched group of nonpregnant female controls. Each subject participates in a series of four identical exercise tests conducted on separate days. Each test consists of a period of resting data collection followed by a step increase in work rate from loadless pedaling (4 min) to a work rate corresponding to 80% or 110% of measured T_{VENT} . A 20 min rest is allowed between levels. Breath-by-breath respiratory gas analysis is conducted at rest, during exercise (8 min) and during post-exercise recovery (15 min) at each level (Hughson *et al.*, 1991). In two of the four exercise sessions, arterialized blood samples are taken following three and six minutes of exercise and at one, four and seven minutes of recovery. Breath-by-breath oxygen

uptake data from the four tests are linearly interpolated (1.0 s) time aligned and ensemble averaged to provide a single data set for each subject at both exercise levels. Phase II kinetics at 80% T_{VENT} are analyzed in accordance with the monoexponential equation of Whipp *et al.* (1982). The slow component (i.e. Phase III) of oxygen uptake kinetics is characterized mathematically and correlated with measures of plasma lactate as described by Barstow (1994) and Kowalchuk *et al.* (1997).

Progress to Date

This study is still in progress. To date, two pregnant subjects and nine nonpregnant subjects have completed all aspects of testing. Apart from some mechanical problems with our respiratory mass spectrometer (which were quickly repaired), the study is proceeding very well from a technical viewpoint.

Factors That Have Impeded Progress

The main limiting factor in studies such as this is the rate of recruitment of pregnant subjects and the rate of dropout from those recruited. As a result of a six month time delay in receiving human ethics clearance for this study, a considerable amount of momentum was lost that needed to be regained. As stated in past correspondence, earlier this year, we were able to recruit a group of 12 pregnant subjects who agreed initially to participate in this study during 34-38 weeks gestation. All of these subjects were offered nutritional evaluations and continuing advice on prenatal fitness. Of the 12 subjects recruited, five did not participate because they developed medical contraindications to exercise (an unusually high number) and five declined to participate because of a lack of time or loss of interest in late gestation (this is not unusual). Once again, two of the 12 pregnant subjects completed the protocol. We have continued to recruit subjects in the meantime and have a list of several women interested in participating later in their pregnancies. We are committed to the successful completion of this study and have stepped up our subject recruitment efforts to ensure this. A sufficient amount of funding has also been conserved within the contract to complete this study.

STUDY #3 - ACID-BASE PHYSIOLOGY

Objectives

This study employed an innovative new approach (Stewart, 1983; Wolfe *et al.* 1998) to examine the effects of human pregnancy on acid-base regulation in the resting state and during exercise above and below T_{VENT} . Stewart's approach is based directly on fundamental physical and chemical principles and hypothesizes that plasma hydrogen ion concentration ($[\text{H}^+]$) is determined by and can be predicted from values for three

independent variables: the partial pressure of carbon dioxide (PCO_2); the strong ion difference ($[\text{SID}] = [\text{Na}^+] + [\text{K}^+] - 2[\text{Ca}^{++}] - [\text{La}^-]$); total weak acid concentration $[\text{Atot}]$. $[\text{Atot}]$ can be calculated from total plasma protein concentration ($[\text{TP}]$) using a simple equation (Stewart, 1983).

Methods

Responses a group of 15 healthy, physically active pregnant women were compared to those of a matched group of 15 healthy nonpregnant female controls. Studies were conducted in the resting state and during upright cycling at work rates corresponding to 70% and 110% of the measured ventilatory anaerobic threshold. Measurements under each experimental condition included arterialized blood gases (PCO_2 , PO_2) and pH, plasma osmolality, total protein and albumin, electrolytes ($[\text{Na}^+]$, $[\text{K}^+]$, $[\text{Ca}^{++}]$), lactate ($[\text{La}^-]$) and circulating hormones (progesterone, angiotensin II, arginine vasopressin). $[\text{Atot}]$ was calculated from values for $[\text{TP}]$, and $[\text{SID}]$ was calculated as described above from values for electrolytes and lactate.

From a practical viewpoint, this study provided important new information on the capacity (and specific mechanisms involved) to control acid-base balance during heavy exercise in late gestation. Note that maternal metabolic acidosis can affect fetal well-being and could, in theory, contribute to fetal asphyxia (Blechner *et al.*, 1967; Parer, 1994) in association with strenuous exercise. The rationale for this study (and a closely-related analysis of the effects of human pregnancy on the control of pulmonary ventilation, described below) has been published as a review article in a well-respected physiological journal (Wolfe *et al.* *Can. J. Physiol. Pharm.* 76:815-827, 1998; Appendix B).

Results

This study has been successfully completed. The results have been presented at scientific meetings and the full manuscript is currently in press in a top tier physiological journal (Heenan and Wolfe. *J. Appl. Physiol.* 86(1):(in press), 2000; Appendix C). Briefly, the study confirmed that lower plasma $[\text{H}^+]$ in the resting state is the combined result of lower values for PCO_2 and $[\text{Atot}]$ (which would reduce $[\text{H}^+]$) and a lower $[\text{SID}]$ (which would increase $[\text{H}^+]$ and partly offset the effects of a lower PCO_2 and $[\text{Atot}]$). The contributions of PCO_2 , $[\text{SID}]$ and $[\text{Atot}]$ to exercise-induced increases in $[\text{H}^+]$ were also similar in the pregnant vs. nonpregnant state, except that the contribution of reductions in $[\text{SID}]$ were smaller in the pregnant group and appeared to require less respiratory compensation. Measured and calculated values for $[\text{H}^+]$ were highly correlated in both groups at rest and at both exercise intensities, however absolute values were slightly underestimated in the pregnant group. Further study was recommended to examine this issue.

Practical Implications

Important practical observations were that $[H^+]$ values in the pregnant group were always lower than those of the nonpregnant controls, and values in the pregnant group did not reach levels high enough to reverse the fetal to maternal gradient for $[H^+]$ (Nava *et al.*, 1996). Therefore, it appears that the maternal capacity to regulate $[H^+]$ is sufficient to protect the fetus from acidosis during brief strenuous exercise in late gestation during a healthy pregnancy.

Parallel Studies

The measurements described above allowed us to examine two other important physiological problems. First, it was not possible to study all members of the control group in the follicular phase of the menstrual cycle for practical reasons. This was not a serious problem and, in fact, it became an advantage since it allowed us to compare acid-base responses of nonpregnant controls during the luteal and follicular phases of the menstrual cycle. Menstrual cycle phase was verified from values for circulating progesterone. Menstrual cycle phase did not significantly alter $[H^+]$ values at rest or during exercise, but women in the luteal phase had lower values for PCO_2 , [SID] and [Atot] compared to the follicular phase (effects of these changes on $[H^+]$ were offsetting). Note that the changes in the luteal phase (where progesterone levels are highest) are in the same direction but of MUCH smaller magnitude than those of pregnancy described above. Also, menstrual cycle phase had no effect on the ability to accurately predict $[H^+]$ from values for PCO_2 , [SID] and [Atot] at rest or during exercise using Stewart's equation. These results have been submitted for presentation at the annual meeting of the *Federation of American Societies for Experimental Biology* (April, 2000) and the full manuscript is currently in preparation for submission to the *Journal of Applied Physiology* (Appendix D).

As described in our recent review (Wolfe *et al.* 1998), D.B. Jennings (1993;1994) has hypothesized, based on a series of experiments involving laboratory animals, that chemical factors, including plasma osmolality, [SID] and circulating water balance hormones (angiotensin II, arginine vasopressin) are involved in the control of pulmonary ventilation. At the same time, it is well known that pulmonary ventilation is increased both at rest and during submaximal exercise in human pregnancy (Wolfe *et al.*, 1994; Ohtake and Wolfe, 1998). This effect has been attributed to increased circulating levels of progesterone (a known respiratory stimulant) and an estrogen-mediated increase in hypothalamic progesterone receptors (Bayliss and Millhorn, 1992). However, it is also known that human pregnancy involves changes in plasma osmolality, [SID] and circulating levels of angiotensin II and arginine vasopressin that are in directions that would stimulate ventilation in accordance with Jennings' hypothesis. Our experiments have demonstrated statistically significant correlations both at rest and during exercise in a pooled group of pregnant and nonpregnant subjects between arterialized plasma PCO_2 (an index of respiratory

sensitivity to carbon dioxide) and plasma osmolality, [SID] and circulating progesterone levels (Appendix D). Thus, our results provide partial support for Jennings's hypothesis and strongly suggest that both the reduced plasma osmolality and reduced [SID] observed in pregnancy contribute (along with augmented progesterone levels) to the increased pulmonary ventilation observed in late gestation. These results have been presented at scientific meetings and the full manuscript is in review in the *American Journal of Physiology*.

STUDY #1 AND STUDY #3 - MATERNAL RESPONSES TO MAXIMAL EXERCISE TESTING

As described in our original application, both Study #1 and Study #3 involved the performance of progressive maximal cycle ergometer tests to measure T_{VENT} . Therefore, pooled data from the pregnant and nonpregnant subjects from these two studies were available for comparison (Appendix E). Following four minutes of pedaling at 20 watts, a ramp increase in cycling work rate of 20 watts/min was applied until subjects reached volitional fatigue (Lotgering *et al.*, 1992; 1995; Kemp *et al.*, 1997) and breath-by-breath respiratory measurements were recorded at rest, during exercise and during the 15 minute post-exercise recovery period. Blood samples were taken at rest and during 1, 3, 5, 7, 10 and 15 minutes of recovery to measure plasma lactate responses. Finally, fetal heart rate was recorded for 20 minutes before the exercise test and during the immediate 20 minute post-exercise period using conventional Doppler ultrasound. Note that the fetal heart rate data from 9 subjects were available from the earlier study of Kemp *et al.* (1997) and were added to the data set on fetal responses.

The results confirmed that absolute aerobic working capacity was not significantly affected by pregnancy, but there appeared to be a blunted capacity to utilize carbohydrate and produce lactate during very heavy exertion. In this regard, there were no significant differences in peak work rate, peak oxygen uptake, T_{VENT} or the point of respiratory compensation. Also, calculated working efficiency was not affected by pregnancy. However, variables such as the respiratory exchange ratio at peak exercise, peak post-exercise lactate concentration and excess post-exercise oxygen consumption which reflect anaerobic energy production were significantly reduced in the pregnant vs. nonpregnant state. These results have been presented at scientific meetings and the full manuscript is currently in review in the *American Journal of Obstetrics and Gynecology*.

STUDY #1 AND STUDY #3 - FETAL RESPONSES TO MAXIMAL EXERCISE TESTING

Fetal heart rate tracings obtained before and immediately after the maximal exercise tests described above were analyzed by two obstetric physicians in accordance with recent guidelines published by the National Institute of Child Health and Human Development (NICHD, 1997). Pre- and post-exercise tracings were divided into two 10 minute segments for the analysis of fetal heart rate baseline, baseline deviations including bradycardia (a symptom of fetal hypoxia) and tachycardia, the frequency of fetal heart rate accelerations (a sign of fetal well-being) and decelerations (another sign of fetal hypoxia), fetal heart rate variability (an index of fetal central nervous system function) and the time to reactivity (fetal heart rate acceleration in association with fetal movement (another sign of fetal well-being).

Fetal heart rate baseline increased significantly in the 20 minute post-exercise period compared to the 20 minute pre-exercise period and there were significantly fewer accelerations in the second post-exercise period compared to the second pre-exercise segment. Variability was reduced in both 10 minute post-exercise time periods compared to the first pre-exercise 10 minute period. Time to reactivity was increased following the exercise test. There were two instances of mild post-exercise tachycardia, and bradycardia occurred in one previously undiagnosed growth restricted fetus. This test was instrumental in saving the child's life and there were no abnormal neonatal outcomes in the group as a whole. In general, it appears that fetal heart rate responses to maximal exercise testing are minimal in this population. These results have been presented at a prominent obstetric meeting and the full manuscript is in review in *Obstetrics and Gynecology* (Appendix F).

The combined results of the maternal and fetal studies described above suggest that brief maximal maternal exertion under controlled conditions is safe for research or diagnostic purposes. The single episode of fetal bradycardia demonstrates the need for medical screening, including estimates of fetal weight, prior to maximal exercise testing.

III. KEY RESEARCH ACCOMPLISHMENTS

- Results from Study #1 have shown that the increased maternal heart rate observed in the resting state heart is the result of reduced vagal/parasympathetic cardiac modulation, and that blunted heart rate responses to strenuous exercise are the result of reduced sympathoadrenal cardiac modulation. These findings have important practical implications for the use of heart rate to prescribe and monitor exercise intensity in prenatal fitness programs.

- Findings from Study #3 have verified that maternal ability to regulate acid-base balance during strenuous exercise is well-preserved in late gestation. In this regard, healthy physically fit pregnant women are able to maintain a lower $[H^+]$ during strenuous exercise than nonpregnant women and therefore an enhanced physiological reserve exists to protect the fetus from metabolic acidosis. This is accomplished via a greater respiratory sensitivity to carbon dioxide and reduction in plasma PCO_2 , as well as plasma volume expansion which leads to a reduction in $[A_{tot}]$. Our findings further suggest that the increase in respiratory sensitivity is not entirely the result of increased circulating progesterone levels and that factors such as reduced plasma osmolality and $[SID]$ make important contributions.
- Findings within the nonpregnant control group in Study #3 have shown that while plasma $[H^+]$ does not differ significantly at rest or during exercise in the luteal vs. follicular phase of the menstrual cycle, the mechanisms of acid-base homeostasis are different. In this regard, women in the luteal phase tend to have lower values for plasma PCO_2 , $[SID]$ and $[A_{tot}]$. The implications of these findings for physical performance remain for future study.
- Results of maximal exercise tests conducted as part of Studies #1 and #3 suggest that maternal aerobic working capacity (expressed in absolute units) and working efficiency are not significantly reduced in women who remain physically active throughout pregnancy. However, the capacity to utilize carbohydrate and produce lactic acid during strenuous exercise appears to be reduced. This may be a protective mechanism to preserve fetal glucose availability and may also be helpful to prevent maternal-fetal metabolic acidosis during and following very strenuous exertion.
- Changes in fetal heart rate characteristics after exercise tests in Studies #1 and #3 were minimal, suggesting that maternal-fetal physiological reserve during a healthy pregnancy is sufficient to protect the unborn child during and following brief maximal exertion.
- Results of Study #2, when it is completed, will provide information not previously available on maternal responses to sudden changes from very low level exertion to both moderate and heavy exercise. Such changes are commonly encountered during occupational and recreational exercise performance and information on the responsiveness of the maternal metabolic and cardiorespiratory systems has important practical value.

IV. REPORTABLE OUTCOMES

M.Sc. Theses and Ph.D. Dissertations

Heenan, A.P. (Ph.D. Dissertation in Progress). The Exercise/Pregnancy Model: Applications to Respiratory and Acid-Base Physiology.

Preston, R.J. (Mini-Masters' Project, 1999). Physicochemical Analysis of Phasic Menstrual Cycle Effects on Acid-base Regulation.

Avery, N. (M.Sc. Thesis 1998). Effects of Human Pregnancy on Cardiac Autonomic Function at Rest and During Exercise Above and Below the Ventilatory Anaerobic Threshold.

Heenan, A.P. (M.Sc. Thesis, 1997). Acid-Base Regulation Above and Below the Ventilatory Anaerobic Threshold in Late Gestation.

Review Article

Wolfe, L.A., J.G. Kemp, A.P. Heenan, R.J. Preston and P.J. Ohtake. Acid-base regulation and control of ventilation in human pregnancy. (*Can. J. Physiol. Pharm.* 76: 815-827, 1998).

Chapters in Books

Wolfe, L.A. and M.F. Mottola. Chapter on Pregnancy In: (D. Kumbhare and J.V. Basmajian, Eds.). *Clinical Decision Making in Sports Medicine. Evidence-Based Practice*. New York: Churchill Livingstone (invited book chapter, **in press**), 2000.

Wolfe, L.A. Chapter 37. Pregnant Women Endurance Exercise. In: (R.J. Shephard, Ed.). *Encyclopedia of Sports Medicine. Endurance in Sports, 2nd Ed.*, Oxford, England: Blackwell Science Ltd. (**in press**), 2000.

Journal Publications

Heenan, A.P., L.A. Wolfe and G.A.L. Davies. Maximal exercise testing in late gestation: Maternal responses. *Am. J. Obstet. Gynecol.* (**in review**).

MacPhail, A., G.A.L. Davies and L.A. Wolfe, Maximal exercise testing in late gestation: Fetal responses. *Obstet. Gynecol.* (**in review**).

Heenan, A.P. and L.A. Wolfe. Control of ventilation in healthy women: Effects of plasma osmolality, [SID] and circulatory hormones. Am. J. Physiol. (in review).

Avery, N.D., L.A. Wolfe, C.E. Amara, G.A.L. Davies and M.J. McGrath. Effects of human pregnancy on cardiac autonomic function above and below the ventilatory threshold. J. Appl. Physiol. (in review).

Heenan, A.P. and L.A. Wolfe. Effects of human pregnancy on acid-base regulation above and below the ventilatory threshold. J. Appl. Physiol. 86: (in press), 2000.

Amara, C.E. and L.A. Wolfe. Reliability of noninvasive methods to measure cardiac autonomic function. Can. J. Appl. Physiol. 23:396-408, 1998.

Abstracts

Preston, R.J., A.P. Heenan and L.A. Wolfe. Physicochemical analysis of phasic menstrual cycle effects on acid-base balance. FASEB J. 14:(in review), 2000.

Preston, R.J. A.P. Heenan and L.A. Wolfe. Comparison of physicochemical approaches to acid-base analysis in healthy women: Effects of menstrual cycle phase. FASEB J. 14:(in review), 2000.

Heenan, A.P. and L.A. Wolfe. Respiratory gas exchange above and below T_{VENT} in late gestation. Can. J. Appl. Physiol. 24: 451, 1999.

Avery, N.D., L.A. Wolfe, C.E. Amara and M.J. McGrath. Sympathoadrenal responses to exercise above and below the ventilatory threshold in late gestation. Can. J. Appl. Physiol. 24: 423, 1999.

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V. CONCLUSION

Traditional medical advice has been for pregnant women to rest and to avoid strenuous exertion. This viewpoint was based on the premise that, during strenuous exercise, contracting maternal skeletal muscle may compete with the developing fetus for blood flow and oxygen delivery, heat dissipation and availability of important substrates. The main purpose of this contract was to examine systematically and under carefully controlled conditions, both the maternal and fetal responses to heavy exercise in late gestation. The results clearly demonstrate that the maternal aerobic working capacity is well-preserved and that sufficient maternal-fetal adaptive reserve exists during a healthy pregnancy to protect fetal well-being during brief periods of strenuous weight-supported work.

Clearly, such information is important to help in the design of programs to help maintain fitness and to facilitate return to military readiness after childbirth. Information gained on cardiac autonomic control has direct application for the validation of revised heart rate target zones to prescribe and monitor exercise intensity. Since the present studies focused on maternal responses to varying exercise intensities, future studies should examine the effects of prolonged exercise on maternal-fetal physiological responses.

It is also noteworthy that military pregnancy is a high-risk category with a significantly elevated risk of preterm labor and the incidence of pre-eclampsia (Fox *et al.* 1977; Ramirez *et al.*, 1990). Pre-eclampsia is a serious maternal-fetal disease that affects approximately 10% of all pregnancies in North America. It is also sometimes called the "disease of theories" because its root causes are unknown and its physiological correlates include hypertension, proteinuria, increased peripheral vascular resistance, plasma volume contraction, altered sympathoadrenal function and changes in the renin-angiotensin system (Broughton Pipkin and Rubin, 1994). In this regard, a substantial amount of new and very basic information was also provided from healthy pregnant women on the mechanisms of pregnancy-induced changes in cardiorespiratory control, acid-base regulation and water balance hormones both in the resting state and during varying intensities of exercise. This information should be helpful to understand the pathological changes that occur in pre-eclampsia.

With reference to recommendations for future study, it is noteworthy that evidence exists from human epidemiological studies Marcoux *et al.* (1989) that regular physical activity may be useful to prevent pre-eclampsia. Other studies support the idea that reproductive tissue blood flow is protected in pregnant hypertensive laboratory animals (Jones *et al.* 1992). Therefore, future studies should explore in a mechanistic manner the potential role of regular exercise to prevent/treat pre-eclampsia. Military women would be an ideal study population because of the high incidence of this disease.

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Appendix A

**Manuscript from Study #1 entitled
"Effects of Human Pregnancy on Cardiac Autonomic Functions
Above and Below the Ventilatory Anaerobic Threshold"
(in review, *Journal of Applied Physiology*).**



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October 29th, 1999

Dr. J. E. Remmers, Editor,
American Physiological Society,
Journal of Applied Physiology,
9650 Rockville Pike,
Bethesda, Maryland
20814-3991 U.S.A.

Dear Dr. Remmers,

Please find enclosed the original and three (3) copies of our manuscript entitled "Effects of Human Pregnancy on Cardiac Autonomic Function Above and Below the Ventilatory Threshold", which we are submitting for publication in the American Journal of Physiology. Please also find enclosed a computer disk copy, glossy prints of figures (2 copies), the mandatory submission form and a list of suggested reviewers.

Thank you in advance for your attention and we look forward to receiving the review of this manuscript.

Yours sincerely,

Larry A. Wolfe, Ph.D.
Corresponding Author

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Encl.

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EFFECTS OF HUMAN PREGNANCY ON CARDIAC AUTONOMIC FUNCTION
ABOVE AND BELOW THE VENTILATORY THRESHOLD.

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Running Head: Maternal heart rate variability in late gestation.

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Abstract

This study examined the effects of human pregnancy on heart rate variability (HRV), spontaneous baroreflex (SBR) sensitivity and plasma catecholamines, at rest and during exercise. Subjects were 14 healthy pregnant, physically active women (PG; mean gestational age, 33.9 ± 1.0 wk). Results were compared to an age-matched nonpregnant control group (NPG, $n=14$) with similar characteristics. The electrocardiographic R-R interval and systolic blood pressure (finger plethysmograph) were measured on a beat-to-beat basis at rest and during upright cycling at 60% and 110% of the ventilatory threshold (T_{vent}). Parasympathetic nervous system (PNS) modulation (as reflected by HRV high frequency/total power and SBR slope), was significantly reduced at rest in the PG vs NPG. During exercise, PNS modulation decreased significantly in both groups, but the magnitude of PNS withdrawal from rest to 110% T_{vent} was smaller in the PG vs NPG. Sympathetic nervous system (SNS) modulation (as reflected by low frequency/high frequency power) increased above resting values at 60% and 110% T_{vent} in the NPG. SNS modulation at 110% T_{vent} was significantly lower in the PG compared to the NPG. Plasma norepinephrine and epinephrine levels were also lower at 110% T_{vent} in the PG. It was concluded that healthy pregnant women exhibit lower PNS modulation at rest and blunted SNS modulation during exercise above T_{vent} in late gestation.

Key Words: spectral analysis, spontaneous baroreflex function, human gestation, exercise intensity

INTRODUCTION

Pregnancy is characterized by profound changes in the function of virtually all of the regulatory systems of the human body (28). These changes are initiated by ovarian and placental hormones in the first trimester, but may also be modified with advancing gestational age by placental and fetal endocrine factors.

Pregnancy-induced effects on cardiovascular function are well-described in the resting state and include increases in heart rate (HR), stroke volume (SV) and cardiac output ($\dot{Q}_c$) (24,25). Current evidence suggests that these changes result from the interactive effects of a primary reduction in peripheral vascular resistance (10), activation of renal volume restoring mechanisms (10), estrogen-mediated increases in cardiac dimensions (15,16) and contractility (18), as well as changes in cardiac autonomic modulation and baroreflex function that lead to a higher resting heart rate. As described below, the exact nature and physiological basis for these cardiac autonomic changes is poorly understood.

In recent years, the study of cardiac autonomic modulation in human subjects has been greatly facilitated by the development of computer-based methods for spectral analysis of heart rate variability (HRV) and spontaneous baroreflex (SBR) function. It is well-established that high frequency power (0.15-0.40 Hz) of HRV is mediated by parasympathetic nervous system (PNS) modulation and respiratory sinus arrhythmia (1,2, 6), whereas low frequency power (<0.15 Hz) reflects both sympathetic nervous system (SNS) and PNS autonomic influences (6, 22). Accordingly, the ratio of high frequency power to total power has been employed as an index of cardiac parasympathetic

modulation (PNS indicator) and the ratio of low frequency power to high frequency power has been used to reflect cardiac sympathetic modulation (SNS indicator).

Beat-to-beat PNS-mediated control of heart rate can also be evaluated non-invasively by the simultaneous recording of an electrocardiogram and arterial blood pressure using a finger plethysmograph. In this technique, sequences of 3 or more beats in which the electrocardiographic R-R interval (RRI) and systolic blood pressure (SBP) change in the same direction are analyzed using linear regression analysis. The average slope of RRI/SBP relationship is then employed as an index of spontaneous baroreflex (SBR) sensitivity (4,23).

Previous studies of cardiac autonomic function in human pregnancy have produced conflicting results. For example, findings of reduced total power (12,13) and attenuated heart rate responses to orthostatic tests and the Valsalva maneuver (12) suggest that there is reduced cardiac parasympathetic modulation in the resting state in mid-pregnancy (22-29 wk gestation). However, a subsequent study from the same laboratory (11) reported reduced low frequency HRV (suggesting reduced SNS modulation), during the day time, and reduced high frequency HRV (suggesting reduced PNS modulation) at night. These studies were conducted in early to mid-gestation (11-27 wk). In contrast to these findings, Eneroth-Grimfors *et al.* (1994) reported reduced high frequency power in late gestation in women with pre-eclampsia, but failed to detect statistically significant differences in either high or low frequency power in healthy pregnant women compared to nonpregnant female controls.

Studies of cardiovascular responses to strenuous exercise in pregnancy are few in number, presumably because of historical concerns about fetal well-being (31).

However, some studies have reported blunted heart rate peak responses to maximal exercise testing in late gestation (19) and others (19,25,32) have reported a reduced heart rate reserve during exercise. In addition Bonen *et al.* (1992) reported lower values for both epinephrine and norepinephrine during strenuous exercise testing in the third trimester compared to mid-pregnancy and the nonpregnant state. Considered together, these findings suggest that sympathoadrenal responses to strenuous exercise are blunted in late gestation.

The purpose of this study was to examine the effects of human pregnancy on cardiac autonomic function in late gestation. Subjects were studied in the resting state and during exercise above and below the ventilatory threshold (T_{vent}). It was hypothesized that indices of cardiac parasympathetic modulation would be reduced in the resting state and that indices of cardiac sympathetic modulation would be reduced during exercise above T_{vent} in the pregnant versus nonpregnant state.

METHODS

Subjects. Inclusion criteria for the pregnant female volunteers included maternal age between 20-40 yr, physically active (minimum; brisk walking 3days/wk), a parity 0 to 2 and a nonsmoker. The nonpregnant female volunteers were physically active, nonsmokers, aged 20-40 yr who were not taking oral contraceptives. Both groups were equated for age, body height, prepregnant body mass and aerobic fitness. Each prospective pregnant subject was screened medically by the obstetrician monitoring her pregnancy using a standard medical screening form, and reviewed by the study obstetrician using the Physical Activity Readiness Medical Examination for Pregnancy (CSEP, 1996). The Physical Activity Readiness Questionnaire was used to screen the

nonpregnant female volunteers. All subjects provided written informed consent before entering the study.

Subjects were recruited by posted announcements, newspaper advertisements as well as contact with local obstetricians, community agencies which provide services to women and prenatal exercise classes. The study design and consent form were approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board and the United States Army Medical Research and Materiel Command.

Each subject participated in two visits to the laboratory. The initial visit consisted of collection of demographic information, anthropometric measurements (body height and mass) and the graded exercise test described below. The final visit consisted of a two-stage submaximal exercise test conducted at least 3 days after the first visit.

Graded Exercise Test. Graded exercise tests were performed in the upright posture on a Sensor Medics (Model 800) constant work rate cycle ergometer to evaluate aerobic fitness and to identify the ventilatory threshold (T_{vent}). The protocol involved a 4 minute warmup at 20 watts followed by a 20 watts/min ramp increase in work rate until a heart rate of 170 beats/min was achieved (31).

Respiratory responses including $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) for the graded exercise test used a computerized system (First Breath Inc.) that incorporates a respiratory mass spectrometer (Perkin-Elmer, MGA-1100) with a volume turbine (Alpha Technologies VMM-110) (17). T_{vent} for all subjects was determined using the V-slope method (5). Oxygen pulse ($\dot{V}O_2/HR$) at peak exercise was used as an index of aerobic working capacity (31). Fetal heart rate monitoring was conducted twenty min

immediately before and after exercise using Doppler ultrasound (Hewlett Packard -Model 8041-A cardiotocograph) and supervised by an experienced obstetric nurse.

Two Stage Submaximal Exercise Test. Subjects performed a two-stage submaximal exercise test on a separate day. Immediately prior to this test, HRV was evaluated at rest in both the left lateral decubitus and sitting postures at a breathing frequency of 16 breaths/min (0.267 Hz) to ensure the respiration-mediated oscillations occurred above 0.15 Hz for proper interpretation of the PNS-mediated activity. A metronome with speaker and light indicator were used to regulate breathing frequency. The test in the left lateral posture preceded the seated posture test in order to study the autonomic response to a change from recumbent to upright posture in late gestation. Subjects rested in the left lateral and sitting positions for at least 5 min prior to data collection. After the resting data collection, the exercise testing protocol involved a 3 min warmup at 20 watts, followed by a 20 watt/min ramp increase in work rate within 30s to a level corresponding to 60% of the work rate at T_{vent} . After 20 min of rest and a 3 min warmup, the subjects performed a second exercise bout at 110% of T_{vent} . Respiratory measurements including breathing frequency (f), tidal volume (V_T), minute ventilation ($\dot{V}_E$) and $\dot{V}O_2$ were studied on a breath-by-breath basis as described above during both postures at rest and both submaximal exercise bouts.

Heart Rate Variability Spectral Analysis. In the resting state in the left lateral and sitting postures and during the two-stage submaximal exercise test protocol the R-R interval output from a Marquette Max-1 exercise electrocardiograph (ECG) was recorded continuously from standard bipolar leads. Analog output from the ECG was stored to a

personal computer via an analog-to-digital converter (Tecmar Lab Master). Both resting measures and the stable portion of the two-stage submaximal test included data collection of approximately 600 heart cycles for HRV and SBR analyses (33). Prior to spectral analysis, all signals were inspected visually in the time domain for artifacts (26). The best window of approximately 600 heart cycles with the smallest number of artifacts were selected with artifacts omitted. HRV analysis at rest and during constant work rate exercise was performed by general spectral analysis (33). General spectral analysis employs the total power spectra from 0 to 0.5 Hz with subdivisions of low frequency power from 0 to 0.15 Hz and 0.15 to 0.5 for the high frequency power. The calculated high frequency/total power ratio was the PNS indicator and the SNS indicator was calculated as the low frequency power/high frequency power ratio (33).

Spontaneous Baroreflex Function. The analysis of SBR function involved the simultaneous collection of heart rate (Max-1 ECG) and systolic blood pressure (SBP) (Ohmeda 2300 Finapres) data on a beat-to-beat basis during both postures at rest, and during both submaximal exercise intensities. During data collection the servo reset mechanism of the Finapres was turned off so that continuous blood pressure could be recorded (23). Also, both pulse rate and pressure alarms were turned off to avoid sudden disturbances which might influence test results. Analog output from both the Finapres and ECG were stored to a personal computer via an analog-to-digital converter (Tecmar Lab Master). Indices of SBR function, including mean slope, mean R-R interval and mean systolic blood pressure were calculated and recorded for each test by a computer software package (SBRX, 4). SBR sequences were determined by matching SBP with the corresponding R-R interval for each beat of data collected. Matched R-R intervals

that changed in the same direction as SBP (increased or decreased in value) at the same time (*lag 0*), or during the next beat (*lag 1*) or the next following (*lag 2*) beat were used as SBR sequences (4). The test-retest reliability of both HRV and SBR variables measured at rest and during exercise in healthy nonpregnant subjects using the present methods was confirmed recently by Amara and Wolfe, 1998.

Blood Biochemistry. Venous blood samples were drawn by a registered nurse using an indwelling catheter from the antecubital vein for the determination of plasma lactate concentrations and plasma catecholamine concentrations. During the progressive cycle exercise test, blood was drawn at rest, and at 1, 3, 5, 7, 10 and 15 minutes post-exercise. During the two-stage submaximal protocol, samples were obtained during the last minute at rest (sitting posture) and during the last minute of exercise at both 60% and 110% T_{vent} . Samples for plasma lactate concentrations were treated with an anticoagulant (potassium oxalate) and an antiglycolytic agent (sodium fluoride). Samples collected for plasma catecholamine concentrations were treated with EGTA and glutathione. All samples were centrifuged (IEC Centra-MP4R) at 4 degrees C, and frozen for later analyses. Lactate samples were analyzed using an automated analyzer (Yellow Springs Instruments, Model 2300 STATPLUS) and catecholamine concentrations were analyzed in duplicate for epinephrine and norepinephrine concentrations by HPLC (Waters) as described by Weiker *et al.* (1984).

Statistical Analyses. The physical characteristics and peak responses to the graded exercise test were compared using an independent Student-t statistic. Postural effects were analyzed by a two-way analysis of variance (group x posture). Cardiac autonomic, metabolic and respiratory responses to exercise were analyzed using a two-way analysis

of variance (group x work rate) for repeated measures. When significant F-ratios were obtained Tukey Honestly Significant Difference tests were used to compare paired means. Results of all statistical tests are considered significant if $p \leq 0.05$.

RESULTS

Subjects. Subjects were 14 healthy nonsmoking, physically active pregnant female volunteers (pregnant group, PG). The mean age of the PG was 30.9 ± 0.9 yr (range 28-39 yr) with a mean gestational age of 33.9 ± 1.0 wk (26-39 wk). Fourteen healthy nonsmoking and physically active nonpregnant female volunteers (nonpregnant group, NPG) with similar age (28.4 ± 1.8 yr; range 21-42 yr) acted as controls (Table 1). As expected, the PG group had significantly higher body mass and body mass index than the NPG group. However, the self-reported prepregnant body mass and body mass index were similar between the two groups. Oxygen pulse at 170 beats/min and oxygen uptake at T_{vent} did not differ significantly between groups.

Metabolic and Respiratory Data. Resting metabolic respiratory data were available for 9 subjects in each group (Table 2). $\dot{V}O_2$ was significantly higher in the PG in both postures. $\dot{V}O_2$ was not affected by a change in posture from left lateral to sitting in either group. There was no difference between or within groups for f . Both groups had f of approximately 16 breaths/min at rest in both postures. The PG had significantly increased values for V_T and $\dot{V}_E$ in both postures. V_T increased significantly in both groups from left lateral to sitting. Only the NPG had an increased $\dot{V}_E$ with a change in posture. As expected, $\dot{V}O_2$, V_T and $\dot{V}_E$ increased significantly with exercise for both groups (Table 2). There was no significant difference in exercise $\dot{V}O_2$, f , V_T and $\dot{V}_E$

between the two groups. Resting and 60% T_{vent} values for plasma lactate were below 4.0 mmol/L. Exercise at 110% T_{vent} elicited values above 4.0 mmol/L for both groups. There was no difference between groups for plasma lactate concentration. The values for plasma lactate indicated that the exercise work rates used were in fact above and below T_{vent} .

Cardiac Autonomic Control. At rest in the left lateral and sitting postures, mean R-R interval was shorter and systolic blood pressure lower in the PG compared to the NPG. R-R interval decreased and SBP increased with a change in posture from left lateral decubitus to sitting in both groups (Table 3). HRV total power spectra and the PNS indicator were significantly lower in the PG than NPG at rest in both postures (Table 3). There was no significant change with a change in posture from left lateral decubitus to sitting in either group. SBR slope was significantly lower in the PG in both postures. There was an interaction in SBR slope with a change in posture, with the NPG showing a larger decrease in SBR slope during sitting than the PG. The SNS indicator was significantly higher in both postures in the PG versus NPG, and was not altered with a change in posture.

Both groups had a significant decrease in R-R interval as a function of exercise. R-R interval values were similar at 60% and 110% T_{vent} for the two groups. However, the decrease in R-R interval from sitting to exercise (significant interaction) at both 60% and 110% T_{vent} was smaller in the PG compared to the NPG (Figure 1A). SBP was similar at rest and throughout exercise for the PG and NPG. There was a significant

increase in systolic blood pressure from rest to 60% T_{vent} and to 110% T_{vent} in both groups (Figure 1B).

In the PG, there was significantly lower HRV total power, low frequency power and high frequency power at sitting rest compared to the NPG. During exercise at 60% T_{vent} the PG had significantly reduced low frequency power compared to the NPG. Total power, low frequency power and high frequency power all decreased from sitting to exercise at 60% and 110% T_{vent} (Figure 2).

Both the PNS indicator and SBR slope were decreased in the PG at sitting rest compared to the NPG (Figure 3). SBR slope decreased from sitting to 60% and from sitting to 110% T_{vent} in both groups. The PNS indicator decreased in the transition from sitting to exercise at 60% to 110% T_{vent} in both groups.

There was no significant difference in the SNS indicator at rest between the groups (Figure 4A). There was a significant increase in the SNS indicator in the transition from sitting to exercise at both 60% and 110% T_{vent} and from 60% to 110% T_{vent} in the NPG. There was no significant effect of intensity on the SNS indicator in the PG. The SNS indicator was significantly decreased at 110% T_{vent} in the PG.

Plasma Catecholamines. There was no significant difference in plasma norepinephrine levels at rest or a 60% T_{vent} between groups, however the PG had significantly lower levels at 110% T_{vent} compared to the NPG (Figure 4B). Plasma epinephrine levels were significantly lower in the PG at rest, 60% and 110% T_{vent} than the NPG (Figure 4C). Both plasma norepinephrine and epinephrine levels increased significantly from rest to 60% to 110% T_{vent} .

DISCUSSION

This study is the first to examine the effects of healthy human pregnancy on cardiac autonomic function both at rest and at exercise intensities above and below T_{vent} . An important strength of this study is the combined use of HRV spectral analysis, noninvasive evaluation of SBR sensitivity and measurement of plasma catecholamines to study the effects of pregnancy and exercise on cardiac autonomic control. The overall results supported our original hypothesis that parasympathetic modulation (as reflected by reductions in HRV high power/total power and SBR slope) would be blunted in the resting state and that sympathetic modulation (as reflected by reductions in HRV low power/high power and plasma catecholamines) would be blunted during exercise above T_{vent} . These results provided a logical and mechanistic explanation for earlier findings that resting heart rate is increased (9), that heart rate responses to strenuous exercise are blunted (19), and that maximal heart rate reserve is reduced (24,25,32) in healthy pregnant women.

Our findings are also consistent with the hypothesis of Duvekot *et al.* (1993) that cardiovascular changes in human pregnancy are initiated by a reduction in peripheral vascular resistance (PVR) mediated by elevated circulating estrogen levels. The decrease in PVR becomes more pronounced as the fetoplacental shunt develops and a greater percentage of the total cardiac output is diverted toward the fetus. A reduction in blood pressure would then be prevented by activation of renal "volume-restoring mechanisms" (ie. renin-angiotensin system, arginine vasopressin release) activated by baroreceptors. At the same time, an estrogen-mediated increase in heart volume occurs that helps to accommodate augmented venous return without an increase in left ventricular preload

(15,16). Finally, a baroreflex-mediated increase in resting heart rate, along with an augmented stroke volume, would explain the so-called "hyperkinetic" cardiac output that has been documented in pregnant women and would help to maintain a normal resting blood pressure even though PVR is reduced. Our results confirmed that the higher resting heart rate is primarily the result of less parasympathetic modulation both in the left lateral and sitting postures. Since the SNS indicator was increased in the PG in both resting postures (but not plasma catecholamines measured in the sitting posture), some evidence was also provided for increased sympathetic modulation at rest in late gestation.

After the transition from the left lateral position to the sitting posture, there was no significant change in either the PNS indicator or SNS indicator in either group. However, SBR slope, an index of vagally-mediated heart rate control, decreased significantly in both groups and a significant group X posture interaction was observed, suggesting that this reflex response was attenuated in the pregnant vs. nonpregnant state. Thus, it appears that both the degree of PNS modulation and vagally-mediated cardiac reflex responses are attenuated in that gestation.

The cardiac autonomic response to exercise in both groups was qualitatively similar to that reported previously by Yamamoto *et al.* (1992) in healthy nonpregnant subjects. In this regard, both groups displayed evidence for progressive vagal withdrawal in the transition from rest to exercise and enhanced sympathetic modulation at work rates above T_{vent} . However, owing to lower baseline levels of PNS modulation, the magnitude of withdrawal was less in the pregnant vs. nonpregnant state. Similarly, plasma catecholamines increased significantly in the transition from rest to strenuous exercise in

both groups, but this effect was greater quantitatively in the NPG and the exercise-induced changes in the SNS indicator within the PG did not reach statistical significance.

The present study also provided strong evidence for blunted cardiac autonomic (HRV SNS indicator) and sympathoadrenal (plasma epinephrine and norepinephrine) responses to exercise above T_{vent} in the pregnant vs. nonpregnant state. Although, no significant between group difference was observed for the R-R interval at 110% T_{vent} in the present study, blunted cardiac autonomic responses would provide a logical mechanistic explanation for attenuated peak heart rate responses to maximal exercise testing that have been reported on earlier studies (19). Reduced epinephrine and norepinephrine responses to strenuous exercise in late gestation were reported previously by Bonen *et al.* (1992). As postulated in a recent review from this laboratory (30), the reduced epinephrine response could also contribute to a lower rate of catecholamine-mediated liver glycogenolysis, an exercise-induced reduction in maternal blood glucose concentration (7) as well as reduced carbohydrate utilization and lactate production during maximal or near maximal exercise (31).

The integrated heart rate response to graded exercise testing in healthy pregnant women has also been described using linear regression analysis of heart rate expressed as a function of $\dot{V}O_2$ (29). Earlier studies have consistently reported a reduced slope and increased Y-intercept of the heart rate vs. $\dot{V}O_2$ regression (19,25,32). The pattern of exercise-induced changes in the R-R interval in this study is consistent with these earlier findings and further suggests that the reduced heart rate vs. $\dot{V}O_2$ slope in late gestation is the combined result of reduced PNS modulation during mild exertion and blunted SNS modulation during strenuous exercise. From a practical viewpoint, it is clear that

maximal heart rate reserve is reduced in late gestation and that the use of heart rate to monitor and prescribe exercise intensity is less precise in the pregnant vs. nonpregnant state. Consistent with this viewpoint, the Canadian Society for Exercise Physiology (8) has published revised heart rate target zones for prenatal exercise that are both narrower (15 vs. 20 beats/min) and have a reduced maximum value compared to conventional age-related heart rate target zones for healthy nonpregnant adults. The concomitant use of other methods (perception of effort scales, the "talk test") was also recommended.

Although the present results provide clear evidence for attenuated parasympathetic cardiac modulation in the resting state and blunted sympathoadrenal responses to strenuous exertion in late gestation, it is important to recognize the limitations of the noninvasive methodologies employed in this study. In this regard, data obtained from HRV spectral analyses reflect changes within the normal cardiac autonomic operating range of individual subjects and do not constitute quantitative measures of cardiac autonomic activity (20). Similar limitations exist for SBR sensitivity data obtained by linear regression analyses of heart rate and systolic blood pressure sequences, since this method provides information on beat-to-beat vagal control of heart rate rather than the full operating range of the baroreflex (23).

Another potential limitation of the use of HRV spectral analysis is the contribution of exercise-induced increases in f and V_T to the estimate of high frequency power (21). There were no significant differences in f or V_T between groups for this study, however the PG had slightly higher values for both respiratory measures in all conditions. This may increase the HRV high frequency power and, therefore increase the estimates of PNS modulation. In this study, we were able to confirm the finding that

sympathoadrenal responses to strenuous exercise are blunted in late gestation by the plasma epinephrine and norepinephrine values.

In conclusion, the findings of this study support our original hypothesis that cardiac parasympathetic/vagal modulation is reduced in the resting state and that sympathoadrenal responses to strenuous exercise above T_{vent} are blunted in healthy women in late gestation. Evidence also existed for a reciprocal increase in SNS modulation in the resting state. These findings have important practical implications for the use of heart rate to monitor and prescribe exercise intensity in prenatal physical conditioning programs. Future research is recommended to examine the effects of advancing gestational age, physical conditioning and maternal-fetal disease states (eg. pre-eclampsia).

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Table 1: Physical Characteristics.

	Pregnant Group (n=14)	Nonpregnant Group (n=14)
Age (yr)	30.9 $\pm$ 0.9 (28-39)	28.4 $\pm$ 1.8 (21-42)
Height (cm)	165.8 $\pm$ 1.5 (157-173)	162.7 $\pm$ 1.8 (153-177)
Body Mass (kg)	74.4 $\pm$ 2.1 (64-88)	61.1 $\pm$ 1.9* (50-72)
Pre-Pregnant Body Mass (kg)	64.0 $\pm$ 2.2 (53-80)	N/A
Body Mass Index (kg/m ²)	27.1 $\pm$ 0.7 (21.9-30.1)	23.6 $\pm$ 0.8* (19.0-29.0)
Pre-Pregnant Body Mass Index (kg/m ²)	23.3 $\pm$ 0.8 (19.8-29.3)	N/A
Gestational Age (wk)	33.9 $\pm$ 1.0 (26-39)	N/A
Ventilatory Threshold (ml/min)	1653 $\pm$ 43 (1225-1882)	1802 $\pm$ 78 (1129-2274)
O ₂ Pulse at 170 beats/min (ml/beat)	12.1 $\pm$ 0.5 (9.3-15.4)	13.2 $\pm$ 0.5 (8.2-15.3)

Values are means $\pm$ SE. *Significant difference between pregnant and nonpregnant groups ($p < 0.05$). N/A = not applicable.

Table 2: Metabolic and respiratory responses at rest (left lateral and sitting) and during submaximal exercise (60% and 110%).

Variable		Pregnant Group	Nonpregnant Group
Oxygen Uptake (ml/min)	Sitting (n=9)	321 $\pm$ 6	287 $\pm$ 15
	60% T _{vent} (n=14)	1114 $\pm$ 37	1163 $\pm$ 54
	110% T _{vent} (n=14)	1790 $\pm$ 67	1968 $\pm$ 90
Breathing Frequency (breaths/min)	Sitting	16.1 $\pm$ 0.6	15.3 $\pm$ 0.6
	60% T _{vent}	24.8 $\pm$ 1.9	24.6 $\pm$ 1.0
	110% T _{vent}	30.6 $\pm$ 2.3	30.2 $\pm$ 1.5
Tidal Volume (ml)	Sitting	666 $\pm$ 37	601 $\pm$ 53
	60% T _{vent}	1407 $\pm$ 63	1202 $\pm$ 62
	110% T _{vent}	2059 $\pm$ 83	1877 $\pm$ 73
Minute Ventilation (L/min)	Sitting	10.6 $\pm$ 0.5	8.9 $\pm$ 0.7
	60% T _{vent}	33.1 $\pm$ 1.6	28.2 $\pm$ 1.1
	110% T _{vent}	61.4 $\pm$ 3.7	55.6 $\pm$ 3.1
Work Rate (watts)	Sitting	N/A	N/A
	60% T _{vent}	59 $\pm$ 3	63 $\pm$ 4
	110% T _{vent}	126 $\pm$ 4	137 $\pm$ 7
Plasma Lactate (mmol/L)	Sitting	0.9 $\pm$ 0.1	1.1 $\pm$ 0.1
	60% T _{vent}	2.1 $\pm$ 0.3	1.5 $\pm$ 0.2
	110% T _{vent}	5.2 $\pm$ 0.5	5.6 $\pm$ 0.7

Values are means $\pm$ SE.

No significant difference between group effects were observed during sitting, 60% or 110% exercise. N/A = not applicable.

Table 3: Cardiac autonomic function at rest in the left lateral and sitting postures.

Variable		Pregnant Group (n=14)	Nonpregnant Group (n=13 ¹ , n=14 ²)
R-R Interval (ms)	Left Lateral	760 $\pm$ 19†	1075 $\pm$ 54*
	Sitting	721 $\pm$ 20†	996 $\pm$ 50
Systolic Blood Pressure (mmHg)	Left Lateral	104 $\pm$ 5†	115 $\pm$ 6*
	Sitting	112 $\pm$ 4†	128 $\pm$ 3
SNS Indicator	Left Lateral	6.9 $\pm$ 2.0†	1.8 $\pm$ 0.4
	Sitting	7.1 $\pm$ 2.6†	1.8 $\pm$ 0.3
PNS Indicator	Left Lateral	0.23 $\pm$ 0.04†	0.46 $\pm$ 0.06
	Sitting	0.26 $\pm$ 0.06†	0.41 $\pm$ 0.05
Total Power (ms ² /Hz)	Left Lateral	617 $\pm$ 122†	5386 $\pm$ 1754
	Sitting	715 $\pm$ 109†	4174 $\pm$ 1226
SBR Slope (mmHg/ms)	Left Lateral	9.0 $\pm$ 1.1†	26.3 $\pm$ 4.1*
	Sitting	8.5 $\pm$ 1.1†	18.8 $\pm$ 3.4*

Values are means $\pm$ SE.

