Uterine artery blood flow and renal sympathetic nerve activity during exercise in rabbit pregnancy

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Submitted 9 May 2003; accepted in final form 10 July 2003

O’Hagan, Kathleen P., and Jennifer A. Alberts. Uterine artery blood flow and renal sympathetic nerve activity during exercise in rabbit pregnancy. Am J Physiol Regul Integr Comp Physiol 285: R1135–R1144, 2003. First published July 17, 2003; 10.1152/ajpregu.00258.2003.—The uterine artery blood flow (UtBF) and renal sympathetic nerve activity (SNA) responses to treadmill exercise were evaluated in 12 nonpregnant (NP) and 17 term pregnant (P) rabbits. UtBF was monitored continuously with a Transonic flowprobe. Rabbits underwent three exercise trials (5-min duration) that varied in absolute workload. The rise in renal SNA with exercise was intensity related. Pregnancy did not affect the average steady-state renal SNA response expressed relative to maximum (P 0.4 ± 1% vs. NP 2.3 ± 2% of maximum smoke-elicited activity) and increased the average renal SNA response expressed relative to resting activity (P 155 ± 19% vs. NP 48 ± 23% from rest, P = 0.03) At rest, UtBF (P 13 ± 3 vs. NP 1.9 ± 0.3 ml/min) and uterine artery conductance (UtC; P 22 ± 5 vs. NP 2.8 ± 0.5 ml·min⁻¹·mmHg⁻¹ × 10⁻⁴) were elevated in the P rabbits. The average exercise-related decreases in UtBF (P –16 ± 4% vs. NP –48 ± 4%) and UtC (P –27 ± 4% vs. NP –54 ± 4%) were attenuated in the P rabbits. Pregnancy does not impair the ability to raise renal SNA but attenuates the uterine artery constrictor response to moderate to heavy dynamic exercise in rabbits. Under normal conditions, the pregnant uterine circulatory bed may be relatively protected from exercise-related redistribution of blood flow.

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http://www.ajpregu.org 0363-6119/03 $5.00 Copyright © 2003 the American Physiological Society

PREGNANCY is associated with physiological alterations in the function of maternal organ systems to meet the increasing metabolic needs of the developing fetus. Systemic cardiovascular adjustments to pregnancy in women and animals include expansion of blood volume, increases in heart rate (HR), stroke volume, and cardiac output, and decrease in total peripheral resistance (3, 10, 26). Blood flow to the uteroplacental circulation increases with a larger fraction of the elevated cardiac output directed to the uteroplacental tissues (10).

Exercise is a common physiological stressor. During dynamic exercise, increased sympathetic nerve activity to nonexercising circulatory beds, such as the splanchic and renal circulations, results in regional vasoconstriction and diversion of blood flow to the central circulation in humans and rabbits (15, 36). Little is known of how neural control of the circulation during exercise is affected by normal pregnancy. An indirect index of global sympathetic activity is plasma catecholamine levels. Bonen et al. (5) and Avery et al. (2) found that plasma norepinephrine and epinephrine levels were lower in third-trimester pregnant women performing cycle ergometry. These results suggest that term pregnancy may be associated with an attenuated sympathoadrenal response to dynamic exercise. Direct measurements of regional sympathetic neural activity in pregnant animals during exercise have not yet been reported. Rabbits have been used to study the cardiovascular responses to and neural control of the circulation during dynamic exercise (15, 32) and pregnancy (33, 35). In this study, we utilized the conscious rabbit to measure sympathetic nerve activity to the kidney during exercise in the nonpregnant and pregnant states. We hypothesized that the renal sympathetic nerve activity (SNA) responses to dynamic treadmill exercise would be attenuated at term pregnancy and that the renal SNA response to exercise would be related to exercise intensity.