* Significant difference ($p < 0.05$) between left lateral and sitting postures within group.

† Significant difference ($p \leq 0.05$) between groups in left lateral or sitting.

n=13¹: 13 subjects completed left lateral position

n=14²: 14 subjects completed sitting position

Figure Legend

Figure 1: A. R-R interval (means $\pm$ SE) at rest, 60%, and 110% T_{vent} in the sitting posture. R-R interval decreased significantly from rest to 60% to 110% T_{vent} in both groups. *Significant difference between groups ($p \leq 0.05$). B. Systolic blood pressure (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. Systolic blood pressure increased significantly from rest to 60% to 110% T_{vent} in both groups.

Figure 2: A. Total power (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. Total power decreased significantly from rest to 60% and rest to 110% T_{vent} in both groups. B. Low frequency (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. Low frequency decreased significantly from rest to 60% to 110% T_{vent} in both groups. C. High frequency (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. High frequency decreased significantly from rest to 60% to 110% T_{vent} in both groups. *Significant difference between groups ($p \leq 0.05$).

Figure 3: A. PNS indicator (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. The PNS indicator decreased significantly from rest to 60% to 110% T_{vent} in both groups. B. SBR slope indicator (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. SBR slope decreased significantly from rest to 60% and rest to 110% T_{vent} in both groups. *Significant difference between groups ($p \leq 0.05$).

Figure 4: A. SNS indicator (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. The SNS indicator increased significantly from rest to 60% to 110% T_{vent} in NPG. B. Plasma norepinephrine (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. Plasma norepinephrine increased significantly from rest to 60% to 110% T_{vent} in both groups. C. Plasma epinephrine (means $\pm$ SE) at rest, 60% and 110% T_{vent} in the sitting posture. Plasma epinephrine increased significantly from rest to 60% to 110% T_{vent} in both groups. *Significant difference between groups ($p \leq 0.05$).

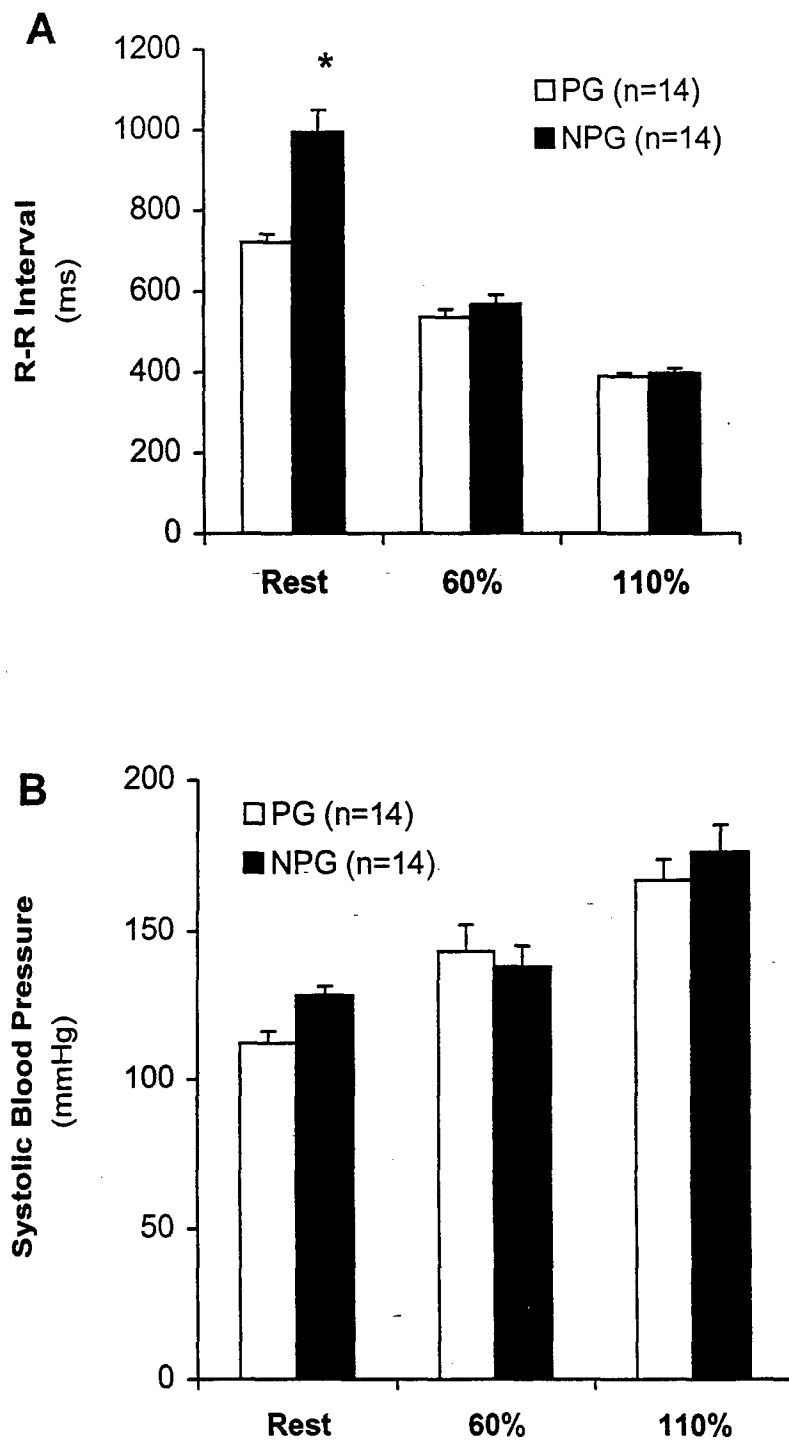


Figure 1

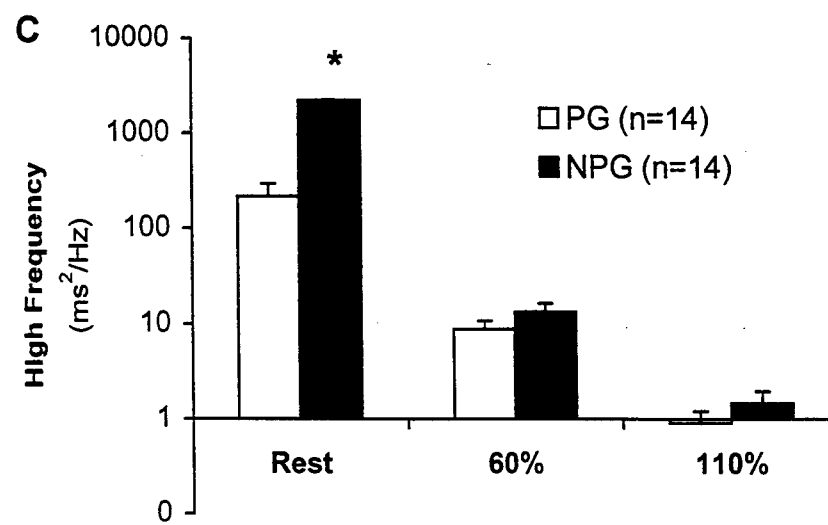
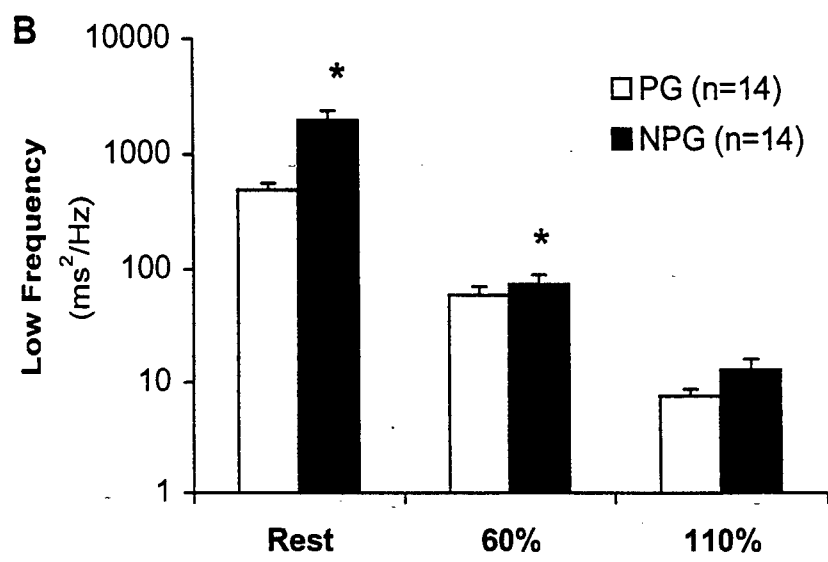
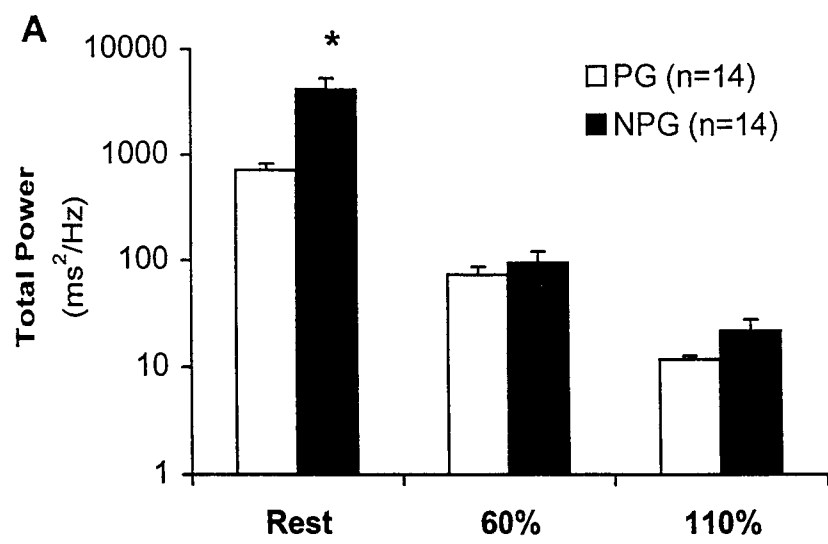


Figure 2

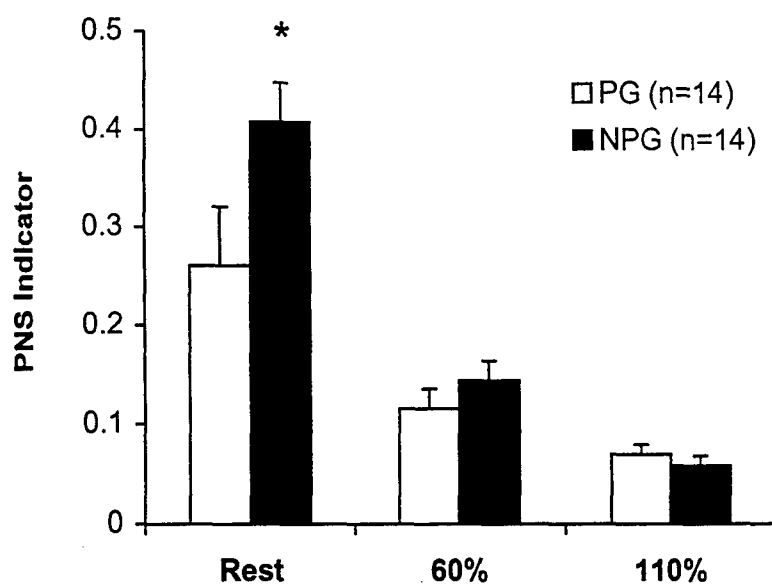
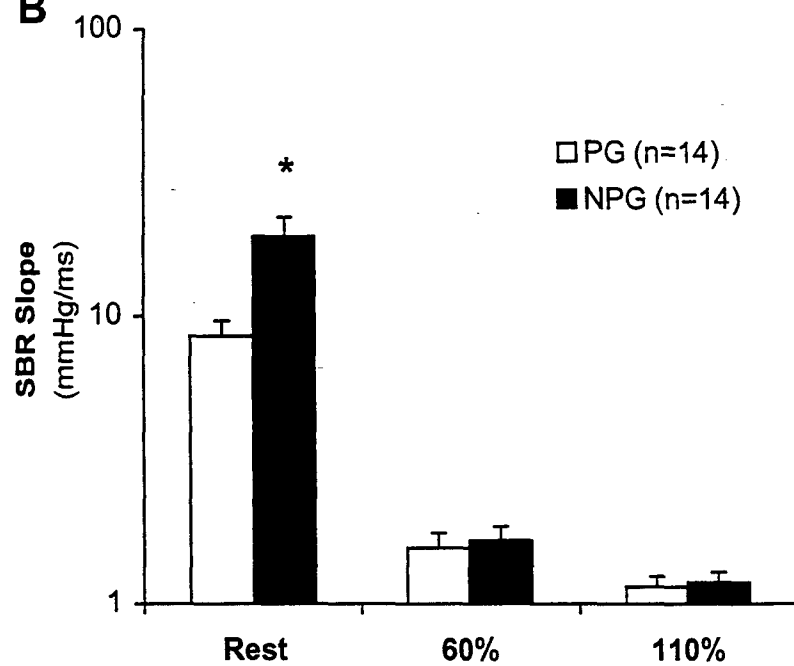
A**B**

Figure 3

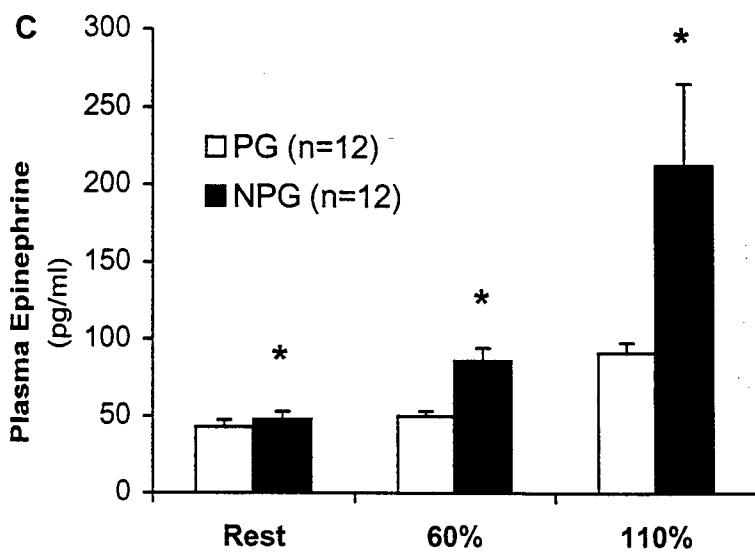
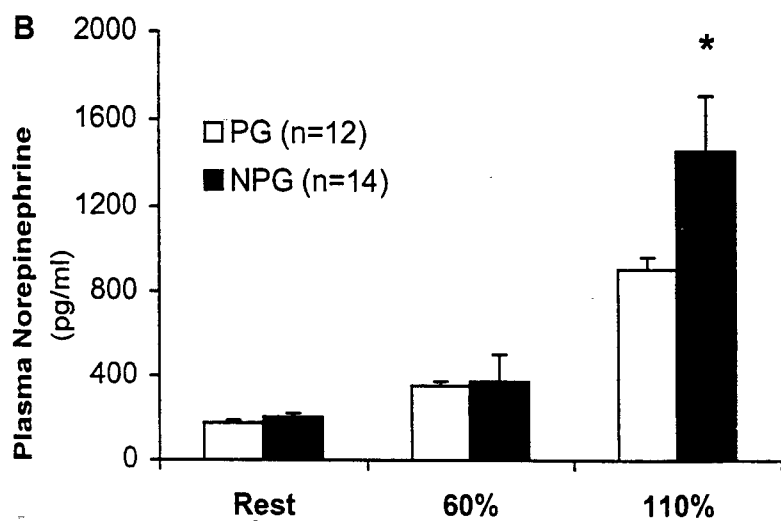
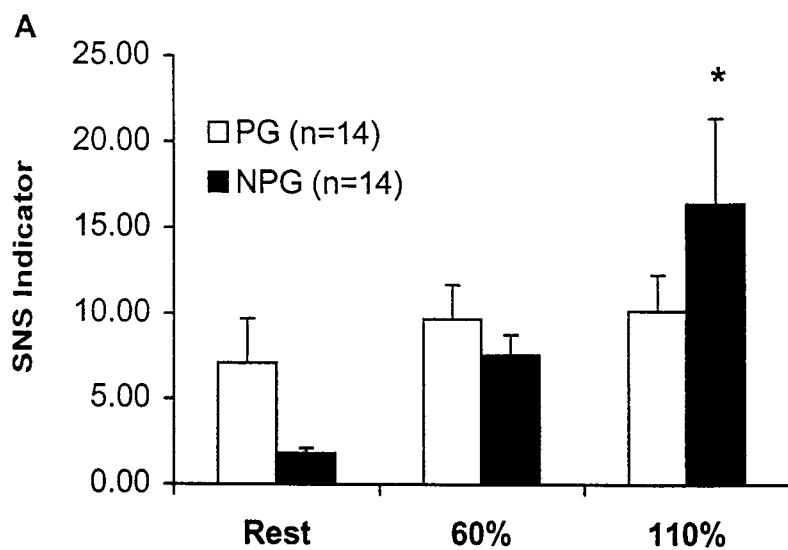


Figure 4

Appendix B

**Review article that provides rationale for Study #3 entitled
"Acid-base Regulation and Control of Ventilation
in Human Pregnancy"
(*Can. J. Physiol. Pharm.* 76:815- 827, 1998).**

SURVEY REVIEW / SYTHÈSE D'ENSEMBLE

Acid-base regulation and control of ventilation in human pregnancy

Larry A. Wolfe, Justin G. Kemp, Aaron P. Heenan, Robert J. Preston, and Patricia J. Ohtake

Abstract: The purposes of this review were twofold: to apply modern physicochemical principles to explain changes in acid-base regulation and the control of ventilation in human pregnancy; and to demonstrate the value of pregnancy as a model for the study of endocrine effects on physiological control systems. Application of P.A. Stewart's approach (P.A. Stewart. *Can. J. Physiol. Pharmacol.* 61: 1444-1461, 1983) shows that lower values of plasma hydrogen ion concentration ($[H^+]$) observed at rest and in association with exercise in pregnancy are the result of lower values for carbon dioxide tension (P_{CO_2}) and total weak acid ($[A_{tot}]$). This effect is partly offset by a lower strong ion difference ($[SID]$). The ability to predict plasma $[H^+]$ at rest and following strenuous exercise in pregnancy (J.G. Kemp, F.A. Greer, and L.A. Wolfe. *J. Appl. Physiol.* 83: 644-651, 1997) supports the validity of Stewart's approach. Jennings and associates (D.B. Jennings. *Can. J. Physiol. Pharmacol.* 72: 1499-1512, 1994) have further demonstrated in animal models the involvement of plasma osmolality and circulating levels of angiotensin II (ANG II) and arginine vasopressin (AVP) in the chemical control of ventilation. We hypothesize that pregnancy-induced increases in respiratory sensitivity to carbon dioxide are the combined result of reduced plasma osmolality, reduced cerebrospinal fluid $[SID]$, and augmented circulating levels of progesterone, ANG II, and AVP.

Key words: human gestation, hydrogen ion concentration, strong ion difference, osmolality, angiotensin II, arginine vasopressin, progesterone.

Résumé : Cet article vise deux objectifs : l'un est de faire appel à des principes physico-chimiques modernes pour expliquer les variations de la régulation acido-basique et le contrôle de la ventilation durant la grossesse humaine; l'autre est de démontrer la valeur de la grossesse comme modèle d'étude des effets endocriniens sur les systèmes de régulation physiologiques. Suivant l'approche de P.A. Stewart (P.A. Stewart. *Can. J. Physiol. Pharmacol.* 61: 1444-1461, 1983), on montre que, durant la grossesse, les plus faibles concentrations en ions hydrogène ($[H^+]$) plasmatiques observées au repos et pendant l'exercice sont dues à de plus faibles valeurs associées à la pression partielle en gaz carbonique (P_{CO_2}) et à la teneur en acide faible total ($[A_{tot}]$). Cet effet est partiellement contrebalancé par une plus faible différence de concentration impliquant les ions forts ($[DIF]$). Cette capacité de prévoir la $[H^+]$ plasmatique au repos et après un exercice exténuant durant la grossesse (J.G. Kemp, F.A. Greer et L.A. Wolfe. *J. Appl. Physiol.* 83: 644-651, 1997) renforce l'approche de Stewart. De plus, Jennings et ses collaborateurs (D.B. Jennings. *Can. J. Physiol. Pharmacol.* 72: 1499-1512, 1994) ont démontré, dans des modèles animaux, la participation de l'osmolalité plasmatique et des taux circulants d'angiotensine II (ANG II) et d'arginine vasopressine (AVP) dans le contrôle chimique de la ventilation. Nous émettons l'hypothèse que, durant la grossesse, les augmentations de la sensibilité respiratoire au gaz carbonique sont le résultat combiné d'une réduction de l'osmolalité plasmatique, d'une réduction de la $[DIF]$ dans liquide céphalo-rachidien et d'une augmentation des taux circulants de progestérone, d'ANG II et d'AVP.

Mots clés : grossesse, concentration en ions hydrogène, différence de concentration entre ions forts, osmolalité, angiotensine II, arginine vasopressine, progestérone.

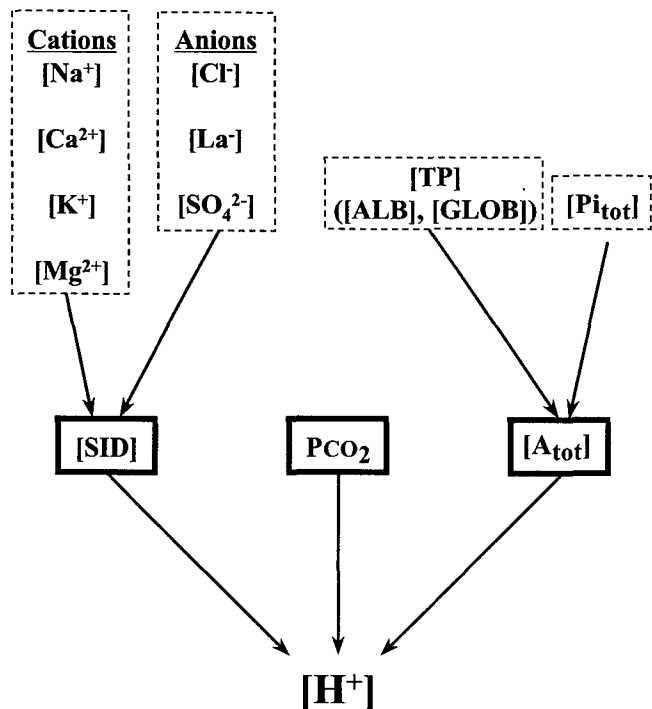
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Fig. 1. Independent determinants of $[H^+]$ in individual body fluid compartments. SID, strong ion difference; P_{CO_2} , partial pressure of carbon dioxide; A_{tot} , total weak acid; Na^+ , sodium ion, Ca^{2+} , calcium ion; K^+ , potassium ion; Mg^{2+} , magnesium ion; Cl^- , chloride ion; La^- , lactate ion; SO_4^{2-} , sulfate ion; TP, total protein; ALB, albumin; GLOB, globulin; Pi_{tot} , total phosphate.

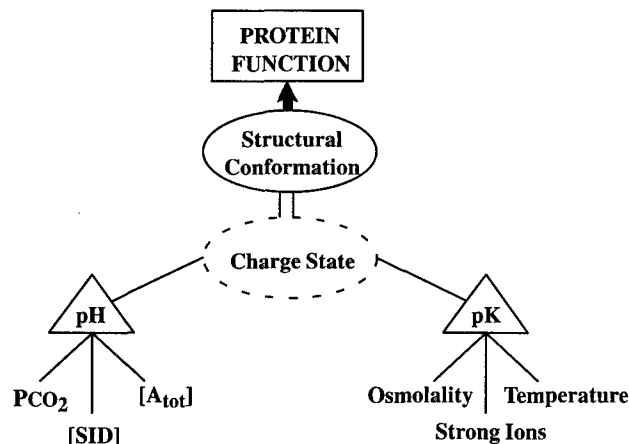


Introduction

Pregnancy is an exceedingly complicated process that has important effects on human regulatory systems. These effects are initiated, maintained, and modified with advancing gestational age by ovarian and placental hormones to accommodate the physiological needs of the fetus (Wolfe et al. 1989; Wolfe and Mottola 1993). Pregnancy-induced physiological effects are substantial in magnitude and include striking changes in carbohydrate metabolism, water balance, cardiovascular function, respiratory control, acid-base balance, and temperature regulation (Wolfe et al. 1989, 1994b). Basic knowledge of the physiology of human pregnancy is important to promote reproductive health via good nutrition and healthy physical activity and is essential for effective medical management of maternal-fetal disease states (e.g., preeclampsia, gestational diabetes mellitus). Since pregnancy-induced changes occur in a predictable time sequence over a 9-month time span, pregnancy also provides a useful model for the study of endocrine effects on physiological control systems.

During the past 10–15 years, several important new hypotheses have been advanced, which have revolutionized scientific thought in the areas of physiology and respiratory control. As shown in Fig. 1, the physicochemical approach of Stewart (1981, 1983) has demonstrated that in any given fluid compartment, $[H^+]$, $[HCO_3^-]$, and the acidic and anionic forms of weak acid ($[HA]$ and $[A^-]$) are dependent variables whose concentrations are determined by three in-

Fig. 2. Factors affecting the relation between the pK and pH of protein, thereby affecting protein charge state and function. (Adapted from O'Connor (1997) with permission.)



dependent variables: the partial pressure of CO_2 (P_{CO_2}); the strong ion difference ($[SID]$); and total weak acid $[A_{tot}]$. The alaphastat hypothesis (Reeves and Rahn 1979) further suggests that pH is controlled to offset changes in protein pK (caused in turn by exercise-induced changes in temperature, osmolality, and strong ions), and thereby preserve the charge state of protein, protein conformation, and ultimately the function of contractile proteins, enzymes, and ion channels (Fig. 2). The most important weak acid that affects the charge state of protein may be the imidazole group of histidine amino acids. Its pK is within the normal physiological range of pH (≈ 7.4), whereas other amino acids with pK values outside the normal physiological range help to promote stability of the system with pH changes. Consistent with the alaphastat hypothesis, D.B. Jennings and associates have also proposed a new hypothesis to explain the interactive effects of angiotensin II (ANG II), arginine vasopressin (AVP), plasma osmolality, and $[SID]$ on the chemical control of ventilation (Jennings 1994a, 1994b). Since human pregnancy involves changes in all of these variables, we hypothesize that Jennings' hypothesis may be useful to explain pregnancy-induced increases in respiratory sensitivity to carbon dioxide in addition to the well-known effects of progesterone as a respiratory stimulant (Lyons and Antonio 1959; Bayliss and Millhorn 1992).

This review has two main purposes: to show how modern physicochemical principles can be applied to gain new information on acid-base regulation and control of ventilation in human pregnancy; and to demonstrate the usefulness of human pregnancy as a model for the validation of new hypotheses of acid-base regulation and respiratory control.

Acid-base regulation

Acid-base balance at rest

Pregnancy is characterized by respiratory alkalosis, which has been documented as early as 8 weeks of gestation (Anderson et al. 1969; Blechner et al. 1968; Gilbert et al. 1962; Lucius et al. 1970) and is maintained until delivery (Gilbert et al. 1962; Lim et al. 1976; Lucius et al. 1970; Machida 1981; Prowse and Gaensler 1965). Arterial pH levels between 7.38 and 7.46 at 12–42 weeks of gestation have

been reported (Blechner et al. 1968), as well as values between 7.44 and 7.52 at 8–42 weeks of gestation (Lucius et al. 1970). No consistent variation in pH was observed with advancing gestational age (Lim et al. 1976; Moore et al. 1987; Pivarnik et al. 1992). As described below, the respiratory alkalosis is attributable to pregnancy-induced increases in minute ventilation ($\dot{V}_E$), which lead to a reduction in arterial carbon dioxide tension (P_{aCO_2}) to approximately 30–32 mmHg (1 mmHg = 133.3 Pa) (Anderson et al. 1969; Lim et al. 1976; Lucius et al. 1970; Lyons and Antonio 1959; Machida 1981; Templeton and Kelman 1976). These maternal responses to pregnancy, which appear in the first trimester (Anderson et al. 1969; Blechner et al. 1968; Gilbert et al. 1962; Machida 1981; Rees et al. 1990), may act to facilitate placental gas exchange prior to development of a functional fetal circulatory system (Liberatore et al. 1984).

Pregnancy-induced respiratory alkalosis is accompanied by renal excretion of bicarbonate (Prowse and Gaensler 1965; Hytten 1968) and a lowering of the plasma bicarbonate concentration (Anderson et al. 1969; Blechner 1993; Dayal et al. 1972; Lucius et al. 1970; Machida 1981). In accordance with conventional acid–base theory (Cameron 1989), the decrease in plasma bicarbonate levels, along with relative anemia (Lund and Donovan 1967) and hypoproteinemia (Pivarnik et al. 1990), leads to a reduced buffering capacity of maternal blood.

Acid–base balance during exercise

The changes in maternal acid–base regulation described above suggest that women may be more prone to metabolic acidosis during pregnancy when working at levels above the onset of blood lactate accumulation (OBLA). Fortunately, limited placental permeability to hydrogen and bicarbonate ions has been reported during acute reductions in maternal blood pH (Blechner et al. 1967; Lotgering et al. 1983) and this is essential to protect the fetus from acute changes in maternal blood pH (e.g., those following strenuous exercise). Under normal resting conditions the fetus has a lower pH than maternal blood (Blechner et al. 1967; Blechner 1993). Therefore, during times of reduced maternal pH the transplacental pH gradient may be eliminated or reversed (Lotgering et al. 1983) and may increase the likelihood of fetal acidosis if maternal acidemia is not quickly corrected.

Only two studies (Lehmann and Regnat 1976; Pivarnik et al. 1992) have examined changes in maternal plasma pH during exercise in pregnancy, using the conventional approaches to acid–base analysis. Pivarnik et al. (1992) observed that arterial pH values decreased during 6 min of treadmill (67 m/min with 2.5 and 12% grade, respectively) and cycle ergometer work (50 and 75 W) in both the pregnant and nonpregnant states. The average absolute pH at rest and exercise was greater in pregnancy in each protocol, and the average absolute reduction in pH was also the same in both groups. However, Lehmann and Regnat (1976) reported slightly larger decreases in arterial pH when 6 min of cycling (50 and 80 W) was performed during pregnancy, as well as lower absolute pH values at 80 W when compared with nonpregnant values.

Reported changes in bicarbonate concentration that occur with exercise during pregnancy are controversial. Compared

with postpartum, decreases in bicarbonate during exercise have been reported to be smaller (Pivarnik et al. 1992) or greater (Lehmann and Regnat 1976). Strenuous exercise in pregnancy also results in smaller increases in both venous (Clapp et al. 1987; McMurray et al. 1988, 1991; Wolfe et al. 1994a) and arterial (Pivarnik et al. 1992) blood lactate concentrations. The apparent reduction in maternal buffering capacity is less critical with lower peak blood lactate concentration. However, the hypothetical effects of metabolic acidosis in the maternal system during exercise remain.

An increase in fetal $[H^+]$ combined with fetal hypoxia due to reduced uterine blood flow (Lotgering et al. 1983) may result in fetal asphyxia (Artal-Mittelmark et al. 1991). Asphyxia appears to be more detrimental to the fetus than equivalent degrees of hypoxia (Cohn et al. 1974) and can lead to fetal brain damage and death. Therefore it is important to study the main determinants of maternal plasma $[H^+]$, since this would help to clarify the mechanisms by which the maternal system restores plasma $[H^+]$ to normal resting levels following strenuous exercise.

Physicochemical approach to acid–base analysis

The innovative physicochemical approach to acid–base analysis of Stewart (1978, 1981, 1983) must be considered when investigating acid–base regulation in human subjects. By direct application of fundamental physical and chemical properties, Stewart's analysis of ionic solutions describes the quantitative relationships that determine $[H^+]$, and thus provides a quantitative method of prediction of hydrogen ion activity in human functions (Heigenhauser 1995). Stewart's hypothesis examines acid–base equilibria separately in individual fluid compartments (e.g., arterial plasma, venous plasma, cerebrospinal fluid (CSF)) with all body fluid compartments being treated as aqueous solutions with the following components: (a) water, (b) strong electrolytes, and (c) weak electrolytes (Table 1). Stewart's quantitative analysis also requires that all systems must behave in accordance with the laws of electroneutrality and conservation of mass, and that all incompletely dissociated substances obey and satisfy dissociation equilibria.

All variables and their quantitative values are defined as either independent or dependent (Stewart 1981). The three independent variables, which can be changed individually and independently in body fluids, include (i) the partial pressure of carbon dioxide (P_{CO_2}); (ii) the strong ion difference ($[SID]$), which is the difference between the sum of the concentrations of all strong cations minus the sum of the concentrations of all strong anions; and (iii) the total concentrations of all the nonvolatile weak acids ($[A_{tot}]$).

The most important constituents of the three independent variables are illustrated in Fig. 1. All other variables within the system are designated as dependent variables and change only if one or more of the independent variables change.

By combining the principles of electroneutrality, conservation of mass, and dissociation equilibria relevant to the species in body fluids, equations can be derived to express any dependent variables (namely, $[H^+]$, $[HCO_3^-]$, $[A^-]$, $[HA]$, $[CO_3^{2-}]$, and $[OH^-]$) in terms of all independent variables and dissociation constants (Stewart 1983). The fourth-order polynomial developed in accordance with these mathematical principles (Stewart 1983) provides a

Table 1. The constituents of plasma important to acid–base balance, as outlined by Stewart (1981, 1983).

Water	High molality and extremely weakly dissociated
Strong electrolytes	Fully dissociated and chemically nonreacting Na^+ , K^+ , Cl^- , and La^-
Weak electrolytes	Partially dissociated (i.e., $\text{HA} \leftrightarrow \text{H}^+ + \text{A}^-$) Obey a dissociation equilibrium (i.e., $[\text{H}^+] \times [\text{A}^-] = K_A \times [\text{HA}]$) (a) Nonvolatile weak acids $[\text{A}_{\text{tot}}]$ (i) Inorganic phosphate (i.e., H_3PO_4 and its dissociation products)* (ii) Proteins*† (b) Volatile weak electrolytes (i) The CO_2 system (dissolved molecular CO_2 in equilibrium with H_2CO_3 and its dissociation products) (ii) $\text{NH}_3 + \text{H}^+ \leftrightarrow \text{NH}_4^+$

Note: For references see the following: Fencel and Leith 1993; Figge et al. 1991, 1992; Stewart 1981.

*The suggestions of Fencel and Leith (1993) and Figge et al. (1991, 1992) for $[\text{A}_{\text{tot}}]$.

†Stewart (1981, 1983) suggests that total plasma protein concentration is representative of $[\text{A}_{\text{tot}}]$.

model that allows the measurement of the independent variables within a system, a meaningful quantitative analysis of their contribution to the system, and calculation of their effect on the dependent variables.

In theory, several methodologic obstacles exist to the application of Stewart's approach. As discussed by Cameron (1989), these include problems in the determination of $[\text{SID}]$, $[\text{A}_{\text{tot}}]$, and the equilibrium constants used in the equation. In Stewart's analysis, $[\text{SID}]$ is calculated as $([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{La}^-])$, where La^- is the lactate ion. However, other cations (e.g., Ca^{2+} , Mg^{2+}) and anions (e.g., ketones, fatty acids, aspartate, glutamate, SO_4^{2-}) exist that make small contributions to the "effective" $[\text{SID}]$, although the mathematical effect of omitting these ions tends to offset one another. The $[\text{SID}]$ is also subjected to the measurement error from the determination of the various strong ions. In the Stewart model, $[\text{TP}]$ (total plasma protein concentration) and a single dissociation constant are used to represent $[\text{A}_{\text{tot}}]$. This representation of $[\text{A}_{\text{tot}}]$ has been criticized as being too simple (Figge et al. 1991, 1992), and an alternative model has been proposed (i.e., the Fencel model) which uses the plasma concentrations of albumin and phosphoric acid (along with dissociation constants for the ionizable groups on albumin and phosphate molecules) to represent $[\text{A}_{\text{tot}}]$. Lastly, the equilibrium constants used in the equation may not be accurate because of the effects of changes in temperature or ionic strength. However, variations in temperature should not be a source of error since all measurements of independent and dependent variables are usually done at 37°C .

Several studies (Kowalchuk et al. 1988a, 1988b, 1992; Kowalchuk and Scheuermann 1994; Weinstein et al. 1991) have examined acid–base regulation in young men at rest and during recovery from exercise, using Stewart's quantitative method of analysis. Close agreement was demonstrated between the mean $[\text{H}^+]$ measured and the mean $[\text{H}^+]$ calculated using Stewart's equations in arterial and femoral venous blood at rest and during recovery from 30 s of maximal cycling (Kowalchuk et al. 1988a). Calculated $[\text{H}^+]$ was also observed to accurately predict measured $[\text{H}^+]$ in upper-arm venous blood obtained before and immediately following a maximal treadmill test (Weinstein et al. 1991). In this study, weak correlations between the three independent variables were observed, thus supporting the theoretical independence

of P_{CO_2} , $[\text{SID}]$, and $[\text{A}_{\text{tot}}]$ (Weinstein et al. 1991). Postexercise $[\text{H}^+]$ values were highly correlated with P_{CO_2} and $[\text{SID}]$ and poorly correlated with $[\text{A}_{\text{tot}}]$, suggesting that the increase in $[\text{H}^+]$ during exercise (measured postexercise) was largely the result of increases in P_{CO_2} and decreases in $[\text{SID}]$ (Weinstein et al. 1991). In early recovery, P_{CO_2} tends to contribute more to the observed $[\text{H}^+]$ changes (Kowalchuk et al. 1988a; Weinstein et al. 1991), whereas later in recovery (9 min), the relative contributions of $[\text{SID}]$ to $[\text{H}^+]$ changes become more evident (Kowalchuk et al. 1988a).

Kowalchuk and Scheuermann (1994) compared the ability of the Stewart model and the Fencel model to calculate measured $[\text{H}^+]$ in exercising young men and found them to be equally effective in predicting $[\text{H}^+]$. Stewart's equation slightly underpredicted $[\text{H}^+]$, whereas Fencel's equation slightly overpredicted and thus offered no improvement over the original Stewart model. Waters et al. (1995) found Stewart's equation to underpredict $[\text{H}^+]$ in rabbits in situations of extreme acidosis and attempted to improve the calculation by including $[\text{Ca}^{2+}]$ and $[\text{Mg}^{2+}]$ in the $[\text{SID}]$ calculation and phosphate in the weak acid calculation. Incorporating these variables in the Stewart equation brought calculated $[\text{H}^+]$ back into agreement with measured $[\text{H}^+]$. The increase in the calculated $[\text{H}^+]$ was the result of adding phosphate, since the addition of $[\text{Ca}^{2+}]$ and $[\text{Mg}^{2+}]$ would by themselves lower $[\text{H}^+]$. Thus, a more accurate prediction of $[\text{H}^+]$ was accomplished by representing the total weak acid component by $[\text{TP}]$ and total phosphate ($[\text{Pi}_{\text{tot}}]$). The addition of phosphate to the weak acid component should be considered in future acid–base studies.

From the above discussion, it appears that the use of Stewart's physicochemical approach to study maternal acid–base regulation is ideal for the following reasons: (i) Stewart's quantitative analysis has not been validated under the conditions of pregnancy at rest or during exercise; (ii) pregnancy is associated with significant alterations in resting P_{CO_2} , $[\text{SID}]$, and $[\text{A}_{\text{tot}}]$ (the three independent variables); and (iii) the concept of independent and dependent variables outlined in Stewart's quantitative analysis provides the opportunity to better understand the acid–base regulatory mechanisms being tested. Since this approach allows quantification of the relative contributions of factors influ-

encing $[H^+]$, important new information on maternal acid-base regulation at rest and during exercise can be gained.

To understand maternal acid-base physiology during rest and in response to exercise, it is essential to examine the changes imposed by pregnancy on the three independent variables. P_{CO_2} , the first independent variable, reflects the relationship between ventilation and cellular metabolism, both of which undergo considerable changes during pregnancy and therefore must be considered. Hormonal changes during gestation mediate changes in the electrolyte composition of plasma, thereby altering the second independent variable, $[SID]$. Finally, maternal blood volume expansion results in changes in plasma proteins and phosphoric acid that will impact $[A_{tot}]$. The effects of both pregnancy and exertion on each of these variables will be considered individually, and then an integrated view of the factors that influence acid-base regulation in the pregnancy-exercise model will be presented.

Effects of pregnancy and exercise on P_{CO_2}

Ventilatory changes during pregnancy are well documented. An increase in resting $\dot{V}_E$ is observed (Bader et al. 1959; Contreras et al. 1991; Clapp et al. 1988; Cugell et al. 1953; Edwards et al. 1981; Field et al. 1991; Knuttgen and Emerson 1974; Pernoll et al. 1975; Rees et al. 1990) beginning as early as 7–8 weeks of gestation (Clapp et al. 1988; Rees et al. 1990) with smaller progressive increases continuing through the second and third trimesters (Contreras et al. 1991; Knuttgen and Emerson 1974; Pernoll et al. 1975). The increase in $\dot{V}_E$ is due primarily to an increased tidal volume (V_T) with little or no change in respiratory frequency (Field et al. 1991; Knuttgen and Emerson 1974; Pernoll et al. 1975). Since inspiratory time (T_i) remains unchanged in pregnancy, the mean inspiratory flow (V_T/T_i) must increase (Dempsey et al. 1986). As discussed in detail below, these effects have been attributed to increased circulating progesterone (a known respiratory stimulant) and an estrogen-dependent increase in hypothalamic progesterone receptors (Bayliss and Millhorn 1992). An increase in resting oxygen uptake ($\dot{V}O_2$) also contributes to the increased respiratory drive (Bader et al. 1959; Cugell et al. 1953; Edwards et al. 1981; Field et al. 1991; Knuttgen and Emerson 1974) due primarily to maternal weight gain and the developing conceptus (Wolfe et al. 1989). An augmented oxygen cost of breathing due to an increase in the diaphragmatic excursion with breathing may also be involved (Bader et al. 1959; McGinty 1938).

The increase in $\dot{V}_E$ reduces resting P_{aCO_2} to approximately 30–32 mmHg (Anderson et al. 1969; Blechner et al. 1968; Dayal et al. 1972; Lim et al. 1976; Lucius et al. 1970; Lyons and Antonio 1959; Machida 1981) and increases resting P_{aO_2} to approximately 100–106 mmHg (Anderson et al. 1969; Blechner et al. 1968; Templeton and Kelman 1976). The low P_{aCO_2} and elevated P_{aO_2} in pregnancy (Gilbert et al. 1962; Lotgering et al. 1984; Wolfe et al. 1989) facilitate the transfer of CO_2 across the placenta from the fetus to the mother, and O_2 transfer from the mother to the fetus (Liberatore et al. 1984). Increases in both physiological dead space (V_D) and alveolar ventilation ($\dot{V}_A$) have been demonstrated (Pernoll et al. 1975; Templeton and Kelman 1976), but $V_D:V_T$ remains unchanged (Templeton and Kelman

1976). The ventilatory equivalent for oxygen ($\dot{V}_E:\dot{V}O_2$) is also elevated over nonpregnant values (Cugell et al. 1953; Knuttgen and Emerson 1974; Pernoll et al. 1975).

$\dot{V}_E$ and V_T are also augmented significantly during steady-state exercise in pregnancy at standard submaximal work rates (Cugell et al. 1953; Edwards et al. 1981; Field et al. 1991; Knuttgen and Emerson 1974; Pernoll et al. 1975; Pivarnik et al. 1992). Values increase progressively throughout gestation, peaking at term (Ohtake and Wolfe 1998; Pernoll et al. 1975). The absolute change in $\dot{V}_E$ (i.e., ventilatory gain) from rest to steady-state exercise in pregnancy is greater than in the nonpregnant state (Edwards et al. 1981). No significant changes have been reported in respiratory frequency (Field et al. 1991; Knuttgen and Emerson 1974; Pernoll et al. 1975; Pivarnik et al. 1992). Increased $\dot{V}_A$ accompanies the greater exercise $\dot{V}_E$ in pregnancy (Pernoll et al. 1975; Pivarnik et al. 1992). Physiological dead space during exercise in pregnancy is increased moderately during exercise in late gestation (Ohtake and Wolfe 1998; Pernoll et al. 1975; Pivarnik et al. 1992), but $V_D:V_T$ is similar to the nonpregnant state.

In contrast with the resting state, studies of arterial blood gases in exercising pregnant women are few in number. Pivarnik et al. (1992) studied changes in blood gases, pH, and respiratory responses in the transition from the resting state (left lateral decubitus posture) to two levels of steady-state cycle ergometer work (50 and 75 W) and treadmill exercise (67 m/min with 25 and 12% grade, respectively). Subjects were primigravid women ($n = 7$) who were permanent residents at 1388 m elevation. They were studied at moderate altitude (barometric pressure = 650 mmHg) at both 36.9 ± 0.9 weeks of gestation and 12.0 ± 1.1 weeks postpartum. As expected, mean resting values for P_{aCO_2} during late pregnancy at altitude were somewhat lower (26.5 ± 2.2 mmHg) than those observed by others at sea level. Values did not change significantly in the transition from rest to any of the four exercise conditions, and the magnitude of change was comparable both in late gestation and postpartum. From this laboratory, Kemp et al. (1997) also reported significantly lower resting baseline values and comparable changes immediately following maximal exercise testing for venous P_{CO_2} in late gestation compared with the nonpregnant state.

Other investigations have measured arterialized blood gases (Lehman and Regnat 1976), end-tidal P_{CO_2} values (Pernoll et al. 1975), or have reported P_{aCO_2} values predicted from end-tidal P_{CO_2} data from exercising pregnant women (Ohtake and Wolfe 1998; McAuley et al. 1997) using the equation of Jones and colleagues (Jones et al. 1979; Robbins et al. 1990). Although more research is needed with actual measurement of P_{aCO_2} , these studies support the concept that P_{aCO_2} is lower in the pregnant versus nonpregnant state under a variety of exercise conditions and that this effect is established early in the first trimester with only very small reductions in P_{aCO_2} with advancing gestational age. Also, changes in P_{aCO_2} induced by either moderate steady-state exercise (Pernoll et al. 1975; Ohtake and Wolfe 1998; McAuley et al. 1997) or strenuous non-steady-state exercise (McAuley et al. 1997) are comparable in the pregnant versus nonpregnant state, even though baseline values are significantly lower during pregnancy.

Table 2. Differences in plasma constituents in the pregnant versus nonpregnant state at rest.

- ↑ Estrogen and progesterone levels
- ↑ hCG (early pregnancy) and relaxin levels
- ↓ $[H^+]$ and $[HCO_3^-]$ in both arterial and venous blood
- ↓ P_{CO_2} in both arterial and venous blood
- ↓ $[Na^+]$, $[K^+]$, and $[SID]$ in both arterial and venous blood; $[Cl^-]$ levels maintained
- ↑ Total blood volume (40–50%)
- ↓ Osmolality
- ↓ $[TP]$, $[ALB]$; slightly ↑ $[GLOB]$; ↓ $[ALB]/[GLOB]$; ↓ $[P]_{tot}$
- ↑ Angiotensin II levels (although ANG II receptors may be downregulated)
- ↓ Osmotic threshold for AVP release; ↓ AVP levels in late gestation

Note: For references see the following: Brandstetter and Schueller 1959; Brown et al. 1988; Devane 1985; Eastman 1930; Gray et al. 1964; Hytten 1968; Kemp et al. 1997; Kydd 1931; Lim et al. 1976; Lindheimer et al. 1991; Lindheimer and Davison 1995; Lucius et al. 1970; Lund and Donovan 1967; Machida 1981; Newman 1957; Pedersen et al. 1985; Pivarnik et al. 1990; Plass and Mathew 1926; Prowse and Gaensler 1965; Ramsey et al. 1992; Wolfe et al. 1989.

Summary

Increases in pulmonary ventilation that appear in early pregnancy cause a substantial reduction in P_{aCO_2} , which would tend to reduce $[H^+]$. After these initial changes, only very small reductions are observed with advancing gestational age. These effects are observed both at rest and during exercise, and existing data suggest that changes in P_{aCO_2} during the transition from rest to exercise of varying intensities are comparable with those observed in the nonpregnant state.

Effects of pregnancy and exercise on $[A_{tot}]$

During pregnancy, maternal blood volume expands approximately 40–50% above nonpregnant levels (Gorski 1985; Lund and Donovan 1967; Pivarnik et al. 1990). This expansion is out of proportion with the increase in red cell volume (approximately 20%), resulting in a relative state of anemia (Lund and Donovan 1967) and a diminished total plasma protein concentration ($[TP]$) (Table 2) (Eastman 1930; Pivarnik et al. 1990; Kemp et al. 1997). Increased capillary leakage of protein (Pivarnik et al. 1990) also contributes to hypoproteinemia as pregnancy progresses. Total plasma proteins are reduced at the expense of the albumin fraction ($[ALB]$) (Eastman 1930; Kydd 1931; Plass and Matthew 1926; Pivarnik et al. 1990; Kemp et al. 1997) as the globulin fraction ($[GLOB]$) undergoes a moderate increase (Eastman 1930; Kydd 1931; Plass and Matthew 1926). The overall outcome is a reduction in the $[ALB]/[GLOB]$ ratio (Eastman 1930; Pivarnik et al. 1990).

Strenuous exercise during pregnancy causes a decrease in absolute plasma volume, as well as increases in the plasma concentrations of total protein and albumin (McMurray et al. 1991; Pivarnik et al. 1990). Greater than normal exercise-induced hemoconcentration occurs in pregnancy and results in an overall increase in $[TP]$ and $[ALB]$, with no change observed in the $[ALB]/[GLOB]$ ratio, when compared with resting values (McMurray et al. 1991; Pivarnik et al. 1990; Kemp et al. 1997).

Summary

Pregnancy results in a decrease in $[TP]$, which would tend to reduce $[H^+]$ in the resting state. However, during strenuous exercise, $[TP]$ increases, and this increase contributes to

increases in plasma $[H^+]$ observed in the transition from rest to exercise.

Effects of pregnancy and exercise on $[SID]$

In the resting pregnant state, plasma $[Na^+]$ and $[K^+]$ are reduced (Kydd 1931; Brandstetter and Schueller 1959; Lucius et al. 1970; Kemp et al. 1997), presumably as a result of pregnancy-induced plasma volume expansion (Table 2), whereas $[Cl^-]$ and $[La^-]$ are reported to be either unchanged or slightly increased. These changes result in a significant reduction in $[SID]$, which in accordance with Stewart's hypothesis, would tend to increase $[H^+]$.

As described above, existing studies (Clapp et al. 1987; McMurray et al. 1988; Wolfe et al. 1994a) have reported that pregnant subjects have lower plasma lactate concentrations following strenuous exercise than in the nonpregnant state. Factors that may contribute to this effect include pregnancy-induced blood volume expansion (Lund and Donovan 1967; Pivarnik et al. 1990); insulin resistance (Wolfe et al. 1994b), and total utilization of lactate as a metabolic fuel (Burd et al. 1975). In accordance with Stewart's hypothesis, lower blood lactate concentrations would tend to attenuate both exercise-induced reductions in $[SID]$ and increases in $[H^+]$.

Summary

During pregnancy, plasma volume expansion plays a role in the decrease in $[SID]$ at rest, which alone would have the effect of increasing $[H^+]$. During exercise, there is the potential for an increase in lactate concentration due to the muscular work, which would lead to a further increase in $[H^+]$. However, during pregnancy, a slower rate of lactate accumulation occurs, relative to the nonpregnant state, thereby decreasing the possibility of further maternal acidosis.

Physicochemical approach to acid–base analysis in human pregnancy

As described above, pregnancy is accompanied by substantial changes in all three independent variables (P_{CO_2} , $[SID]$, and $[A_{tot}]$) depicted in Stewart's physicochemical approach to acid–base analysis. A recent study from this laboratory (Kemp et al. 1997) was the first to examine acid–base regulation during pregnancy either at rest or during exercise,

using modern physicochemical principles. Responses of healthy, physically active pregnant ($n = 9$) and nonpregnant ($n = 14$) women were compared at rest and at specific times (1, 3, 5, 7, 15 min) during recovery from a progressive maximal cycle ergometer test. As expected, mean values in both groups for venous plasma $[H^+]$, P_{CO_2} , and $[TP]$ increased significantly in the transition from rest to maximal exercise, whereas those for [bicarbonate] and [SID] decreased. However, at rest and during postexercise recovery, significantly lower mean values were observed in the pregnant group for P_{CO_2} , $[HCO_3^-]$, and $[TP]$. [SID] was significantly lower in the pregnant group at rest and during early recovery from exercise. Venous plasma $[H^+]$ was always 3–4 nequiv/L lower in the pregnant group at all measurement times, but the difference compared with the nonpregnant group was statistically significant only in the resting state because of greater variability of values during the postexercise period. Measured and calculated values for $[H^+]$ were not significantly different from one another, although nonsignificant data trends were observed within both groups to underestimate measured values at rest and to overestimate during postexercise recovery.

Changes in measured $[H^+]$ were also analyzed during the transition from rest to peak exercise, during early postexercise recovery (1–7 min postexercise) and in late postexercise recovery (7–15 min postexercise). Change scores were similar in the pregnant and nonpregnant groups for all three time periods. Analysis of the percentage contributions of independent variables to these changes also revealed a similar pattern in both groups. In this regard, reductions in [SID] made substantial contributions ($\approx 60\%$) to increases in $[H^+]$ in the transition from rest to peak exercise, with smaller relative contributions caused by increased P_{CO_2} ($\approx 10\%$) and $[A_{tot}]$ as reflected by $[TP]$ ($\approx 30\%$). [SID] continued to decrease in early recovery, but this was compensated by substantial reductions in P_{CO_2} during early recovery, resulting in a modest net reduction in $[H^+]$. Further reductions in P_{CO_2} , increases in [SID], and decreases in $[A_{tot}]$ (as reflected by $[TP]$) contributed to reductions in $[H^+]$ in late recovery. Overall it appears that a lower $[H^+]$ in the resting state in late gestation is the result of reductions in P_{CO_2} and $[A_{tot}]$. These effects on $[H^+]$ are partly offset by a reduction in [SID]. Changes in $[H^+]$ induced by strenuous exercise and the percent contributions of the three independent variables to these changes are not altered significantly by pregnancy. Contributions of the independent variables to return $[H^+]$ to resting levels are also similar in the pregnant versus nonpregnant state.

Summary

During pregnancy, values for P_{aCO_2} , [SID], and $[A_{tot}]$ appear to adequately predict $[H^+]$. The physiological changes in $[H^+]$ in response to maternal exercise are also explained by the changes in P_{aCO_2} , [SID], and $[A_{tot}]$. Therefore, evidence suggests that Stewart's quantitative analysis provides a useful conceptual framework for the study of acid-base regulation during pregnancy at rest and during exercise. It appears that the lower $[H^+]$ observed during pregnancy in the resting state is caused by reductions in P_{aCO_2} and $[A_{tot}]$, which not completely offset by the effects of a lower [SID]. Increases in $[H^+]$ in response to strenuous maternal exercise

are mainly due to a reduction in [SID] with a smaller contribution from an increased $[A_{tot}]$. The mechanisms by which the changes in these independent variables occur during pregnancy are not well understood. Progesterone is thought to be the major contributor to the changes that occur during pregnancy; however, it appears that other humoral systems may be involved in pregnancy-related changes in respiration and acid-base balance.

Control of ventilation in pregnancy

Progesterone and the respiratory response

It is well established that the augmented ventilatory response during pregnancy is associated with increased levels of circulating progesterone (Lyons and Antonio 1959; Moore et al. 1987; Regensteiner et al. 1989) causing an increase in the slope of the ventilatory response to carbon dioxide (Kimura et al. 1984). The luteal phase of the menstrual cycle is also a time of increased circulating progesterone and is accompanied by ventilatory changes similar to those that occur during pregnancy. This includes increased resting $\dot{V}_E$ values (Dempsey et al. 1986; Milne et al. 1977; Schoene et al. 1981), a decrease in alveolar carbon dioxide tension (P_{aCO_2}) (England and Farhi 1976; Milne et al. 1977), and an increase in P_{aO_2} (Machida 1981). This response appears to be specific to progesterone because, as noted in both female and male cats, the increased $\dot{V}_E$ following exogenous progesterone administration could not be reproduced with identical doses of other classes of steroid hormones (Bayliss et al. 1987).

The effects of progesterone on ventilatory drive in pregnancy are maintained during exercise. Administration of the synthetic progestin medroxyprogesterone acetate (MPA) in men for 14 days induced ventilatory responses to progressive submaximal and maximal exercise that were greater than those observed following placebo administration (Schoene et al. 1979). Greater values for the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) during steady-state exercise in pregnancy (Edwards et al. 1981; Ohtake and Wolfe 1998; Pivarnik et al. 1992) as well as the decreased P_{aCO_2} in pregnancy both support the hypothesis that respiratory sensitivity to CO_2 is increased at rest and during exercise.

Although the pregnancy-induced increase in CO_2 sensitivity has been attributed to progesterone, the mechanism of action remains unclear. Expression of the augmented ventilation produced by increased levels of circulating progesterone appears to involve estrogen, which also increases during pregnancy. A dose-dependent enhancement of phrenic nerve activity (an index of central respiratory output) was observed in response to repeated intravenous doses of progesterone (0.1, 0.2, 0.5, and 1.0 g/kg, cumulative) only when ovariectomized female cats were pretreated with estrogen on each of 3 days prior to study (Bayliss et al. 1990). This response was weakened with pretreatment of estrogen receptor or progesterone receptor antagonists. Indeed, the synergistic effect of chronic progesterone and estrogen administration produces a greater increase in ventilation than that with either hormone alone (Brodeur et al. 1986), and the stimulatory effect is more consistent (Regensteiner et al. 1989).

Existing evidence indicates that the increased ventilation during pregnancy depends on functional progesterone receptors. Blockade of progesterone receptors with the antagonist RU486 abolished the increase in ventilation in response to exogenously administered progesterone (Bayliss et al. 1987), demonstrating that the enhanced ventilation is receptor mediated. Recent animal studies, where respiratory feedback mechanisms and exogenous levels of steroid hormones were strictly controlled, found that the respiratory response to progesterone was mediated by hypothalamic cells containing progesterone receptors (Bayliss et al. 1990). Furthermore, removal of the diencephalon attenuated the stimulatory effect of progesterone on respiration, implicating the diencephalon as a critical neuroanatomical region involved in the response (Bayliss et al. 1990). In this regard, estrogen has been shown to induce an increased number of progesterone receptors in the hypothalamus and preoptic areas (MacLusky and McEwan 1978). This observation was confirmed by recent reports that the largest population of progesterone receptors was observed in the preoptic area and the ventromedial nucleus of the hypothalamus (DonCarlos and Morrell 1990). Subsequent investigation of the process of progesterone-receptor induction via estrogen demonstrated a dependence on RNA and protein synthesis (Bayliss et al. 1990; Bayliss and Millhorn 1991). Cumulatively, this evidence suggests that progesterone may act within the brain to increase the ventilatory response to CO_2 through actions on hypothalamic receptors involved in respiratory control (Bayliss et al. 1990) and that this proposed mechanism depends at least in part on estrogen.

Although progesterone is associated with an increased respiratory sensitivity to carbon dioxide, it is unknown to what extent the peripheral and central chemoreceptors are involved. The effect of progesterone on peripheral chemoreceptors has been investigated in one study (Tatsumi et al. 1997). In response to endogenous reductions in progesterone caused by ovariectomy, the hypercapnic ventilatory response was unchanged, whereas in response to hypoxia, carotid sinus nerve firing decreased relative to control (Tatsumi et al. 1997). Although this suggests that progesterone exerts an effect on peripheral chemoreceptors, it remains to be determined how increased levels of progesterone alter peripheral chemoreceptor responsivity.

Direct involvement of the central chemoreceptors in the increase in respiratory sensitivity to CO_2 is unlikely since progesterone receptors have not been identified in the medulla. However, there is evidence to suggest a role for hypothalamic disinhibition of central chemoreceptors resulting in the augmentation of the ventilatory response to CO_2 . Progesterone receptors are present in the hypothalamus, and the numbers of these receptors increase in the presence of estrogen. Suprapontine structures are known to be involved in modulating the respiratory response to hypercapnia. Indeed, unilateral microinjection of a GABA synthesis inhibitor (3-mercaptopropionic acid) into the posterior hypothalamus elicits an increase in resting minute diaphragmatic activity and greatly accentuates the respiratory responses to hypercapnia (Peano et al. 1992). Similar findings have been reported in response to microinjections of GABA antagonists into the posterior hypothalamus (Waldrop et al. 1988; Waldrop 1991). These findings suggest that a

GABAergic inhibition of posterior hypothalamic neurons modulates the respiratory response to hypercapnia.

Interestingly, it has been observed that, although estradiol increases GABA in hypothalamic sites, progesterone administration to estradiol-primed female rats results in a rapid decline in GABA levels (Luine et al. 1997). Similarly, progesterone metabolites have been shown to decrease $[\text{K}^+]$ -induced GABA release from nerve terminals (Taubill et al. 1993). Taken together, it appears that following estrogen priming, progesterone and (or) its metabolites may decrease hypothalamic levels of GABA, thereby removing an inhibitory influence on ventilation. This disinhibition would result in augmented ventilation at rest and an accentuated response to hypercapnia, as is observed during pregnancy. This mechanism requires further investigation.

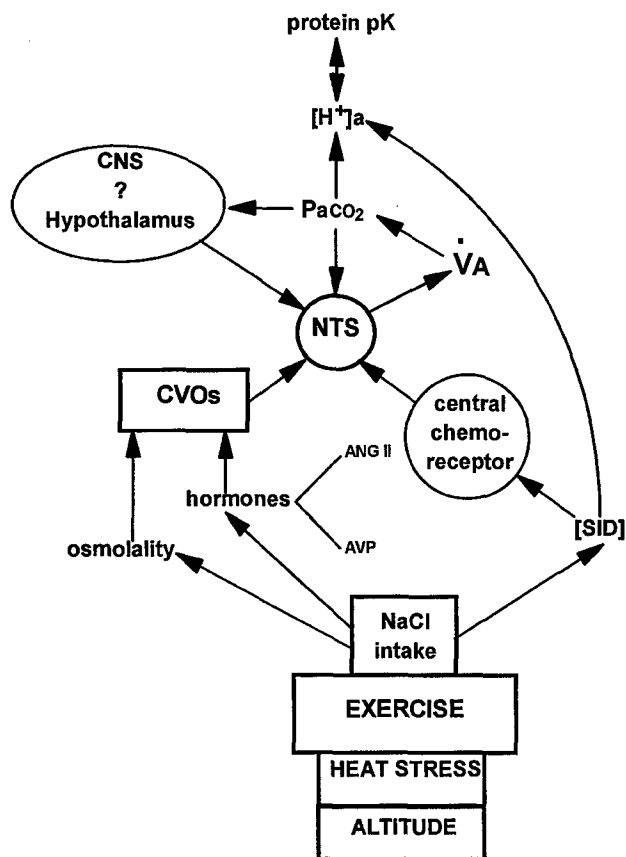
While progesterone appears to stimulate respiration, several lines of evidence suggest that there are other factors involved in addition to progesterone. The major concern with the progesterone theory is that the time course of the increase in ventilation and the increase in circulating levels of progesterone are not well correlated. Therefore, it is necessary to consider alternative hypotheses.

Jennings' hypothesis of respiratory control

Recently, Jennings (1994a) proposed an integrated model to explain how humoral and chemical factors interact to affect the control of $\dot{V}_A$ and Paco_2 (Fig. 3). Central to Jennings' hypothesis is the concept described above, that $[\text{H}^+]$ is controlled in relation to pK in order to maintain the charge state and conformation of critical proteins. Central chemoreceptors regulate $\dot{V}_A$ and Paco_2 in relation to CSF $[\text{SID}]$ (Jennings 1993). Recent studies of Jennings and associates have also demonstrated the importance of plasma osmolality (Anderson and Jennings 1988a, 1988b) and circulating levels of ANG II (Anderson et al. 1990; Ohtake and Jennings 1993; Ohtake et al. 1993) to stimulate pulmonary ventilation in animal preparations. Conversely, AVP appears to modulate ventilation by inhibiting both brain and systemic renin-angiotensin systems (Gregory et al. 1988; Suzuki et al. 1989; Walker and Jennings 1994). AVP reduces the slope of the ventilatory response to CO_2 (Ohtake and Jennings 1993; Ohtake et al. 1993). However, the effects of ANG II and AVP on ventilation do not appear to be present in rats (Walker and Jennings 1996) or in dogs subjected to moderate hypoxia or hypoxic isocapnia and hypercapnia (Overgaard et al. 1996). Jennings has hypothesized that the central effects of plasma osmolality, ANG II, and AVP are mediated via circumventricular organs (CVOs) of the brain, which lack a blood-brain barrier and have receptors for ANG II and numerous other hormones.

During strenuous exercise, body temperature rises, lactic acid production increases, the plasma strong ion difference $[\text{SID}]$ decreases, and plasma osmolality increases as a result of fluid shifts and loss of water and electrolytes via sweating. In addition, arginine vasopressin (AVP) is released and the renin-angiotensin system is activated, resulting in augmented plasma concentrations of AVP and ANG II (Convertino et al. 1983; Freund et al. 1987). These variables may be involved in ventilatory control during exercise.

Fig. 3. Schematic representation of the humoral and chemical factors affecting the regulation of $\dot{V}_A$ and P_{aCO_2} . CNS, central nervous system; CVOs, circumventricular organs; NTS, nucleus of the tractus solitarius; ANG II, angiotensin II; AVP, arginine vasopressin. (Adapted from Jennings (1994a) with permission.)

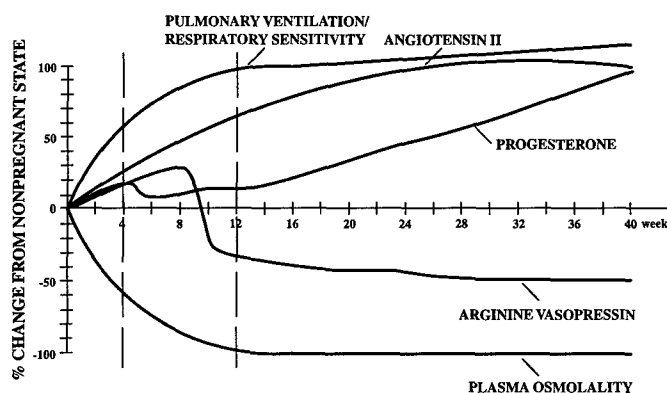


Jennings' hypothesis and human pregnancy

In addition to the effects of progesterone as a respiratory stimulant, there are also striking pregnancy-induced changes in several other important variables involved in respiratory control as described in Jennings' hypothesis. Recently, Duvekot et al. (1993) provided convincing evidence to support the hypothesis that the vessel-dilating effect of gestational hormones leads to a reduction in systemic vascular tone and a decrease in mean arterial blood pressure (MAP). These effects in turn cause activation of "volume restoring mechanisms," and an early increase in blood volume and reduction in plasma osmolality.

It is postulated that, in early pregnancy, volume and pressure receptors cause an increase in AVP release from the neurohypophysis and thirst in response to the decrement in "effective" blood volume described above (Fig. 4). There also appears to be a reduction in the osmotic threshold for AVP release caused by gestational hormones (Lindheimer and Davison 1995). However, later in pregnancy the metabolic clearance rate of AVP is greatly increased (Lindheimer et al. 1991) so that plasma levels in late gestation are somewhat lower than those in the nonpregnant state (Devane 1985; Pedersen et al. 1985) (Fig. 4). Although stimulation of

Fig. 4. Hypothetical time course of changes in pulmonary ventilation and respiratory sensitivity plasma osmolality, ANG II, AVP, and progesterone in human pregnancy (Clapp et al. 1988; Davison et al. 1988; Duvekot et al. 1993; Ohtake and Wolfe 1998; Rees et al. 1990; Wilson et al. 1980; Wolfe et al. 1994a). Values are percentages of the total pregnancy-induced change for each variable relative to prepregnant baseline.



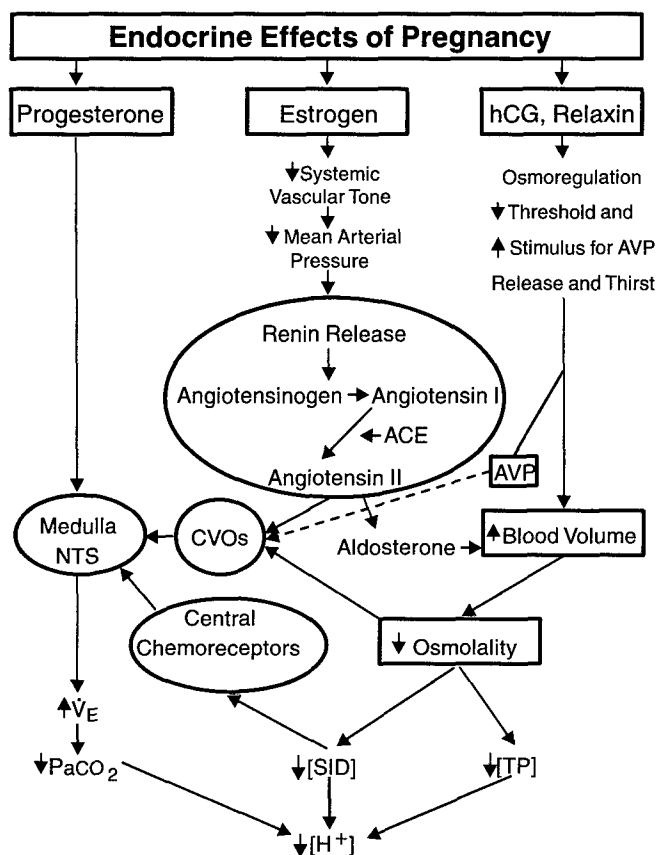
the renin-angiotensin system would be expected as a result of the relative hypovolemia in early pregnancy, renin, ANG II, and aldosterone levels are elevated throughout pregnancy but do not peak until the third trimester (Brown et al. 1988) (Fig. 4). This could be the result of lower AVP levels in late gestation, since AVP inhibits renin release by the kidney (Gregory et al. 1988). With advancing gestational age, there is also a reduced pressor response to infusion of ANG II (Gant et al. 1973; Ramsay et al. 1992), suggesting a downgrading of the receptor sensitivity of vascular smooth muscle. Other important pregnancy-induced changes that must be considered include a small increase in body core temperature (Clapp et al. 1987; Clapp 1991) and an increase in baroreflex sensitivity in the resting state (Leduc et al. 1991; Brooks and Keil 1994).

Integrated hypothesis of acid-base regulation and respiratory control in human pregnancy

As described above, pregnancy is accompanied by substantial changes in all three independent variables (P_{CO_2} , $[SID]$, and $[A_{tot}]$) described in Stewart's physicochemical approach to acid-base analysis. In addition, plasma levels of progesterone (a known respiratory stimulant) increase with advancing gestational age, the renin-angiotensin system is activated, AVP secretion is altered, and plasma osmolality is reduced (Fig. 4). These changes may interact to alter the control of ventilation and to regulate $[H^+]$ in relation to protein pK in order to preserve the function of enzymes, ion channels, contractile proteins, etc. (Fig. 5).

The view that progesterone plays a role in the ventilatory changes that accompany pregnancy is widely accepted and is not being questioned here, though the mechanism by which progesterone receptors in the hypothalamus are able to communicate with the medullary respiratory center has, thus far, not been identified. Mechanisms to explain why the changes

Fig. 5. Postulated mechanisms of acid-base regulation and respiratory control in human pregnancy. hCG, human chorionic gonadotropin; AVP, arginine vasopressin; ACE, angiotensin converting enzyme; NTS, nucleus of the tractus solitarius; CVOs, circumventricular organs; $\dot{V}_E$, expired minute ventilation; P_{aCO_2} , arterial partial pressure of carbon dioxide; SID, strong ion difference; TP, total protein; H^+ , hydrogen ion.



in progesterone and ventilation do not follow the same time course still need to be identified, and the possibility that other endocrine changes in pregnancy may affect control of ventilation cannot be excluded.

Jennings has demonstrated a clear relationship between changes in ANG II, AVP, and osmolality with changes in ventilation in the dog model. In pregnancy, all of these factors change along with the change in ventilation (Fig. 4). Clapp et al. (1988) demonstrated that a large increase in ventilation occurs by the 7th week of pregnancy. Duvekot et al. (1993) observed that plasma renin concentration (an indicator of ANG II levels) between 5 and 8 weeks of pregnancy was much higher than postpartum values, while osmolality was lower. With this in mind, it seems very possible that changes in the renin-angiotensin system and osmolality could be playing a role in the early ventilatory changes observed in pregnancy. Investigation into these relationships is needed.

Conclusions

A lower plasma $[H^+]$ is observed at rest throughout pregnancy compared with the nonpregnant state. Analyses in accordance with modern physicochemical principles suggests

that this is the net result of reductions in P_{CO_2} and $[A_{tot}]$ (which will lower $[H^+]$) and a reduction in $[SID]$ (which will increase $[H^+]$). Available evidence suggests that changes in $[H^+]$ induced by strenuous exercise are similar in the pregnant versus nonpregnant state, and percentage contributions of independent variables are also comparable.

It is generally accepted that increases in respiratory sensitivity to carbon dioxide are caused by augmented circulating progesterone levels and an estrogen-dependent increase in hypothalamic progesterone receptors. However, the mechanism by which these changes lead to augmented respiratory sensitivity remains unclear, and involvement of other neuroendocrine factors cannot be excluded. In this regard, recent research by Jennings and associates have demonstrated in laboratory animals the involvement of CSF $[SID]$, osmolality, and circulating levels of ANG II and AVP in the chemical control of ventilation. Since human pregnancy involves substantial changes in these variables, we hypothesize that these factors in concert with progesterone contribute to pregnancy-induced increases in respiratory sensitivity.

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Appendix C

**Manuscript from Study #3 entitled
"Plasma Acid Base Regulation Above and Below the Ventilatory
Threshold in Late Gestation"
(*Journal of Applied Physiology*, Vol 86(1): (in press), 2000).**

The American Physiological Society

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September 14, 1999

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RE: JAP Ms #A0006-9 R2
TITLE: Plasma acid-base regulation above and below the ventilatory threshold in late gestation

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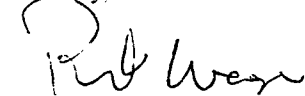
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BOOKS

Plasma acid-base regulation above and below the ventilatory threshold in late gestation.

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Stewart's physicochemical approach was used to study the effects of pregnancy on acid-base regulation in arterialized blood. Responses of a group of 15 healthy pregnant women (PG; gestational age, 37.1 (0.2 wk) were compared to those of 15 nonpregnant controls (CG) at rest and during cycling at 70 and 110% of the ventilatory threshold (TVENT). Hydrogen ion concentration ([H⁺]) was lower in the PG vs. CG at rest (37.6 vs. 39.9 nEq/L) and during exercise (39.5 vs. 41.8 nEq/L at 70% TVENT; 43.5 vs. 45.1 nEq/L at 110% TVENT; $p < 0.05$ at rest and 70% TVENT). Exercise-induced changes in [H⁺] were similar between groups. Lower resting [H⁺] values in the PG vs. CG resulted from lower values for CO₂ tension (PaCO₂; 33.3 vs. 39.5 mmHg) and total weak acid ([Atot]; 15.1 vs. 17.3 mEq/L) which were partly offset by a lower strong ion difference ([SID]; 36.8 vs. 39.9 mEq/L). Reductions in [Atot] and [SID] at rest were primarily the result of reductions in albumin [ALB] and sodium [Na⁺], respectively. In the transition from rest to 70% TVENT, small increases in PaCO₂ and [Atot] contributed to moderate increases in [H⁺] in both groups, however [SID] increased in the PG and decreased in the CG ($p < 0.05$ between groups). In the transition from rest to 110% TVENT, decreases in [SID] made a significantly greater contribution to changes in [H⁺] in the CG vs. PG. Exercise-induced increases in [H⁺] are similar in the pregnant vs. nonpregnant state, but there is a reduced contribution of [SID] both above and below TVENT during pregnancy.

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**PLASMA ACID-BASE REGULATION ABOVE AND BELOW THE
VENTILATORY THRESHOLD IN LATE GESTATION**

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Abstract

Stewart's physicochemical approach was used to study the effects of pregnancy on acid-base regulation in arterialized blood. Responses of a group of 15 healthy pregnant women (PG; gestational age, 37.1 ± 0.2 wk) were compared to those of 15 nonpregnant controls (CG) at rest and during cycling at 70 and 110% of the ventilatory threshold (T_{VENT}). Hydrogen ion concentration ($[\text{H}^+]$) was lower in the PG vs. CG at rest (37.6 vs. 39.9 nEq/L) and during exercise (39.5 vs. 41.8 nEq/L at 70% T_{VENT} ; 43.5 vs. 45.1 nEq/L at 110% T_{VENT} ; $p < 0.05$ at rest and 70% T_{VENT}). Exercise-induced changes in $[\text{H}^+]$ were similar between groups. Lower resting $[\text{H}^+]$ values in the PG vs. CG resulted from lower values for CO_2 tension (PaCO_2 , 33.3 vs. 39.5 mmHg) and total weak acid ($[\text{A}_{\text{tot}}]$; 15.1 vs. 17.3 mEq/L) which were partly offset by a lower strong ion difference ($[\text{SID}]$; 36.8 vs. 39.9 mEq/L). Reductions in $[\text{A}_{\text{tot}}]$ and $[\text{SID}]$ at rest were primarily the result of reductions in albumin $[\text{ALB}]$ and sodium $[\text{Na}^+]$, respectively. In the transition from rest to 70% T_{VENT} , small increases in PaCO_2 and $[\text{A}_{\text{tot}}]$ contributed to moderate increases in $[\text{H}^+]$ in both groups, however $[\text{SID}]$ increased in the PG and decreased in the CG ($p < 0.05$ between groups). In the transition from rest to 110% T_{VENT} , decreases in $[\text{SID}]$ made a significantly greater contribution to changes in $[\text{H}^+]$ in the CG vs. PG. Exercise-induced increases in $[\text{H}^+]$ are similar in the pregnant vs. nonpregnant state, but there is a reduced contribution of $[\text{SID}]$ both above and below T_{VENT} during pregnancy.

Keywords: hydrogen ion, carbon dioxide tension, strong ion difference, total weak acid

INTRODUCTION

Pregnancy-induced changes in respiratory control and acid-base regulation have been studied extensively in the resting state. These include increases in minute ventilation ($\dot{V}_E$), tidal volume (V_T) and alveolar ventilation ($\dot{V}_A$) and a reduction in arterial carbon dioxide tension (P_{aCO_2}) (1, 17, 24, 29). In accordance with conventional acid-base theory, these changes are accompanied by renal excretion of bicarbonate ($[HCO_3^-]$), resulting in a state of partly compensated respiratory alkalosis (arterial pH $\simeq$ 7.43-7.47) (13, 17). These effects appear in the first trimester and may promote placental gas exchange prior to development of an effective fetal circulatory system (13).

Existing studies of acid-base balance during and after maternal exercise have reported conflicting results. Lehmann and Regnat (12) studied healthy pregnant women at rest and during six minutes of stationary cycling at both 50 and 80 watts. They reported greater decreases in blood pH during exercise at both 50 and 80 watts in pregnancy compared to measurements at 12 weeks postpartum. Significantly lower absolute pH values were also encountered during the exercise at 80 watts in pregnancy compared to the nonpregnant state. Conversely, Pivarnik et al. (24) reported higher arterial pH values in pregnant women at 37 weeks gestation compared with postpartum during exercise bouts lasting six minutes on a cycle ergometer (50 and 75 watts) and on a treadmill (67m/ min, 2.5% grade and 67m/min, 12% grade). Similar changes in pH in the transition from rest to exercise were reported under all exercise conditions in both groups, but bicarbonate values decreased to a lesser extent in the pregnant group.

Lehman and Regnat (12) and Pivarnik *et al.* (24) employed the conventional Henderson-Hasselbalch approach to the study of acid-base balance in pregnancy and

exercise. Unfortunately, this provides limited insight into the mechanisms controlling acid-base balance (6). In contrast, Stewart's physicochemical approach to acid-base analysis (26, 27) allows examination of the specific physicochemical determinants of changes in hydrogen ion concentration ($[H^+]$) in individual fluid compartments. All variables are defined as independent or dependent and all systems are assumed to behave in accordance with the principles of electroneutrality, conservation of mass and dissociation equilibria. If the values for the independent variables (i.e. carbon dioxide tension (PCO_2), the strong ion difference ($[SID]$) and total weak acid ($[A_{tot}]$)) and dissociation constants are known, values for dependent variables ($[H^+]$, $[HCO_3^-]$, dissociated weak acid $[A^-]$, weak acid $[HA]$, carbonate $[CO_3^{2-}]$ and hydroxide $[OH^-]$) can be determined mathematically. This approach to acid-base analysis has been validated in an animal model (23) and at rest and during recovery from exercise in young men (11, 14).

Only one study has used Stewart's approach to study acid-base regulation in healthy women. Kemp *et al.* (9) compared the responses of physically active pregnant women (mean gestational age, 33 ± 1 wk) to those of a nonpregnant control group in both the resting state and during recovery from a maximal cycle ergometer test. During pregnancy significantly lower values for $[H^+]$ in venous plasma in the resting state were the result of lower values for PCO_2 and $[A_{tot}]$, (which would reduce $[H^+]$). This effect was only partly offset by a lower $[SID]$ (which would increase $[H^+]$). Increases in $[H^+]$ in the transition from rest to maximal exercise were quantitatively similar in the two groups and calculated contributions of PCO_2 , $[SID]$ and $[A_{tot}]$ to changes in $[H^+]$ in the transition from rest to peak exercise, during early post-exercise recovery (1-7 min post-exercise)

and late post-exercise (7-15 min) did not differ significantly in the pregnant versus nonpregnant state. These findings suggested that pregnancy-induced changes in $[H^+]$ are established in the resting state and that exercise-induced changes in $[H^+]$ and its determinants are not affected by human pregnancy.

Unfortunately, the value of the study of Kemp *et al.* (9) to describe the effects of human pregnancy on $[H^+]$ and its independent determinants was limited by the use of venous plasma in the analyses. The composition of venous blood reflects the metabolic activity of the tissues that it drains, whereas that of arterial blood is consistent throughout the body. In this regard, Kemp *et al.* (9) studied venous blood drawn from the antecubital vein in the arm, whereas exercise was performed on a leg cycle ergometer. Clearly, the use of arterial (or arterialized) blood would have been more accurate and sensitive to analyze changes in acid-base regulation induced by pregnancy and exercise.

The purpose to this study was to examine, using Stewart's physicochemical approach, the effects of human pregnancy on arterialized plasma $[H^+]$ and its determinants in the resting state, as well as changes in $[H^+]$ in the transition from rest to both steady-state and nonsteady-state exercise. It was hypothesized that the results would confirm the earlier findings of Kemp *et al.* (9) from venous blood that lower plasma $[H^+]$ in the resting state is the combined result of lower values for PCO_2 and $[A_{tot}]$ and this effect is partly offset by a lower $[SID]$. It was further hypothesized that changes in $[H^+]$ in the transition from rest to both steady-state and nonsteady-state exercise would be similar in the pregnant versus nonpregnant state and that the contributions of $PaCO_2$, $[A_{tot}]$ and $[SID]$ to these changes would not differ significantly between groups.

METHODS

Subjects

Subjects were 15 healthy, nonsmoking, physically active pregnant women (pregnant group, PG). Results from the PG were compared to those of 15 healthy nonpregnant women with similar physical and demographic characteristics (control group, CG). Prospective subjects were recruited from local prenatal fitness classes and from the general population, via media advertisements, posters, flyers, and contact with local obstetricians. Medical clearance for pregnant subjects was obtained from the physician or midwife monitoring their pregnancy using a standard form (Canadian Physical Activity Fitness and Lifestyle Assessment). Nonpregnant subjects completed the revised Physical Activity Readiness Questionnaire.

Written informed consent was obtained from all subjects before entry into the study. The study protocol, described below, and consent form were approved by the Research Ethics Board, Faculty of Medicine, Queen's University and the U.S. Army Medical Research and Materiel Command, Human Subjects Protection Branch.

Basic physical measurements included body height, body mass and resting blood pressure. Body mass index was calculated as body mass (kg)/body height² (m²). The PG and CG were matched for mean age, body height, pre-pregnant body mass, parity and aerobic fitness. Members of the PG were tested between 34 and 38 weeks of their gestation. Subjects in the CG were not using oral contraceptives and menstrual cycle status at the time of the second exercise test was calculated using the first day of their last menstrual cycle and the average length of their cycle, and verified using serum progesterone samples taken at rest on the day of the test (29).

Exercise Testing Protocols

Subjects performed two exercise tests on a Sensor Medics (Model 800S) constant work rate cycle ergometer at least one day apart. Subjects consumed a standard meal (350 kcal, 40% carbohydrate, 40% fat, 20% protein) 1-2 h prior to both tests and avoided strenuous physical activity and caffeine on the day of testing. The first test was used to determine the ventilatory threshold (T_{VENT}) and to assess aerobic working capacity. The protocol involved five minutes of resting data collection and a four min warm-up at 20 watts, followed by an increase in work rate of 20 watt/min until a heart rate of 170 beats/min was reached (16, 9). Respiratory responses were measured on a breath-by-breath basis using a computerized system (First Breath Inc.) that incorporates a respiratory mass spectrometer (Perkin-Elmer, MGA 1100) with a volume turbine (VMM-1100) as described by Hughson *et al.* (1991). Breath-by-breath alveolar gas exchange was calculated using the algorithm of Beaver *et al.* (1981) and T_{VENT} was identified using the V-slope method (3). Heart rate (HR) was monitored with both a Polar Vantage monitor and a Marquette Max-1 electrocardiograph. Oxygen pulse ($\dot{V}O_2/\text{HR}$) at a heart rate of 170 beats/min was calculated as an index of aerobic working capacity (Wolfe *et al.*, 1994).

The second exercise test involved a 10 min resting data collection, followed by a three min warm-up at 0 watts and a ramp increase in work rate, over a 30-second time period, to a work rate corresponding to 70% or 110% of T_{VENT} . Both work rates were continued for seven minutes after achievement of the prescribed work rate. Subjects rested for 20 minutes between levels. Prior to this test, an indwelling catheter was inserted into a dorsal hand vein situated as far from the thumb as possible. The hand and

lower arm were soaked in a warm water bath prior to insertion of the catheter, and then placed in a plexiglass heating box (45 degrees C) to promote vasodilation. Arterialized blood samples were then collected at rest and during the sixth minute of exercise at 70% or 110% of T_{VENT} . Measured PaO_2 values averaged were 79 ± 4 mmHg, 74 ± 3 and 71 ± 2 at rest, 70% T_{VENT} and 110% T_{VENT} , respectively, and confirmed adequate arterialization.

Blood samples for the determination of oxygen tension, $PaCO_2$, $[HCO_3^-]$ and $[H^+]$ were collected in a syringe containing lyophilized heparin and analyzed immediately using a Radiometer ABL 30 acid-base analyzer at a standard temperature of 37°C. Correction of blood gas values for changes in temperature were not necessary, since tympanic temperature measurements confirmed no significant deviation from 37°C with pregnancy or exercise using the present protocol. Quality control checks using four control liquids were done on all testing days. The remaining blood was then centrifuged for 10 minutes at 2500 rpm and frozen at -80 °C for later analysis, as described below.

Total protein concentration ($[TP]$) was measured using the direct Biuret method. $[A_{tot}]$ (mEq/l) was calculated from $[TP]$ (g/L) using the conversion factor 0.243 (Kowalchuk and Scheuermann, 1993). Albumin concentration ($[ALB]$) was determined using a conventional dye-binding method. Plasma concentrations of sodium ($[Na^+]$), potassium ($[K^+]$), calcium ($[Ca^{2+}]$) and chloride ($[Cl^-]$) were analyzed using ion-selective electrodes. Plasma osmolality was determined using the freezing point depression technique. Globulin concentration ($[GLOB]$) was calculated by subtracting the $[ALB]$ from $[TP]$ so that the A/G ratio could be determined. The interassay coefficient of variability was less than three percent for all of the procedures listed above.

Plasma lactate concentration $[La^-]$ was determined using an automated analyzer (Yellow Springs Instruments, Model 2300). The analyzer was calibrated before analysis using five and 15 mmol/L standards and at regular intervals during the analysis. The test-retest reliability of $[La^-]$ measurements was described in an earlier publication from this laboratory (29). $[SID]$ was then calculated as: $([Na^+] + [K^+] + 2 [Ca^{2+}]) - ([Cl^-] + [La^-])$.

Stewart's Physicochemical Analysis

Stewart's physicochemical equation (26,27) was used to calculate $[H^+]$ using values for the three independent variables (9, 11) and to calculate the contributions of the three independent variables to changes in $[H^+]$ in each group in response to exercise (9, 14):

$$\begin{aligned} & [H^+]^4 + (K_A + [SID]) [H^+]^3 \\ & + \{K_A ([SID] - [A_{tot}]) - (K_C \times PCO_2 + K'_w)\} [H^+]^2 \\ & - \{K_A(K_C \times PCO_2 + K'_w) + (K_3 \times K_C \times PCO_2)\} [H^+] \\ & - (K_A \times K_3 \times K_C \times PCO_2) = 0 \end{aligned}$$

where $K'_w = 4.4 \times 10^{-14}(\text{eq/L})^2$, $K_C = 2.46 \times 10^{-11}(\text{eq/L})^2/\text{Torr}$, $K_3 = 6.0 \times 10^{-11}(\text{eq/L})$, $K_A = 3.0 \times 10^{-7}(\text{eq/L})$.

As previously described by Lindinger *et al.* (1992), the contribution of each independent variable to a change in $[H^+]$ can be determined by solving the above equation while using resting values for the variables and changing variables singly or in combination to their measured values.

Statistical Analyses

Physical characteristics, T_{VENT} , oxygen pulse at 170 beats/min and measured changes in $[\text{H}^+]$ at the two exercise levels were compared between groups using Student's t -statistics for independent samples. Data at rest and during exercise at 70% and 110% T_{VENT} were compared within and between subjects using a two-way ANOVA (groups vs. rest/exercise level) with repeated measures on the second factor. When a significant between group main effect was observed, separate independent Student t -statistics were used to identify significant differences between group means at rest, at 70% T_{VENT} and at 110% T_{VENT} . When a significant within-subjects main effect was observed, paired Student t -statistics were also used to detect significant differences between rest, 70% T_{VENT} and 110% T_{VENT} within each group.

$[\text{H}^+]$ was calculated using Stewart's physicochemical equation and compared to measured $[\text{H}^+]$ within both groups under each experimental condition using paired Student t -statistics. The corresponding associations between calculated and measured $[\text{H}^+]$ were examined using Pearson product-moment correlation coefficients (Pearson r). Contributions of the 3 independent variables to change in $[\text{H}^+]$ at each work rate were compared within and between groups using a two-way ANOVA (group vs. independent variables contribution) with repeated measures on the second factor. When a significant between-group main effect was observed or group x contribution interaction, separate independent t -statistics were used to identify significant differences between group means at rest, at 70% T_{VENT} and at 110% T_{VENT} . When a significant within-subjects effect or group x time interaction was observed paired Student t -statistics were used to detect significant differences among variables within each group.

All statistical tests were considered significant if $p < 0.05$. Since comparisons between groups and across variables were planned comparisons and the number of comparisons was small in each case, the critical alpha level for significance was maintained at $p < 0.05$ (10). Results were identified as trends when $0.05 < p < 0.08$.

RESULTS

Subjects. Subjects in both groups were aged between 25 and 40 y and the mean values were 29.5 ± 0.9 y and 26.9 ± 1.6 y for the PG and CG, respectively (Table 1). Mean gestational age of the PG was 37.1 ± 0.2 wk. Within the CG, nine women were in the follicular phase of their menstrual cycle and six women were in the luteal phase. As expected, body mass and body mass index (BMI) were significantly higher in the PG compared to the CG at the time of testing. However, the PG's pre-pregnancy body mass and BMI were not different from those of the CG. There were no significant differences in mean age, body height, parity, oxygen uptake ($\dot{V}O_2$) at T_{VENT} and oxygen pulse (ml/beat) at 170 beats/min.

Ventilatory Variables and Heart Rate. Heart rate was significantly higher in the PG compared to the CG at rest and 70% T_{VENT} , but the difference narrowed with increasing exercise intensity (Table 2). $\dot{V}O_2$ and the respiratory exchange ratio (RER) did not differ significantly between groups, at rest or either exercise level. $\dot{V}_E$ and the end-tidal oxygen tension ($P_{ET}O_2$) were significantly higher in the PG at all measurement times. Ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) were significantly higher in the PG at all measurement times except for $\dot{V}_E/\dot{V}CO_2$ at rest. The

end-tidal carbon dioxide tension ($P_{ET}CO_2$) was significantly lower in the PG at all measurement times and increased from rest to both work rates.

Dependent Acid-Base Variables. During all three experimental conditions $[H^+]$ and $[HCO_3^-]$ were lower in the PG vs. CG (Figures 1A, 1B). Results were statistically significant except for $[H^+]$ at 110% T_{VENT} . $[H^+]$ increased significantly in the transition from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} in both groups. $[HCO_3^-]$ was also significantly lower at 110% T_{VENT} compared to rest and 70% T_{VENT} in both groups. Calculated mean changes in measured $[H^+]$ from rest to 70% T_{VENT} and rest to 110% T_{VENT} were similar between groups (Figure 2).

Independent Acid-Base Variables. $PaCO_2$ was significantly lower in the PG vs. CG at rest and both exercise levels (Figure 3). $PaCO_2$ did not change significantly with exercise, except for an increase from rest to 70% T_{VENT} in the PG. However, a trend for $PaCO_2$ values to decrease from 70% T_{VENT} to 110% T_{VENT} was present in the CG. $[SID]$ was significantly lower in the PG vs. CG at rest and 70% T_{VENT} , but not at 110% T_{VENT} (Figure 4). There was a significant group $\times$ time interaction for $[SID]$. $[SID]$ decreased significantly in the transition from rest to 110% T_{VENT} within both groups and was significantly lower at 110% T_{VENT} compared to 70% T_{VENT} . $[SID]$ increased significantly in the PG from rest to 70% T_{VENT} .

Both $[Na^+]$ and $[K^+]$ increased in the transition from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} in both groups (Table 3). $[Na^+]$ was significantly lower at rest and both exercise levels in the PG compared to the CG. $[K^+]$ was significantly lower at rest and 70% T_{VENT} in the PG compared to the CG. As expected, osmolality exhibited the

same significant trends between groups and measurements as those for $[\text{Na}^+]$. $[\text{Ca}^{2+}]$ was greater at 110% T_{VENT} in the PG than at rest and 70% T_{VENT} . Values for $[\text{Ca}^{2+}]$ in the PG were significantly higher than those of the CG at 70% and 110% T_{VENT} . There were no differences in $[\text{Cl}^-]$ between groups at any level. $[\text{Cl}^-]$ increased significantly in the transition from rest to both 70% and 110% T_{VENT} except for in the PG at 70% T_{VENT} . $[\text{La}^-]$ increased significantly from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} as expected. There were no significant between group differences in absolute values for $[\text{La}^-]$ and increases from rest to both exercise intensities were not significantly different.

In both groups, $[\text{TP}]$ and $[\text{ALB}]$ increased significantly in the transition from rest to both 70% T_{VENT} and 110% T_{VENT} (Table 4). $[\text{GLOB}]$ significantly increased from rest to 110% T_{VENT} in the PG. $[\text{TP}]$, $[\text{ALB}]$ and $[\text{GLOB}]$ also increased significantly from 70% to 110% T_{VENT} , except for $[\text{TP}]$ and $[\text{GLOB}]$ in the CG. There were no significant changes across measurement conditions for the A/G ratio. At rest, 70% T_{VENT} and 110% T_{VENT} the values for $[\text{TP}]$, $[\text{ALB}]$ and the A/G ratio were significantly lower in the PG compared to the CG. The values for $[\text{GLOB}]$ were significantly higher in the PG compared to the CG at rest and both exercise levels. Differences between groups and across exercise levels for the calculated values for $[\text{A}_{\text{TOT}}]$ (Figure 5) followed those of $[\text{TP}]$.

Relationship Between Measured and Calculated $[\text{H}^+]$. Calculated $[\text{H}^+]$ values from Stewart's equation are compared to measured in Table 5. Calculated $[\text{H}^+]$ was not significantly different from measured $[\text{H}^+]$ at rest or during exercise in the CG. However, a small but statistically significant underestimation was present in the PG. Strong

statistically significant correlations were also observed between measured and calculated $[H^+]$ in both groups. The only exception to this was the relationship at rest in the CG. This effect was attributed to the low variability of data in the resting state.

Contributions of Independent Variables to Changes in $[H^+]$. $[SID]$ was the only variable to make a significantly different contribution to change in $[H^+]$ between the groups (Figure 6). At 70% T_{VENT} an increase in $[SID]$ in the PG attenuated the rise in $[H^+]$, whereas a decrease in $[SID]$ in the CG contributed to the rise. At 110% T_{VENT} , the contribution of $[SID]$ to the rise in $[H^+]$ was significantly greater in the CG vs. PG. This appeared to be offset by a modest reduction in $PaCO_2$ ($p>0.05$) in the CG. This was reflected in a trend for a different contribution of $PaCO_2$ between groups from rest to 110% T_{VENT} in which $PaCO_2$ contributed to the rise in $[H^+]$ in the PG but attenuated the rise in $[H^+]$ in the CG.

Discussion

The central objective of this study was to examine, using the physicochemical approach of Stewart (26,27), the effects of human pregnancy on mechanisms of acid-base regulation at rest and during exercise above and below T_{VENT} . The two exercise intensities were chosen to examine the effects of pregnancy on acid-base regulation during moderate steady-state exercise and during strenuous nonsteady-state exertion that represented a more severe challenge to maternal acid-base homeostasis. This study adds significantly to information available from the earlier study of Kemp *et al.* (9) since arterialized rather than venous plasma was employed for the analysis and the effects of

exercise both below and above T_{VENT} (i.e. steady-state and nonsteady-state exercise conditions) were examined. It was hypothesized that acid-base balance would be significantly altered at rest in pregnancy, and that absolute changes in $[H^+]$ in the transition from rest to exercise and the mechanisms responsible would be similar to the nonpregnant state.