In 1956, Morris et al. (28) reported that the clearance of radioactive sodium from the myometrium in pregnant women decreased with exercise, which suggested an exercise-induced decrease in uterine artery blood flow (UtBF). More recent studies have utilized Doppler ultrasonography of the uterine artery to study the uteroplacental circulatory response to dynamic exercise in pregnant women. Due to exercise-related movement artifacts, data have been recorded within the 1st min postexercise (14, 29) or during brief pauses during a graded exercise test (11). The ratio of the systolic to diastolic flow velocities, called the S/D ratio or resistance index, has been used as an indicator of uteroplacental vascular resistance. Morrow et al. (29) and Hackett et al. (14) found that brief, light cycling exercise increased the uterine artery resistance index and Errkola et al. (11) described progressive increases in the resistance index during moderate to heavy cycle exercise. In contrast, others have reported no change in uterine artery resistance (27) with exercise in pregnancy. Studies in exercising pregnant sheep (23) and
METHODS

A question that has been largely unaddressed is whether pregnancy alters qualitative or quantitative aspects of the uterine artery constrictor response to dynamic exercise. Due to the large resting flow to the uteroplacental circulation in pregnancy, comparable or enhanced reduction in vascular conductance during exercise would divert a considerable volume of blood away from the uterine circulation to support increased oxygen demand by working muscle. Uterine blood flow measurements in the nonpregnant state during exercise are not available for the sheep or goat, species in which uteroplacental flow during pregnancy is known to decrease (18, 23). Dowell and Kauer (10), utilizing microspheres to measure blood flow at steady-state exercise, reported that the rise in uterine resistance to treadmill exercise was enhanced in term pregnant rats (−50%) compared with nonpregnant rats (−25%). Continuous measurement of UtBF during exercise in nonpregnant and pregnant animals would facilitate comparison of the uterine circulatory responses at the onset and cessation of exercise as well as during steady-state conditions.

In this study, we utilized rabbits chronically instrumented with a uterine artery flowprobe to investigate the uterine artery circulatory response to dynamic treadmill exercise in the nonpregnant and term pregnant states. We tested the following hypotheses: first, that UtBF and uterine artery conductance (UtC) decrease during exercise in both pregnant and nonpregnant rabbits; second, that the relative changes in UtBF and UtC during exercise would be attenuated with pregnancy; and third, that the uterine circulatory responses to exercise were related to exercise intensity.

Surgical Preparation

General. Rabbits were anesthetized with Telazol (tiletamine hydrochloride and zoletil hydrochloride: 15 mg/kg im, Elkins-Sinn, Cherry Hill, NJ) and xylazine (xylazine hydrochloride, 5 mg/kg im, Butler, Columbus, OH) and intubated with a cuffed endotracheal tube. To maintain a surgical plane of anesthesia, the rabbits were mechanically ventilated with 2.0–2.5% isoflurane in room air. Buprenorphine hydrochloride (0.03 mg/kg im, Reckitt and Colman, Richmond, VA) was given immediately and at 5–8 h postoperatively for pain management.

Implantation of uterine artery flowprobe. In the nonpregnant state, all rabbits were chronically instrumented with an ultrasonic transit-time flowprobe (1.0–1.5 mm R series; Transonic Systems, Ithaca, NY) on the left or right uterine artery via a midline lower abdominal incision. The rabbit has a bicornate uterus. A uterine horn receives arterial blood flow from an ipsilateral uterine artery and a smaller contribution from the ipsilateral ovarian artery (6); thus the flow signal we received did not represent the entire arterial flow to the uterine horn. This may be a contributing factor to the observation that our resting values for uterine arterial flow in the nonpregnant (2 ml/min) and pregnant (13 ml/min) conscious rabbit are somewhat lower than the values reported for uterine (−5–6) or uteroplacental flow (−13–18 ml/min) in previous studies in rabbits utilizing microspheres (22, 38).