Generalized metabolic and cardiorespiratory responses at rest and during both exercise tests and differences between groups were consistent with previous studies of exercising pregnant women. It is well documented that respiratory sensitivity to CO_2 is increased, resulting in higher values for $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ as well as an increased $P_{ET}O_2$ and reduced $P_{ET}CO_2$ both at rest and during submaximal exercise relative to the nonpregnant state (22, 21). RER does not appear to be altered at work rates below the onset of blood lactic acid accumulation (29, 16). It is well documented that HR is augmented both at rest and during submaximal exercise and these differences in HR compared to the nonpregnant state decrease with increasing exercise intensity (21). Finally, while the effects of pregnancy on maximal aerobic power are controversial (30), existing studies indicate that T_{VENT} is not changed (16, 29). Thus, our results are consistent with and confirm the results of earlier studies of the effects of human pregnancy on generalized metabolic and cardiorespiratory responses to exercise.

Measured $[H^+]$ values in the PG were lower than in the CG at rest and at both exercise levels. Differences were statistically significant at rest and 70% T_{VENT} , but significance was lost at 110% T_{VENT} where the variability of measurements increased. Despite the difference in acid-base status at rest, both groups exhibited similar increases in $[H^+]$ in response to the acid-base balance challenge provided by exercise, as

demonstrated by the lack of difference between groups in the measured changes in $[H^+]$ from rest to both work rates. These findings agree with those of Kemp *et al.* (9) and Pivarnik *et al.* (24), but differ from those of Lehmann and Regnat (12) who observed larger reductions in pH in pregnant subjects compared to nonpregnant controls in the transition from rest to submaximal exercise.

The present data also show that strenuous exercise in pregnancy does not produce high levels of $[H^+]$ in the maternal circulation that could have potentially detrimental effects on the fetus. The pH of the maternal blood at 110% T_{VENT} (pH=7.36) did not decrease to a greater extent than what would be expected in fetal venous blood at 37 weeks gestation (pH=7.36; (20)). This suggests that the increases in the maternal $[H^+]$ with the exercise intensity above T_{VENT} should not affect the fetal $[H^+]$ since changes in maternal $[H^+]$ are transient (9) and the maternal-fetal $[H^+]$ gradient was not reversed.

Values for $[HCO_3^-]$ were lower in the PG vs. CG at rest and both exercise intensities. The decrease in $[HCO_3^-]$ from rest to either exercise intensity was no greater in the PG than the CG. These results are in agreement with the earlier findings of Kemp *et al.* (9) from this laboratory but differ from those of Lehmann and Regnat (1976) who found that exercise-induced decreases in base-excess were greater in pregnancy and those of Pivarnik *et al.* (24) who reported smaller exercise-induced decreases in $[HCO_3^-]$.

In accordance with either Stewart's physicochemical approach, or traditional acid-base analysis, significantly lower $PaCO_2$ values in the PG vs. the CG would contribute to the maintenance of a lower $[H^+]$ in the PG at all measurement times. This confirms the importance of pregnancy-induced increases in respiratory sensitivity (2) to reduce $PaCO_2$ and to maintain a lower $[H^+]$ than in the nonpregnant state. Augmented respiratory

sensitivity in pregnancy has been attributed to increased circulating levels of progesterone, a known respiratory stimulant, and estrogen (5, 18). The increased estrogen level elevates the number of progesterone receptors in the hypothalamus (2, 5). In accordance with recent findings of Jennings and associates (8), the increase in $\dot{V}_E$ in pregnancy may also be due to changes in osmolality, [SID] and angiotensin II levels which have been implicated in the control of ventilation. During pregnancy, osmolality decreases, [SID] decreases, and angiotensin II levels increase. In theory, all of these effects could contribute to the increase in $\dot{V}_E$ in pregnancy in concert with the effects of progesterone (28).

The lower [SID] in the PG compared to the CG at rest and both work rates resulted primarily from lower values for $[\text{Na}^+]$ and to a lesser extent $[\text{K}^+]$ in the PG, since there were no significant differences in $[\text{Cl}^-]$ or $[\text{La}^-]$ between groups. The reductions in $[\text{Na}^+]$ and $[\text{K}^+]$ may have been the result of pregnancy-induced hemodilution (or perhaps other mechanisms), since blood volume in pregnancy increases by 40-50% over nonpregnant levels (15, 25). Expansion of blood volume during pregnancy is attributed to an estrogen-mediated stimulation of the renin-angiotensin system, which in turn augments aldosterone secretion, and as well as Na^+ and water retention (15). Reduced $[\text{Na}^+]$ and $[\text{K}^+]$ values at rest in pregnancy have been observed previously (9, 17). As reported previously, pregnancy did not cause reductions in $[\text{Cl}^-]$ (9, 18). This could be due to changes in renal absorption of chloride, ionic shifts between fluid compartments or altered binding of chloride by plasma proteins.

The decrease in [SID] observed in both groups during the transition from rest to exercise at 110% T_{VENT} was primarily the result of an increase in $[\text{La}^-]$. $[\text{La}^-]$ did not

differ significantly between groups at either exercise intensity and increases were not significantly different between groups, although there have been reports of lower $[La^-]$ for exercising pregnant women at work rates above T_{VENT} (19, 29). Blunted $[La^-]$ responses in pregnancy would, in theory, contribute to the maintenance of a lower $[H^+]$.

$[A_{tot}]$ was lower, as a result of reductions in $[ALB]$, in the PG vs. the CG at rest and both work rates, thus contributing to the lower $[H^+]$ in the PG. The lower $[A_{tot}]$ in the PG was attributed to pregnancy-induced blood volume expansion and altered synthesis of proteins by the liver as suggested by the decreased A/G ratio. The present results for $[TP]$, $[ALB]$, $[GLOB]$ and A/G ratio also agree with previous findings. $[TP]$ and $[ALB]$ decrease in pregnancy whereas $[GLOB]$ increases moderately (9). The overall result is a decrease in the A/G ratio (9, 25). $[TP]$ and thus $[A_{tot}]$ increase during exercise, likely the result of exercise-induced hemoconcentration.

Similar absolute changes in $[H^+]$ in the transition from rest to 70% and 110% T_{VENT} in the PG and CG suggested that the contributions of independent variables to the increase in $[H^+]$ in response to strenuous exercise were similar in the pregnant vs. nonpregnant state, as reported previously by Kemp *et al.* (9) in venous plasma. To examine this hypothesis further, Stewart's equation was utilized to calculate the contributions of the independent variables to changes in $[H^+]$ from rest to each work rate. The contribution of $[A_{TOT}]$ was not significantly different between groups at either exercise intensity. As discussed below, a trend ($p=0.07$) was present for a different contribution of $PaCO_2$ between groups at 110% T_{VENT} . The contributions of $[SID]$ to changes in $[H^+]$ were significantly different between groups at both exercise intensities and a significant group $\times$ time interaction was observed for the absolute $[SID]$ values. The

altered behavior of [SID] in the pregnant state resulted in a negative contribution to the rise in $[H^+]$ at the 70% T_{VENT} work rate and a smaller positive contribution to the $[H^+]$ rise at the 110% T_{VENT} work rate. These findings are different from those of Kemp *et al.* (9) who found no pregnancy-induced effect on the contributions of any of the independent variables to changes in $[H^+]$ in recovery from a maximal exercise test. This discrepancy was attributed to the use of venous as opposed to arterial or arterialized plasma in this earlier study.

A trend for $PaCO_2$ values to decrease from 70% T_{VENT} to 110% T_{VENT} was present in the CG ($p=0.06$), but not in the PG ($p=0.32$), suggesting that respiratory compensation for the rising $[H^+]$ was present in the CG at this work rate but not in the PG. The reduction in $PaCO_2$ in the CG but not the PG could be easily explained if the rise in $[H^+]$ from 70% to 110% T_{VENT} was greater in the CG vs. PG, but this was not observed. However, if [SID] rather than $[H^+]$ is the stimulus to chemoreceptors and ventilation as hypothesized by Jennings (8), the decrease in [SID] in the CG in the transition from rest to 110% T_{VENT} (approximately twice that of the PG) would account for the differences in the behavior of $PaCO_2$ at 110% T_{VENT} .

Excellent agreement was observed between measured and calculated values for $[H^+]$ both at rest and during exercise in the CG and, except for values in the CG at rest (owing to low variability of measurements), strong statistically significant correlations were observed between measured and calculated $[H^+]$ in both groups under all experimental conditions. In accordance with earlier studies of exercising men (11), these results provide strong support for the validity and utility of Stewart's approach.

Within the PG, there was a small (2-3 mEq/L) but statistically significant underestimation of $[H^+]$ using Stewart's equation and values for the independent variables. In accordance with modern acid-base theory (8) this could be an effect of changes in temperature, $[SID]$ and/or osmolality on the dissociation constants used in Stewart's analysis. Indeed, our data showed significant differences in plasma osmolality and $[SID]$ (but not temperature) in the pregnant vs. nonpregnant state. Given the small differences involved, it is unlikely that this introduced important mathematical errors in our calculation of contributions of the independent variables to changes in $[H^+]$. It is also important to keep in mind that the purpose of using Stewart's approach is not to predict $[H^+]$ but to allow a more mechanistic approach to acid-base analysis than is possible using the conventional Henderson-Hasselbalch approach by itself. The prediction of $[H^+]$ is usually done to show the validity of Stewart's approach and to provide assurance that no serious errors are involved in the measurement or calculation of the three independent variables. Taken by themselves, the results from the PG provide strong support for Stewart's approach based on the highly significant correlations between measured and calculated $[H^+]$. Indeed, although the difference between the measured and calculated $[H^+]$ in the PG was significantly greater than in the CG it was still quite small and in the same range observed in earlier validation studies (9, 11). Nevertheless, this effect should be considered in future studies of acid-base regulation in human pregnancy.

The present study confirmed earlier findings (1, 13, 17, 24, 29) that human pregnancy is accompanied by a partly compensated respiratory alkalosis as reflected by significantly reduced values for $[H^+]$, $PaCO_2$ and $[HCO_3^-]$ in arterialized plasma in the resting state. Application of Stewart's physicochemical approach was helpful to clarify

the involvement of metabolic, hepatic and renal contributions to a reduction in $[H^+]$ in the resting state. The reduction of $[A_{tot}]$ can be attributed in part to dilution of plasma proteins (and other weak acids) in an expanded maternal blood volume. However, a significant decrease in the A/G ratio also suggests altered synthesis of plasma proteins by the liver. Pregnancy-induced reduction in $[SID]$ was the result of lower values for $[Na^+]$ and $[K^+]$, again presumably as a result of hemodilution. The reasons why $[Cl^-]$ and $[La^-]$ were not significantly reduced should be examined in future investigations of metabolic, renal and ionic factors. The present study results also confirmed earlier findings that exercise-induced reductions in $[H^+]$ are quantitatively similar in the pregnant vs. nonpregnant state (9, 25). We also observed no significant differences between groups in the change in $[HCO_3^-]$ in the transition from rest to either moderate (70% T_{VENT}) or strenuous (110% T_{VENT}) exercise. Application of Stewart's physicochemical approach demonstrated that there is a blunted $[SID]$ response to exercise above and below T_{VENT} in late pregnancy.

In conclusion, our results support our original hypothesis that lower $[H^+]$ of arterialized plasma in the resting state is the combined result of lower values for $PaCO_2$ and $[A_{tot}]$ and this effect is partly offset by a lower $[SID]$. Whereas exercise-induced increases in $[H^+]$ are quantitatively similar in the pregnant vs. nonpregnant state, the mechanisms of adaptation from rest to exercise are different. The altered behavior of $[SID]$ above and below T_{VENT} in pregnancy is beneficial to maintain a lower $[H^+]$. In addition, since there is a lesser contribution of $[SID]$ to changes in $[H^+]$ induced by strenuous exercise in pregnancy, acid-base regulation may require less respiratory compensation at work rates above T_{VENT} .

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Table 1. Physical Characteristics of Subjects

VARIABLE	PREGNANT GROUP (n=15)	CONTROL GROUP (n=15)
Age (years)	29.5 $\pm$ 0.9	26.9 $\pm$ 1.6
Gestational Age (weeks)	37.1 $\pm$ 0.2	N/A
Height (cm)	163.6 $\pm$ 2.0	163.5 $\pm$ 1.5
Body Mass (kg)	77.9 $\pm$ 2.7*	61.9 $\pm$ 1.9
Body Mass Index	29.0 $\pm$ 0.7*	23.1 $\pm$ 0.6
Pre-Pregnancy Body Mass (kg)	64.4 $\pm$ 2.7	N/A
Pre-Pregnancy Body Mass Index	24.0 $\pm$ 0.8	N/A
Parity	0.4 $\pm$ 0.2	0.4 $\pm$ 0.2
VO ₂ @ T _{VENT} (L/min)	1.76 $\pm$ 0.06	1.81 $\pm$ 0.04
O ₂ Pulse @ 170 beats/min (ml/beat)	12.7 $\pm$ 0.5	13.4 $\pm$ 0.4

Values are means $\pm$ SE.

* Significant difference ($p < 0.05$) between groups.

Table 2. Ventilatory Variables and Heart Rate

Variable	HR (beats/ min)	RER	$\dot{V}O_2$ (L/min)	$\dot{V}_E$ (L/min)	$\dot{V}_E/\dot{V}O_2$	$\dot{V}_E/\dot{V}CO_2$	$P_{ET}O_2$ (mmHg)	$P_{ET}CO_2$ (mmHg)
REST								
PG	87 ± 2 [*]	0.91 ± 0.02	0.38 ± 0.01	11.0 ± 0.4 [*]	30.0 ± 1.4 [*]	32.9 ± 1.1	113.1 ± 0.6 [*]	32.5 ± 0.4 [*]
CG	70 ± 2	0.87 ± 0.02	0.34 ± 0.01	8.2 ± 0.4	25.9 ± 1.1	30.2 ± 1.1	107.4 ± 1.1	37.4 ± 0.5
70% T _{VENT}								
PG	130 ± 3 ^{*†}	0.96 ± 0.01 [†]	1.34 ± 0.06 [†]	38.2 ± 2.0 ^{*†}	28.6 ± 1.1 [*]	29.6 ± 0.8 ^{*†}	110.5 ± 1.0 ^{*†}	35.3 ± 0.7 ^{*†}
CG	119 ± 4 [†]	0.96 ± 0.01 [†]	1.34 ± 0.04 [†]	31.3 ± 1.3 [†]	23.5 ± 0.5 [†]	24.3 ± 0.4 [†]	105.2 ± 0.8 [†]	41.4 ± 0.5 [†]
110% T _{VENT}								
PG	160 ± 3 ^{†§}	1.04 ± 0.01 ^{†§}	2.00 ± 0.09 ^{†§}	63.6 ± 2.8 ^{*†§}	32.3 ± 1.3 ^{*§}	30.9 ± 1.0 ^{*§}	113.4 ± 1.1 ^{*§}	34.4 ± 0.9 ^{*†}
CG	155 ± 4 ^{†§}	1.02 ± 0.01 ^{†§}	2.03 ± 0.05 ^{†§}	55.6 ± 2.0 ^{†§}	27.6 ± 0.7 [§]	27.0 ± 0.5 ^{†§}	109.7 ± 1.0 ^{†§}	38.7 ± 0.7 ^{†§}

PG - Pregnant Group (n=15); CG - Control Group (n=15)

^{*} Significant difference ($p \leq 0.017$) between groups.[†] Significant change ($p \leq 0.017$) within groups from Rest.[§] Significant change ($p \leq 0.017$) within groups from cycling at 70% T_{vent} to cycling at 110% T_{vent}.

Table 3. Plasma Strong Ions at Rest and at Two Work Rates

VARIABLE	[Na ⁺] (mmol/l)	[K ⁺] (mmol/l)	[Ca ⁺⁺] (mmol/l)	[Cl ⁻] (mmol/l)	[La ⁻] (mmol/l)	Osmolality (mOsm/kg H ₂ O)
REST						
PG	136 ± 0.3 [*]	3.9 ± 0.1 [*]	1.18 ± 0.02	104 ± 0.6	1.5 ± 0.1	277 ± 1 [*]
CG	139 ± 0.4	4.3 ± 0.1	1.15 ± 0.01	105 ± 0.5	1.2 ± 0.2	284 ± 1
70% T _{VENT}						
PG	137 ± 0.4 ^{*‡}	4.5 ± 0.1 ^{*‡}	1.21 ± 0.01 [*]	104 ± 0.6	2.5 ± 0.3 [‡]	280 ± 1 ^{*‡}
CG	141 ± 0.4 [‡]	4.8 ± 0.1 [‡]	1.14 ± 0.01	106 ± 0.6 [‡]	2.5 ± 0.4 [‡]	288 ± 1 [‡]
110% T _{VENT}						
PG	138 ± 0.5 ^{*‡§}	4.9 ± 0.1 ^{‡§}	1.23 ± 0.02 ^{*‡§}	105 ± 0.7 [‡]	5.8 ± 0.4 ^{‡§}	284 ± 1 ^{*‡§}
CG	141 ± 0.5 ^{‡§}	5.2 ± 0.1 ^{‡§}	1.16 ± 0.01	106 ± 0.6 [‡]	5.9 ± 0.6 ^{‡§}	293 ± 1 ^{‡§}

Values are means ± SE.

PG - Pregnant Group (n=15); CG - Control Group (n=15)

^{*} Significant difference (p<0.05) between groups.

[‡] Significant change (p<0.05) within groups from Rest.

[§] Significant change (p<0.05) within groups from cycling at 70% T_{vent} to cycling at 110% T_{vent}.

Table 4. Plasma Protein at Rest and During Two Work Rates

VARIABLE	[TP] (g/L)	[ALB] (g/L)	[GLOB] (g/L)	A/G
REST				
PG	62 ± 1.1 [*]	30 ± 0.6 [*]	32 ± 0.9 [*]	0.93 ± 0.03 [*]
CG	71 ± 1.6	42 ± 0.6	28 ± 1.4	1.55 ± 0.06
70% T _{VENT}				
PG	66 ± 1.2 ^{†‡}	32 ± 0.6 ^{†‡}	34 ± 0.8 [*]	0.94 ± 0.02 [*]
CG	74 ± 1.7 [†]	44 ± 0.5 [†]	31 ± 1.3	1.46 ± 0.05
110% T _{VENT}				
PG	69 ± 1.6 ^{†‡§}	33 ± 0.8 ^{†‡§}	36 ± 1.1 ^{†‡§}	0.93 ± 0.03 [*]
CG	76 ± 1.4 [†]	46 ± 0.4 ^{†,§}	31 ± 1.4	1.51 ± 0.06

Values are means ± SE.

PG - Pregnant Group (n=15); CG - Control Group (n=15)

^{*} Significant difference (p<0.05) between groups.

[†] Significant change (p<0.05) within groups from Rest.

[§] Significant change (p<0.05) within groups from cycling at 70% T_{vent} to cycling at 110% T_{vent}.

Table 5. Values of measured $[H^+]$ and calculated $[H^+]$ at rest and at two work rates

Variable	Measured $[H^+](nEq/L)$	Calculated $[H^+](nEq/L)$	Mean Difference (nEq/L)	r
REST				
PG	37.6 ± 0.4	$35.4 \pm 0.7^*$	2.2	0.78
CG	39.9 ± 0.4	39.6 ± 0.7	0.3	0.10
70% T_{VENT}				
PG	39.5 ± 0.5	$36.4 \pm 0.8^*$	3.1	0.86
CG	41.8 ± 0.6	42.2 ± 1.3	-0.4	0.80
110% T_{VENT}				
PG	43.5 ± 0.7	$40.8 \pm 1.1^*$	2.7	0.74
CG	45.1 ± 0.8	45.9 ± 1.1	-0.8	0.74

Values are means $\pm$ SE.

PG - Pregnant Group (n=15); CG - Control Group (n=15)

* Significant difference ($p < 0.05$) between measured and calculated $[H^+]$

LIST OF FIGURES

Figure 1. A. Measured $[H^+]$ at rest and at two work rates. * Significant difference between groups. † Significant change within group from Rest. § Significant change within group from cycling at 70% T_{VENT} to cycling at 110% T_{VENT} . $[H^+]$, hydrogen ion concentration. B. Calculated $[HCO_3^-]$ at rest and at two work rates. * Significant difference between groups. † Significant change within group from Rest. § Significant change within group from cycling at 70% T_{VENT} to cycling at 110% T_{VENT} . $[HCO_3^-]$, bicarbonate ion concentration.

Figure 2. Changes in measured $[H^+]$. The changes in measured $[H^+]$ from rest to both 70% and 110% T_{VENT} were not significantly different between groups.

Figure 3. Arterialized plasma $PaCO_2$ at rest and at two work rates. * Significant difference between groups. † Significant change within group from Rest. $PaCO_2$, partial pressure of carbon dioxide.

Figure 4. Calculated plasma $[SID]$ at rest and at two work rates. * Significant difference between groups. † Significant change within group from Rest. § Significant change within group from cycling at 70% T_{VENT} to cycling at 110% T_{VENT} . SID , strong ion difference.

Figure 5. $[A_{\text{tot}}]$ as reflected by $[TP]$ at rest and at two work rates. * Significant difference between groups. † Significant change within group from Rest. § Significant change within group from cycling at 70% T_{VENT} to cycling at 110% T_{VENT} . A_{tot} , total weak acid; TP, total protein.

Figure 6. Calculated contributions of independent variables to changes in $[H^+]$. See text for explanation of significant differences between groups.

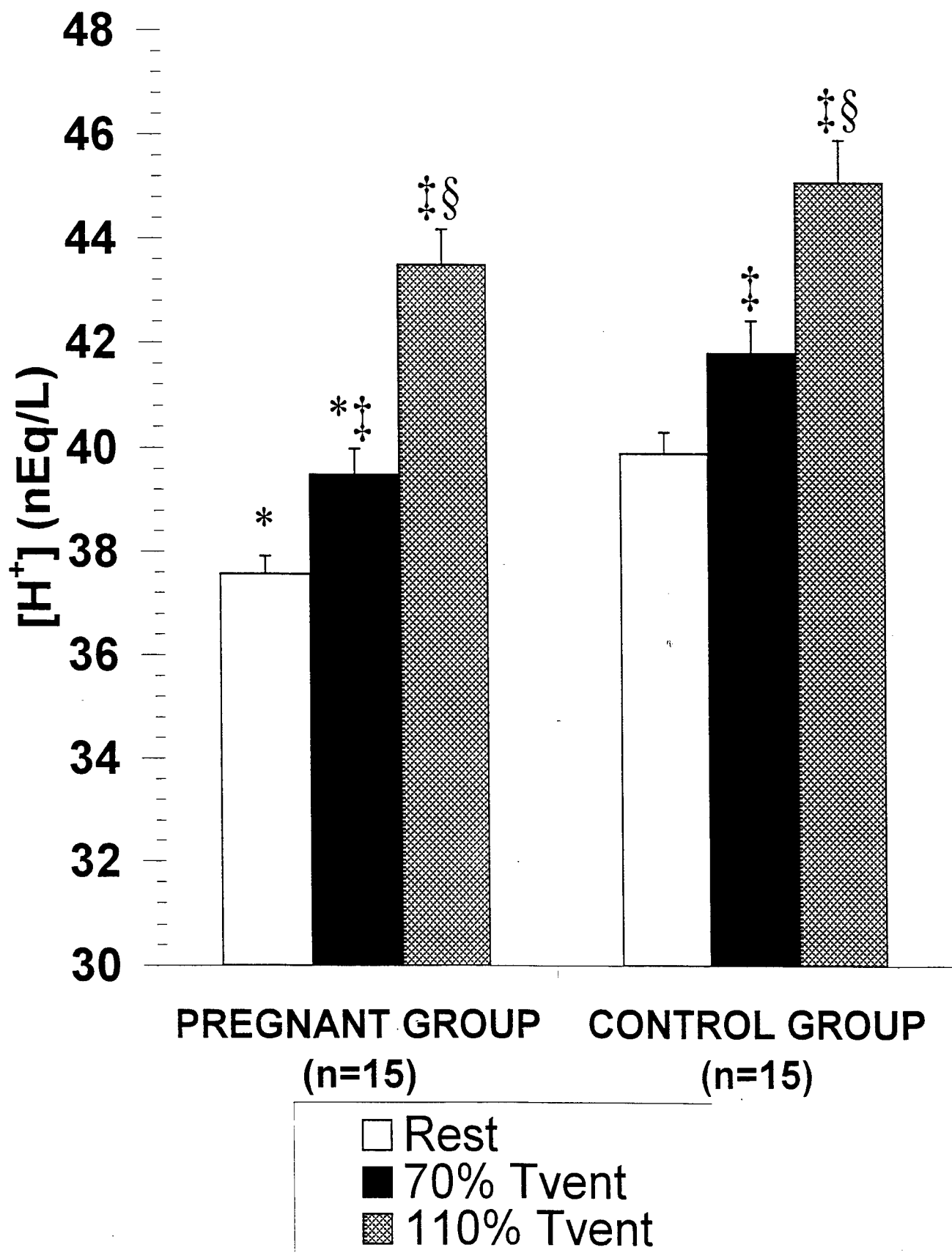


FIGURE 1 - A

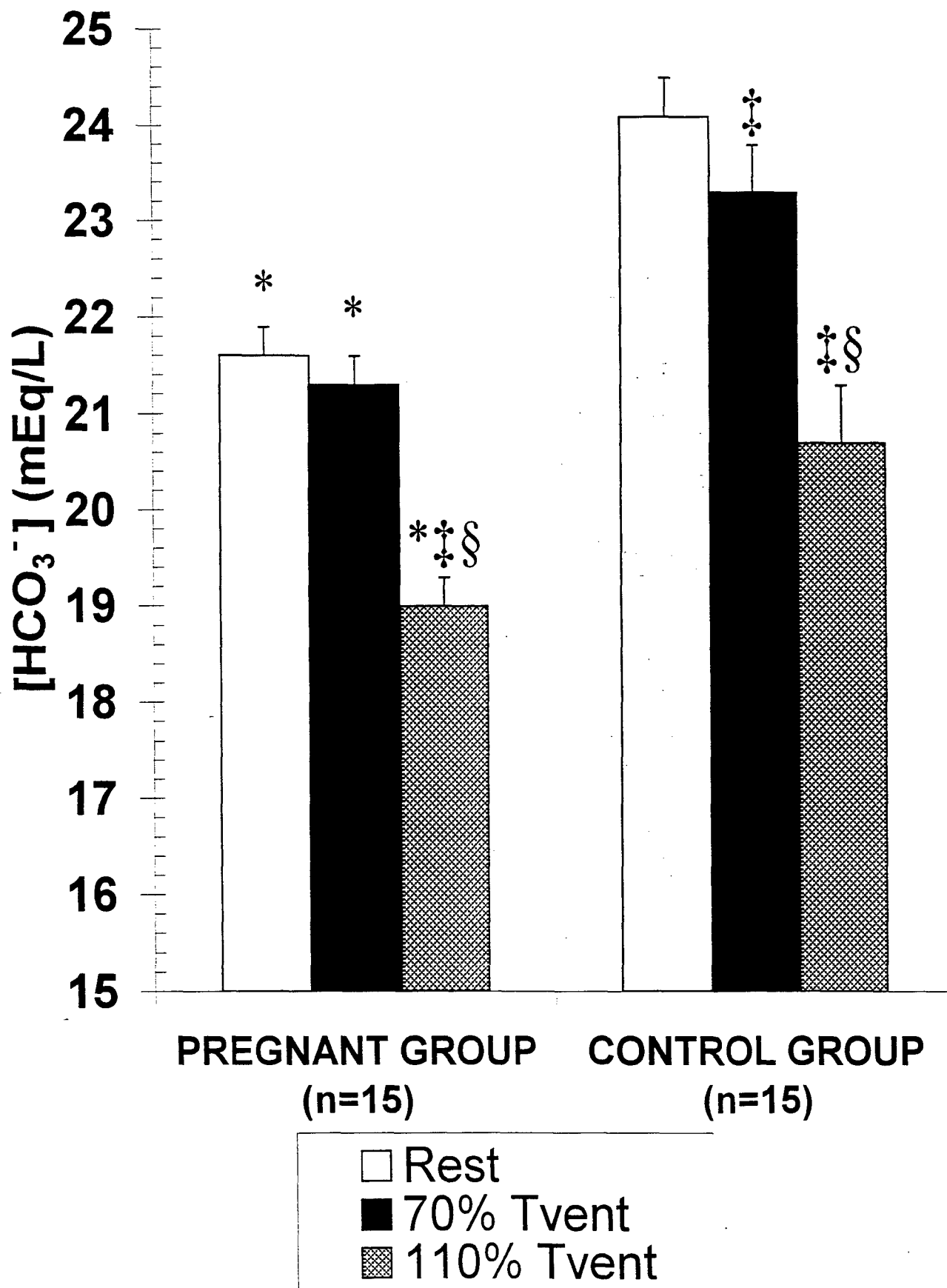


FIGURE 1 - B

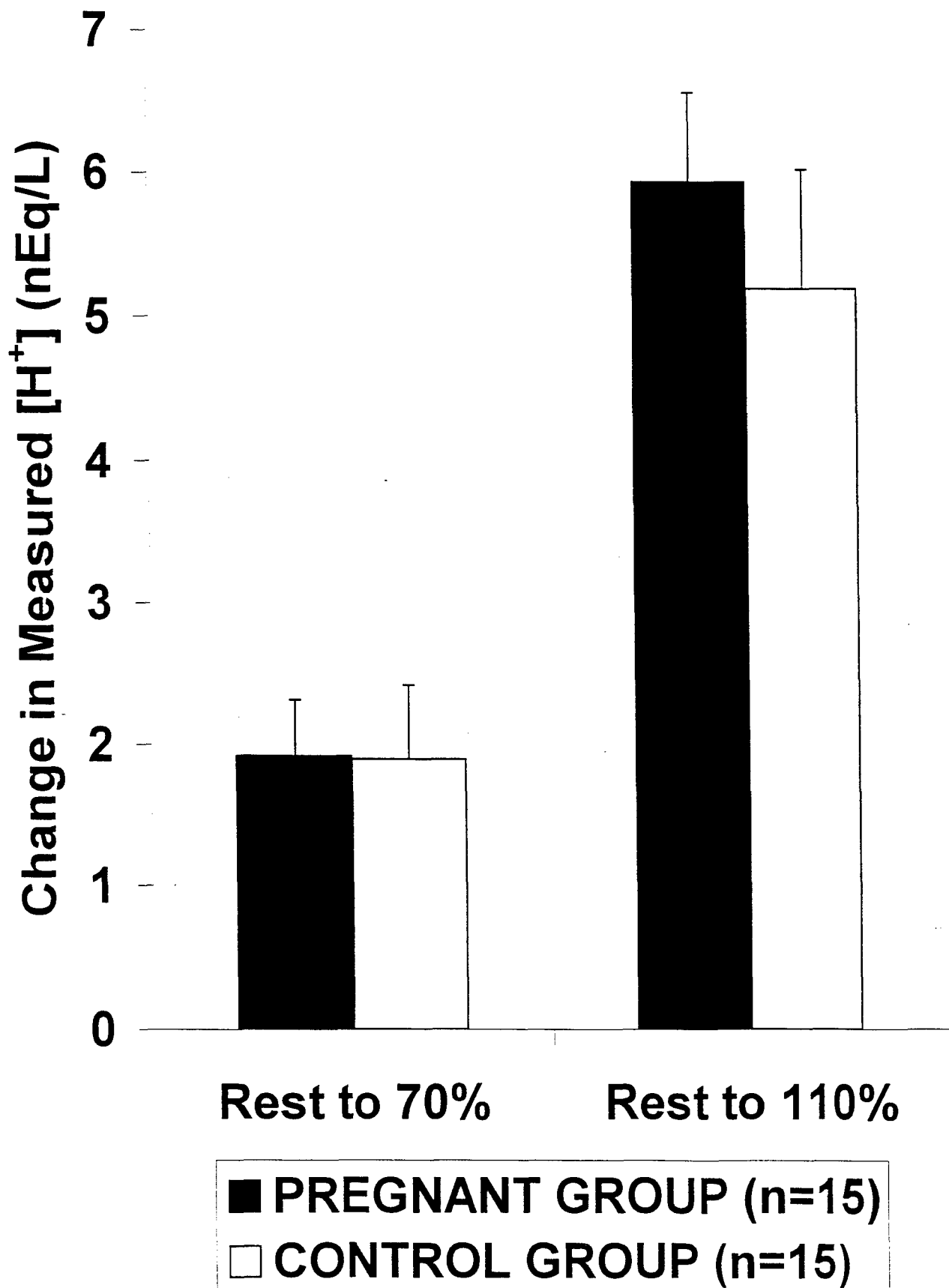


FIGURE 2

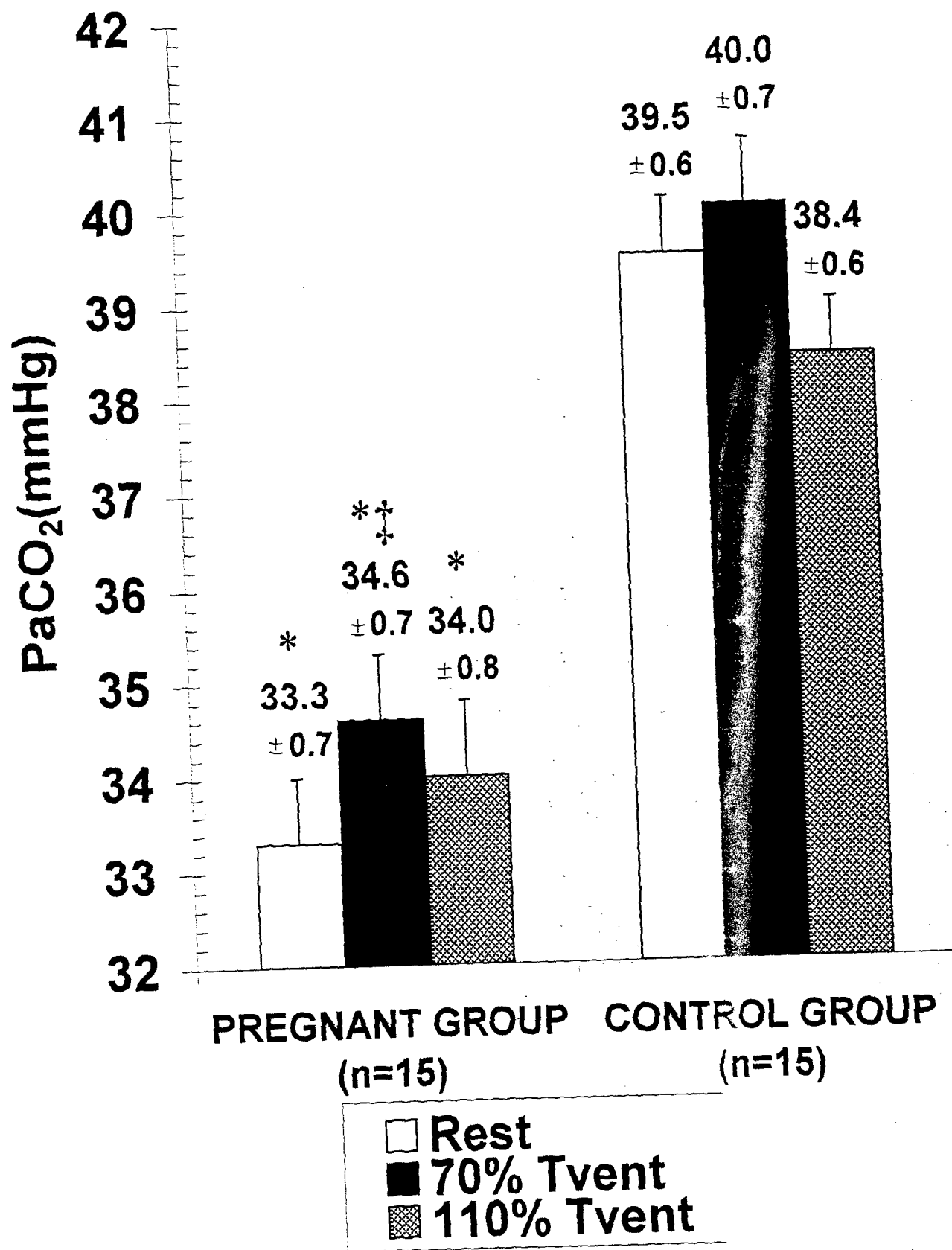


FIGURE 3

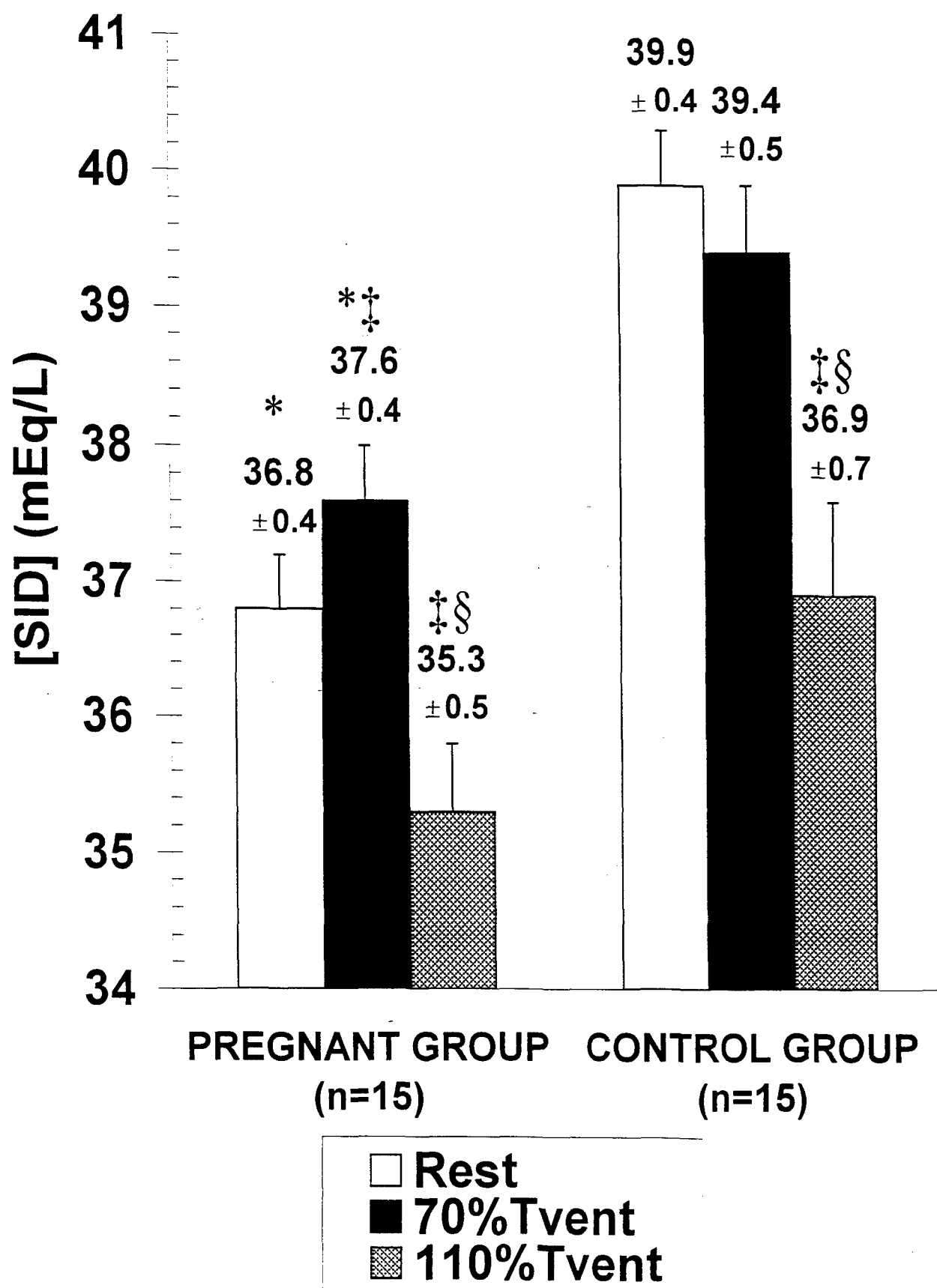


FIGURE 4

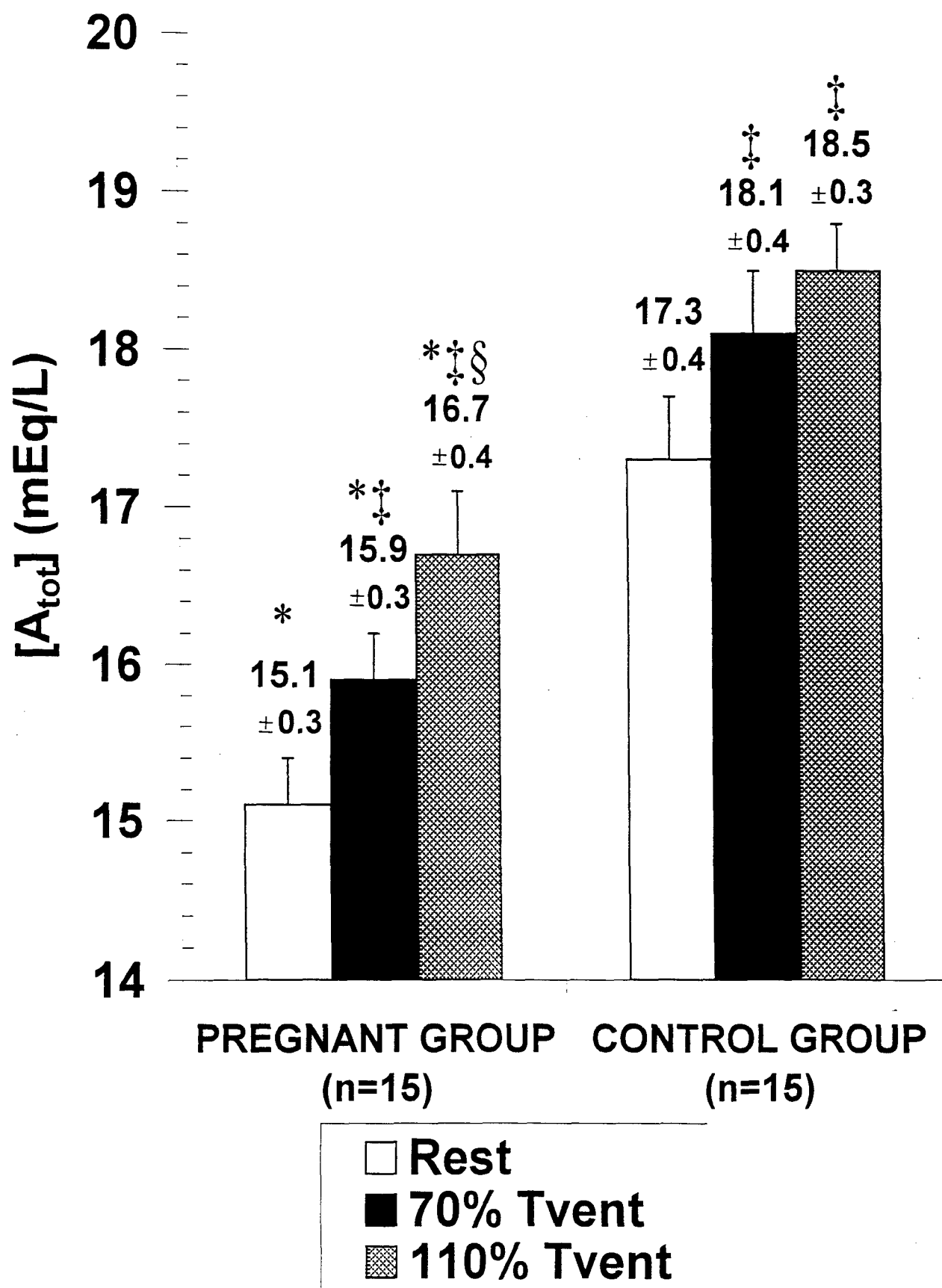


FIGURE 5

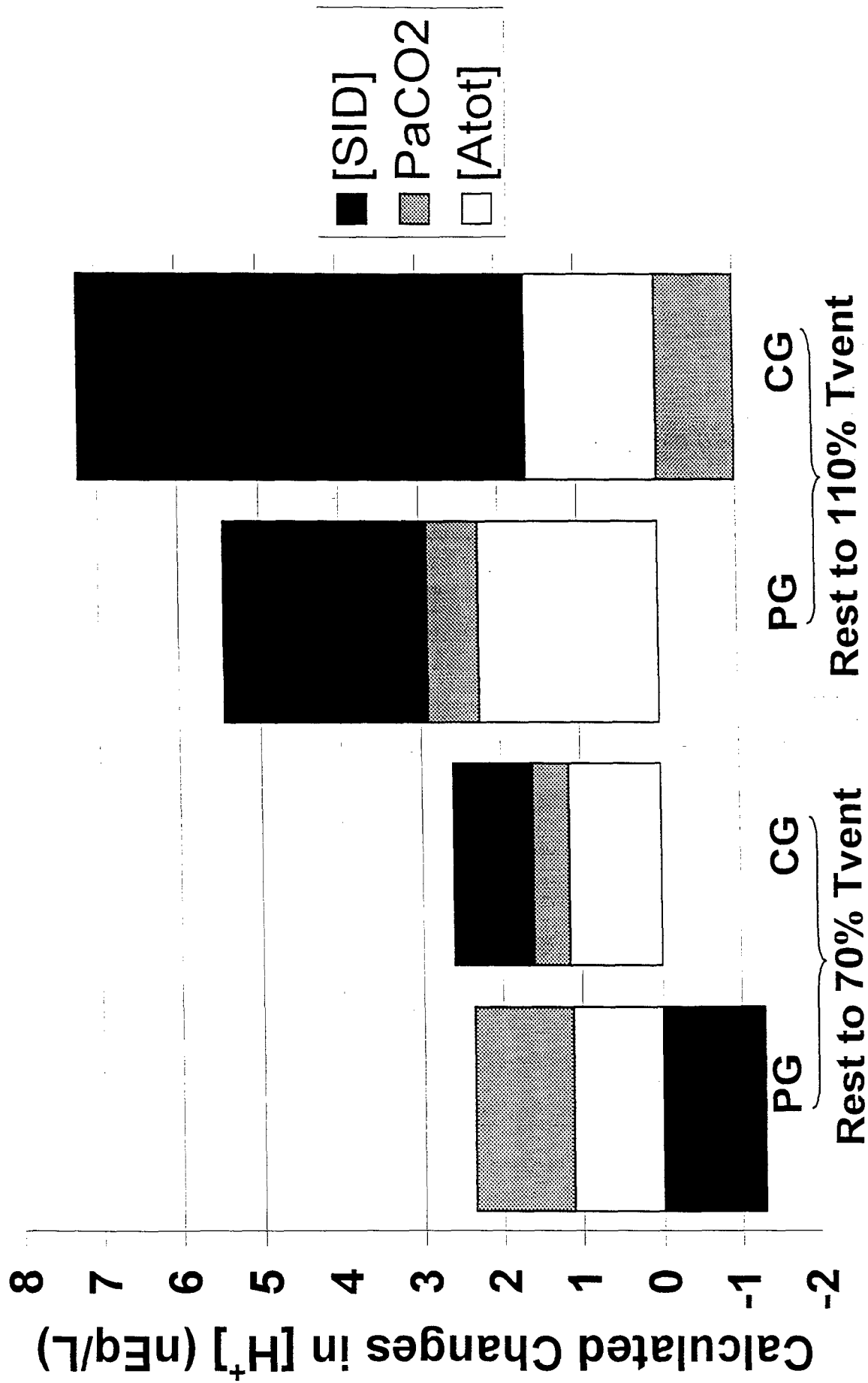


FIGURE 6

Appendix D

**Manuscript from Study #3 entitled
"Control of Ventilation in Healthy Women : Effects of Plasma
Osmolality [SID] and Circulating Hormones"
(in review, *American Journal of Physiology*).**



SCHOOL OF PHYSICAL AND HEALTH EDUCATION

Queen's University
Kingston, Canada
K7L 3N6

October 28th, 1999

Dr. J. E. Hall,
American Physiological Society,
American Journal of Physiology
(Regulatory, Integrative and Comparative Physiology)
9650 Rockville Pike,
Bethesda, Maryland
20814-3991
USA

Dear Dr. Hall,

Please find enclosed the original and three (3) copies of our manuscript entitled "Control of Ventilation in Healthy Women: Effects of Plasma Osmolality, [SID] and Circulating Hormones", which we are submitting for publication in the American Journal of Physiology. Please also find enclosed ~~a computer disk copy~~, laser prints of figures (2 copies) on camera ready paper, the mandatory submission form and a list of suggested reviewers. Also, four (4) copies of a closely related review article which provides a detailed rationale for the present study are enclosed. Finally, four (4) copies of the abstract are enclosed for a parallel study on acid-base regulation in human pregnancy which is currently in press in the *Journal of Applied Physiology*, (Volume 86, January issue).

Thank you in advance for your attention and we look forward to receiving the review of this manuscript.

Yours sincerely,

Larry A. Wolfe, Ph.D.
Corresponding Author

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CONTROL OF VENTILATION IN HEALTHY WOMEN: EFFECTS OF PLASMA
OSMOLALITY, [SID] AND CIRCULATING HORMONES

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Natural Sciences and Engineering Research Council of Canada (N.S.E.R.C.).

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Short title: Chemical control of ventilation

ABSTRACT

This study tested the hypothesis that plasma osmolality, the strong ion difference ([SID]) and circulating hormones modulate respiratory sensitivity at rest and during exercise in healthy women. Subjects were physically active pregnant women (PG, n=22, gestational age 37.0 ± 0.2 wk) and a matched group of nonpregnant subjects (CG, n=17) in varying stages of the menstrual cycle. Arterialized blood gases, hydrogen ion concentration ($[H^+]$), plasma osmolality, [SID] and circulating levels of progesterone, angiotensin II (ANG II) and arginine vasopressin (AVP) were measured at rest and during upright cycling at work rates corresponding to 70% and 110% of the ventilatory threshold (T_{VENT}). Osmolality increased significantly in response to exercise in both groups and values were significantly lower in the PG vs. CG at all measurement times. [SID] decreased significantly in both groups in response to the 110% T_{VENT} work rate and was significantly lower in the PG vs. CG at rest and 70% T_{VENT} . Pooling of data from the two groups revealed significant correlations between measures of respiratory sensitivity ($PaCO_2$, $\dot{V}_E/\dot{V}CO_2$) at rest and during both exercise conditions for plasma osmolality, [SID] and progesterone. The results support the hypothesis that, in concert with the effects of progesterone, plasma osmolality, and [SID] are important factors in the modulation of respiratory sensitivity in healthy women. Additional study of human subjects is recommended to clarify the roles of ANG II and AVP in the chemical control of ventilation.

Key words: respiratory sensitivity, strong ion difference, progesterone, angiotensin II, arginine vasopressin

INTRODUCTION

Human pregnancy is accompanied by striking changes in both the chemical control of ventilation and acid-base balance. These effects are established during the first trimester and are observed both at rest and during standard submaximal exercise (34). Specific changes include increases in minute ventilation ($\dot{V}_E$), tidal volume (V_T), alveolar ventilation ($\dot{V}_A$), the ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$), inspiratory flow rate (V_T/T_i) and alveolar oxygen tension (P_{AO_2}) as well as reductions in alveolar and arterial carbon dioxide tensions ($P_{ET}CO_2$, $PaCO_2$) and plasma hydrogen ion concentration ($[H^+]$) (9, 26, 33, 34). Recent studies from this laboratory have established, using Stewart's physicochemical approach (30), that the lower plasma $[H^+]$ is the result of substantial reductions in $PaCO_2$ and total weak acid concentration ($[A_{tot}]$) that are partly offset by the effects of a lower strong ion difference ($[SID]$) (20, 14).

Previous studies have also shown that the augmented respiratory sensitivity in pregnancy is due, at least in part, to increased circulating progesterone levels and an estrogen-mediated increase in hypothalamic progesterone receptors (3, 6). Thus, there appears to be an increase in sensitivity to carbon dioxide that is mediated by central neural mechanisms (3). However, evidence also exists for increased sensitivity to hypoxia and involvement of peripheral sites of action in the response to estrogen and progesterone (13, 31).

Recently, Jennings (17, 18, 19) proposed an innovative model to explain the interactive roles of humoral and chemical factors in the control of pulmonary ventilation. Jennings' model is based on the "alphastat" hypothesis which postulates that both $\dot{V}_E$

and $[H^+]$ are controlled in order to maintain the charge state and conformation of critical proteins in the body (29). Other important elements of this model include the concept that the central chemoreceptors regulate $\dot{V}_A$ and $PaCO_2$ in relation to CSF [SID] (17, 18, 19) and that reduced plasma osmolality (1, 2) and increased circulating levels of angiotensin II (ANG II) (2, 24, 25) stimulate ventilation. On the other hand, increased circulating levels of arginine vasopressin (AVP) are thought to modulate ventilation by inhibiting both the brain and systemic renin-angiotensin systems (32). Finally, it is postulated that the central neurophysiological effects of plasma osmolality, ANG II and AVP are expressed via circumventricular organs (CVOs) which do not have a blood-brain barrier and which have receptors sensitive to osmolality, ANG II and many other hormones.

In association with augmented circulating levels of progesterone and estrogen, there are also pregnancy-induced reductions in plasma [SID] (14, 20), osmolality (14) and AVP (27) as well as increased circulating levels of ANG II (27). As discussed in detail in a recent review from this laboratory (34), pregnancy-induced changes in these variables are in directions that would stimulate breathing in accordance with Jennings' hypothesis. Therefore, it is logical to postulate that these factors, in concert with the effects of estrogen and progesterone, are responsible for pregnancy-induced increases in respiratory sensitivity.

The overall objective of this study was to employ pregnancy as a human model to test Jennings' hypothesis that changes in plasma osmolality, [SID], and circulating hormones (ANG II, AVP) are important modulators of respiratory sensitivity. It was hypothesized that these variables would be significantly correlated both at rest and during exercise with

measures of respiratory sensitivity to carbon dioxide in healthy women, both in late gestation and at various stages of the menstrual cycle in the nonpregnant state. It was assumed that plasma levels of [SID] reflect CSF[SID] under steady-state conditions. The results also provided new information on renal and endocrine responses to exercise of different intensities in late gestation.

METHODS

Subjects

Subjects were healthy, nonsmoking, physically active pregnant women (pregnant group (n=22), PG) and healthy nonpregnant women (control group (n=17), CG) with similar physical and demographic characteristics. Prospective subjects were recruited from local prenatal fitness classes and from the general population, via media advertisements, posters, flyers, and contact with local obstetricians. Medical clearance for pregnant subjects was obtained from the physician or midwife monitoring their pregnancy using a standard form (7). Nonpregnant subjects completed the revised Physical Activity Readiness Questionnaire.

Written informed consent was obtained from all subjects before entry into the study. The study protocol, described below, and consent form were approved by the Research Ethics Board, Faculty of Medicine, Queen's University and the U.S. Army Medical Research and Materiel Command, Human Subjects Protection Branch.

Basic physical measurements included body height, body mass (BM) and resting blood pressure. Body mass index (BMI) was calculated as body mass (kg)/body height² (m²). The PG and CG were matched for mean age, body height, pre-pregnant body mass,

parity and aerobic fitness. Members of the PG were tested between 34 and 38 weeks of their gestation. Subjects in the CG were not using oral contraceptives.

Exercise Testing Protocols

Subjects performed two exercise tests on a Sensor Medics (Model 800S) constant work rate cycle ergometer at least one day apart. Subjects consumed a standard meal (350 kcal, 40% carbohydrate, 40% fat, 20% protein) 1-2 h prior to both tests and avoided strenuous physical activity and caffeine on the day of testing. The first test was used to determine the ventilatory threshold (T_{VENT}) and to assess aerobic working capacity. The protocol involved five minutes of resting data collection and a four min warm-up at 20 watts, followed by an increase in work rate of 20 watt/min until a heart rate of 170 beats/min was reached (14). Respiratory responses were measured on a breath-by-breath basis using a computerized system (First Breath Inc.) that incorporates a respiratory mass spectrometer (Perkin-Elmer, MGA 1100) with a volume turbine (VMM-1100) as described by Hughson *et al.* (16). Breath-by-breath alveolar gas exchange was calculated using the algorithm of Beaver *et al.* (4) and T_{VENT} was identified using the V-slope method (5). Heart rate (HR) was monitored with both a Polar Vantage monitor and a Marquette Max-1 electrocardiograph. Oxygen pulse (oxygen uptake ($\dot{V}O_2$)/heart rate (HR)) at a heart rate of 170 beats/min was calculated as an index of aerobic working capacity (33).

The second exercise test involved a 10 min resting data collection, followed by a three min warm-up at 0 watts and a ramp increase in work rate, over a 30-second time period, to a work rate corresponding to 70% or 110% of T_{VENT} . Both work rates were

continued for seven minutes after achievement of the prescribed work rate. Subjects rested for 20 minutes between levels. Prior to this test, an indwelling catheter was inserted into a dorsal hand vein situated as far from the thumb as possible. The hand and lower arm were soaked in a warm water bath prior to insertion of the catheter, and then placed in a plexiglass heating box (45 degrees C) to promote vasodilation. Arterialized blood samples were then collected at rest and during the sixth minute of exercise at 70% or 110% of T_{VENT} .

Blood samples for the determination of oxygen tension, $PaCO_2$ and $[H^+]$ were collected in a syringe containing lyophilized heparin and analyzed immediately using a Radiometer ABL 30 acid-base analyzer at a standard temperature of 37°C. Correction of blood gas values for changes in temperature were not necessary, since tympanic temperature measurements confirmed no significant deviation from 37°C with pregnancy or exercise using the present protocol. Quality control checks using four control liquids were done on all testing days. The remaining blood was then centrifuged for 10 minutes at 2500 rpm and frozen at -80 °C for later analysis, as described below.

Plasma concentrations of sodium ($[Na^+]$), potassium ($[K^+]$), calcium ($[Ca^{2+}]$) and chloride ($[Cl^-]$) were analyzed using ion-selective electrodes. Plasma osmolality was determined using the freezing point depression technique (1). ANG II was measured using 125I-labelled angiotensin II as described by Walker and Jennings (32). AVP and progesterone were also measured by radioimmunoassay (32, 33). Plasma lactate concentration $[La^-]$ was determined using an automated analyzer (Yellow Springs Instruments, Model 2300). The analyzer was calibrated before analysis using five and 15 mmol/L standards and at regular intervals during the analysis. The test-retest reliability

of $[La^-]$ measurements was described in an earlier publication from this laboratory (33).

$[SID]$ was then calculated as: $([Na^+] + [K^+] + 2 [Ca^{2+}]) - ([Cl^-] + [La^-])$.

Statistical Analyses

Physical characteristics, $\dot{V}O_2$ at T_{VENT} and oxygen pulse at 170 beats/min were compared between groups using Student's *t*-statistics for independent samples. Data at rest and during exercise at 70% and 110% T_{VENT} were compared within and between subjects using a two-way ANOVA (groups vs. rest/exercise level) with repeated measures on the second factor. When a significant between group main effect was observed, separate independent Student *t*-statistics were used to identify significant differences between group means at rest, at 70% T_{VENT} and at 110% T_{VENT} . When a significant within-subjects main effect or group x contribution interaction was observed, paired Student *t*-statistics were also used to detect significant differences between rest, 70% T_{VENT} and 110% T_{VENT} within each group. Since comparisons between groups and across variables were planned and since the number of comparisons was small in each case, the critical alpha for significance was maintained at $p < 0.05$ (21). Results were identified as trends when $0.05 < p < 0.10$.

To investigate associations between measures of respiratory sensitivity and factors postulated to affect respiratory sensitivity, separate Pearson product-moment correlation matrices were constructed for $PaCO_2$ and $\dot{V}_E/\dot{V}CO_2$ with plasma osmolality, $[SID]$, progesterone, ANG II and AVP at rest, 70% T_{VENT} and 110% T_{VENT} , respectively, within both groups and for pooled results from both groups. Data from the PG and CG were pooled to provide a wide range of values for correlations. This was followed by

stepwise linear regression for pooled results to analyze the contribution of each independent variable to respiratory control. Results were considered significant at $p < 0.05$.

RESULTS

Subjects in the PG and CG were aged 30.0 ± 0.8 y and 27.1 ± 1.4 y, respectively. Mean gestational age of the PG was 37.0 ± 0.2 wk. There were no significant between group differences in age, body height or parity (Table 1). As expected, BM and BMI of the PG was significantly greater than the CG's at the time of testing. However, the PG's pre-pregnancy BM and BMI were closely matched to those of the CG. There were also no significant differences between the groups in $\dot{V}O_2$ at T_{VENT} or O_2 pulse at 170 beats/min indicating the two groups were at a similar level of aerobic fitness.

Significant increases in $\dot{V}_E$ were observed in both groups from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} . The $\dot{V}_E$ of the PG was significantly higher than that of the CG at all three measurement times (Figure 1). $\dot{V}_E/\dot{V}CO_2$ decreased significantly from rest to 70% T_{VENT} and increased significantly from 70% T_{VENT} to 110% T_{VENT} in both groups. $\dot{V}_E/\dot{V}CO_2$ exhibited a trend for higher values in the PG vs. CG at rest and was significantly higher in the PG vs. CG at both work rates (Figure 2). $[H^+]$ increased significantly from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} in both groups. The $[H^+]$ of the PG was significantly lower than that of the CG at all measurement times (Figure 3). $PaCO_2$ increased significantly from rest to 70% T_{VENT} in the PG and decreased significantly from 70% T_{VENT} to 110% T_{VENT} in the CG. $PaCO_2$ in the PG was significantly lower at all three measurement times vs. the CG (Figure 4).

Osmolality increased significantly from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} in both groups. Osmolality was significantly lower in the PG vs. CG at rest and at both work rates (Figure 5). [SID] increased significantly in the PG from rest to 70% T_{VENT} and decreased significantly in both groups from rest and 70% T_{VENT} to 110% T_{VENT} . A significantly lower [SID] was observed in the PG vs. CG at rest and 70% T_{VENT} with a trend for a lower value in the PG vs. CG at 110% T_{VENT} (Figure 6).

Progesterone levels significantly increased in both groups from rest to 110% T_{VENT} and in the PG from 70% T_{VENT} to 110% T_{VENT} . Progesterone levels were significantly higher in the PG vs. CG (Figure 7). [ANG II] increased significantly in the CG from rest to 110% T_{VENT} , while a trend was present in the PG for a decrease in concentration. There was a significant group $\times$ time interaction for [ANG II]. [ANG II] was significantly higher in the PG vs. CG at rest and a trend was present for higher values in the PG vs. CG at 70% T_{VENT} (Figure 8). [AVP] increased significantly from rest to 110% in the CG. [AVP] was significantly lower in the PG vs. CG at rest and both work rates (Figure 9).

PaCO_2 was significantly correlated with [SID], osmolality and progesterone levels at rest and at both work rates when data from both groups were pooled (Table 2). PaCO_2 was significantly correlated with [SID] at rest in the CG and with [SID] and [AVP] at 110% T_{VENT} within the CG. $\dot{V}_E/\dot{V}\text{CO}_2$ was significantly correlated with [SID], osmolality and progesterone concentration at both work rates when data from both groups were pooled (Table 3). $\dot{V}_E/\dot{V}\text{CO}_2$ was significantly correlated with [SID] and progesterone at 70% T_{VENT} within the PG and with progesterone at 110% T_{VENT} within the PG.

Stepwise linear regression for PaCO_2 with plasma osmolality, [SID], progesterone, ANG II and AVP as the independent variables entered progesterone at rest 70% and 110% T_{VENT} , while also including AVP at 70% T_{VENT} . At rest progesterone accounted for 46% of the variability of PaCO_2 , 67% at 70% T_{VENT} (with the addition of AVP improving this to 76%), and 39% at 110% T_{VENT} . Stepwise linear regression for $\dot{V}_E/\dot{V}\text{CO}_2$ with plasma osmolality, [SID], progesterone, ANG II and AVP as the independent variables, entered progesterone at 70% and 110% T_{VENT} . Progesterone levels accounted for 73% of the variability of $\dot{V}_E/\dot{V}\text{CO}_2$ at 70% T_{VENT} and 62% at 110% T_{VENT} .

DISCUSSION

This study employed human pregnancy as a human model to test Jennings' hypothesis that osmolality, [SID] and ANG II and AVP are important contributors to the chemical control of ventilation (17, 18, 19). Both at rest and during exercise, pregnancy-induced changes in these variables were in directions (i.e. reduced plasma osmolality, [SID], [AVP] and increased [ANG II]) that would be expected to increase respiratory sensitivity in addition to the well-documented effects of augmented circulating levels of progesterone and estrogen. Statistical analysis of pooled data from pregnant and nonpregnant subjects identified significant correlations between measures of respiratory sensitivity (i.e. PaCO_2 , $\dot{V}_E/\dot{V}\text{CO}_2$) at rest (PaCO_2 only) and during exercise below and above T_{VENT} with plasma progesterone, osmolality and [SID]. This supports the hypothesis that plasma osmolality and [SID] are involved in ventilatory control. Reasons for the lack of significant correlations of plasma ANG II and AVP with measures of respiratory sensitivity are discussed below.

It is well established that the increased respiratory sensitivity in pregnancy is associated with a gradual increase in circulating progesterone levels with advancing gestational age (33, 34). Since progesterone receptors in the medulla have not been identified, this effect has been attributed to an estrogen-mediated increase in hypothalamic progesterone receptors (3,6) and disinhibition of central chemoreceptors via the hypothalamus (34). Evidence also exists for a peripheral effect of progesterone, although the mechanism remains to be clarified (31).

As described in a recent review from this laboratory (34), increases in circulating progesterone levels during pregnancy and those for pulmonary ventilation follow a different time course. In this regard, a substantial increase in pulmonary ventilation is observed as early as 7-8 wks gestation (8, 28) whereas placental progesterone output is only beginning to compensate for regression of the corpus luteum at this time (34). Therefore, factors other than progesterone need to be considered to explain increases in respiratory sensitivity.

In addition to small increases in progesterone in early pregnancy, there are significant effects on plasma osmolality and circulating ANG II and AVP levels. In this regard, the findings of Duvekot *et al.* (11) support the hypothesis that the vessel-dilating effects of gestational hormones in early pregnancy leads to a reduction in systemic vascular tone, reduced mean arterial pressure and activation of "volume restoring mechanisms." This includes activation of the renin-angiotensin system, retention of sodium and water, an increase in plasma volume and reduced plasma osmolality (11, 22, 27). As well, the osmotic threshold for AVP release is reduced by gestational hormones in early pregnancy, thus contributing to the increase in blood volume. However, the

metabolic clearance rate of AVP is increased as well (22), resulting in lower plasma AVP levels (10, 27). Although data are not available for studies in early pregnancy, a reduction in plasma [SID] would also be expected based on available information (14, 20, 34).

A role for plasma osmolality in the control of ventilation was hypothesized after experiments using dogs on high and low NaCl diets found that changes in plasma osmolality were positively correlated with changes in PaCO_2 (1). Osmolality is postulated to influence ventilation through the circumventricular organs of the brain which have receptors sensitive to osmolality and possibly through peripheral osmoreceptors as well (1, 18). The lowered osmolality of pregnancy would thus be expected to stimulate ventilation. Indeed, in the present study osmolality was positively correlated to PaCO_2 at rest and during exercise.

Recently, Jennings (17, 18, 19) also postulated that [SID] rather than $[\text{H}^+]$ is the stimulus to chemoreceptors involved in the control of ventilation. Based on the law of electroneutrality, $[\text{HCO}_3^-]$ can be used as an index of [SID] in studies which do not measure [SID] and Jennings has used this relationship to reanalyze the data of other researchers (12, 23). Although earlier studies had interpreted $[\text{H}^+]$ as the stimulus for peripheral (12) and central chemoreceptors (23) to adjust ventilation, the stimulus could equally well have been [SID]. Jennings has also noted in his own experiments on dogs that while CSF[SID] was an excellent predictor of ventilatory regulation of PaCO_2 , $\text{CSF[H}^+]$ was not (17, 19). Pregnancy is characterized by augmented pulmonary ventilation, but since $[\text{H}^+]$ is lower relative to the nonpregnant state, it is not the likely stimulus. However, [SID] which is reduced in pregnancy would appear a likely

candidate. Decreasing [SID] during exercise of increasing intensity also suggests that this variable contributes to exercise hyperpnea. The strong correlations in the present study between measures of respiratory sensitivity and plasma [SID] during rest and exercise support the hypothesis that [SID] is involved in the control of ventilation.

A stimulatory role for ANG II in the control of ventilation has been demonstrated in animal preparations (24, 25, 32), while AVP appears to modulate ventilation by inhibiting a brain renin-angiotensin system (32). It is postulated that the effects of ANG II and AVP are mediated via the CVOs of the brain which possess receptors for these hormones (18,19). We did not find significant correlations between plasma ANG II and AVP levels and indexes of respiratory sensitivity in our subjects. The reason for the poor correlation with plasma ANG II levels may be that ventilatory responses to ANG II are dependent on the brain renin-angiotensin system as opposed to the systemic renin-angiotensin system. This point has been illustrated in studies that have found that while ANG II receptor blockade abolishes ventilatory stimulation observed in response to hypoxia (15) and AVP receptor blockade (32), thus demonstrating the stimulatory affect that ANG II has on ventilation, plasma ANG II levels had actually decreased (15) or remained unchanged relative to control (32). It was thus, concluded that the stimulation of ventilation by ANG II was accomplished through activation of the brain rather than systemic renin-angiotensin system (15, 32).

Detection of associations between plasma AVP and indexes of respiratory sensitivity may be difficult since AVP has an indirect effect on ventilation through inhibition of ANG II formation. However, despite the lack of significant correlations between AVP and indexes of respiratory sensitivity in this study, stepwise linear

regression did reveal that AVP levels were associated with changes in PaCO_2 at 70% T_{VENT} for the pooled data set. The lower plasma AVP levels in the PG would be expected to result, via the CVOs, in a disinhibition of the brain renin-angiotensin system leading to subsequent stimulation of ventilation by higher ANG II levels. While this study was conducted in late gestation, it may be useful to conduct serial studies during early pregnancy in order to detect effects of ANG II and AVP on ventilation when progesterone levels are low and to compare the time course of changes in respiratory sensitivity and its postulated chemical determinants.

The stepwise linear regression for the dependent measures of respiratory sensitivity with the independent variables of interest only brought in progesterone, while excluding both osmolality and [SID]. This was due to high correlations between progesterone levels and both [SID] and osmolality. The fact that osmolality and [SID] were not included in the linear regression suggests that their effect on respiratory sensitivity is similar to that of progesterone. Plasma ANG II was likely not included in the stepwise linear regression since the brain renin-angiotensin is likely the important system as opposed to the systemic. Since AVP is postulated to indirectly affect ventilation by inhibiting the formation of ANG II, its mechanism of action is clearly different than that of progesterone and explains why it was able to be included in the linear regression for P_aCO_2 at 70% T_{VENT} .

This study supports the hypothesis that plasma osmolality and [SID] are involved in the control of ventilation. Based on plasma measurements, a role for ANG II in ventilatory control could not be detected. However, as discussed, this may be the result of ventilatory responses to ANG II being contingent on the brain rather than systemic

renin-angiotensin system. Alternatively, effects of AII and AVP may be more easily identified in early pregnancy when progesterone levels are relatively low. Further study is recommended to clarify the role of ANG II and AVP on ventilation in humans. These studies should examine the time course of changes in respiratory sensitivity and its postulated humoral determinants in early pregnancy.

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Table 1. Physical Characteristics of Subjects

VARIABLE	PREGNANT GROUP (n=22)	CONTROL GROUP (n=17)
Age (years)	30.0 $\pm$ 0.8	27.1 $\pm$ 1.4
Gestational Age (weeks)	37.0 $\pm$ 0.2	n/a
Height (cm)	163 $\pm$ 2	165 $\pm$ 1
Body Mass (kg)	75.8 $\pm$ 2.0*	61.4 $\pm$ 1.7
Body Mass Index (kg/m ²)	28.4 $\pm$ 0.6*	22.5 $\pm$ 0.5
Pre-Pregnant Body Mass (kg)	62.4 $\pm$ 2.0	n/a
Pre-Pregnant Body Mass Index	23.3 $\pm$ 0.6	n/a
Parity	0.5 $\pm$ 0.2	0.4 $\pm$ 0.2
$\dot{V}O_2$ @ T _{VENT} (L/min)	1.67 $\pm$ 0.06	1.80 $\pm$ 0.04
O ₂ Pulse @ 170 beats/min (ml/beat)	12.1 $\pm$ 0.5	13.0 $\pm$ 0.4

Values are means $\pm$ SE.

*Significant difference between groups ($p < 0.05$)

Table 2. Correlations with $P_a\text{CO}_2$.**REST**

	$P_a\text{CO}_2$ (Pooled)	$P_a\text{CO}_2$ (PG)	$P_a\text{CO}_2$ (NP)
[SID]	0.689*	0.247	0.507*
Osmolality	0.489*	-0.405	-0.046
Progesterone	-0.735*	-0.374	-0.239
Angiotensin II	-0.263	0.093	0.292
Arginine Vasopressin	0.251	0.297	-0.313

70% T_{VENT}

	$P_a\text{CO}_2$ (Pooled)	$P_a\text{CO}_2$ (PG)	$P_a\text{CO}_2$ (NP)
[SID]	0.545*	0.393	0.295
Osmolality	0.580*	-0.219	0.174
Progesterone	-0.758*	-0.302	0.126
Angiotensin II	-0.374	-0.017	-0.447
Arginine Vasopressin	0.157	-0.050	-0.328

110% T_{vent}

	$P_a\text{CO}_2$ (Pooled)	$P_a\text{CO}_2$ (PG)	$P_a\text{CO}_2$ (NP)
[SID]	0.390*	0.154	0.491*
Osmolality	0.465*	-0.066	-0.155
Progesterone	-0.659*	-0.223	0.092
Angiotensin II	0.038	0.274	-0.142
Arginine Vasopressin	0.158	0.518	-0.591*

*Correlation is significant at the 0.05 level

Table 3. Correlations with $\dot{V}_E/\dot{V}CO_2$.**REST**

	$\dot{V}_E/\dot{V}CO_2$ (Pooled)	$\dot{V}_E/\dot{V}CO_2$ (PG)	$\dot{V}_E/\dot{V}CO_2$ (NP)
[SID]	-0.227	-0.165	0.057
Osmolality	-0.297	-0.020	-0.227
Progesterone	0.282	0.165	-0.205
Angiotensin II	0.299	0.356	-0.159
AVP	-0.017	0.219	0.328

70% T_{VENT}

	$\dot{V}_E/\dot{V}CO_2$ (Pooled)	$\dot{V}_E/\dot{V}CO_2$ (PG)	$\dot{V}_E/\dot{V}CO_2$ (NP)
[SID]	-0.555*	-0.550*	-0.068
Osmolality	-0.594*	0.192	-0.420
Progesterone	0.780*	0.503*	-0.012
Angiotensin II	0.124	-0.257	-0.090
AVP	-0.291	-0.006	0.219

110% T_{vent}

	$\dot{V}_E/\dot{V}CO_2$ (Pooled)	$\dot{V}_E/\dot{V}CO_2$ (PG)	$\dot{V}_E/\dot{V}CO_2$ (NP)
[SID]	-0.418*	-0.382	-0.316
Osmolality	-0.432*	0.130	-0.009
Progesterone	0.734*	0.527*	0.117
Angiotensin II	-0.194	-0.534	0.226
AVP	-0.359	-0.090	-0.130

*Correlation is significant at the 0.05 level

LIST OF FIGURES

1. $\dot{V}_E$ at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group. $\dot{V}_E$, minute ventilation.
2. Ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}\text{CO}_2$) at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group.
3. $[\text{H}^+]$ at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group. H^+ , hydrogen ion concentration
4. Arterialized P_aCO_2 at rest and two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group. P_aCO_2 , carbon dioxide tension.
5. Plasma osmolality at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group.
6. Calculated plasma $[\text{SID}]$ at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group. SID , strong ion difference.
7. Plasma [progesterone] at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group.

8. Plasma [ANG II] at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group. ANG II, angiotensin II.
9. Plasma [AVP] at rest and at two work rates. * Significant difference ($p < 0.05$) between pregnant group and control group. AVP, arginine vasopressin.

Figure 1

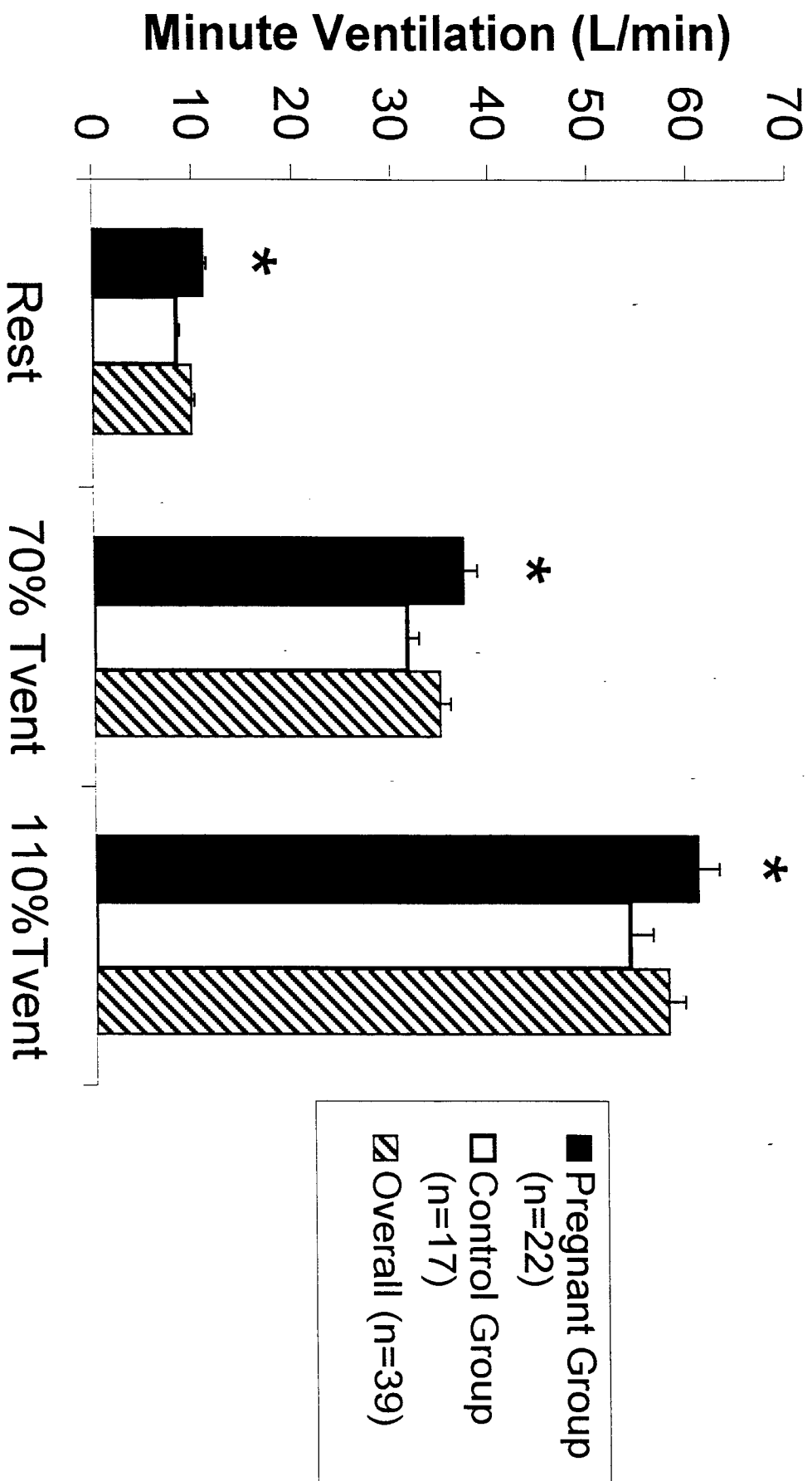


Figure 2

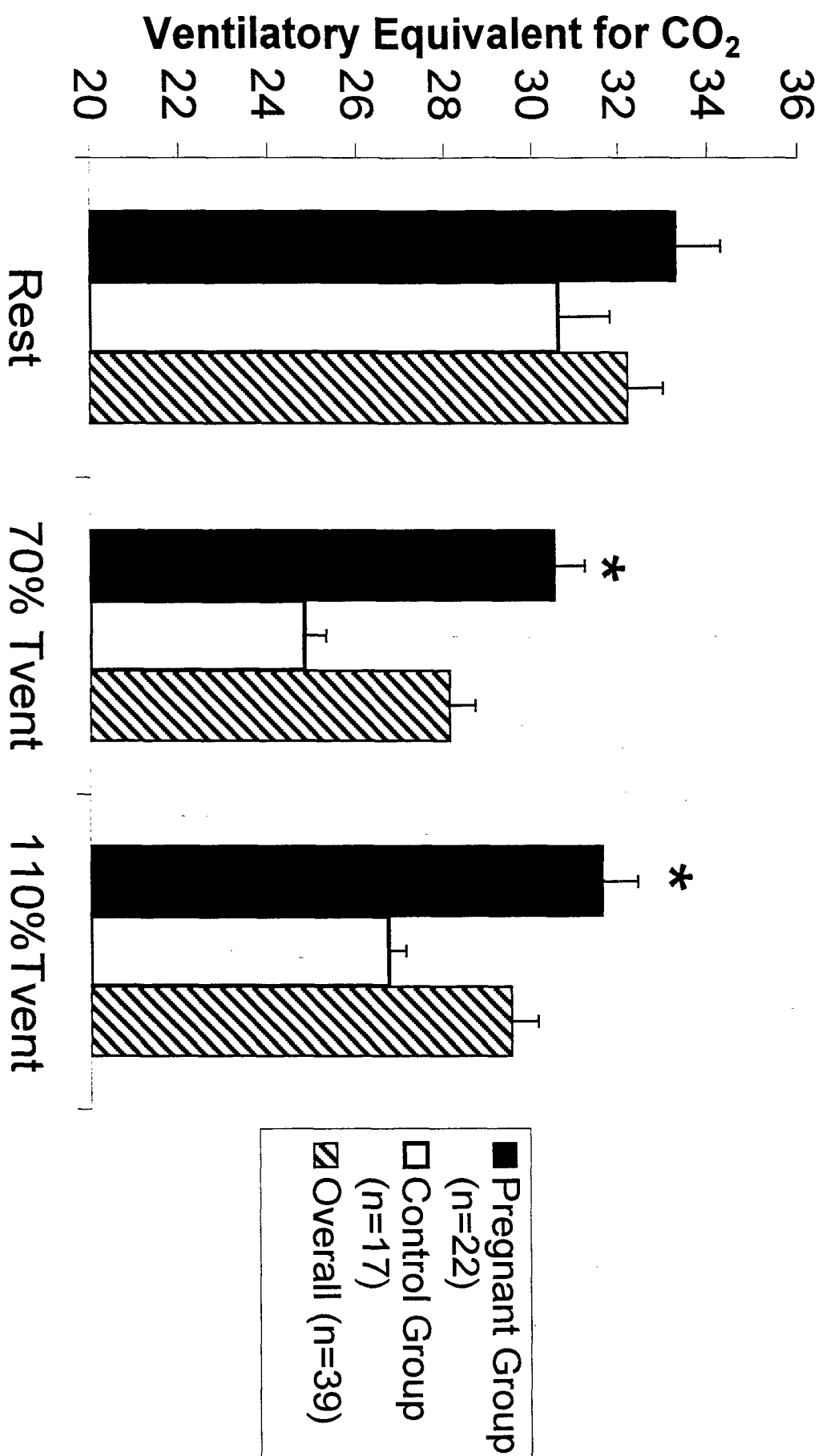


Figure 3

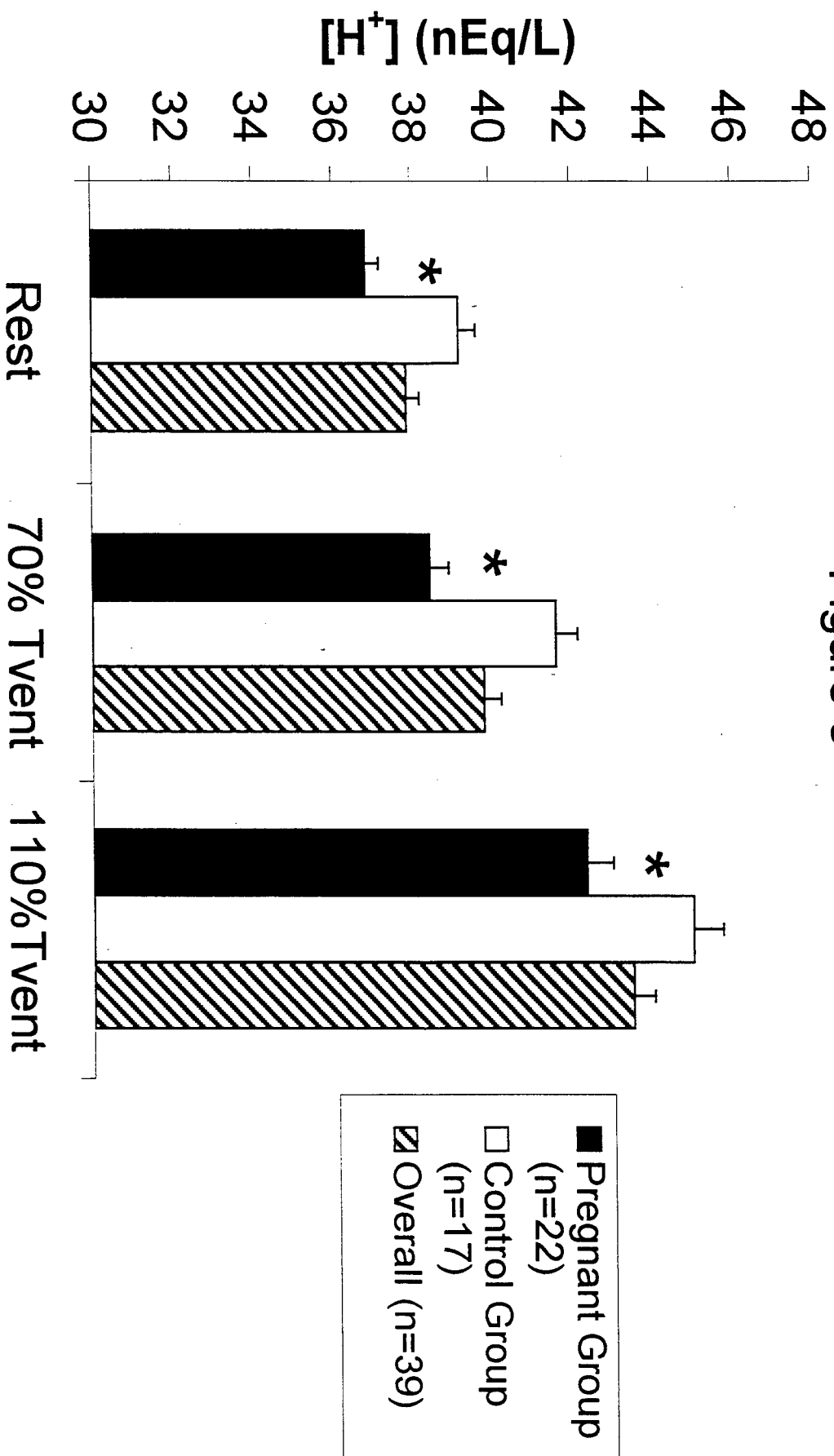


Figure 4

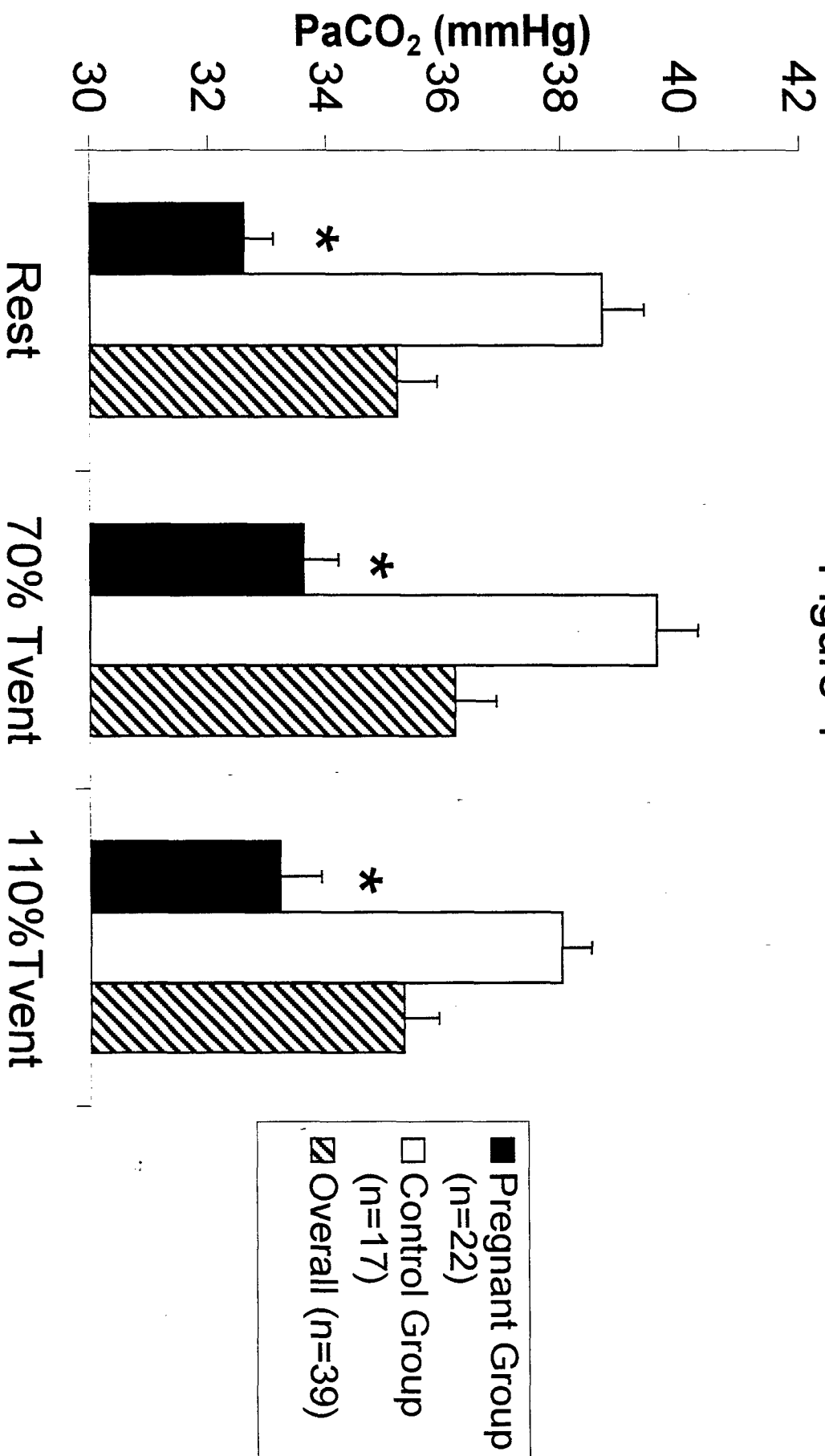


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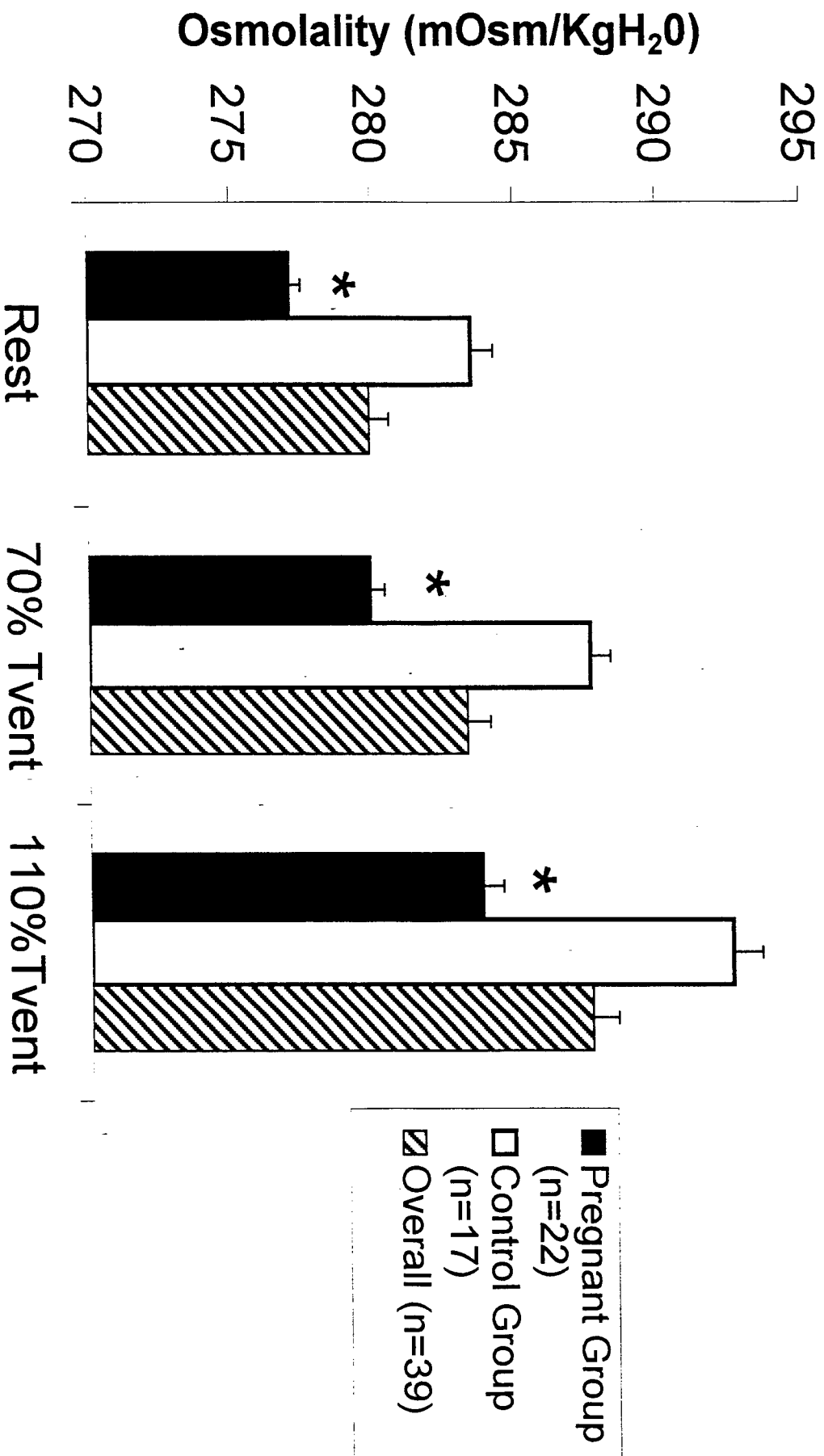


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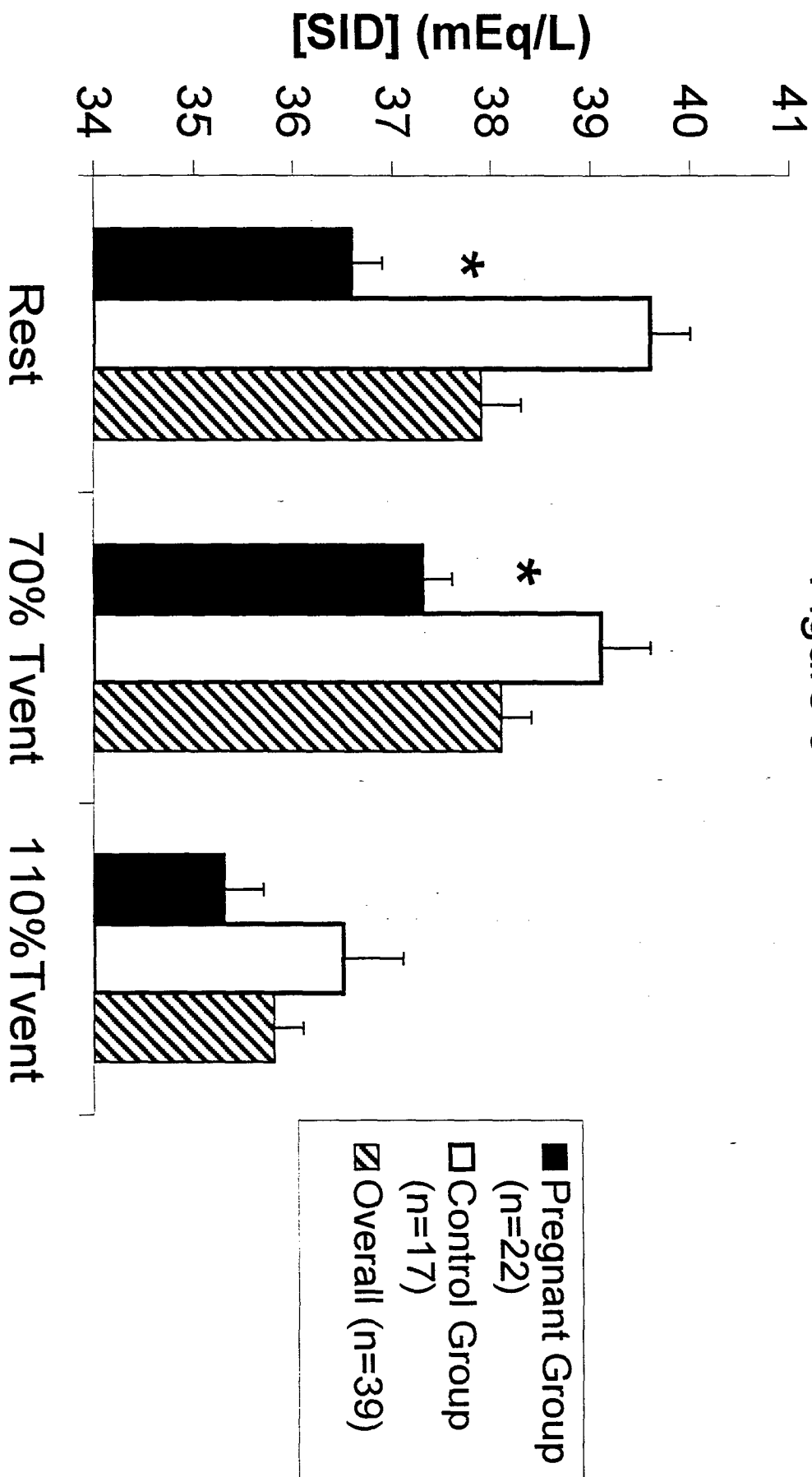