The artery-probe complex was wrapped with a small piece of medical grade silicone elastomer (Technical Products of GA, Decatur, GA) to stabilize the probe orientation and avoid trapping adipose tissue in the reflecting bracket during the ingrowth phase. The free end of the flowprobe was routed out of the abdominal cavity and was stored in a small subcutaneous pocket on the right flank. After the abdominal surgery was complete, the rabbits underwent a left thoracotomy for placement of a silicone catheter in the pericardial space. The pericardial catheter was utilized for a separate experimental protocol, performed on the day before the current study, which investigated the cardiac sensory receptor control of renal SNA and uterine circulatory responses to exercise. At least 14 days of recovery elapsed before rabbits resumed treadmill running or underwent plasma volume determination. Usable recordings of UtBF were obtained in 8 nonpregnant and 11 pregnant rabbits.

Implantation of renal nerve recording electrodes. In nonpregnant and pregnant rabbits, chronic recording electrodes were implanted on intact left renal nerves, as previously described (32). This surgery was performed in pregnant rabbits on day 25 of gestation (gestation duration = 31–32 days), which was not earlier than 48 days (median = 69 days) after the first surgery. In the nonpregnant rabbits, the renal nerve implantation surgery occurred not earlier than 35 days (median = 64 days) after the flowprobe implantation. Rabbits were studied on the 4th day postsurgery. This time corresponded to day 29 of gestation (term pregnancy) in the pregnant rabbits. Usable recordings of renal SNA during exercise were obtained in six nonpregnant and nine pregnant rabbits.

Experimental Procedures

Instrumentation. On the day of the experiment, the rabbit was brought to the laboratory. The skin overlying the central ear artery and marginal vein was anesthetized with topical EMLA cream (lidocaine 2.5% and prilocaine 2.5%; Astra, Westborough, MA). Arterial blood pressure (BP) was obtained from a small Teflon catheter [Angiocath 24 gauge (OD = 0.7 mm), Deseret, Sandy, UT] placed into the central
ear artery by percutaneous placement. The arterial catheter was connected to a solid-state pressure transducer that was strapped to the rabbit’s back. HR was derived from the arterial pressure pulse using a Grass tachograph. Venous access was obtained by percutaneous placement of a 24-gauge Teflon catheter into the contralateral ear vein. In animals with functioning flowprobes, the free end of the uterine artery flowprobe was retrieved from the flank subcutaneous pocket under a local anesthetic block (2% lidocaine). The probe end was connected by a 2-m extension cable to the Transonic flowmeter (model T206) for measurement of UtBF.

**Plasma volume determination.** Plasma volume was determined twice. The first determination was made no earlier than 14 days after the first surgery, when all animals were in the nonpregnant state (as part of the Initial study protocol). The second determination was made on the day of the experiment, before the commencement of the exercise protocol. Plasma volume was determined with the Evans blue dye-dilution technique (T1824; Sigma) (1). At time 0, 2 mg of dye (in 4 ml of saline) was infused intravenously. At 5 min postinfusion, a 1.0-ml arterial blood sample was taken, and the hematocrit (Hct) of the plasma was used to calculate plasma volume. Blood volume was calculated as plasma volume/(1 – hematocrit). Hematocrit was multiplied by 0.96 to account for trapped plasma. At least 60 min separated the plasma volume determination and the start of the exercise protocol.

**Quantification of renal SNA.** In conscious animals, renal SNA recordings are limited to whole nerve recordings. We used two complementary methods to express the renal SNA data during exercise: as a percentage of renal SNA at rest immediately before exercise and as a percentage of renal SNA measured during maximal activation of the nasopharyngeal reflex.