Figure 7

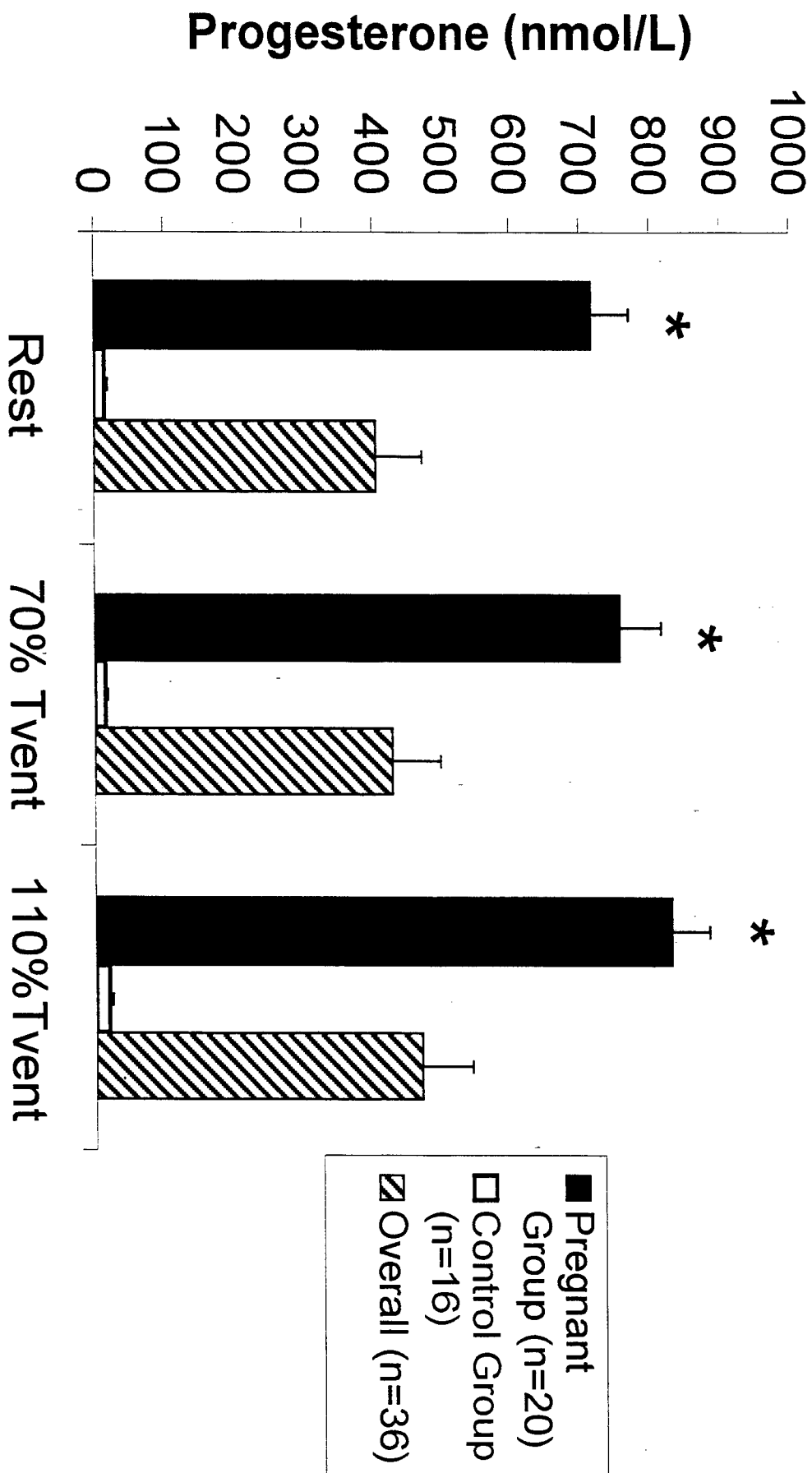


Figure 8

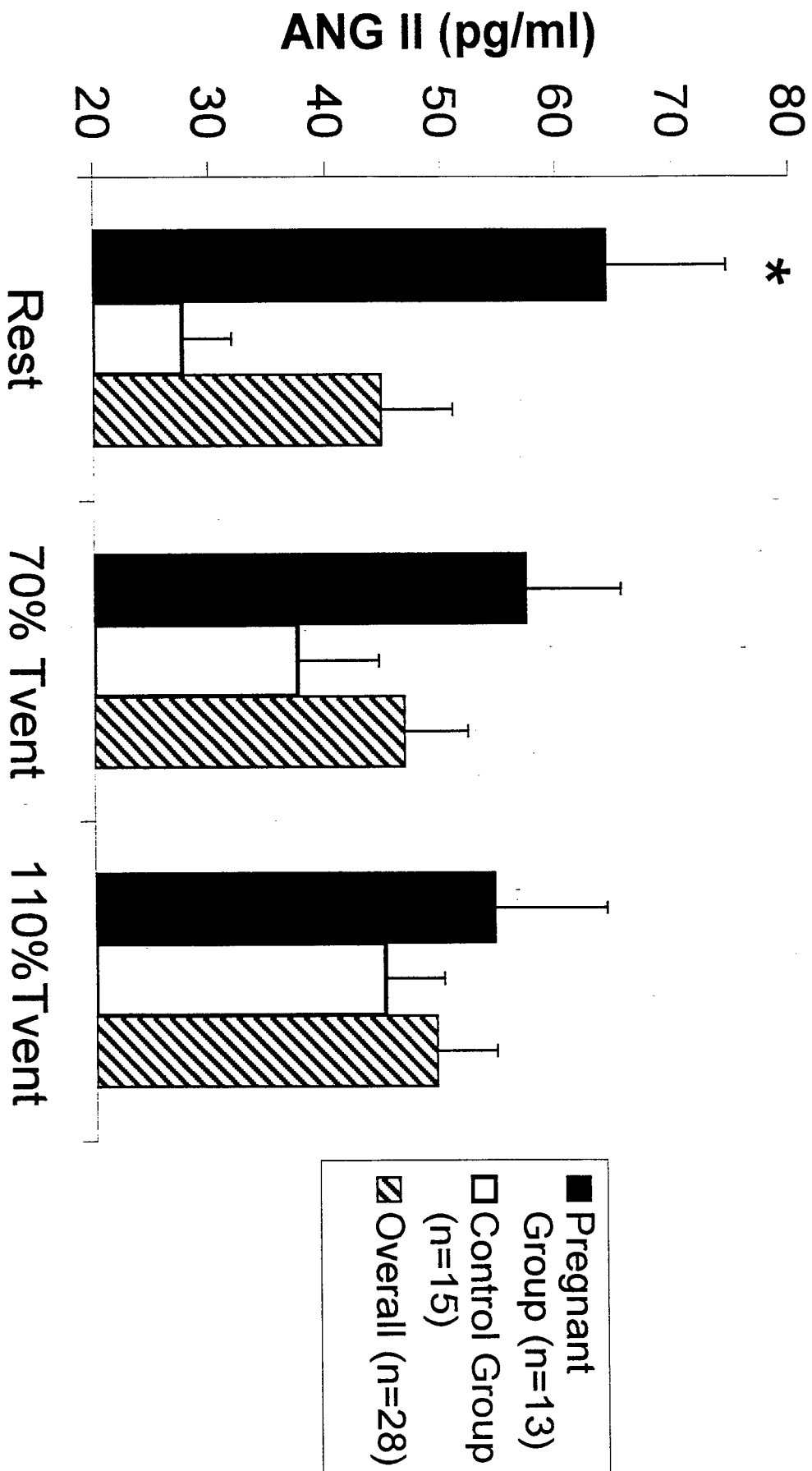
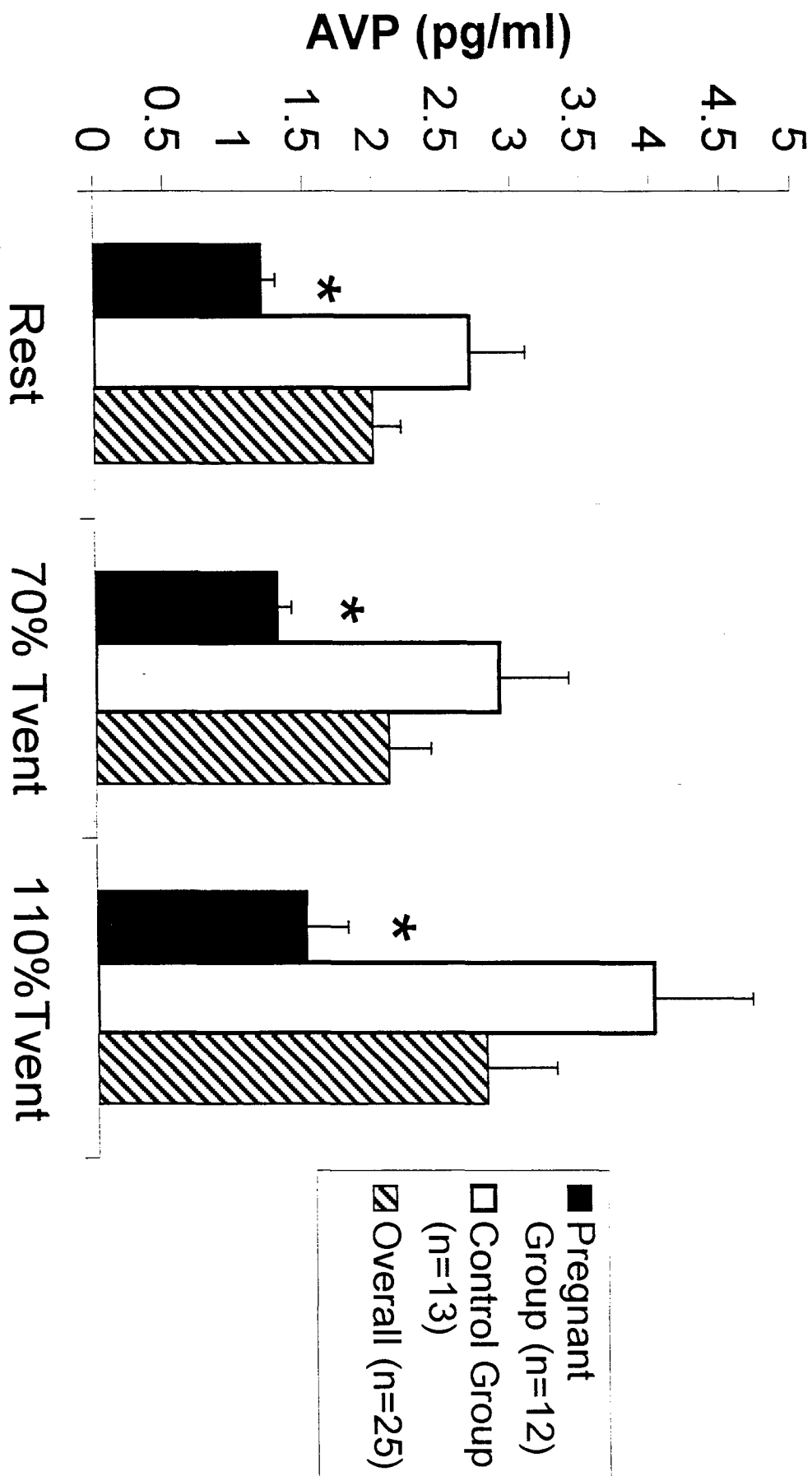


Figure 9



Appendix E

**Manuscript from Studies #1 and #3 entitled
“Maximal Exercise Testing in Late Gestation: Maternal Response”
(in review, *American Journal of Obstetrics and Gynecology*).**

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Manuscript No. 100919

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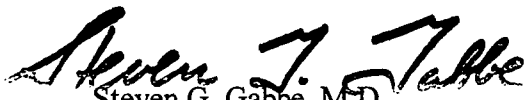
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Receipt of your manuscript is acknowledged. Your paper has been submitted to our consultant(s) for peer review. We will report to you as promptly as possible.

Thank you for your submission to the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*. Please refer to the manuscript identification number (100919) in any communication regarding this manuscript.

Sincerely,


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MAXIMAL EXERCISE TESTING IN LATE GESTATION:
MATERNAL RESPONSES

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Short Title: Strenuous exercise in late pregnancy

Condensation: Aerobic working capacity is preserved in late gestation but carbohydrate utilization and anaerobic energy production is blunted above the point of respiratory compensation (RC).

Abstract

Objective: To study the effects of human pregnancy on metabolic and respiratory responses to maximal cycle ergometer testing and to test the hypothesis that the respiratory exchange ratio (RER) at maximal exercise and peak post-exercise lactate concentration ($[La^-]$) are lower in the pregnant vs. nonpregnant state and that these effects are associated with a lower excess post-exercise oxygen consumption (EPOC) during pregnancy.

Study Design: The pregnant (PG, $n=14$, gestational age= 34.7 ± 0.4 wk) and nonpregnant control (CG, $n=14$) groups included healthy, physically-active women matched for age, body height and parity. Breath-by-breath gas exchange was measured at rest, during exercise and 15 min post-exercise.

Results: Maximal oxygen uptake, the ventilatory threshold (T_{vent}), the point of respiratory compensation (RC) and calculated work efficiency (η) did not differ significantly between groups. However, RER at maximal exercise, peak post-exercise $[La^-]$ and EPOC were significantly lower in the PG. Peak $[La^-]$ was significantly correlated with RER and EPOC.

Conclusion: The capacity for weight supported work is preserved in late gestation and η is unchanged. However, carbohydrate utilization appears to be blunted at high levels of exertion. Blunted respiratory responses were attributed to reduced lactate production and/or dilution of lactate in an expanded blood volume.

Key Words: human pregnancy, oxygen uptake, gas exchange, lactic acid

INTRODUCTION

Pregnancy is accompanied by significant changes in substrate utilization, cardiovascular and respiratory control and acid-base regulation.^{1, 2} Each of these variables play an integral role in responses to exercise and therefore tolerance for strenuous exercise may be altered, especially in late gestation, to accommodate the needs of the growing fetus.

In recent years, there has been a substantial increase in the involvement of young women in nontraditional activities that involve high levels of physical exertion (military service, police work, fire fighting, construction work, strenuous sports and recreational activities). When physically active women become pregnant, it is important for health care providers to understand the normal maternal/fetal responses to strenuous exercise in order to advise these women on appropriate physical activities at various stages of gestation.

Previous investigations of strenuous exertion in pregnancy are few in number, have used simple conventional methodologies and have examined a limited number of variables. There is very little information available on the effects of pregnancy on the ventilatory anaerobic threshold (T_{vent})^{3, 4} and the point of respiratory compensation (RC).⁴ Excess post exercise oxygen consumption (EPOC), an improvement over the "oxygen debt" concept, has not been examined in response to strenuous exercise. However, reports of blunted catecholamines⁵ and lactate concentration ($[La^-]$)^{3, 6, 7} in response to strenuous exercise suggest that EPOC should be lower in the pregnant state. Reports of a lower respiratory exchange ratio (RER) at maximal or near maximal exercise^{8, 9-10} in the pregnant state combined with the reports of lower $[La^-]$ ^{3, 6, 7}, also suggest that carbohydrate utilization may be blunted during intense exercise. However, peak RER and $[La^-]$ have never been reported together in any of the small number of studies that have examined maximal exercise responses in the pregnant state. Work efficiency (η) has been

examined in only one study.¹¹ Information on these variables would add significantly to our understanding of the effects of pregnancy on maternal/fetal exercise tolerance.

This study employed modern breath-by-breath gas analyses to study maternal metabolic responses and gas exchange to a maximal cycle ergometer stress test in late gestation. It was hypothesized that RER at maximal exercise and peak post-exercise $[La^-]$ would be lower in the pregnant subjects compared to the nonpregnant control group and that this would be associated with a lower EPOC in the pregnant group.

MATERIALS AND METHODS

Subjects

Subjects were 14 healthy, nonsmoking, physically active pregnant women (pregnant group, PG) and 14 healthy nonpregnant women with similar physical and demographic characteristics (control group, CG). Prospective subjects were recruited from local prenatal fitness classes and the general population via media announcements, posters, flyers, and communications with local obstetricians. Medical clearance for pregnant subjects was obtained from the physician or midwife monitoring their pregnancy using a standard form, published by the Canadian Society for Exercise Physiology, and reviewed by the study obstetrician (GD).¹² Nonpregnant subjects completed the Physical Activity Readiness Questionnaire. Written informed consent was obtained from all subjects before entry into the study. The study protocol and consent form were approved by the Research Ethics Board, Faculty of Medicine, Queen's University and the U.S. Army Medical Research and Materiel Command, Human Subjects Protection Branch.

Basic physical measurements included body height, body mass and resting blood pressure. Body mass index (BMI, kg/m^2) was calculated as body mass /body height². The PG and CG were matched for mean age, body height, pre-pregnant body mass, parity and aerobic fitness. Members of the PG were studied between 34 and 38 weeks gestation. Subjects in the CG were not using oral contraceptives and menstrual cycle status at the time of the second exercise test was calculated using the first day of their last menstrual cycle and the average length of their cycle.

Exercise Testing Protocol

Subjects performed a progressive maximal exercise test on a Sensor Medics (Model 800S) constant work rate cycle ergometer. Subjects consumed a standard meal (350 kcal, 40% carbohydrate, 40% fat, 20% protein) 1-2 h prior to testing and avoided strenuous physical activity and caffeine intake on the day of testing. The protocol involved five minutes of resting data collection and a four min warm-up at 20 watts, followed by a progressive increase in work rate of 20 watt/min to volitional fatigue.^{4, 9, 13, 14} Following the maximal exercise test, data collection continued into the recovery period for 15 min.

Respiratory Measurements

Respiratory responses were measured on a breath-by-breath basis at rest, during and following exercise using a computerized system (First Breath Inc.) that incorporates a respiratory mass spectrometer (Perkin-Elmer, MGA 1100) with a low dead space, bidirectional volume turbine (VMM-1100) as described by Hughson *et al.*¹⁵ The mass spectrometer was calibrated with a precision analyzed gas mixture and the volume turbine was calibrated before each test

using a syringe of known volume (3.004 L). Respiratory gases (O_2 , CO_2 , N_2) were sampled at the mouth at a flow rate of 60 ml/min. Electrical signals from the equipment were converted from analog to digital and stored on a microcomputer. Heart rate (HR) was monitored with both a Polar Vantage monitor and a Marquette Max-1 electrocardiograph. Thirty seconds of data were averaged for each subject for between group comparisons of submaximal and maximal exercise. Submaximal exercise was taken at an oxygen uptake ($\dot{V}O_2$) 100 ml below measured T_{VENT} for each subject.

Breath-by-breath alveolar gas exchange was calculated using the algorithm of Beaver *et al.*¹⁶ Arterial carbon dioxide tension (P_aCO_2) was calculated from end-tidal CO_2 tension ($P_{ET}CO_2$) and tidal volume (V_T) using the following equation: $P_aCO_2 = 5.5 - 0.90 P_{ET}CO_2 - 0.0021 V_T$.¹⁷ T_{VENT} was identified using the V-slope method.¹⁸ The V-slope method involves a two-segment linear regression (constrained at one point) that is fit on the carbon dioxide output ($\dot{V}CO_2$) and $\dot{V}O_2$ pairs within the region of interest. This is done to provide an unbiased estimate of the $\dot{V}O_2$ where the $\dot{V}CO_2$ vs. $\dot{V}O_2$ relationship breaks from linearity.

RC was identified by using a modified version of the V-slope method where the lower limit for the analysis was placed at or slightly beyond the T_{VENT} and the upper limit was placed near maximal exercise. The break from linearity calculated in this way was also inspected visually to verify correct identification of RC. EPOC was calculated by subtracting mean resting $\dot{V}O_2$ from the mean recovery $\dot{V}O_2$ of the 15 minute recovery period and then multiplying by 15 min.¹⁹

Work efficiency (η) was calculated as described by Davis *et al.*²⁰ using the following equation: $\eta = ((\Delta \text{Work Rate} \times 2.39^{10^{-4}} \times 60) / (\Delta \dot{V}O_2 \times 4.985)) \times 100$, where units for $\Delta \text{Work Rate}$, $\Delta \dot{V}O_2$ and the constants $2.39^{10^{-4}}$ and 60 are watts, L/min, s/min, and kcal/s/watt;

4.985(kcal/min) corresponds to the caloric expenditure per litre of O₂ consumed for the best estimate of the substrate mixture utilized.

Blood Biochemistry

An indwelling venous catheter was inserted prior to the test and venous blood samples were obtained at rest and 1, 3, 5, 7, 10 and 15 min post-exercise. Blood samples were centrifuged for 10 min at 2500 rpm and the plasma was frozen at -80 °C for later analysis. Plasma lactate concentration [La⁻] was determined using an automated analyzer (Yellow Springs Instruments, Model 2300). The analyzer was calibrated before analysis using five and 15 mmol/L standards and at regular intervals during the analysis. The test-retest reliability of [La⁻] measurements was described and confirmed in an earlier publication from this laboratory.³

Statistics

Student's *t*-statistics for independent samples were used for between group comparisons of physical characteristics, T_{VENT}, RC, EPOC and work efficiency. One-tailed Student *t*-statistics were used to compare EPOC, RER at peak exercise and peak post-exercise lactates between groups, since it was hypothesized based on previous studies that values would be lower in the PG vs. CG. Similarly, a one-tailed Student *t*-statistic was used to test the hypothesis that peak [La⁻] would be positively correlated with both RER and EPOC using the Pearson product-moment correlation coefficient.

Data at rest and at submaximal and maximal exercise were compared within and between subjects using a two-way ANOVA (groups vs. rest/exercise level) with repeated measures on the second factor. When a significant between group main effect or group × time interaction was

observed, separate independent Student *t*-statistics (two-tailed) were used to identify significant differences between groups at rest, and submaximal and maximal exercise. When a significant within-subjects main effect was observed, paired Student *t*-statistics (two-tailed) were used to detect significant differences between rest, submaximal exercise and maximal exercise within each group. The statistical package utilized was SPSS version 7.5 (SPSS Inc., Chicago, Illinois).

Statistical tests were considered significant if $p < 0.05$. Since comparisons between groups and across variables were planned and the number of comparisons was small in each case, the critical alpha level for significance was maintained at $p < 0.05$.²¹

RESULTS

The PG (gestational age 34.7 ± 0.4 wk) and CG were well matched in terms of age, body height and parity (Table I). As expected, the body mass and BMI of the PG were significantly greater than those of the CG. However, the pre-pregnant body mass and BMI of the PG were similar to those of the CG. Normal fetal heart rate tracings were confirmed immediately prior to and after exercise for all pregnant subjects. Pregnancy outcome was also normal for all subjects.

As expected, HR, $\dot{V}O_2$, $\dot{V}CO_2$, and RER increased significantly from rest to submaximal exercise and from submaximal to maximal exercise in both groups. Heart rate was significantly higher in the PG vs. CG at rest, but this difference decreased with increasing exercise intensity and was not observed at maximal exercise (Table II). $\dot{V}O_2$ and $\dot{V}CO_2$ were not different between groups at rest or either exercise intensity, although a trend was present for a higher $\dot{V}O_2$ in the PG vs. CG at rest (Table 2). $\dot{V}O_2$ adjusted for body weight (ml/kg/min) was not different in the PG vs. CG at rest (5.0 ± 0.2 vs. 5.2 ± 0.2), but was significantly lower at both the submaximal and maximal exercise intensities in the PG (21.0 ± 0.9 ; 30.9 ± 1.4 , respectively) vs. the CG ($26.3 \pm$

1.4; 36.9 ± 1.8 , respectively). Work rate at maximal exercise was not significantly different between groups (i.e. PG, 190 ± 7 watts vs. CG, 202 ± 6 watts).

$\dot{V}O_2$ at T_{VENT} and RC were not different between groups (Figure 1). The only significant difference in the respiratory exchange ratio (RER) between groups occurred at maximal exercise, where the RER was significantly greater in the CG vs. the PG (Figure 2-A). $[La^-]$ was not different between groups at rest, but peak $[La^-]$ was significantly lower in the PG vs. CG (Figure 2-B). EPOC was significantly higher in the CG vs the PG (Figure 2-C). Peak $[La^-]$ was significantly correlated with both RER ($r=0.39$) and EPOC ($r=0.35$) within the pooled data of the two groups. Work efficiency was not different between groups (Figure 3).

Significant increases in minute ventilation ($\dot{V}_E$), breathing frequency (f) and V_T were observed from rest to submaximal exercise and from submaximal to maximal exercise in both groups. Inspiratory time (T_I), $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ significantly decreased in the transition from rest to submaximal exercise. T_I further decreased from submaximal to maximal exercise while $\dot{V}_E/\dot{V}O_2$ increased in the transition from submaximal to maximal exercise. $\dot{V}_E/\dot{V}CO_2$ increased in the transition from submaximal to maximal exercise in the CG only. $\dot{V}_E$, f , V_T , (T_I) and V_T/T_I were not significantly different between groups. The PG exhibited higher values for $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ at submaximal exercise than the CG (Table III). A group $\times$ time interaction was observed for V_T as the PG started higher at rest and showed a trend ($p=0.10$) for lower values at maximal exercise compared to the CG.

Alveolar ventilation ($\dot{V}_A$) was not significantly different between groups and increased significantly from rest to submaximal exercise and from submaximal to maximal exercise in both groups (Table IV). End-tidal oxygen tension ($P_{ET}O_2$) was not significantly different between groups and decreased significantly from rest to submaximal exercise and increased significantly

from rest to maximal exercise in both groups. $P_{ET}CO_2$ and predicted P_aCO_2 were significantly lower in the PG vs. CG at rest and submaximal exercise and both increased significantly from rest to submaximal exercise and significantly decreased from submaximal to maximal exercise. $P_{ET}CO_2$ at max was also significantly higher than its value at rest.

COMMENT

This study examined, using modern breath-by-breath technology, the effects of pregnancy on the response to strenuous exercise in healthy, active women. Breath-by-breath analysis facilitates the measurement of an expanded number of ventilatory variables compared to conventional open circuit spirometry (i.e. T_I , V_T/T_I , $P_{ET}O_2$ and $P_{ET}CO_2$) and allows for greater precision in the determination of T_{VENT} and RC. Only one previous study²² has utilized breath-by-breath analysis during exercise testing in pregnancy. Unfortunately their report did not include any of the variables cited above and was limited to the study of responses to moderate submaximal (50 watt) exercise.

It is well documented that there is an increase in respiratory sensitivity in pregnancy and this is attributed to augmented circulating levels of progesterone, a known respiratory stimulant²³, and an estrogen-mediated increase in hypothalamic progesterone receptors.^{23, 24} In addition, augmented respiratory sensitivity may be mediated by changes in plasma osmolality, cerebrospinal fluid strong ion difference concentration (CSF [SID]) and circulatory angiotensin II levels which have been demonstrated in laboratory animals to play a role in the control of ventilation.²⁵ Indeed, human pregnancy is accompanied by decreases in plasma osmolality and [SID] and increases in circulating angiotensin II levels and therefore any or all of these factors could contribute to the increase in ventilatory responses in pregnancy.² Although the differences

in the resting $\dot{V}_E$, $\dot{V}_A$ and V_T between the PG and CG did not reach significance, statistical trends were observed in the expected directions and an augmented respiratory sensitivity in the PG was confirmed by the significantly lower values for $P_{ET}CO_2$ and P_aCO_2 at rest and during submaximal exercise. However, the ventilatory response of the PG was blunted at maximal exercise as reflected by the loss of significance for $P_{ET}CO_2$ and P_aCO_2 between the groups. This effect is likely the result of the lower peak lactate values in the PG vs. CG which would contribute to blunted pH responses to maximal exercise and a milder stimulus to increase CO_2 output above the point of RC and during recovery from maximal exercise.¹²

The lack of difference in the $\dot{V}O_{2max}$ of pregnant and nonpregnant subjects is consistent with other studies that have examined maximal or peak $\dot{V}O_2$ using the same women in the pregnant and postpartum state.^{9, 10, 26-28} The physiological changes of pregnancy do not seem to affect maximal aerobic power, provided the woman remains physically active. However, the higher resting $\dot{V}O_2$ of pregnant women can be expected to cause a small, nonsignificant reduction in peak power output since more O_2 is devoted to resting maternal/fetal metabolism and less is available to perform external work. The mean peak power output of the pregnant subjects in this study (190 ± 7 watts) was nearly identical (± 3 watts) to other reports^{9, 12} of the peak power output of pregnant women during maximal cycling exercise and was only slightly lower ($p=0.20$) than the nonpregnant controls (202 ± 6 watts). The mean HR (178 ± 2 beats/min) and $\dot{V}O_2$ (2.25 ± 0.10 L/min) at maximal exercise of the pregnant subjects were also in the upper range of reported values (ie. 171-181 beats/min and 1.94 – 2.36 l/min, respectively) for maximal cycling exercise.^{9, 12, 26, 28}

T_{VENT} , an index of the onset of blood lactate accumulation, was also similar in the PG and CG. This confirms the findings of two previous studies^{3, 4} that examined T_{VENT} in women tested

during pregnancy and postpartum. Since T_{VENT} reflects the peak intensity that an individual can sustain without progressive accumulation of lactic acid, pregnancy should not affect the capacity for prolonged weight-supported work. As well, our finding of the same point of respiratory compensation between the PG and CG is also in agreement with Lotgering *et al.*⁴

Several findings considered together suggest that the ability to metabolize carbohydrate and produce lactate is reduced in late gestation. The RER of the CG was significantly higher at maximal exercise than that of the PG. This is consistent with other studies that have compared RER in the pregnant and nonpregnant states at maximal or near maximal exercise.^{3, 8-10} A lower RER during strenuous exercise in pregnancy may result from a greater reliance on fat as an energy source with a reduction in carbohydrate utilization. In support of this hypothesis, we observed lower peak post exercise lactates in the PG vs. the CG. Unfortunately only one of the earlier studies³ that observed lower RER values during strenuous exercise in pregnancy also measured lactate, but the finding of lower peak lactate values during pregnancy compared to postpartum in that study support the hypothesis of reduced carbohydrate utilization during strenuous exercise in pregnancy. Other studies have also reported lower lactate responses to strenuous exercise in pregnancy.^{6, 7}

Reduced carbohydrate utilization during strenuous exercise may be the result of the development of insulin resistance with advancing gestational age²⁹, blunted catecholamine responses⁵ and reduced liver glycogen storage.³⁰ The recent finding²⁹ of reduced GLUT 4 glucose transporter expression in pregnancy that remained low despite physical conditioning provides one mechanism by which carbohydrate utilization would be reduced during exercise in pregnancy. Blunted sympathoadrenal responses to exercise in pregnancy⁵ may result in reduced glycogenolysis and combined with decreased liver glycogen storage, as found in pregnant rats³⁰,

could contribute to maternal hypoglycemic responses and decreased carbohydrate utilization during exercise. Other factors that may contribute to reduced lactate values following strenuous exercise in pregnancy include dilution of lactate in the expanded maternal blood volume⁷ and fetal utilization of lactate as a metabolic fuel.³¹ However, the significant positive correlation of lactate to RER, suggests that reduced carbohydrate utilization was primarily responsible for the reduced lactate concentration in the pregnant group.

Previous studies have examined O₂ debt or EPOC following steady-state exercise in pregnancy and have reported no change²² or a greater EPOC³² in pregnancy compared to postpartum. However, the present study is the first to measure EPOC after maximal exercise in pregnancy. A lower EPOC in the pregnant state suggests that changes in temperature, catecholamines, calcium ions, fatty acids or restoration of glycogen, adenosine triphosphate and creatine phosphate stores¹⁹ may contribute less to EPOC following strenuous exercise in pregnancy. Indeed, blunted catecholamine responses to strenuous exercise have been reported in late gestation⁵. The lower peak lactate values in the PG also suggest that less gluconeogenesis and/or oxidation of lactate is necessary in recovery from strenuous exercise in late gestation compared to the nonpregnant state. This conclusion is also supported by the significant positive correlation between lactate concentration and EPOC.

In contrast to an earlier study¹¹ that used a weight-bearing treadmill protocol and reported that the caloric cost of the exercise was reduced in the second trimester compared to postpartum, we did not find any change in η using our non-weight bearing cycling protocol in late gestation. Still, this result supports the idea that pregnancy does not adversely affect a woman's working capacity.

In summary, the two most important determinants of aerobic fitness, $\dot{V}O_{2\text{MAX}}$ and T_{VENT} , are unaffected by pregnancy. The lack of change in η in pregnancy is another indicator that the working capacity of a woman is largely unaffected by pregnancy. While maximal aerobic power was unchanged by pregnancy, anaerobic energy metabolism was affected during strenuous exercise. The lower peak post-exercise lactate values and RER at peak exercise indicate blunting of carbohydrate utilization above the point of RC. This may be a protective mechanism to spare glucose for the fetus/placenta. In addition, the maintenance of a lower $[H^+]$ during pregnancy at rest and in response to strenuous exercise¹² is beneficial in protecting the fetus from changes in pH. While absolute aerobic capacity (L/min) is unaffected by pregnancy, relative aerobic capacity adjusted for weight gain (ml/kg/min) will decline throughout pregnancy. Weight bearing activities will thus become progressively more difficult for the pregnant woman, but return to normal after childbirth and subsequent loss of weight gain, as long as an active lifestyle is maintained. While the physiological effects of pregnancy do not affect a woman's overall aerobic capacity, alterations in energy metabolism and acid-base regulation appear to aid in the maintenance of fetal well-being during strenuous exercise.

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LIST OF FIGURES

Figure 1. The ventilatory anaerobic threshold (T_{VENT}) and the point of respiratory compensation (RC).

Figure 2. A. Peak respiratory exchange ratio. B. Rest and peak post-exercise lactate. C. Excess post-exercise oxygen consumption (EPOC). * Significant difference between groups ($p < 0.05$).

Figure 3. Work Efficiency (η).

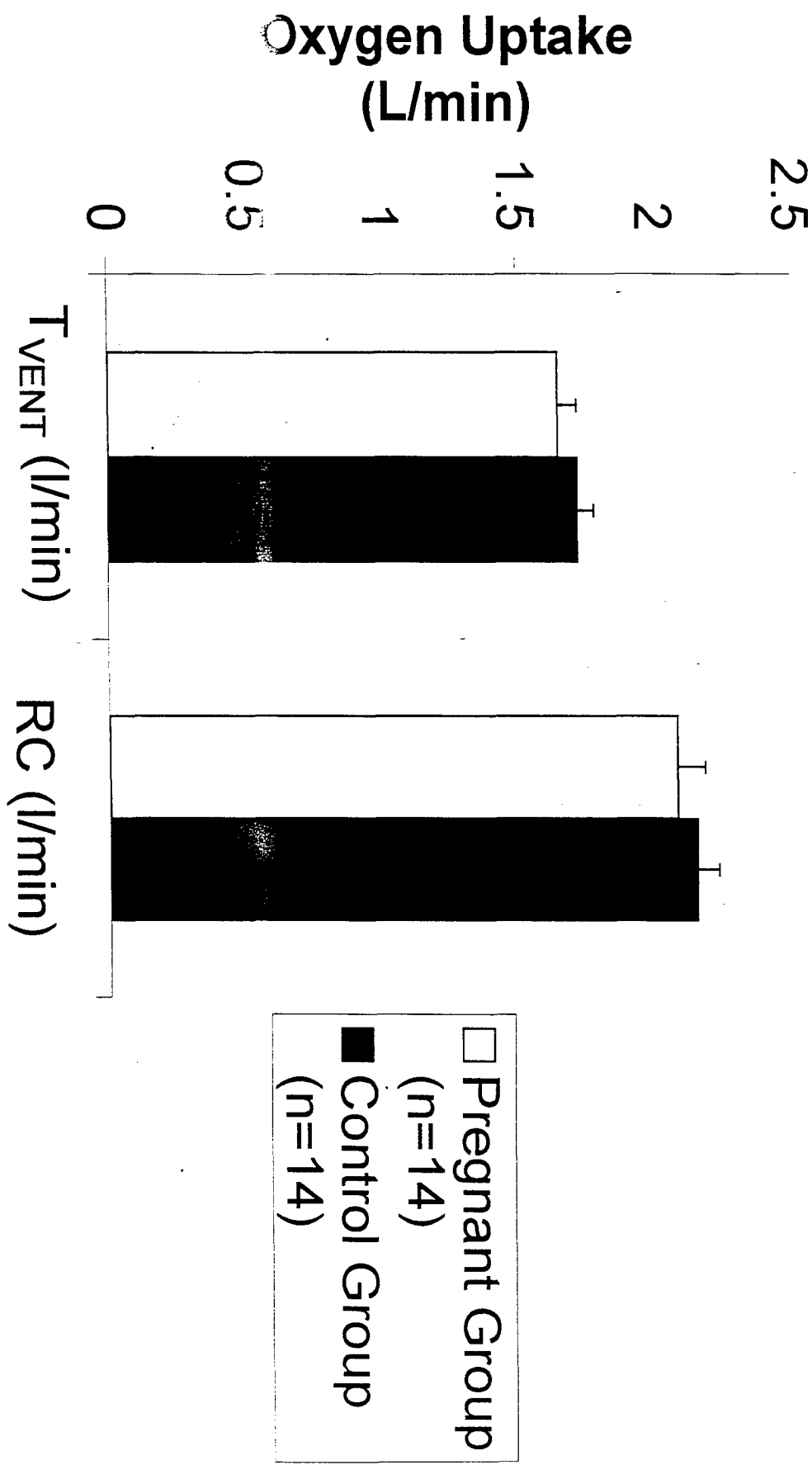


Figure 1

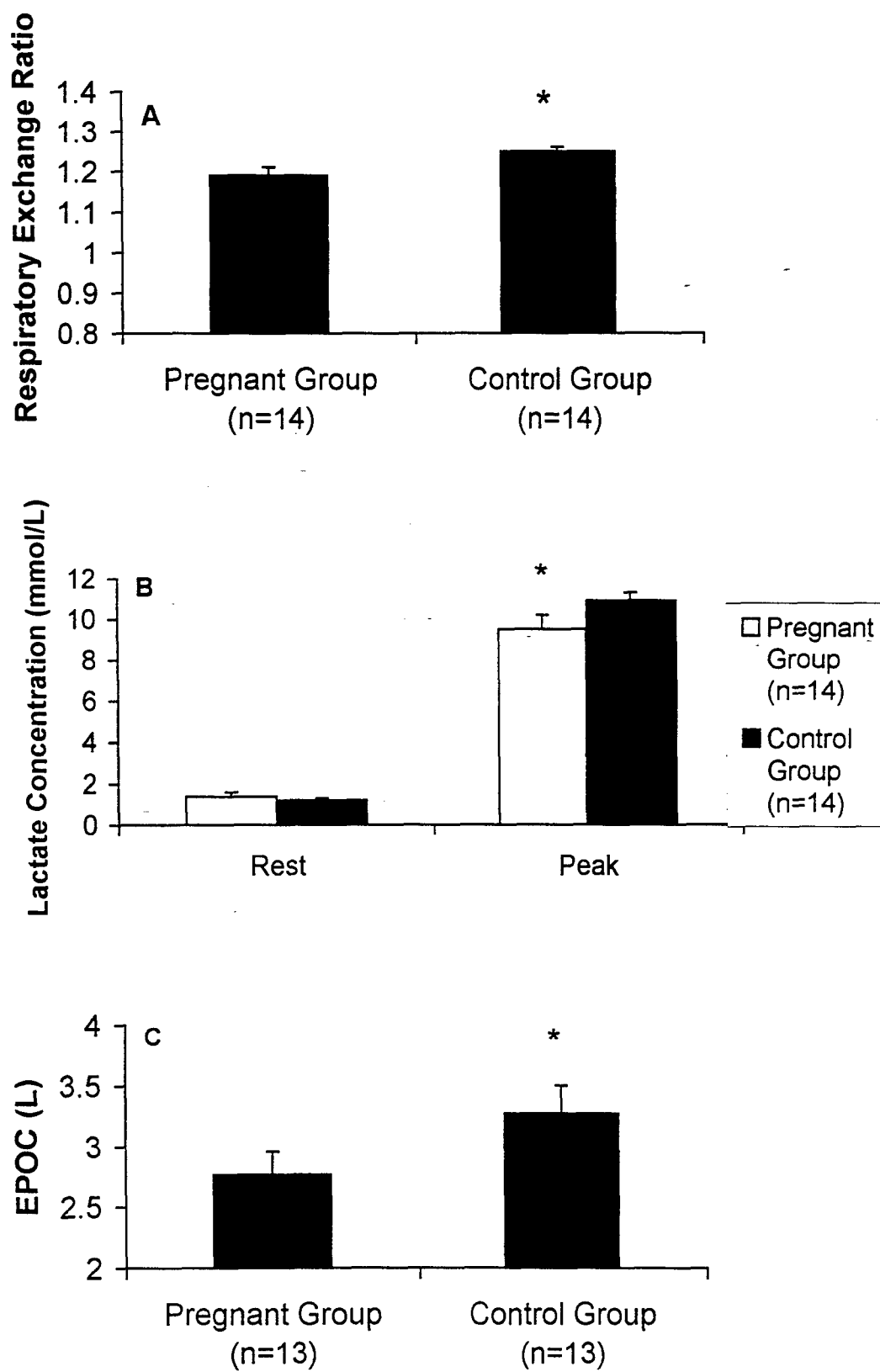


Figure 2

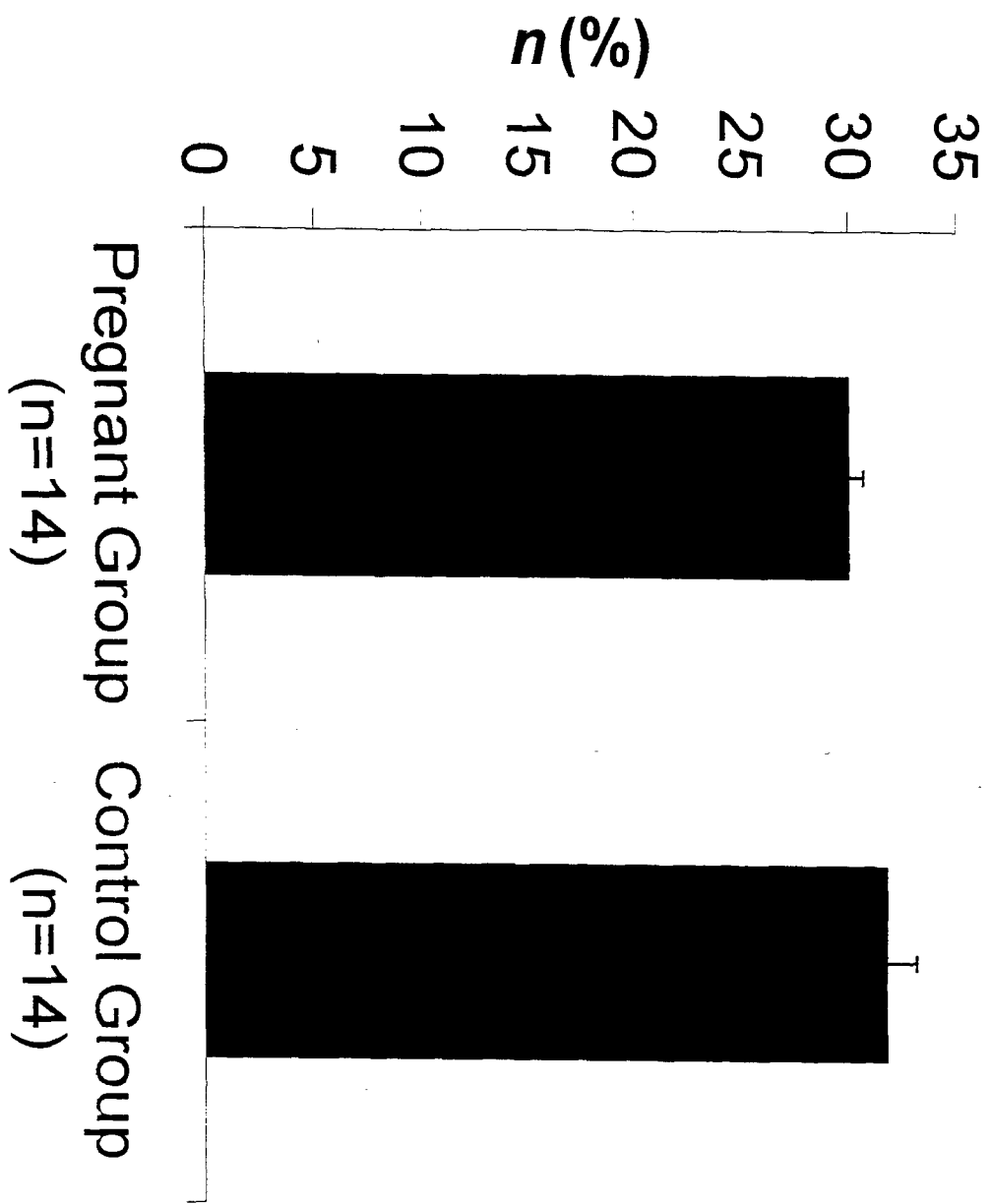


Figure 3

Table I. Physical Characteristics of Subjects

VARIABLE	PREGNANT GROUP (n=14)	CONTROL GROUP (n=14)
Age (years)	30.8 $\pm$ 1.0	30.8 $\pm$ 2.0
Gestational Age (weeks)	34.7 $\pm$ 0.4	N/A
Height (cm)	162.7 $\pm$ 1.5	161.9 $\pm$ 1.4
Body Mass (kg)	73.3 $\pm$ 2.0*	62.6 $\pm$ 2.0
Body Mass Index	27.7 $\pm$ 0.5*	23.9 $\pm$ 0.6
Pre-Pregnancy Body Mass (kg)	61.1 $\pm$ 2.0	N/A
Pre-Pregnant Body Mass Index	23.1 $\pm$ 0.6	N/A
Parity	0.6 $\pm$ 0.2	0.6 $\pm$ 0.2

Values are means $\pm$ SE.

*Significant difference ($p < 0.05$) between groups

Table II. Metabolic Responses

		REST		Submaximal Exercise		Maximal Exercise
HR (beats/min)	PG	93 ± 3 *	PG	148 ± 3	PG	178 ± 2
	CG	79 ± 4	CG	140 ± 3	CG	179 ± 2
$\dot{V}O_2$ (L/min)	PG	0.36 ± 0.01	PG	1.53 ± 0.07	PG	2.25 ± 0.10
	CG	0.32 ± 0.01	CG	1.62 ± 0.06	CG	2.28 ± 0.08
$\dot{V}CO_2$ (L/min)	PG	0.33 ± 0.01	PG	1.53 ± 0.07	PG	2.66 ± 0.11
	CG	0.29 ± 0.01	CG	1.65 ± 0.07	CG	2.84 ± 0.10
RER	PG	0.90 ± 0.01	PG	1.00 ± 0.01	PG	1.19 ± 0.02 *
	CG	0.89 ± 0.02	CG	1.02 ± 0.02	CG	1.25 ± 0.01

Values are means ± SE.

PG = Pregnant Group (n=14); CG = Control Group (n=14)

* Significant difference ($p < 0.05$) between groups

Table III. Ventilatory Responses

		REST		Submaximal Exercise		Maximal Exercise
$\dot{V}_E$ (L/min)	PG	10.9 ± 0.4	PG	42.7 ± 1.6	PG	78.5 ± 3.9
	CG	9.2 ± 0.4	CG	40.9 ± 1.7	CG	84.3 ± 4.3
f (breaths/min)	PG	14.7 ± 0.9	PG	25.1 ± 1.0	PG	40.2 ± 2.3
	CG	15.1 ± 0.6	CG	24.9 ± 1.5	CG	39.3 ± 3.0
V_T	PG	0.83 ± 0.08	PG	1.77 ± 0.10	PG	2.01 ± 0.08
	CG	0.68 ± 0.07	CG	1.75 ± 0.09	CG	2.20 ± 0.08
$\dot{V}_E/\dot{V}O_2$	PG	30.4 ± 0.8	PG	$28.1 \pm 0.5 *$	PG	35.2 ± 1.4
	CG	28.9 ± 0.9	CG	25.7 ± 0.9	CG	37.2 ± 1.6
$\dot{V}_E/\dot{V}CO_2$	PG	33.5 ± 0.7	PG	$28.2 \pm 0.5 *$	PG	29.6 ± 0.9
	CG	32.2 ± 1.2	CG	25.1 ± 0.8	CG	29.7 ± 1.2
T_I	PG	1.79 ± 0.16	PG	1.17 ± 0.05	PG	0.77 ± 0.05
	CG	1.70 ± 0.12	CG	1.18 ± 0.06	CG	0.78 ± 0.04
V_T/T_I	PG	0.47 ± 0.02	PG	1.50 ± 0.05	PG	2.67 ± 0.12
	CG	0.39 ± 0.02	CG	1.49 ± 0.06	CG	2.92 ± 0.14

Values are means $\pm$ SE.

PG = Pregnant Group (n=14); CG = Control Group (n=14)

* Significant difference ($p < 0.05$) between groups

Table IV. Respiratory Gas Exchange

		REST		Submaximal Exercise		Maximal Exercise
$\dot{V}_A$	PG	8.9 ± 0.4	PG	37.8 ± 1.6	PG	69.8 ± 3.3
	CG	7.3 ± 0.4	CG	36.3 ± 1.5	CG	74.5 ± 3.6
$P_{ET}O_2$	PG	112.7 ± 0.7	PG	108.9 ± 0.8	PG	115.8 ± 1.1
	CG	111.6 ± 1.0	CG	106.3 ± 1.2	CG	116.6 ± 1.0
$P_{ET}CO_2$	PG	$31.6 \pm 0.5 *$	PG	$37.7 \pm 0.6 *$	PG	35.6 ± 1.1
	CG	34.0 ± 0.9	CG	42.0 ± 0.9	CG	37.3 ± 1.1
P_aCO_2	PG	$32.2 \pm 0.6 *$	PG	$35.7 \pm 0.5 *$	PG	33.4 ± 0.9
	CG	34.6 ± 0.9	CG	39.6 ± 0.7	CG	34.5 ± 0.9

Values are means $\pm$ SE.

PG = Pregnant Group (n=14); CG = Control Group (n=14)

* Significant difference ($p < 0.05$) between groups

Appendix F

**Manuscript from Studies #1 and #3 entitled
“Maximal Exercise Testing in Late Gestation : Fetal Responses”
(in review, *Obstetrics and Gynecology*).**



SCHOOL OF PHYSICAL AND HEALTH EDUCATION

November 9th, 1999

Queen's University
Kingston, Canada
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The Editor,
Obstetrics and Gynecology,
10921 Wilshire Boulevard, Suite 403
Los Angeles, California
90024 - 3908 USA

Dear Sir/Madam,

Please find enclosed, the original and two complete copies of an original research report entitled **"Maternal Exercise Testing in Late Gestation : Fetal Responses"** which we are submitting for publication in Obstetrics and Gynecology. Please note that two papers on maternal responses to the exercise tests also exist. One has been published in the Journal of Applied Physiology (Kemp, *et al.*, *J. Appl. Physiol.* 83:644-651, 1997) and the other by A.P. Heenan, *et al.* is in review in the *American Journal of Obstetrics and Gynecology* (1 copy of each enclosed). Note that the finding and data presentation in these two papers (except for listing of maternal physical characteristics) do not overlap with the present one and the maternal findings are properly cited and referenced in the present paper.

In closing, we thank you for your attention and look forward to hearing the results of the review of this paper.

Yours sincerely,

Larry A. Wolfe, Ph.D.
Corresponding Author

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Enc.

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MAXIMAL EXERCISE TESTING IN LATE GESTATION:
FETAL RESPONSES

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Short Title:

Fetal Heart Responses

Precis

Fetal responses to maximal exercise testing of healthy women in late gestation were increased fetal heart rate, fewer accelerations, decreased variability and increased time to reactivity.

Abstract

Objective: To determine the fetal response to and safety of maximal maternal exercise in the third trimester.

Methods: Twenty-three active women with uncomplicated singleton pregnancies underwent maximal exercise testing in late gestation using a progressive maximal cycle ergometer protocol. Fetal heart rate (FHR) responses were monitored and classified using National Institute of Child Health and Human Development guidelines. Statistical analyses involved the use of Student's t-statistics, repeated measures ANOVA with Tukey-Kramer multiple comparisons posttest and chi-squared analysis.

Results: There was an increase in baseline FHR in the 20 min posttest time period compared to the 20 min pretest time period. There were significantly fewer accelerations in the second posttest 10 min segment compared to the second pretest 10 min segment. Variability was reduced in both posttest time periods compared to the first 10 min pretest. Time to reactivity increased after testing. Mild tachycardia occurred in 2 tracings and bradycardia occurred in a previously undiagnosed growth-restricted fetus. There were no abnormal neonatal outcomes.

Conclusion: Maximal exercise testing in late gestation led to minimal changes in the fetal heart rate. Fetal bradycardic responses were not seen in normally grown fetuses, suggesting that brief maximal maternal exertion for research or diagnostic purposes is safe in this group.

Introduction

Research on exercise in pregnancy has increased over the years resulting in more specific and less conservative guidelines for physical activity for healthy women with normal pregnancies^{1,2}. Since most studies have focussed on moderate exercise, limited information is available about the effects of strenuous exercise on the fetus.

Fetal heart rate (FHR) characteristics are important indicators of human fetal well being or distress. FHR responses associated with hypoxia include tachycardia, bradycardia, reductions in variability or accelerations, and an increase in decelerations³.

FHR tracings have been inconsistently analyzed in the past due to different definitions of normal FHR patterns, interpreter variability and incorrect assessment of motion artifacts (from Doppler ultrasound recording) as bradycardia^{4,5}. These drawbacks, combined with poor descriptions of the exercise performed and incomplete clinical and physical descriptions of subjects, result in knowledge gaps about the effects of strenuous maternal exercise on FHR responses⁴.

Strenuous maternal exercise involves metabolic and cardiovascular changes that have the potential to compromise fetal well-being⁴. Studies of laboratory animals⁶ suggest that redistribution of blood flow from visceral organs to contracting maternal skeletal muscle could compromise uterine, umbilical and fetal blood flow, causing fetal hypoxia. The combined effects of reduced maternal liver glycogen storage⁷, blunted maternal sympathoadrenal responses⁸ and recruitment of fast twitch motor units in maternal skeletal muscle at high work rates could also contribute to maternal hypoglycemia⁸ and reduced fetal glucose availability in the immediate post-exercise period⁹. Finally, maternal blood lactate accumulation during strenuous exercise could, in

theory, reverse the transplacental gradient for hydrogen ion concentration ($[H^+]$), possibly contributing to fetal asphyxia³.

A growing body of evidence also supports the existence of maternal-fetal protective mechanisms that could help to prevent fetal hypoxia and preserve fetal glucose availability in association with strenuous exertion. As discussed in a recent review from this laboratory⁴, these may include redistribution of uterine blood flow to favor the cotyledons vs. myometrium, exercise-induced hemoconcentration and increased fetal arteriovenous oxygen extraction.

The purpose of this study was to examine the effects of maximal maternal exercise testing on FHR responses using standardized subject inclusion criteria, a testing protocol tailored to pregnant women, fetal monitoring before and immediately after exercise, and analyzing tracings with standardized measurement criteria definitions recently proposed by the National Institute of Child Health and Human Development¹⁰. The hypothesis tested was that FHR responses to a single bout of strenuous exercise by aerobically-conditioned women in late gestation would be minimal and transient. Results are discussed in relation to maternal physiological data from the same exercise tests^{11,12}.

Materials and Methods

Subjects

Subjects were recruited via newspaper advertisements, posted announcements and contact with physicians, midwives and community agencies which provide services to women in Kingston, Ontario, Canada. Prospective subjects were screened by their obstetrician/family physician/midwife using the Physical Activity Readiness Medical Examination for Pregnancy (PARmed-X for Pregnancy), a standardized medical

screening questionnaire designed to determine whether exercise in pregnancy is considered safe for that individual². Inclusion criteria were: gestational age, 31 – 38 wk with single fetus; nonsmoker; physically active throughout pregnancy (minimum energy expenditure equivalent to walking 30 min three times per week); nonobese (body mass index < 27); age, 20 – 40 y; parity, 0 – 2; taking no medications other than prenatal vitamins; absence of absolute or relative contraindications to exercise in pregnancy based on response to PARmed-X for Pregnancy by physician. Written informed consent was obtained before entry into the study. The study design and informed consent form were approved by the Research Ethics Board, Faculty of Medicine, Queen's University and the Human Subjects Protection Branch, U.S. Army Medical Research and Materiel Command.

Exercise Testing Protocol

Before exercise testing, subjects abstained from caffeine intake for at least 6 hr and strenuous physical activity for at least 12 hr. They also consumed a standard meal (350 kcal) two hours before testing. Subjects exercised on a constant work rate cycle ergometer at 20 W for 4 min followed by a ramp increase in work rate of 20 W to volitional fatigue¹¹⁻¹⁴. Subjects were monitored by an experienced obstetric nurse using a cardiotocometer (Hewlett-Packard Model 8041-A) for 20 min prior to and 20 min immediately after the maximal exercise test. Any significant abnormalities identified by the nurse were referred to the on-call obstetrician for further assessment.

FHR tracings were interpreted independently by two researchers (GD, RV) experienced in the interpretation of FHR tracings in both clinical and research situations.

Measurements were made of the baseline heart rate, frequency of accelerations and decelerations and variability using research guidelines for interpretation of electronic FHR monitoring developed by the National Institute of Child Health and Human Development¹⁰.

The FHR tracing was separated into two pretest 10 min segments and two posttest 10 min segments. According to the National Institute of Child Health and Human Development guidelines, the baseline FHR is the approximate mean FHR rounded to increments of 5 beats/min during a 10 min segment. To be interpretable, the baseline FHR must be of at least 2 min duration within the 10 min segment, without periodic or episodic changes, or periods of marked variability or segments of the baseline that differ by > 25 beats/min. Bradycardia is defined as baseline FHR less than 110 beats/min. Tachycardia is a FHR baseline greater than 160 beats/min. Accelerations are defined as abrupt increases in FHR from the baseline of at least 15 beats/min lasting at least 15 s and no longer than 2 min before the return to baseline. Variable decelerations of the FHR are defined as abrupt decreases in the FHR below the baseline of at least 15 beats/min lasting at least 15 s and no longer than 2 min before the return to baseline. Prolonged decelerations of the FHR are defined as decreases in the baseline heart rate of at least 15 beats/min lasting more than 2 min, but less than 10 min from onset to return to baseline.

The National Institute of Child Health and Human Development guidelines also include definitions for early and late decelerations. However, none of the exercising patients were contracting or in labor. As these definitions depend on the fetal heart response to uterine contractions, these definitions are not included. The National Institute of Child Health and Human Development guidelines do not differentiate between beat to

beat (short term) and long term variability. Baseline FHR variability is defined as fluctuations in the baseline FHR of two cycles per minute or greater. The fluctuations are irregular in amplitude and frequency and are determined visually as the amplitude of the peak-to-trough in beats per minute as follows:

1. Amplitude range undetectable: absent FHR variability
2. Amplitude range $> \text{undetectable} \leq 5$ beats/min: minimal FHR variability
3. Amplitude range 6 to 25 beats/min : moderate FHR variability
4. Amplitude range > 25 beats/min: marked FHR variability

Time to Reactivity is defined as the time (min) required for two accelerations from the baseline > 15 beats/min lasting at least 15 s^{15} .

Statistics

Four 10 minute FHR segments, two before exercise and two after, were available for interpretation. These were analyzed for baseline FHR, number of accelerations from the baseline, number of decelerations from the baseline and degree of FHR variability. The time to a reactive FHR was determined both before and after exercise testing. The mean of the data from the two interpreters was used for analysis, except for the categorical definition of variability where data from a single interpreter was used (GD). Averaged data from the two interpreters were used in the assessment of continuous variables: baseline heart rate, accelerations, decelerations and time to reactive. Observer means are presented in Table I. Paired Student *t*-statistics were used when comparing the means of continuous variables. Repeated measures ANOVA was used to compare continuous data during the four 10 min time periods followed by application of the Tukey-Kramer multiple comparisons posttest. Chi-squared analysis was used for

comparison of categorical data. Results were considered statistically significant if $p < 0.05$.

Results

Twenty-three women with uncomplicated singleton pregnancies underwent a graded cycle ergometer test to volitional fatigue. The mean gestational age was 32 ± 4 wk. Maternal physical characteristics appear in Table II. All pregnancies resulted in live births. Neonatal characteristics appear in Table III. FHR tracings were available for all subjects for at least 20 min prior to and after maximal exercise testing. A summary of FHR characteristics stratified by the four 10 minute time segments, two pretest and two posttest, can be found in Table IV.

There was a significant difference in baseline FHR over the four time periods analyzed noted on repeated measures analysis of variance. The Tukey-Kramer multiple comparisons posttest identified a significantly higher baseline FHR in the second posttest 10 min segment (mean = 145 beats/min $\pm$ 12) as compared to the first pretest 10 min segment (mean = 139 beats/min $\pm$ 9, $p < 0.05$) and the second pretest 10 min segment (mean = 139 beats/min $\pm$ 10, $p < 0.01$). There were significantly fewer accelerations in the second posttest 10 min segment (mean = 1.5 ± 1.2) when compared to the second pretest 10 min segment, (mean = 2.4 ± 1.6 , $p < 0.01$). FHR decelerations were uncommon regardless of the time segment and no significant differences were found between time segments. For each time segment, assessment of variability was categorized into either undetectable/minimal or moderate/marked. Chi-squared analysis identified no significant differences in the amount of variability in the two consecutive time segments before or

after maximal exercise testing. However, there was a significant reduction in FHR variability between the first pretest time segment and both the first posttest time segment, ($p < 0.01$) and the second posttest time segment, ($p < 0.05$). There was also a significant decrease in FHR variability between the second pretest time segment and the first posttest time segment, ($p \leq 0.01$). There was a significantly increased time to achieve reactivity after maximal exercise testing. The mean difference was 8.5 min, ($p \leq 0.0001$). No fetuses demonstrated tachycardia or bradycardia before maternal exercise. Posttest tachycardia occurred with 2 tracings, one at 165 beats/min for 20 min from a pretest baseline of 150 and a second at 163 beats/min during the second 10 min posttest segment from a pretest baseline of 143 beats/min and first 10 min posttest baseline of 160 beats/min. A single episode of transient bradycardia was seen. Immediately posttest the FHR was 60 beats/min and climbed gradually to 120 beats/min over 6 min. This subject further medical evaluations which identified previously undiagnosed intrauterine growth restriction which led to induction of labor three days posttest.

Discussion

This study was conducted to characterize the effects of an acute bout of strenuous exercise performed by healthy, physically active women in late gestation on FHR characteristics. Particular attention was paid to standardization of inclusion criteria, the exercise protocol and testing, and analysis of fetal responses. As hypothesized, FHR responses were minimal and transient under these conditions.

The results of this study confirm that the most common FHR response to an acute bout of strenuous exercise is an increase in FHR immediately post-exercise¹⁶⁻²⁵. Mild tachycardia occurred in 9% of tracings. The baseline FHR was significantly higher (~ 6

beats/min) in the second posttest 10 min segment compared to the first and second 10 min pretest segments. This difference is not likely to be clinically significant. Mean baseline FHR did not return to pre-exercise value within 20 min post exercise. Others have reported return to pre-exercise baseline within 20 to 30 minutes^{4,17,19,22,23,24,27}. Integrated fetal chemoreceptor, baroreceptor and adrenal responses appear to influence transient increases in FHR resulting in increased fetal cardiac output and hence, increased oxygen availability²¹. This may be a protective mechanism or reflex response to compensate for relative hypoxia resulting from reduced uterine blood flow during maternal exercise^{21, 26}.

Post exercise fetal bradycardia has been reported to occur in 15-20% of fetuses after strenuous exercise^{4,17,19,22,27}. Except for the case of significant fetal growth restriction, no episodes of fetal bradycardia occurred in our study. Bradycardia is a reflex vagal response to significant hypoxia due to maternal hypotension and/or reduced uterine blood flow during recovery. It protects the fetus by preserving blood flow and oxygen delivery to vital organs including the brain and heart³.

Bradycardia may not have occurred frequently in this study for several reasons. Subjects were conditioned, thus may have maternal and fetal compensatory mechanisms to prevent fetal hypoxia^{4,22,25,28}. Such women may be able to perform at a higher work rate before inducing fetal hypoxic stress as less cardiac output is redistributed toward skeletal muscle and away from the placenta^{22,25} and they may have greater placental volume²⁸. The exercise protocol of this study was shorter than that of other studies such as Manders et al.²⁴ and involved the use of a cycle ergometer instead of modes requiring

greater muscle mass. Shorter duration and reduced percentage of maternal muscle mass both contribute to smaller reductions in uterine blood flow thereby maintaining greater fetal PO_2 ⁶. Another reason why bradycardia has been reported in some studies but not in others is due to varied definitions of this FHR characteristic⁴.

Variability was reduced following exercise but returned toward pretest values in the second 10 min period following exercise cessation. Reduced variability was also observed by Artal¹⁷ in 22.5% of cases lasting 6 - 7 min, and by Manders et al. in association with bradycardic incidents for 20 min post exercise²⁴. Carpenter et al.²⁷ observed bradycardia with normal FHR variability within 3 min of cessation of exercise in 16.2 percent of maximal cycle ergometer tests. (Bradycardia was defined as $FHR < 110$ beats/min for ≥ 10 s.) No change in variability occurred in fetuses of healthy pregnant women in the studies of O'Neill²³ or vanDoorn et al.²⁰. Variability is thought to indicate CNS integrity, adequate oxygenation and fetal well-being^{3,4}. However, a reduction in variability in the absence of other ominous findings such as decelerations may not imply an asphyxial insult³.

The present study observed a reduction in accelerations, no change in decelerations and an increase in time to achieve reactivity after exercise. Few studies report information about these fetal characteristics. O'Neill observed no FHR decelerations or reduction in accelerations with strenuous maternal exercise²³. Accelerations in Artal's study¹⁷ were similar before and after strenuous exercise. VanDoorn et al. found no change in pattern pre- to postexercise²⁰. Carpenter et al. observed normal reactive tracings within 30 min post exercise²⁷.

An important advantage of the present study over previous investigations of fetal

responses to maximal exercise testing is the availability of very detailed information on maternal physiological responses to the same maximal exercise tests⁴. In this regard, Kemp et al.¹¹ used a modern physicochemical approach to study acid-base responses of nine of the present study subjects and Heenan et al.¹² employed state of the art breath-by-breath methodologies to study metabolic and respiratory responses of the remaining 14 subjects during and following the exercise test. It is noteworthy that both studies reported no significant differences in the peak work rate achieved in healthy active pregnant subjects compared to the nonpregnant controls.

Heenan et al.¹² also observed no significant differences between pregnant and nonpregnant subjects for absolute maximal oxygen uptake (expressed in L/min), oxygen uptake at the ventilatory anaerobic threshold, oxygen uptake at the point of respiratory compensation or calculated working efficiency. However, the respiratory exchange ratio at peak exercise was significantly reduced during pregnancy, suggesting reduced carbohydrate utilization. These findings were also consistent with the earlier reports of Lotgering et al.^{13,14} who studied the exercise responses of healthy pregnant women using the same cycle ergometer testing protocol. In association with the blunted respiratory exchange ratio at peak exercise, Heenan et al. also reported significantly lower values during pregnancy for peak post-exercise lactate concentration and excess post-exercise oxygen consumption (ie. oxygen debt). All of these results suggest that maternal ability to utilize carbohydrate and produce lactic acid during heavy exercise above the point of respiratory compensation is reduced in late gestation. This was attributed to augmented insulin resistance caused by gestational hormones and may be an important mechanism to protect fetal glucose availability from the maternal blood

glucose pool⁴.

The parallel study of Kemp et al. demonstrated that the pregnant subjects were able to maintain lower plasma hydrogen ion concentrations (higher pH) than nonpregnant controls in the resting state, at peak exercise and during the immediate 15 min post-exercise recovery period via a combination of respiratory and metabolic adaptations. Thus, maternal capacity for weight-supported work is well-preserved and the ability to regulate acid-base balance during and following brief strenuous exercise is maintained in healthy active pregnant women in late gestation.

In summary, the results of this study reveal minimal changes in FHR in response to maximal exercise testing of active pregnant women in the third trimester. Fetal bradycardic responses were not seen in normally grown fetuses and the pregnancy outcome of all healthy women with uncomplicated pregnancies was normal. Considered in relation to the maternal data summarized above, the present study results suggest that maximal maternal exercise testing using a brief cycle ergometer testing protocol is safe in this group under carefully controlled conditions for research or medical diagnostic purposes. However, use of maximal exercise intensities in chronic physical conditioning programs may not be safe and could result in altered fetal growth^{4,29}. The single episode of bradycardia demonstrates the need for screening, including estimates of fetal weight prior to maximal exercise testing.

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Table IA Observer FHR, Accelerations and Decelerations

FHR	Pretest 1 st 10 min		Pretest 2 nd 10 min		Posttest 1 st 10 min		Posttest 2 nd 10 min	
	GD	RV	GD	RV	GD	RV	GD	RV
FHR (beat/min)	139 ± 10	139 ± 9	136 ± 10	140 ± 10	139 ± 16	145 ± 9	146 ± 13	146 ± 10
Accelerations (#/10 min)	2 ± 2	2 ± 2	3 ± 3	2 ± 2	1 ± 1	2 ± 2	2 ± 2	1 ± 1
Decelerations (#/10 min)	0 ± 0.2	0.3 ± 0.6	0 ± 0.02	0 ± 0	0.2 ± 0.4	0.3 ± 0.8	0 ± 0	0.3 ± 0.4

Values are means ± SD

Table 1B Observer Time to Reactivity (min)

Pretest (20 min)		Posttest (20 min)	
GD	RV	GD	RV
9.4 ± 8.9	10.7 ± 7.2	14.1 ± 7.4	19.2 ± 13

Values are means ± SD

Table II. Maternal Physical Characteristics

Variable			
Age (y)	32	±	4
Body height (cm)	162	±	6
Body mass (kg)	74.3	±	7.9
Body Mass Index (kg/m ²)	28	±	2.6
Sum of seven skinfolds (mm)	130	±	43
Resting heart rate (beats/min)	91	±	11
Peak Heart Rate (beats/min)	176	±	6
Parity	0.7	±	0.9
Gestational Age (wk)	35.0	±	1.6
Peak Work Rate (watts)	184	±	28
Resting Lactate (mmol/l)	1.3	±	0.6
Peak Post-exercise Lactate (mmol/l)	9.8	±	2.4
Resting blood pressure (mmHg)	120/68	±	3.7/9.5

Values are means ± SD

Table III. Neonatal Characteristics

Variable	
Apgar score - 1 min	7.9 ± 1.5
- 5 min	9.0 ± 0.2
Birth weight (g)	3454 ± 446
Birth length (cm)	51.0 ± 2.5
Head circumference (cm)	34.4 ± 1.5
Cord artery pH/buffer base (base excess)	$7.2 \pm 0.1/38.8 \pm 4.2$

Values are means $\pm$ SD

Table IV. Fetal Heart Rate Characteristics After Maximal Exercise

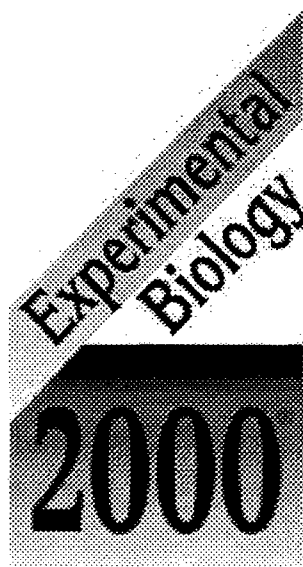
Fetal Heart Characteristic	Time 1 First 10 minutes Pretest	Time 2 Second 10 minutes Pretest	Time 3 First 10 minutes Posttest	Time 4 Second 10 minutes Posttest
Baseline FHR (beats/min)	139 ± 9 ^a	139 ± 10 ^b	142 ± 11	145 ± 12
Accelerations	2.1 ± 1.4	2.4 ± 1.6	1.7 ± 1.4	1.5 ± 1.2 ^c
Decelerations	0.2 ± 0.39	0.02 ± 1.0	0.3 ± 0.4	0.1 ± 0.2
Variability				
• Absent/minimal	2 ^{d,e}	3 ^f	12	9
• Moderate/ marked	21	20	11	14
Time to Reactivity (min)	10.6 ± 7.3 ^g		19.1 ± 9.7	

Values are means ± SD

- a. significantly less than Time 4 at $p < 0.05$
- b. significantly less than Time 4 at $p < 0.01$
- c. significantly less than Time 2 at $p \leq 0.01$
- d. significantly less than Time 3 at $p < 0.01$
- e. significantly less than Time 4 at $p < 0.05$
- f. f. significantly less than Time 3 at $p \leq 0.01$
- g. significantly less than posttest time to reactive at $p \leq 0.0001$

Appendix G

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Comparison of Physicochemical Approaches to Acid-Base Analysis in Healthy Women: Effects of Menstrual Cycle Phase

R.J. Preston, A.P. Heenan and L.A. Wolfe

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The ability to calculate $[H^+]$ using three physicochemical approaches to acid-base analysis was compared across different phases of the menstrual cycle. As described by Stewart (*Can. J. Physiol. Pharm.* 61:1444, 1983), plasma $[H^+]$ is determined by three independent variables: the partial pressure of carbon dioxide (PCO_2), the strong ion difference ($[SID]$), and total weak acid ($[A_{TOT}]$). The three models differ in their representation of $[A_{TOT}]$: the Stewart model represents it as total protein ($[TP]$), the Fencil model (*J. Clin. Lab. Med.* 120:713, 1992) as the concentrations of albumin ($[albumin]$) and total phosphate ($[Pitot]$), and the modified Stewart (*Anesth. Analg.* 81:1043, 1995) as $[TP]$ and $[Pitot]$. The menstrual cycle is an ideal model since phase-related differences in the hormonal milieu exist causing alterations in the weak acid component. Subjects were healthy, physically active women with similar physical characteristics tested during either the follicular (FP, n=14) or luteal phase (LP, n=14) of the menstrual cycle. Arterialized blood samples were obtained at rest and following 5 minutes of upright cycling at both 70% and 110% of the ventilatory threshold (T_{VENT}). Measurements included plasma $[H^+]$, PCO_2 , $[TP]$ to reflect total weak anion ($[A_{TOT}]$), $[albumin]$, $[Pitot]$, and the strong ion difference ($[SID]$). Regardless of menstrual cycle phase, the Stewart model accurately predicted measured $[H^+]$ at rest and during exercise above and below T_{VENT} . Also in both groups, the Fencil model underpredicted measured $[H^+]$ at rest and during exercise above and below T_{VENT} . Finally, the Modified Stewart model overpredicted measured $[H^+]$ at rest and during exercise above and below T_{VENT} in the FP, and at rest and below T_{VENT} at 70% T_{VENT} in the LP. In conclusion, the Stewart model accurately predicts $[H^+]$ in healthy women regardless of their menstrual cycle phase.

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Physicochemical Analysis of Phasic Menstrual Cycle Effects on Acid-Base Balance

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This study employed Stewart's physicochemical approach (*Can. J. Physiol. Pharm.* 61:1444, 1983) to examine the mechanisms of plasma $[H^+]$ homeostasis at rest and during exercise during different phases of the menstrual cycle. Subjects were two groups of healthy, physically active women with similar physical characteristics tested during the follicular (FP, $n=14$) and luteal phase (LP, $n=14$) of the menstrual cycle, respectively. Arterialized blood samples were obtained at rest and following 5 minutes of upright cycling at both 70% and 110% of the ventilatory anaerobic threshold (T_{VENT}). Measurements included arterialized plasma $[H^+]$, PCO_2 , total protein ($[TP]$) to reflect total weak anion ($[A_{TOT}]$) and the strong ion difference ($[SID]$). No significant between group differences for $[H^+]$ were observed at rest or in response to exercise. This is consistent with previous reports that $[H^+]$ is unaffected by menstrual cycle phase. At rest, significant reductions in $[A_{TOT}]$ and PCO_2 during the luteal phase (stresses to decrease $[H^+]$) were offset by a reduction in $[SID]$. During exercise, significantly lower values for $[A_{TOT}]$ persisted during the luteal phase. Since $[H^+]$ is affected by the cumulative effects of all three independent variables and the trends for PCO_2 and $[SID]$ were similar to the resting state, these trends must have offset the tendency of a reduced $[A_{TOT}]$ to lower $[H^+]$. The transition from rest to exercise in both the FP and LP resulted in a significant increase in $[H^+]$ at 70% T_{VENT} vs. rest, and at 110% T_{VENT} vs. both rest and 70% T_{VENT} . Analysis of the contributions of each independent variable to exercise-induced changes in $[H^+]$ revealed no significant phase-related differences. In conclusion, mechanisms of acid-base regulation appear to be unaffected by menstrual cycle phase. $[H^+]$ homeostasis at rest and during exercise is maintained during the luteal vs. follicular phase by significant reductions in all three independent variables.

Supported by U.S. Army Medical Research & Materiel Command Contract #DAMD17-96-C-6112; Ontario Thoracic Society; N.S.E.R.C. (Canada).

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Volume 24, Number 5, October 1999

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CONTENTS

Exercise & Nutrition Update

Dietary Carbohydrate and its Effects on Metabolism and
Substrate Stores in Sedentary and Active Individuals

Terry E. Graham and Kristi B. Adamo 393

Book Reviews 416

Proceedings of the 7th Annual Meeting of the
Canadian Society for Exercise Physiology

419

Conference Proceedings Index 490

Editorial Statement 494

fighters: A 20 Year

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Trunk mm	LBM kg	FM kg
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Sympathoadrenal Responses to Exercise Above and Below the Ventilatory Anaerobic Threshold in Late Gestation

N.D. Avery, L.A. Wolfe, C.E. Amara and M.J. McGrath. School of Physical and Health Education and Departments of Physiology and Obstetrics & Gynaecology, Queen's University, Kingston, Ontario (Sponsor: L.A. Wolfe).

The study examined the effects of human pregnancy on sympathoadrenal responses to exercise. Plasma catecholamines (epinephrine, norepinephrine) were measured via HPLC in 12 healthy, physically active pregnant women (PG: mean gestational age 34 ± 1 wk) at rest and following 6 min of cycle ergometer exercise at both 60% and 110% of the ventilatory anaerobic threshold (Tvent, V-slope method). Results were compared to an age-matched nonpregnant control group (NPG, n=14). As expected, both epinephrine and norepinephrine values increased significantly in response to strenuous exercise in both groups. However, significantly lower values were observed in the PG for epinephrine under all experimental conditions and for norepinephrine at 110% Tvent. These findings considered in relation to heart rate variability data for the same subjects (Avery *et al.*, *Can. J. Appl. Physiol.* 23:462, 1998) support the hypothesis that sympathoadrenal responses to strenuous exercise are blunted in late gestation. Supported by U.S. Army Medical Research and Materiel Command Contract # DAMD17-96-C-6112 and NSERC (Canada).

Metabolic Profile of Distance Running Intermittent Training Programs.

C. Babineau and L. Léger. École d'éducation physique et loisir, Université de Moncton, Moncton, NB, and Département de Kinésiologie, Université de Montréal, Montréal, Qc

Six different intermittent training workouts with different work to rest ratios (WR) were compared using both the VO_2 -power and the HR-power regressions to determine O_2 deficit and energy contributions on 7 runners. The energy requirement of each workout as determined by the O_2 deficit method follows:

Event	Intervals	WR ratio	%Aerobic	%Anaerobic
1500m	1. 4 x ~400m @ 60s	1/1	74	26
	2. 4 x ~400m @ 60s	2/1	78	22
	3. 8 x ~200m @ 30s	1/1	73	27
	4. 8 x ~200m @ 30s	1/5	56	44
5000m	1. 5 x ~800m @ 2:30	2/1	89	11
	2. 5 x ~800m @ 2:30	5/1	95	05

Also these intermittent workouts require more than 90% VO_2max . Even though the aerobic contribution was slightly higher with the heart rate deficit method, the overall energy profile was similar to the one obtained with the VO_2 deficit. The simulation of 1500m and 5000m are best accomplished using WR ratios of 1/1 or 2/1 and 5/1, respectively.

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Respiratory Gas Exchange Above and Below T_{VENT} In Late Gestation

A.P. Heenan and L.A. Wolfe. School of P.H.E. and Dept. of Physiology,
Queen's University, Kingston, Ont. (Sponsor: L.A. Wolfe)

Effects of pregnancy on gas exchange were studied above and below the ventilatory threshold (T_{VENT}). The pregnant group (PG; $n=15$; gestational age 37.1 ± 0.2) and nonpregnant control group (CG; $n=15$) were healthy, active women matched for age and fitness. Breath-by-breath measurements, plasma lactate and serum progesterone, were measured at rest and both 70% and 110% T_{VENT} during upright cycling. Oxygen uptake and lactate responses did not differ between groups at either exercise level, indicating similar metabolic stress. Minute and alveolar ventilation were significantly higher in the PG vs. CG at rest and both exercise levels as a result of higher breathing frequencies and tidal volumes (V_T). End-tidal O_2 tension, V_T /inspiratory time (T_i) and the ventilatory equivalents for CO_2 ($\dot{V}_E/\dot{V}CO_2$) and O_2 were higher in the PG vs. CG at all measurement times, except for $\dot{V}_E/\dot{V}CO_2$ at rest and V_T/T_i at 110% T_{VENT} . End-tidal CO_2 tension was lower in the PG at all measurement times. Serum progesterone was significantly correlated with $\dot{V}_E/\dot{V}CO_2$ at both exercise levels and V_T/T_i at rest and 110% T_{VENT} . Respiratory gas exchange during exercise is altered by pregnancy, but does not limit aerobic exercise performance. Supported by U.S. Army Medical Research and Materiel Command Contract # DAMD17-96-C-6112, Ontario Thoracic Society, and NSERC (Canada).

Maximal Accumulated Oxygen Deficit in Running and Cycling.

D.W. Hill and K.M. Davey, Department of Kinesiology, University of North Texas, Denton, Texas USA. (Sponsored by D.W. Hill).

The purpose of this study was to compare anaerobic capacity in running and in cycling, with accumulated oxygen deficit in fatiguing short-duration exercise as the measure of anaerobic capacity. Five women and two men performed a series of constant-speed treadmill tests and constant-power cycle ergometer tests, each on a different day, at a variety of speeds and power outputs selected to elicit fatigue in 3 to 10 min. Overall, mean time to fatigue was 328 s in running tests and 374 s in cycle ergometer tests. In each test, the $\dot{V}O_2$ was determined using a MedGraphics CPX cart (St. Paul, MN USA). Accumulated oxygen deficit was calculated for each participant for each exercise mode. As expected, peak 30-s $\dot{V}O_2$ was higher ($p = 0.03$) in running ($2.63 \pm 0.66 \text{ l}\cdot\text{min}^{-1}$, or $38.0 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) than in cycling ($2.41 \pm 0.71 \text{ l}\cdot\text{min}^{-1}$, or $34.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). However, oxygen deficit tended to lower ($p = 0.10$) in running ($2.97 \pm 1.21 \text{ l}$, or $43.0 \text{ ml}\cdot\text{kg}^{-1}$) than in cycling ($3.27 \pm 1.04 \text{ l}$, or $47.4 \text{ ml}\cdot\text{kg}^{-1}$). It was concluded that exercise mode may be a factor in determining the available anaerobic contribution to fatiguing short-duration exercise.

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ABSTRACTS PART II

Abstracts 487.1-857.4

Tutorials T1-T15

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790.25

EXHAUSTIVE EXERCISE SUPPRESSION OF MACROPHAGE ANTIGEN PRESENTATION IS NOT MEDIATED BY SOLUBLE FACTORS

M.A. Coddia & J.A. Woods. Dept. of Kinesiology, Univ. of Illinois at U-C, Urbana, IL 61801

The macrophages (Mφ's) ability to present antigen is central to the development of specific T cell mediated immunity. Previously, we have reported that exhaustive exercise (EXH) significantly suppresses Mφ antigen presentation (AP). However, the mechanism by which EXH decreases Mφ AP is unknown. Therefore, this study determined if soluble mediators (i.e. IL-1, PGE₂) produced by Mφ's during *in vitro* culture were responsible for the depressed AP. In 3 experiments male Balb/c mice (n=18, 8 wk) were randomly assigned to either exhaustive (EXH, n=9) or a home cage control (HCC, n=9) groups. The mice were exercised on a treadmill exhaustively (15-40 m/min, 5% grade, 3 hr/d) for 4 d during a peritoneal TG inflammation. The HCC group remained in their cages during the exercise protocol. Mice were sacrificed post-exercise on Day 4 and Mφ's were harvested by i.p. lavage. The Mφ's were washed, plated and adhered for 3 hr. The non-adherent cells were washed off and the Mφ's were incubated with chicken ovalbumin for 4 hr. Then the Mφ's were either fixed (0.5% P-Form) or not fixed and cultured with ova specific T cells for 48 hr. The fixation renders the Mφ incapable of producing any soluble factors that might influence AP. The supernatants were harvested for IL-2 and the amount was used as an indication of Mφ AP. No differences in Mφ number or adherence was observed. A significant suppression in AP was observed in the EXH both in the fixed [F(1,15)=74.6, P=0.0001] and not fixed [F(1,17)=24.7, P=0.0003] cultures. These data indicate that the changes in AP following EXH are likely mediated by *in vivo* as opposed to *in vitro* influences on Mφ's.

790.27

ADDITIVE EFFECTS OF MAGNESIUM-POTASSIUM GLYCINATE AND GINSENG ON EXERCISE TIME OF RATS. Q.L. Tulp and S. Ritter, Drexel University, Philadelphia, PA 19104

Both ginseng (G) and chelated magnesium-amino acid complexes have been reported to demonstrate ergogenic effects when administered to animals or man. To determine the ergogenic effects of ginseng (G) vs a chelated magnesium glycinate and potassium glycinate complex (MgKGly) or a combination of both (MgKGlyG) on exercise capacity, groups of age 4 months adult lean weight stable normally fed (Purina Chow #5001 plus house water) and housed (50% RH, 20°C, 12-12 light cycle[0800-2000 h light]) sedentary virgin female LA/N rats were administered water (Controls), MgKGly, G, or a combination of MgKGly+G via gavage for 3 consecutive days, and subjected to a determination of the swim time to fatigue (SWTF) under controlled environmental conditions exactly 2 hours following the final gavage. Animals were exercised in 30 cm of water maintained at 30°C at weekly intervals. Control animals were administered an equal volume of water, or equimolar amounts of magnesium oxide (MgO) in a volume of 1 ml of water. The SWTF was greatest in MgKGlyG > MgKGly+G > MgO > Water. These results indicate the MgKGly demonstrated significant ergogenic effects in sedentary rats, and that addition of G to the nutritional regimen resulted in a further enhancement of the ergogenic effects of Mg in untrained rats.

790.29

NET K⁺ UPTAKE IN HUMAN ERYTHROCYTES (RBCs).

S.P. Grudzien and M.I. Lindinger. Dept. of Human Biology and Nutritional Sciences, University of Guelph, Guelph, ON, Canada. N1G 2W1

There is controversy concerning the rate at which RBCs transport K⁺ in vivo in response to the rapidity and magnitude of changes in plasma status during high intensity exercise in humans. The present pilot study examined net K⁺ uptake (J_{netK}) in human RBCs incubated in an exercise simulated (ES) plasma that mimicked the increased plasma osmolality (370 mosmol/kg), epinephrine (10 nM), [K⁺] (7 mM), and lactic acid (30 mM) seen with high intensity exercise. Plasma [K⁺] was measured *in vitro* (35°C) with a K⁺ selective electrode. Contributions of the Na,K ATPase and NaK2Cl cotransporter to RBC J_{netK} were quantified using ouabain (0.1 mM) and bumetanide (0.1 mM), respectively. Blood obtained from resting males (n = 4, age 22 to 24 y) was separated into RBCs and plasma. Addition of each subject's RBCs to their control plasma, (n = 4; no additions) to give a hematocrit of about 40%, had no effect on plasma [K⁺]. In contrast, RBCs added to ES plasma (n = 3), rapidly reduced plasma [K⁺] to 5.27 ± 0.25 mM within 100s, with no change thereafter. Calculated peak J_{netK} occurred within the first 15 s and was 2.52 mmol/L plasma/min. The K⁺ channels, Na,K ATPase and NaK2Cl contributed 83%, 19%, and 2.4%, respectively, to the peak J_{netK}. It is concluded that RBC J_{netK} occurs at high rates upon exposure to the combined stimulatory effects of increased plasma osmolality, epinephrine, [K⁺] and lactic acid seen during high intensity exercise. This initial high rate of net K⁺ transport supports the gain of RBC [K⁺] previously shown in *in vivo* studies of very high intensity exercise in humans. Supported by Natural Sciences and Engineering Research Council of Canada.

790.26

EFFECTS OF AGING AND EXERCISE TRAINING ON INSULIN RECEPTOR, IRS-1 AND PI 3-KINASE IN RAT SKELETAL MUSCLE.

M. Nagasaki, N. Nakai, Y. Shimomura, T. Murakami, N. Fujitsuka, Y. Oshida, and Y. Sato. Nagoya Univ. and Nagoya Institute of Technology, Nagoya, Japan, 4640814.

Exercise training prevents an aging-induced decrease in insulin sensitivity. In the present study, we examined effects of aging and training on gene expression and protein content of insulin signaling molecules in rat skeletal muscle. A half of rats was allocated to sedentary rats and another half was trained by voluntary running. At 4, 12 and 27 wk old, rats in both groups were killed, and then gastrocnemius muscle was removed. The level of insulin receptor substrate-1 (IRS-1) mRNA, measured by RT-PCR, in sedentary rats was significantly decreased with aging: 74% for 12 wk old and 49% for 27 wk old relative to that of 4 wk old, but that in trained rats was not decreased with aging and was significantly higher than that in sedentary rats at 27 wk old. The IRS-1 protein, measured by Western blotting, in sedentary rats was significantly decreased with aging: 63% for 27 wk old relative to that of 4 wk old, but that in trained rats was not decreased with aging. Although the level of phosphatidylinositol 3-kinase (PI 3-kinase) mRNA in sedentary rats was not altered with aging. The PI 3-kinase protein in the same group was significantly decreased with aging: 73% for 27 wk old relative to that of 4 wk old. However, PI 3-kinase protein in trained rats was not decreased with aging. These results suggest that the improvement of insulin sensitivity by training may be due, at least in part, to maintain protein contents of IRS-1 and PI 3-kinase and that exercise training may affect transcriptional regulation for IRS-1 and posttranscriptional regulation for PI 3-kinase.

790.28

THE EFFECTS OF A MAGNESIUM-ASPARTATE SUPPLEMENT ON SERUM MAGNESIUM, LACTATE, AND EXERCISE OUTCOME IN RATS. C. Johnston, S. Ritter, D. Jones, A. Parkman, and Q.L. Tulp, Drexel University, Philadelphia, PA 19104

Magnesium (Mg) plays a pivotal role in numerous aspects of energy metabolism, where it functions as an essential cofactor in ATP-dependent biochemical reactions of energy transfer, while muscle or blood lactate accumulation may impede exercise performance. To determine the effects of MgAsp on exercise outcome, groups of lean LA/Ntl rats were administered a mixture of MgAsp+KAsp for 3 days, where the minerals were present either as a chelated or a salt form via intragastric gavage, followed by subjecting the animals to a swim to the onset of fatigue (STTF) under controlled conditions (30°C water temp, 30 cm depth) exactly 2 hr after the last gavage. Controls received 1 ml dH₂O via gavage. Additionally, measures of blood glucose (BG), lactate (BL), and Mg were obtained before and immediately after completion of the swim exercise. Serum Mg concentration increased after Mg administration (MgAsp chelate > MgAsp Salt), and decreased following exercise in all groups. The STTF of MgAsp+KAsp chelate > MgAsp+KAsp salt > controls. BG decreased modestly and BL increased significantly in all rats, but the exercise-induced increase in BL was of lesser magnitude in rats administered the chelated vs. the salt or control treatments. These results indicate that luminal absorption of Mg may be improved when administered as an amino acid chelate vs a salt form, and thus attenuate the exercise induced decreases in Mg availability which may occur during exercise. Moreover, the improved substrate and Mg availability of MgAsp chelate was associated with lesser increments in BL following exercise, and thus may contribute to the enhanced ergogenic responses which were observed via enhancement of Mg-dependent elements of metabolism and energy transfer of muscle.

790.30

Chemical Control of Ventilation at Rest and During Exercise in Healthy Women

A.P. Heenan, L.A. Wolfe. Queen's University, Kingston, Ontario, Canada

This study addressed the hypothesis (*Can. J. Appl. Physiol.* 19:334-349, 1994) that plasma osmolality, the strong ion difference ([SID]: ([Na⁺] + [K⁺] + 2[Ca²⁺]) - ([Cl⁻] + [La⁻])) and circulating water balance hormones influence chemical control of breathing in healthy women. Subjects were healthy, physically active pregnant women (PG, n=19, gestational age=37.0±0.2 wk) and healthy nonpregnant women (CG, n=15) in varying stages of the menstrual cycle with similar characteristics. Arterialized blood gases (PaCO₂, PaO₂), hydrogen ion concentration ([H⁺]), plasma osmolality, [SID], progesterone, angiotensin II and arginine vasopressin (AVP) were measured in the resting state and during cycle ergometer exercise at work rates corresponding to 70% and 110% of the ventilatory anaerobic threshold (T_{VENT}). Pooling of the data from the two groups revealed significant correlations (Pearson r) at rest and the 70% T_{VENT} work rate between PaCO₂ (a measure of respiratory sensitivity) and plasma progesterone (r=-0.80, -0.80), plasma osmolality (r=0.57, 0.54) and plasma [SID] (r=0.72, 0.56), respectively. The correlations weakened slightly at 110% T_{VENT}, but remained significant. PaCO₂ was also significantly correlated (r=0.64) with AVP at rest. These results support the hypothesis that in addition to circulating progesterone levels, AVP, osmolality and [SID] are involved in the chemical control of ventilation in pregnant and nonpregnant female subjects. Supported by U.S. Army Medical Research and Materiel Command Contract # DAMD17-96-C-6112, Ontario Thoracic Society and N.S.E.R.C. (Canada).

790.31

Interactive Effects of Pregnancy and Exercise on Plasma Osmolality, Electrolytes and Circulating Hormones
 R.J. Preston, A.P. Heenan, L.A. Wolfe. Queen's University, Kingston, Ontario, Canada

This study examined the interactive effects of pregnancy and exercise on plasma osmolality, electrolytes and hormones involved in the regulation of water balance. Subjects were a group of healthy, active pregnant women PG, $n=19$, gestational ages 24-38 wk and a nonpregnant female control group CG, $n=15$ with similar characteristics. Plasma osmolality, electrolyte concentrations $[Na^+]$, $[Cl^-]$ and the salt and water balance hormones angiotensin II AII, arginine vasopressin AVP and atrial natriuretic peptide ANP were measured in arterialised blood in the resting state and during cycle ergometer exercise at work rates corresponding to 70% and 110% of the ventilatory anaerobic threshold T_{vent} . As expected, osmolality, $[Na^+]$, AVP, and ANP increased significantly in response to exercise in both groups. Values for osmolality, $[Na^+]$, and AVP were significantly lower in the PG vs. CG at all measurement times, but no significant between group differences were observed for AII. However, trends were observed for higher values at rest in the PG vs. CG, and an exercise-induced increase in the CG concomitant with an exercise-induced reduction in the PG. Pregnancy-induced changes in plasma osmolality, electrolytes, AVP and ANP exist in the resting state and persist during exercise. All responses to strenuous exercise in pregnancy warrant further investigation. Supported by U.S. Army Medical Research and Materiel Command Contract # DAMD17-96-C-6112; Ontario Thoracic Society; and N.S.E.R.C. (Canada).

790.33

In vivo net muscle protein balance in human muscle during exercise.

K.D. Tipton, S.E. Miller, B.B. Rasmussen, S.E. Wolf and R.R. Wolfe. Univ. of Texas Medical Branch, Galveston, TX, 77550.

Previously, we found that there was an anabolic response of muscle protein metabolism following exercise. However, the response of muscle protein metabolism during exercise has never been directly measured. We used a primed, continuous infusion of L- $[^2H_5]$ phenylalanine to directly measure muscle protein synthesis (MPS), breakdown (MPB) and net muscle protein balance (NB) from human muscle in vivo in the fasted state at rest and during a resistance exercise bout. Protein metabolic parameters were determined from a 3-compartment model with blood samples from femoral arterial and venous catheters and muscle biopsies from the vastus lateralis. Leg blood flow was increased from 3.63 ± 0.60 mL/min-100mL leg vol. $^{-1}$ at rest to 11.09 ± 1.66 mL/min-100mL leg vol. $^{-1}$ ($p=0.03$) during exercise. During exercise, both MPS and MPB tended to be reduced from resting levels, but the differences did not reach statistical significance ($p=0.06$). During resistance exercise, mean MPS was 66% (from 56 ± 13 to 19 ± 7 nmol phexmin $^{-1}$ x 100mL leg vol. $^{-1}$) lower during exercise compared to rest, while mean MPB was reduced by 52% from 75 ± 14 to 36 ± 7 nmol phexmin $^{-1}$ x 100mL leg vol. $^{-1}$) from rest. Thus, NB (protein synthesis - protein breakdown) was unchanged from rest to exercise (-18 ± 2 to -17 ± 4 nmol phexmin $^{-1}$ x 100mL leg vol. $^{-1}$, respectively). From these data, we conclude that there is no anabolic response of muscle protein metabolism during resistance exercise, thus the anabolic response must be initiated at some point following exercise. Supported by NIH RO1 38010 and NIH GCRC Grant 00073.

790.32

DETERMINATION OF GLUCOSE RATE OF APPEARANCE (R_a) DURING EXERCISE: ONE VS. TWO-POOL MODELS.

A.R. Coggan, B.C. Ruby, and T.W. Zderic. Univ. of Maryland Sch. of Med., Baltimore, MD 21201, Univ. of Montana, Missoula, MT 59812, and Univ. of Texas, Austin, TX 78712

The purpose of this study was to compare estimates of glucose R_a during exercise calculated using the simplified single-pool model of Steele with those obtained using a more realistic representation of the glucose system. Six healthy but untrained subjects were studied at rest and during 50 min of continuous exercise (25 min each at 45% and 60% of VO_{2peak}) while $[6,6-^2H]$ glucose was infused at a constant rate and blood was sampled every 5 min. Glucose R_a was calculated A) using the Steele equation, assuming effective volumes of distribution (V_d) ranging from 50 to 250 mL/kg, and B) using a two-pool model with parameters specific for exercise (FASEB J. 10:A1652, 1996). Based on the two-pool model, glucose R_a increased 3-fold during exercise, rising from 13.5 ± 0.6 μ mol $\cdot$ min $^{-1}$ kg $^{-1}$ at rest to 38.9 ± 4.0 μ mol $\cdot$ min $^{-1}$ kg $^{-1}$ after 50 min. Not unexpectedly, no single V_d in the Steele equation gave results comparable to the two-pool model at all time points during exercise. However, from 15 min on the results obtained using a V_d of 150 mL/kg were essentially the same as those obtained using the more complicated two-pool model. Except for the early phases of exercise, the classical Steele approach appears to be adequate for estimating glucose R_a during low to moderate intensity exercise.

790.34

Occult alveolitis is related to proinflammatory cytokine levels in patients with sarcoidosis.

S. Nanas, A. Samakovli, E. Pappa, A. Papamichalopoulos, K. Konstantinou, D. Sakellariou, E. Kavada, Koutsouris, Ch. Roussos. Department of Pulmonary and Critical Care Medicine, Kapodistrian University, Athens, GREECE.

Proinflammatory cytokine (PC) levels have been found to increase in various materials in patients with sarcoidosis. In order to investigate the relationship between PC levels and the presence of occult alveolitis we studied 22 patients with sarcoidosis and 13 healthy subjects [mean $\pm$ SD (age: 44 ± 13 and 30 ± 5 yrs, respectively)]. All patients had normal PFTs and were not on any form of corticosteroid treatment. Participants underwent an incremental symptom-limited exercise test on a treadmill. VO_2 , VCO_2 and VE were measured on a breath-by-breath basis throughout exercise and 5 min of recovery. Expiratory flow limitation (EFL) during exercise was detected by superimposition of the tidal flow-volume loop on the forced maximal flow-volume loop at rest. Blood samples for PC determination by an ELISA high sensitivity analysis, were taken prior to and at peak exercise, and 15 min into the recovery. IL-6 serum levels at rest were significantly ($P < 0.01$) higher in patients as compared to healthy subjects [mean $\pm$ SEM (3.12 ± 0.64 vs 1.09 ± 0.21 pg/ml)]. During exercise IL-6 serum levels were significantly ($P < 0.05$) higher in patients with EFL as compared to those without EFL (4.5 ± 1.1 vs 1.8 ± 0.5 pg/ml). However, multivariate factor analysis revealed that changes during exercise and recovery occurred in a parallel fashion in both patient groups. In conclusion, PC serum levels were found to be related to EFL during exercise (occult alveolitis) in patients with sarcoidosis who had normal PFTs at rest.

EXERCISE/VASCULAR CONTROL (791.1-791.2)

791.1

HEART RATE RECOVERY POST EXERCISE AS AN INDEX OF PARASYMPATHETIC ACTIVITY.

G. Pierpont, D. Stolpmann and C. Gormick (SPON: E.K. Weir). Minneapolis VA Med. Center, Minneapolis, MN 55417 and Univ. of MN, Minneapolis, MN 55455.

The time constant (T) obtained by fitting post-exercise heart rate (HR) recovery to a first order exponential decay curve has recently been promoted as an index of parasympathetic activity. However, acceptance of the technique has been limited, perhaps because reported data have been inadequate to: 1) assess goodness of fit for the model, 2) determine the most appropriate exercise protocol, or 3) optimize the duration of post exercise monitoring. Consequently, we assessed how well exercise HR recovery fit a first order exponential decay model for 9 healthy volunteers (age 24-46) following a Bruce protocol treadmill exercise test performed at both maximal (max) and 2 stages sub-max exercise levels. T stabilized after 3 min of monitoring following both max and sub-max exercise. At max exercise, T varied unacceptably in response to changes in time of onset of monitoring, e.g. -16.7 ± 16.6 (-13.2%) in first 5 sec, and residuals of the fitted curve were non-random. In contrast, sub-max exercise produced consistent T values, e.g. -1.9 ± 3.2 (-4.2%) in the first 5 sec, and residuals were more nearly random. In conclusion, first order decay is an inadequate model for HR recovery post max exercise, but may be reasonable for sub-max exercise.

791.2

FOREARM BLOOD FLOW IS NOT AUGMENTED IN MCARDLES PATIENTS FOLLOWING MILD RHYTHMIC HANDGRIP EXERCISES. S. Wilson, A. Reed, A. Iyanoye, L. Berry, D. Proctor, and M. Joyner, Department of Anesthesia, Mayo Clinic, Rochester, MN, 55905

During large muscle mass exercise, skeletal muscle vasodilation may be augmented in patients with glycogen myophosphorylase deficiency (McArdles disease; JAP 61:391-401, 1996). To determine the time course and magnitude of muscle vasodilation, five McArdles patients (3 females and 2 males, ages 30-52) and five matched controls were studied. Forearm blood flow (FBF) was measured using venous occlusion plethysmography after 1, 5, 10, and 20 rhythmic (30/min) handgrip (HG) contractions of a 4.5 kg pulley-based dynamometer system. Reactive hyperemia (RH) was also measured after five min of forearm ischemia. The table below details mean FBFs, standard errors, and p values in the experimental forearm after each maneuver. None of these values were significantly different at a $p < 0.05$.

	Baseline	1HG	5HG	10HG	20HG	RH
McArdles	2.2	8.0	9.6	9.9	11.2	22.6
FBF	± 0.6	± 1.6	± 2.1	± 2.5	± 2.8	± 2.5
Control	2.3	8.4	11.1	14.5	18.2	31.1
FBF	± 0.5	± 0.9	± 2.2	± 3.6	± 2.9	± 4.9
P value	.876	.803	.622	.322	.127	.158

We conclude McArdles patients do not demonstrate augmented vasodilator responses to brief periods of mild rhythmic forearm handgripping.

SOCIETY FOR MATERNAL-FETAL MEDICINE
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**Society for Maternal-Fetal Medicine
19th Annual Meeting - January 18-23, 1999**

October 15, 1998

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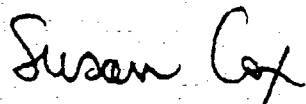
Congratulations! Your abstract *Fetal Heart Response To Strenuous Exercise In Late Gestation*, has been selected for presentation during Poster Session II, which is scheduled for 3:30 pm - 5:30 pm on Thursday, January 21 at the 1999 SMFM Meeting. Out of a total of 1,055 submissions, this abstract was one of 575 accepted for presentation at one of the five Poster Sessions. In order to maximize the impact of your poster presentation on the anticipated 1,400 attendees, please refer to the enclosed guidelines. Your abstract has been assigned a final ID# of 252. Please refer to this number for any inquiries or in any correspondence.

Poster presentations will be judged on site and award-winning posters will be announced at the SMFM's Annual Banquet on Friday evening, January 22. For work presented on Saturday, prizes will be awarded at the end of the Saturday poster session.

If you have any questions or concerns regarding the preparation of your poster, please do not hesitate to contact either Michael L. Socol, MD, 1999 Poster Chair, or me.

Again, congratulations, and we look forward to seeing your work in San Francisco.

Sincerely yours,



Sue Cox, M.D.
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PRINT TYPE 3.5 PT. OR LARGER

FETAL HEART RESPONSE TO STRENUOUS EXERCISE IN LATE GESTATION. A. MacPhail^x, G.A.L. Davies^x, R. Victory^x, L. A. Wolfe^x. School of PHE and Depts. of Ob/Gyn and Physiology, Queen's University, Kingston, ON

OBJECTIVE: To determine the fetal response to and safety of maximal maternal exercise in the third trimester.

STUDY DESIGN: Twenty-three active women with uncomplicated singleton pregnancies between 31-38 wks gestation underwent maximal exercise testing by cycling at 20W for 4 min followed by a ramp increase in work rate of 20W to exhaustion. The fetal heart rate was monitored for two consecutive 10 min segments before and after testing. Fetal heart rate characteristics were classified using NICHD guidelines. Paired Student's t-statistics were used to compare continuous variables before and after testing. Repeated measures ANOVA with the Tukey-Kramer multiple comparisons post-test was used for comparison of continuous data over the 4 time periods. Chi-squared analysis was used for comparison of ordinal data.

RESULTS: There was an increase in baseline fetal heart rate in the second post-test period (mean 145.2 beats/min $\pm$ 11.8) compared to the 2 pretest periods, (means 139.2 beats/min $\pm$ 8.7, $p < 0.05$ and 138.5 beats/min $\pm$ 9.6, $p < 0.01$). There were fewer accelerations in the second post-test period (mean 1.48 $\pm$ 1.23) compared to the second pretest period, (mean 2.43 $\pm$ 1.6, $p < 0.01$). Decelerations were infrequent and no differences were noted. There was an increased time to reactive post-testing (19.1 min $\pm$ 9.7) compared to pretesting, (10.6 min $\pm$ 7.3, $p < 0.0001$). One undiagnosed growth restricted fetus had a bradycardia lasting 6 min which resolved. There were no abnormal neonatal outcomes.

CONCLUSIONS: Maximal third trimester maternal exertion leads to minimal changes in the fetal heart rate. Fetal bradycardic responses were not seen in normally grown fetuses, suggesting that maximal maternal exertion is safe in this group.

Supported by U.S. Army Medical Research and Materiel Command Contract # DAMD17-96-C-6112, Ontario Thoracic Society and NSERC (Canada)

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Revue Canadienne de Physiologie Appliquée

Canadian Journal of Applied Physiology

Contains Abstracts for the
Canadian Society for Exercise Physiology Conference
October 21-24, 1998

Activité Physique, Santé,
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Physical Activity,
Health, and Fitness

Volume 23, Numéro 5, Octobre 1998

Volume 23, Number 5, October 1998

CONTENTS

Research Contributions

- Effects of Split Exercise Sessions on Excess Postexercise
Oxygen Consumption and Resting Metabolic Rate
Khalid S. Almuzaini, Jeffrey A. Potteiger, and Samuel B. Green 433

- Association Between Aerobic Capacity and Carotid-Cardiac
Baroreflex Responsiveness in Women
Tania L. Culham and Gabrielle K. Savard 444

- Book Reviews 456

- Proceedings of the 6th Annual Meeting of the Canadian Society
for Exercise Physiology 461

- Instructions for Authors 524

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Effects of Human Pregnancy on Spontaneous Baroreflex (SBR) Function Above and Below the Ventilatory Anaerobic Threshold.

N.D. Avery, L.A. Wolfe, and M.J. McGrath, Queen's University, Kingston, Ontario. (Sponsored by L.A. Wolfe).

This study examined the effects of human pregnancy on SBR function at rest and during exercise. Subjects were 14 healthy, physically active pregnant women (PG; mean gestational age, 33.9 ± 1.0 wks). Results were compared to an age-matched nonpregnant control group (NPG $n=14$) with similar characteristics. Systolic blood pressure (finger plethysmograph) and the electrocardiographic R-R interval were measured on a beat-to-beat basis as described by Parati *et al.* (*Hypertension* 12:214-22, 1988) at rest and during upright cycling at 60% and 110% of the ventilatory anaerobic threshold (T_{vent}). SBR slope, an index of cardiac vagal modulation, was significantly ($p \leq 0.05$) reduced at rest in the PG versus NPG. During exercise SBR slope decreased significantly in both groups, however the magnitude of vagal withdrawal from rest to 110% T_{vent} was smaller in the PG versus NPG. It was concluded that healthy pregnant women exhibit lower cardiac vagal modulation at rest with a decreased operational range in response to exercise. Implications for exercise prescription during pregnancy will be discussed.

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112 and N.S.E.R.C. (Canada).

Aerobic Intermittent Testing and its Relationship to Triathlon Performance.

C. Babineau, J. Jodoin and L. Léger, École d'éducation physique et de loisir, Université de Moncton, Moncton, New Brunswick and Département de kinésiologie, Université de Montréal, Montréal, Québec.

The purpose of this study was to further document the relationship between physiological variables, aerobic intermittent testing (AIT) conducted at a work to rest ratio (WR) of 5/1 and Olympic distance triathlon (ODT) performance. Ten triathletes with a mean treadmill VO_{2max} of $67.8 (\pm 3.55)$ $ml \cdot kg^{-1} \cdot min^{-1}$ performed three intermittent field sessions and completed one competitive triathlon. The subjects were further divided in an elite (ETR) and a recreational (RTR) triathlete groups based respectively on a sub-2h or 2h-plus performance. The interval workouts performed during regular training sessions consisted of a 5x200m swim, a 6x4000m bike and a 8x800m run. The results showed that the ETR were superior than the RTR in VO_{2max} , running economy, swim distance per stroke, running distance per cycle and mean speed in the intermittent sessions and individual triathlon events. The AIT swim, bike and run sessions were correlated to their respective ODT events (0.95, 0.94, 0.92) and overall triathlon time (0.84, 0.90, 0.73). Although the mean speed of the AIT sessions were slightly faster and some physiological responses greater, the 5/1 WR ratio can represent a useful tool for estimation of triathletes' race potential.

athletes.

A. and Warburton, D.E.R.
Edmonton, AB

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the 1997 World Bench Press
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R. Rasmussen. Dept. of
Antigonish, NS; Dept. of
of Health and Human
ponsored by D. Burke)

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/Natraceuticals Inc.

Metabolic Adaptations to Maximal Exercise in Late Gestation

A.P. Heenan and L.A. Wolfe. School of Physical and Health Education.
Queen's University, Kingston, Ontario. (Sponsored by L.A. Wolfe).

This study examined the effects of human pregnancy on metabolic responses to a maximal cycle ergometer test. The pregnant (gestational age=34.7 $\pm$ 0.4wk; n=14) and nonpregnant control (n=14) groups were healthy, physically active women matched for age, height and parity. The exercise protocol involved a ramp increase in work rate of 20watts/min until fatigue (Lotgering *et al.* J Appl Physiol 78: 1772-1777, 1995). Peak oxygen uptake, heart rate and oxygen pulse did not differ significantly between groups. Work efficiency (calculated as described by Davis *et al.*, Med Sci Sports Exercise 14: 339-343, 1982) was not different between groups. In contrast to earlier findings (Am J Obstet Gynecol. 161: 1458-1464, 1989), obtained using a treadmill protocol, our results, using non-weight bearing exercise, fail to support the hypothesis of increased work efficiency during pregnancy. Our findings do show that the capacity for weight supported work is preserved in late gestation and that cycling is an appropriate modality for the exercise testing of pregnant women.

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112 and N.S.E.R.C. (Canada).

Respiratory Adaptations to Maximal Exercise in Late Gestation

A.P. Heenan and L.A. Wolfe. School of Physical and Health Education.
Queen's University, Kingston, Ontario. (Sponsored by L.A. Wolfe).

This study examined the effects of human pregnancy on respiratory responses to maximal exercise. The pregnant (gestational age=34.7wks $\pm$ 0.4; n=14) and nonpregnant control (n=14) groups were healthy, physically active women matched for age, height, parity and fitness level. Subjects were evaluated using a cycle ergometer protocol with a ramp increase in work rate of 20watts/min until fatigue (Lotgering *et al.*, J Appl Physiol 78: 1117-1777, 1995). Breath-by-breath respiratory data were collected at rest, during exercise and 15 min post-exercise using a computerized system (Comp Biom Res 24: 118-128, 1991) and venous blood samples were taken to measure plasma lactate. The ventilatory threshold and the point of respiratory compensation were not altered in pregnancy, but the peak respiratory exchange ratio was reduced and a trends were observed for a lower peak minute ventilation and peak carbon dioxide production. Since both peak post-exercise lactate and excess post-exercise oxygen consumption were significantly lower in pregnancy, it appeared that blunted respiratory responses reflected reduced buffering of lactic acid.

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112 and N.S.E.R.C. (Canada).

Myofibrillar Performance in the Endurance Athlete.

G. D. Arthur. School of Rehabilitation Science. University of British Columbia, Vancouver, British Columbia.

Adaptations to skeletal muscle at the myofibrillar level in response to acute and chronic exercise are somewhat stereotypical. This gives the physiologist clues as to which aspects / systems of the muscle may be limiting its performance. In terms of myofibrillar force production there are significant alterations that occur during and following training. The limits of these adaptations are likely pre-determined by the underlying characteristics of any individual. This suggests that a "single limiting factor" to performance within muscle will be difficult to find. However, for any individual during the progression of exercise training the "weak links" of the muscle will adapt in order to better handle the demands associated with the exercise. Whether ultimately the limiting factor(s) or ceiling of performance of an endurance athlete is determined at the level of the myofibrillar apparatus will be discussed.

Effects of Human Pregnancy on Heart Rate Variability (HRV) Above and Below the Ventilatory Anaerobic Threshold.

N.D. Avery, L.A. Wolfe, and M.J. McGrath. Queen's University, Kingston, Ontario. (Sponsored by L.A. Wolfe).

This study examined the effects of human pregnancy on cardiac autonomic function at rest and during exercise. Spectral components of HRV were studied in 14 healthy, physically active women (PG: mean gestational age, 33.9 ± 1.0 wk). Results were compared to an age-matched nonpregnant control group (NPG, $n=14$) with similar characteristics. The electrocardiographic R-R interval was measured on a beat-to-beat basis at rest and during upright cycling at 60% and 110% of the ventilatory anaerobic threshold (T_{vent}). Parasympathetic nervous system (PNS) modulation (as reflected by total power and high frequency/total power) was significantly ($p \leq 0.05$) reduced at rest in the PG. Vagal withdrawal from rest to 110% T_{vent} was also smaller in the PG. Sympathetic nervous system (SNS) modulation (as reflected by low frequency/high frequency power) increased above resting values at 60% and 110% T_{vent} in the NPG. SNS modulation at 110% T_{vent} was significantly lower in the PG compared to the NPG. Healthy women exhibit lower PNS modulation at rest and blunted SNS modulation during exercise above T_{vent} in late gestation.

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112 and N.S.E.R.C. (Canada).

Effects of Human Pregnancy on Heart Rate Variability (HRV) Above and Below the Ventilatory Anaerobic Threshold.
N.D. Avery, L.A. Wolfe, and M.J. McGrath. Queen's University, Kingston, Ontario. (Sponsored by L.A. Wolfe).

This study examined the effects of human pregnancy on cardiac autonomic function at rest and during exercise. Spectral components of HRV were studied in 14 healthy, physically active women (PG: mean gestational age, 33.9 ± 1.0 wk). Results were compared to an age-matched nonpregnant control group (NPG, $n=14$) with similar characteristics. The electrocardiographic R-R interval was measured on a beat-to-beat basis at rest and during upright cycling at 60% and 110% of the ventilatory anaerobic threshold (T_{vent}). Parasympathetic nervous system (PNS) modulation (as reflected by total power and high frequency/total power) was significantly ($p \leq 0.05$) reduced at rest in the PG. Vagal withdrawal from rest to 110% T_{vent} was also smaller in the PG. Sympathetic nervous system (SNS) modulation (as reflected by low frequency/high frequency power) increased above resting values at 60% and 110% T_{vent} in the NPG. SNS modulation at 110% T_{vent} was significantly lower in the PG compared to the NPG. Healthy women exhibit lower PNS modulation at rest and blunted SNS modulation during exercise above T_{vent} in late gestation.

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112 and N.S.E.R.C. (Canada).

Aerobic Intermittent Exercise and Heart Rate Variability (HRV) Above and Below the Ventilatory Anaerobic Threshold.
C. Babineau, J. Jodoin, and M. Jodoin. Université de Moncton, Moncton, New Brunswick, Canada.

The purpose of this study was to examine the effects of aerobic intermittent exercise on heart rate variability (HRV) above and below the ventilatory anaerobic threshold (T_{vent}) in competitive triathletes and recreational runners. Ten triathletes (mean age 33.9 ± 1.0 years, mean VO_{2max} 58.5 ± 2.5 ml·kg⁻¹·min⁻¹) and ten recreational runners (mean age 33.9 ± 1.0 years, mean VO_{2max} 38.5 ± 2.5 ml·kg⁻¹·min⁻¹) were studied. HRV was measured at rest and during exercise at 60% and 110% T_{vent} . The results showed that HRV was significantly lower at rest and during exercise at 60% and 110% T_{vent} in the triathletes compared to the recreational runners. This suggests that the triathletes have a more efficient autonomic nervous system (ANS) modulation during exercise. The results also showed that HRV was significantly lower at rest and during exercise at 60% and 110% T_{vent} in the triathletes compared to the recreational runners. This suggests that the triathletes have a more efficient ANS modulation during exercise.

Annual Meeting Abstracts



American College of Sports Medicine 45th Annual Meeting

June 3-6, 1998
Orange County Convention Center
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Medicine & Science in Sports & Exercise.

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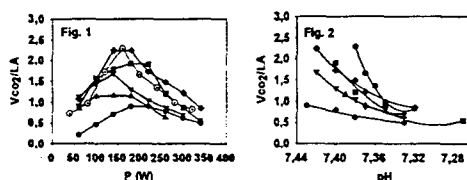
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C-52 FREE COMMUNICATION/SLIDE PRESENTATION PULM VENT ACID-BASE BAL

740 THE RELATIONSHIP BETWEEN $\dot{V}_{CO_2}$, LACTATE AND pH DURING INCREMENTAL EXERCISE TEST

Usaj A., Starc V., Kandare F., Faculty of Sport, Physiological Institute and Clin. Dept. Pulmonary Diseases, University of Ljubljana, Slovenia

The aim of this study was to ascertain the relative importance of $\dot{V}_{CO_2}$ and lactate concentration (LA) represented as $\dot{V}_{CO_2}/LA$ ratio, in regulation of blood pH, during incremental test on cycle ergometer. In six healthy subjects tested, power dependent increase of $\dot{V}_{CO_2}/LA$ ratio reached an individual peak values (mean 178 ± 28 W, Lactate Threshold 171 ± 37 W), which thereafter characteristically decrease (Fig. 1). The convergence shape was observed in dependence to pH (Fig. 2). The different peak values of $\dot{V}_{CO_2}/LA$ ratio and pH converge by an individual shape to common values of $\dot{V}_{CO_2}/LA$ between 0.5 and 1, at the pH values between 7.34 and 7.32. Therefore, neither the higher, nor the lower peak $\dot{V}_{CO_2}/LA$ values didn't represent an advantage in the regulation of pH, at particular testing conditions.



742 BUFFERING AND RESPIRATORY COMPENSATION OF LACTIC ACIDOSIS AFTER THE WINGATE TEST

D. Böning, M. Hütter, R. Beneke, FACSM, Dept. Sports Medicine, Free University Berlin (Sponsor: R. Beneke, FACSM)

The "pH-defense" in the extracellular space after rapid addition of lactic acid by performing 30 s anaerobic exercise was studied in 13 subjects. Acid-base status and lactate concentration in earlobe blood were determined before and up to 30 min after the test. After this time [lactate] was still increased and pH as well as pCO_2 decreased. $-\Delta[\text{lactate}]/\Delta pH$ as a measure of total pH defense (bicarbonate and nonbicarbonate buffering, respiratory compensation) increased steadily from 61 ± 14 (SE) to 120 ± 9 mmol/L. $\Delta[\text{HCO}_3^-]_{\text{baseline}}/\Delta pH$ (bicarbonate buffering and respiratory compensation) rose in a parallel manner from 42 ± 10 to 96 ± 7 mmol/L. The difference between $-\Delta[\text{lactate}]/\Delta pH$ and $\Delta[\text{HCO}_3^-]_{\text{baseline}}/\Delta pH$ amounted to 17 ± 3 mmol/L. The nonbicarbonate buffer value can be used to estimate the effect of hyperventilation and to calculate buffer capacities for constant pCO_2 and thus nonrespiratory (nr) pH changes. $-\Delta[\text{lactate}]/\Delta pH_{\text{nr}}$ was initially higher than $-\Delta[\text{lactate}]/\Delta pH$ (71 ± 8 mmol/L) because of temporarily increasing pCO_2 , reached a minimum of 57 ± 1 mmol/L after 6 min and then increased again up to the initial values. $\Delta[\text{HCO}_3^-]_{\text{baseline}}/\Delta pH_{\text{nr}}$ followed an equal time course but at a lower level (difference 17 mmol/L). Calculation of $\Delta[\text{HCO}_3^-]_{\text{baseline}}/\Delta pH_{\text{nr}}$ from initial values by use of the Henderson-Hasselbalch equation yielded only slightly different values demonstrating that no considerable bicarbonate exchange occurred with the cells. The apparently increasing total pH defense after the Wingate test resulted from a consistently decreased pCO_2 . The relative importance of this respiratory compensation increases with decreasing lactic acid concentration and thus decreasing total pH changes.

741 THE EXERCISE/PREGNANCY MODEL: COMPARISON OF PHYSICO-CHEMICAL APPROACHES TO ACID-BASE ANALYSIS

A.P. Heenan and L.A. Wolfe, FACSM
Queen's University, Kingston, ON, Canada (Sponsor: L.A. Wolfe, FACSM)

The exercise/pregnancy model was utilized to compare the ability of three physicochemical approaches to acid-base analysis to accurately calculate $[H^+]$. As described by Stewart (*Can. J. Physiol. Pharm.* 61:1444, 1983), plasma $[H^+]$ is determined by three independent variables: the partial carbon dioxide tension (PCO_2), the strong ion difference ($[SID]$), and total weak acid ($[A_{TOT}]$). The three models differ in their representation of $[A_{TOT}]$: the Stewart model represents it as total protein ($[TP]$), the Fencel model (*J. Clin. Lab. Med.* 120:713, 1992) as [albumin] and [total phosphate], and the modified Stewart (*Anesth. Analg.* 81:1043, 1995) as $[TP]$ and [total phosphate]. Pregnancy was chosen as a model to make comparisons because the weak acid component is altered in pregnancy. Subjects were 15 healthy, physically active pregnant women (mean gestational age = 37.0 ± 0.3 wks) and 9 age-matched nonpregnant controls. Arterialized blood samples were obtained during rest and in the sixth minute of exercise at work rates corresponding to 70% T_{VENT} and 110% T_{VENT} . In the control group (CG) the Fencel model underestimated measured $[H^+]$ except at 110% T_{VENT} , while the modified Stewart model overpredicted $[H^+]$. In the pregnant group (PG) the Stewart and Fencel model underpredicted $[H^+]$. The Stewart model provided the best estimate of measured $[H^+]$ for the CG. $[H^+]$ in the PG may have been underestimated from the Stewart equation as a result of altered dissociation constants caused by changes in osmolality and strong ions. Although the modified Stewart model provided the best estimate of measured $[H^+]$ in the PG, this may have been the result of inflating the $[H^+]$ by adding [total phosphate] without correcting the underlying problem of dissociation constants poorly suited for an altered physiological state.

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112, Ontario Thoracic Society, and N.S.E.R.C. (Canada).

743 PHYSICO-CHEMICAL ANALYSIS OF EXERCISE-INDUCED CHANGES IN $[H^+]$ IN HUMAN PREGNANCY

R.J. Preston, A.P. Heenan and L.A. Wolfe, FACSM
Queen's University, Kingston, ON, Canada (Sponsor: L.A. Wolfe, FACSM)

This study employed Stewart's physicochemical approach (*Can. J. Physiol. Pharm.* 61:1444, 1983) to examine mechanisms of exercise-induced changes in $[H^+]$ during late gestation. Subjects were 15 healthy, physically active pregnant women (mean gestational age, 37.0 ± 0.3 weeks) and 9 age-matched nonpregnant controls. Arterialized blood samples were obtained at rest and following 5 minutes of cycle ergometer exercise at both 70% and 110% of the ventilatory anaerobic threshold (T_{VENT}). Measurements included plasma $[H^+]$, PCO_2 , total protein ($[TP]$) and the strong ion difference ($[SID]$). As reported previously (*Can. J. Appl. Physiol.* 22:26P, 1997), $[H^+]$ increased significantly from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} in both groups. $[H^+]$ was significantly lower in the pregnant vs. nonpregnant state at rest and at 70% T_{VENT} . Analysis of the contributions of PCO_2 , $[SID]$, and total weak acid ($[A_{TOT}]$), as reflected by $[TP]$ to exercise-induced changes in $[H^+]$ using Stewart's equation indicated that the relative contributions were similar in the pregnant vs. nonpregnant state at 70% T_{VENT} . Above T_{VENT} , however, there was a significantly greater contribution of $[SID]$ in the control group. This effect of $[SID]$ on $[H^+]$ appeared to be offset by a reduction in the contribution of PCO_2 . Mechanisms of exercise-induced changes in $[H^+]$ appear to be altered during pregnancy at exercise levels above T_{VENT} .

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112, Ontario Thoracic Society, and Natural Sciences and Engineering Research Council of Canada (N.S.E.R.C.).

C-53 CLINICAL CASE SLIDE PRESENTATION WRIST INJURIES

744 WRIST INJURY - SNOWBOARDING

T.P. Moore, FACSM
Rocky Mountain Sports Medicine, Crested Butte, CO

HISTORY - A twenty one year old male snowboarder came over a rise, lost it and sustained a tumbling type fall. He was able to ride to the bottom of the mountain. However he then presented to the ski area clinic complaining of right wrist pain.

PHYSICAL EXAM - Obvious deformity of his right wrist with mild distal dorsal angulation. There is pain on palpation of both dorsal and volar aspects of his wrist. There is mild paresthesia of the volar aspect of his fingers. He can actively flex and extend his fingers with complaint of pain.

WRIST INJURY - SNOWBOARDING
T.P. Moore FACSM
Rocky Mountain Sports Medicine, Crested Butte, CO

DIFFERENTIAL DIAGNOSIS:

1. Distal radius fracture
2. Scaphoid fracture
3. Transcaphoid perilunate dislocation
4. Perilunate dislocation
5. Lunate dislocation - no other bony abnormality

TESTS

1. Plain radiographs
2. 3-view x-rays of wrist - lunate dislocation

FINAL WORKING DIAGNOSIS

1. Lunate dislocation

TREATMENT

1. Closed reduction in the emergency department under fluoroscopic guidance
2. Open repair of dorsal and volar ligamentous structures
3. Immobilization for six weeks followed by an active rehab program.

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of the

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**Société Canadienne de Physiologie
de l'Exercice**

at

The Delta Chelsea Hotel
Toronto, Ontario, Canada

October 22-25, 1995

Left Ventricular Wall Stress During Leg-Press Resistance Exercise.

M. Haykowsky, D. Taylor, A. Quinney, K. Teo, D. Humen. Faculty of Physical Education, University Of Alberta, Edmonton, Alberta. (Sponsored by G. Bell)

Left ventricular wall stress (WS) was assessed in 5 healthy males (27.6 ± 2.9 ys) during submaximal (80%, 95 % 1RM) and maximal leg-press exercise (LPE) incorporating a Valsalva Maneuver (VM). Transesophageal echocardiography, intra-arterial pressure and intra-thoracic pressure (ITP) recordings were obtained to derive fractional area change (FAC), end-systolic pressure (ESP), transmural pressure (ESTMP) and WS. Results are as follows: *P < 0.05 vs. rest

Variable	Rest	80%	95%	100%
HR(beats/min)	89.8±10.5	164.5±28.3*	151.2±15.6*	139.4±10.4*
ESP(mmHg)	122.6±12.0	251.3±9.5*	261.7±10.4*	247.8±16.7*
ITP(mmHg)	6.3±9.5	124.8±32.8*	114.9±19.2*	115.2±14.6*
ESTMP(mmHg)	116.3±9.7	126.5±23.6	142.3±14.6	127.6±25.7
WS(dynes/cm ² ×10 ³)	88.3±16.5	69.5±24.8	80.1±21.0	83.3±18.5
FAC(%)	49.9±5.8	53.7±10.1	54.8±6.3	52.0±4.9

Submaximal or maximal LPE performed with a VM is associated with a significant elevation in HR, ESP, ITP with no alterations in ESTMP, WS, or FAC. In young healthy males LPE performed with a VM appears to offset the abrupt increase of ESP on ESTMP, an important determinant of WS. Thus, in young healthy males, the VM should not be discouraged during LPE.

The Effect of β -Blocker on Static Exercise. A. Kinesiology¹ and Med.

Nine males (22.3 ± 1.7 ys) performed static exercise of the right knee extensor (metoprolol, 100 mg) (propranolol, 80-120 mg) Brachial arterial and femoral nerve to evoke a twitch for 15 min following the femoral nerve to evoke a twitch. The exercise-induced re-uptake during recovery was significant. evoked M-waves were evoked. Propranolol resulted in a significant decrease following the 3 min placebo (38.9 ± 3.6 % homeostasis during is membrane excitability. Supported by NSERC

Acid-Base Regulation Above and Below the Ventilatory Anaerobic Threshold in Late Gestation.

A.P. Heenan and L.A. Wolfe. School of Physical and Health Education, Queen's University, Kingston, Ontario.

This study examined mechanisms of acid-base regulation in healthy, physically active pregnant women at rest and during upright cycling at 70% and 110% of the ventilatory anaerobic threshold (T_{VENT}). Results were compared to those of an age matched control group (n=9) with similar characteristics. Hydrogen ion concentration ($[H^+]$), PCO_2 , the strong ion difference ($[SID]$) and total weak acid ($[A_{TOT}]$) were measured in arterialized blood at rest and after 5 minutes of exercise at each work rate. $[H^+]$ increased significantly from rest to 70% T_{VENT} and from 70% T_{VENT} to 110% T_{VENT} in both groups. $[H^+]$ was significantly lower in the pregnant vs. nonpregnant state at rest and at 70% T_{VENT} . A trend for lower $[H^+]$ values in the pregnant group at 110% T_{VENT} was also observed. $[SID]$ decreased significantly from rest to 110% T_{VENT} in both groups. Significantly lower $[SID]$ values were observed in the pregnant group at rest and at 70% T_{VENT} . $[A_{TOT}]$ increased significantly from rest to both work rates in both groups. Values for both PCO_2 and $[A_{TOT}]$ were significantly lower in the pregnant group at all measurement times. Analyses of data using Stewart's physicochemical approach (*Can. J. Physiol. Pharmacol.* 61:1444, 1983) indicated that the lower plasma $[H^+]$ values observed during pregnancy are the result of a lower PCO_2 and $[A_{TOT}]$ that offset the effects of a lower $[SID]$. These changes are present in the resting state and are maintained during sustained exercise above and below T_{VENT} .

Supported by U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112, Ontario Thoracic Society and N.S.E.R.C. (Canada).

Effect of Induced Acidosis on High-Intensity Exercise. M.G. Hollidge-Horvath, G.J.F. Heigenhauser, G.J.F. Heigenhauser

The purpose of this study was to examine the effect of induced acidosis on glycogen utilization and energy expenditure during high intensity exercise. Exercise was performed in a control condition (CON) and in an acidotic condition (ACID). Biopsies of muscle were taken before and after exercise. Pyruvate Dehydrogenase (PDH) activity was 0.75 ± 0.14 vs 0.65 ± 0.14 (vs CON (3.84 ± 0.14 vs 29.9 ± 6.3)) (208.4±29.2 vs 158.4±29.2) were significantly lower during acidosis than during CON. This study was supported by NSERC

Annual Meeting Abstracts

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May 28 - 31, 1997
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American College of Sports Medicine 44th Annual Meeting

**May 28-31, 1997
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Medicine & Science in Sports & Exercise
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A-13 SLIDE PREGNANCY AND EXERCISE

19 CATECHOLAMINE RESPONSES OF PREGNANT WOMEN DURING AEROBIC DANCE AND WALKING

R.G. McMurray, FACSM, V.W. Brabham & A.C. Hackney, FACSM.
University of North Carolina, Chapel Hill, NC.

Previously we have reported a disproportional greater heart rate/oxygen uptake when pregnant women participate in aerobic dance compared to walking. We hypothesized that this result was due to differences in catecholamine levels. Thus, we measured the catecholamine responses of 10 pregnant women (20-25 wk gestation) during walking (W) and aerobic dance (AD) at the same heart rates. HPLC with electrochemical detection was used to measure catecholamines at rest, 20, 30 and 40 min of exercise. Heart rates were similar comparing trials ($AD=138 \pm 8$ vs. $W=141 \pm 7$ b/min; $p>0.10$), but aerobic dance resulted in a lower percent of VO_{2max} (40% vs. 60%). Resting epinephrine (E) and norepinephrine (NE) levels were similar for both trials ($p>0.05$). Both forms of exercise increased E and NE over resting levels ($p<0.05$); the increases were similar for both forms of exercise ($p>0.05$). Correlations for NE and heart rate were high for both trials ($W=r=0.82$, $AD=r=0.88$; $p<0.01$). Correlations between NE and VO_2 were significant during walking ($r=0.98$; $p<0.001$), but not during AD ($r=0.30$; $p>0.10$).

Catecholamine Trial	Rest	20 min	30 min	40 min
E	AD 229 $\pm$ 20	628 $\pm$ 56	734 $\pm$ 80	502 $\pm$ 84
(pmol/L)	W 240 $\pm$ 16	464 $\pm$ 49	540 $\pm$ 43	464 $\pm$ 45
NE	AD 1.68 $\pm$ 0.12	2.56 $\pm$ 0.23	3.55 $\pm$ 0.40	2.80 $\pm$ 0.53
(nmol/L)	W 1.70 $\pm$ 0.11	2.36 $\pm$ 0.24	2.60 $\pm$ 0.15	1.78 $\pm$ 0.18

These results indicate that the elevated heart rate/oxygen uptake relationship was related to a greater than expected catecholamine response during aerobic dance.

21 IS BREAST MILK COMPOSITION IN LACTATING WOMEN ALTERED BY EXERCISE INTENSITY OR DIET?

T. J. Quinn, FACSM and G.B. Carey, FACSM. Dept. of Kinesiology and Dept. of Animal and Nutritional Sciences, University of New Hampshire, Durham, NH.

This study examined the relationships among diet, exercise intensity, and breast milk composition in lactating women. Fourteen lactating women were randomly assigned to either a high ($n=7$) or moderate ($n=7$) carbohydrate (CHO) diet (CHO=60.3% vs 50.3%, respectively). Milk and blood samples were collected after a resting session (rest) and 3 bouts of exercise including maximal, lactic acid threshold (LAT), and 20% below the LAT (LAT-20) intensities. Blood was collected via finger-stick 0 min pre and 0, 30, 60, and 90 mins post-exercise or rest and analyzed for lactic acid (LA). Milk was collected via a breast pump at 30 and 0 mins pre and 0, 30, 60, and 90 mins post and analyzed for LA, pH, and volume. Diet did not significantly effect any of the variables so groups were collapsed. A repeated-measures ANOVA showed that milk LA was significantly elevated at 0 mins following maximal (1.39 $\pm$ 48) and LAT (0.25 $\pm$ 15) exercise when compared to rest (0.08 $\pm$ 04). This was not observed following the LAT-20 exercise (0.10 $\pm$ 07). The elevated milk LA after maximal exercise persisted through the 30 min collection point. LA in blood mirrored these changes. These data suggest that in lactating women whose caloric needs are being met: (1) changing the carbohydrate content of the diet does not impact LA in breast milk; (2) LA appearance in the milk is a function of exercise intensity; and (3) moderate intensity exercise (RPE=12) will not increase breast milk LA levels.

Supported by the Gatorade Sports Nutrition Research Grant, ACSM Foundation and Medela, Inc.

23 EFFECTS OF HUMAN PREGNANCY ON CARDIAC AUTONOMIC ACTIVITY ABOVE AND BELOW THE VENTILATORY ANAEROBIC THRESHOLD.

C.E. Amara & L.A. Wolfe, FACSM Queen's University, Kingston, ON, CAN. (Sponsor: L.A. Wolfe, FACSM)

This study was conducted to test the hypothesis that cardiac autonomic balance is altered by human pregnancy. Subjects were 5 physically active pregnant volunteers studied between 27-37 weeks gestation. A reference group of 5 nonpregnant subjects matched according to age, height, pre-pregnant body mass and parity was also studied. Subjects exercised on a constant work rate cycle ergometer for 4 minutes at 20 watts followed by a ramp increase in work rate of 20 watts/min until fatigue. Ventilatory threshold (T_{vent}) was determined using the V-slope method (*J. Appl. Physiol.* 60:2020, 1986). Subjects then performed 2 additional submaximal exercise tests on a separate day. The testing protocol involved 4 minutes of pedalling at a work rate of 20 watts followed by a ramp increase to a level which corresponds to 60 or 110% of the work rate at T_{vent} . R-R interval data were collected (≥ 512 cycles) and stored using a computerized system. Fast Fourier Transform Analysis was performed to plot the R-R interval spectrum. Low frequency (0-0.15 Hz) and high frequency (0.15-0.5 Hz) power were calculated from data obtained at rest and at each level of exercise. The ratio of high frequency power:total power was used as an index of cardiac parasympathetic activity and the ratio of low to high frequency power was used as an index of sympathetic activity (*J. Appl. Physiol.* 71: 1136, 1991). Blood pressure in the finger (Ohmeda 2300 Finapres) was measured at rest and during exercise on a beat-to-beat basis for evaluation of spontaneous baroreflex function (*Hypertension* 12:214, 1988). In the resting state, cardiac parasympathetic modulation (as reflected by HRV high frequency power/total power and spontaneous baroreflex slope) were reduced and cardiac sympathetic modulation (as reflected by low frequency power/high frequency power) was increased in late gestation ($p<0.05$). At work rates above T_{vent} , cardiac sympathetic modulation was reduced in late gestation vs the nonpregnant state. These findings support our original experimental hypothesis.

Supported by Ontario Thoracic Society, ARC Queen's University, N.S.E.R.C. (Canada), & U.S. Army Medical Research and Materiel Command Contract #DAMD17-96-C-6112

20 PREGNANCY TRAINING VOLUME - EFFECT ON PLACENTAL GROWTH AND SIZE AT BIRTH

J.F. Clapp, J. Tomaselli*, S. Rizdon*, M. Kortan*, B. Lopez*, & K.D. Little. Dept. of Obstetrics & Gynecology, CWRU at MetroHealth Medical Center, Cleveland, OH

This study tested the hypothesis that training volume is an important exercise (EX) variable which modulates the effect of regular EX on fetal-placental growth. At 8 wks. gestation women were randomized to perform sustained antigravitational EX at 55% VO_{2max} for either: 20 min. 3-5 x wk. (LEX); 40min. 5 x wk. (HEX); 20 min. 5 x wk. in early pregnancy increasing to 60 min. 5 x wk. after the 24th wk. (LHEX); or no exercise (C). Training was monitored & EX VO_2 was checked q 2 wks. Placental growth rate (PG) was measured between 16 & 24 wks. At delivery placental weight (PW), birth weight (BW) & other anthropometric measures were obtained including fat mass (FM). The results are reported below as the $x \pm$ s.e.m.

PARAMETER	C	LEX	HEX	LHEX
PG (cc/wk)	22 $\pm$ 3	32 $\pm$ 3	33 $\pm$ 3	30 $\pm$ 3
PW (gm)	438 $\pm$ 27	545 $\pm$ 31	517 $\pm$ 32	482 $\pm$ 34
BWT (gm)	3680 $\pm$ 83	4005 $\pm$	3237 $\pm$	3516 $\pm$
FM (gm)	475 $\pm$ 35	520 $\pm$ 40	260 $\pm$ 30	315 $\pm$ 35

We conclude that weekly training volume alters BW, FM, & PG, that the effects are time specific, have different thresholds, and may explain the diverse findings reported concerning the impact of EX on BW and other pregnancy outcome variables.

Support: NIH grants #HD21268 & 11089, #RR0080 & MMHC.

22 AEROBIC EXERCISE DURING PREGNANCY: RELATION TO DELIVERY OUTCOME

P. Gandolfi, B. Franklin, FACSM, T. Catlin, William Beaumont Hospital, Royal Oak, Michigan (Sponsor: B. Franklin, FACSM)

To clarify the relationship between regular aerobic exercise ($\geq$ three 20-min sessions/week), labor/delivery and neonatal outcome, 146 women ($\bar{x} \pm$ SD age = 30.0 $\pm$ 5.7 years) were randomly surveyed on an inpatient, post-natal basis. Responses were verified via patient chart. Maternal weight gain, type of delivery, labor time, delivery time, delivery complications, number of symptoms in the last trimester, gestational time, newborn weight, newborn length and 1- and 5-minute newborn APGAR scores were compared between exercisers and non-exercisers. Selected results ($\bar{x} \pm$ SD values) were:

Variable	Exercisers	Non-Exercisers	p
Maternal weight gain (kg)	14.5 $\pm$ 5.5	15.3 $\pm$ 6.1	0.51
# symptoms, last trimester	3.0 $\pm$ 1.5	3.8 $\pm$ 1.8	0.06
Delivery complications	14.3% (4 of 28)	28.0% (33 of 118)	0.21
Vaginal deliveries	78.6% (22 of 28)	61.0% (72 of 118)	0.12

Twenty-eight of the 146 women (19.2%) exercised throughout their pregnancy; 22 of the 28 used walking as their primary exercise modality. Exercisers tended to gain less weight, experience fewer symptoms and delivery complications, and have a greater proportion of vaginal deliveries than did their non-exercising counterparts. Labor time, delivery time, gestational time, newborn weight, newborn length, and 1- and 5-minute newborn APGAR scores were not significantly different. Conclusion: Regular aerobic exercise throughout pregnancy may help to maintain relative maternal body weight, decrease symptoms, lessen delivery complications, and reduce caesarean deliveries.

24 CHRONIC EXERCISE EFFECTS ON SUBSTRATE UTILIZATION IN HUMAN PREGNANCY.

A.P. Heaman, L.A. Wolfe, FACSM, B.R. Caven, R.M.C. Walker and A. Bonen. Queen's University, Kingston, ON, and University of Waterloo, Waterloo, ON, Canada.

(Sponsor: L.A. Wolfe, FACSM)

This study was conducted to test the hypothesis that aerobic conditioning prevents exercise-induced hypoglycemia and preserves the capacity to utilize carbohydrate and produce lactate during heavy exercise in late gestation. Effects of closely-monitored cycle ergometer conditioning (HR = 143 $\pm$ 2 beats/min, 25 min/day, 3 days/week) during the 2nd and 3rd trimesters (Tms) were studied in 18 previously sedentary women (exercised group, EG). A nonexercising pregnant control group (CG, n=9) was also studied. Data collection times were: start of 2nd Tm (Entry), end of both 2nd and 3rd Tms (post-training), and 3 months postpartum (nonpregnant control). Respiratory gas exchange was studied and venous blood samples were obtained before, during and following a graded cycle ergometer test terminated at a peak HR of 170 beats/min. Measurements included plasma glucose, insulin and free fatty acids (FFAs), as well as the respiratory exchange ratio (RER) at peak exercise and peak post-exercise lactate. A significant aerobic conditioning effect in the EG was confirmed by a 17% increase in O_2 pulse at peak exercise between Entry and the end of Tm3. As expected, values for plasma insulin and FFAs in the CG rose with advancing gestational age under all experimental conditions. Also, peak exercise RER and peak post-exercise lactate were significantly reduced in late gestation and plasma glucose decreased significantly following end of 3rd Tm testing. Effects of pregnancy to reduce peak post-exercise lactate and to reduce plasma glucose following exercise at the end of Tm3 were significantly attenuated in the EG. These effects were attributed to attenuation of pregnancy-induced insulin resistance (as reflected by insulin/glucose ratio) by physical conditioning. These findings support our original experimental hypothesis.

Supported by Health Canada (N.H.R.D.P.) and Canadian Fitness and Lifestyle Research Institute (C.F.L.R.I.).

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Identifiers: WOMEN'S HEALTH

DTIC Please correct to final read for period 1 Oct 99 to 30 Sep 99

Abstract: This research contract examined the effects of healthy human pregnancy on cardiac autonomic function(Study #1), oxygen uptake kinetics (Study #2)and acid-base regulation (Study #3) at rest and during upright cycling at intensities above and below the ventilatory anaerobic threshold(T to the vent). Results from Study #1 support the hypothesis that cardiac vagal/parasympathetic modulation is reduced in the resting state and that sympathoadrenal modulation is blunted during strenuous exercise above T to the vent in late gestation. These findings have important implications for the use of heart rate to regulate exercise intensity during pregnancy. Study #2 is still in progress. Findings from Study #3 demonstrated that plasma H+ is lower at rest and during exercise in the pregnant vs. nonpregnant state. Exercise-induced increases in H+ were similar quantitatively in the pregnant vs. nonpregnant state, but pregnant subjects have lesser reductions in the strong ion difference (SID)and require less respiratory compensation. Findings also suggested that plasma osmolality and SID contribute, in addition to circulating progesterone, to pregnancy- induced increases in pulmonary ventilation at rest and during exercise. Maximal exercise tests conducted as part of Studies #1 and #3 confirmed that maximal aerobic power and work efficiency are well-preserved in healthy physically active pregnant women and that such tests involve minimal changes in fetal heart rate.

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