In rabbits, nasopharyngeal stimulation with cigarette smoke produces a dramatic increase in renal SNA that has been used to normalize renal SNA in baroreflex and exercise studies (9, 32, 33). We have operationally defined the renal SNA response to activation of the nasopharyngeal reflex as the “maximum” renal SNA that we elicit by physiological means in a conscious rabbit. Increases in renal SNA elicited by other physiological stimuli, such as hypotension (9, 33), severe hypoxemia (31), and dynamic exercise (32), elicit sympathetic responses that are typically 30–50% of the renal SNA measured during the nasopharyngeal reflex. We have observed that the renal SNA response to parturition can at times exceed the renal SNA elicited by nasopharyngeal stimulation (33).

We calculated the relative change in renal SNA from rest in response to nasopharyngeal stimulation and found no difference between the nonpregnant (798 ± 132%) and pregnant (992 ± 104%) groups, which suggests that pregnancy does not affect the ability to raise renal SNA in response to nasopharyngeal stimulation with smoke. No current normalization method can definitively quantify absolute sympathetic activity; thus we are unable to ascertain whether renal SNA outflow, in absolute terms, is affected during pregnancy.

The nasopharyngeal reflex was assessed either at the beginning or end of the experimental protocol. To elicit the nasopharyngeal reflex, cigarette smoke contained in a syringe was intermittently puffed toward the nares of the rabbit for a period of 60–120 s. The five 2-s intervals with the highest renal SNA were averaged, and this average was operationally defined as maximal renal SNA. Minimum renal SNA (background noise) was obtained at the beginning of the day’s experiment in response to phenylephrine hydrochloride (10 µg/kg iv; Sigma Chemical, St. Louis MO) and at end of the day’s experiment after suppression of postganglionic activity (trimethaphan camysylate 5 mg/kg iv, Arfonad, Roche Laboratories or hexamethonium bromide, 10 mg/kg iv, Sigma). Phenylephrine administration increased BP to a similar extent in the nonpregnant (+36 ± 8 mmHg) and pregnant (+33 ± 2 mmHg) animals. The lower of the two voltage values resulting from phenylephrine administration or ganglionic blockade was subsequently used to define the reference renal SNA recordings. Renal SNA recorded during the experiment was then expressed as a percentage of the maximal renal SNA and as a percentage of the resting activity immediately before a bout of dynamic exercise.

**Experimental Protocols**

**Initial study protocol.** No earlier than 14 days after the first surgery for flowprobe implantation, rabbits were brought to the laboratory and acutely instrumented with ear arterial and venous lines as described above. At this time, all rabbits were in the nonpregnant state. After 60 min of rest in the transport box, BP, HR, and UtBF were measured for 10 min. After these measurements, plasma volume was determined with the Evans blue dye-dilution technique as described above.

**Exercise protocol.** All hemodynamic and sympathetic activity measurements on the day of the exercise protocol were made while the animal was on the treadmill. After the assessment of the nasopharyngeal reflex (if applicable), the rabbit was allowed to rest for at least 15 min. Each rabbit completed three exercise trials. For each trial, data were continuously recorded during a 2-min baseline period (rest) followed by 5 min of treadmill exercise and 5 min of recovery. At least 45 min of rest were allowed between exercise trials. As the treadmill belt began to move and increase in speed, rabbits rode the belt for −1–2 s before taking their first hop. Thus time 0 for analyzing the hemodynamic and renal SNA responses to exercise was defined as the start of the first hop, as visually identified by one of the investigators.

Three exercise trials were performed: 7 m/min, 0% grade; 10 m/min, 7% grade; 10 m/min, 11% grade. The order of the trials was alternated among animals. The decision to emphasize increases in grade rather than speed to increase workload was to minimize the risk of incurring mechanical artifacts in the renal SNA recording. In our laboratory, the observed upper limit for exercise HR in rabbits is 400 beats/min. With the use of percentage of maximal HR as an index of relative exercise intensity, the fixed workloads corresponded to relative intensities of 79 ± 2, 87 ± 2, and 89 ± 2% of maximum HR in the nonpregnant group and 83 ± 1, 86 ± 1, and 89 ± 2% of maximum HR in the pregnant group.

**Data Analysis**

Renal SNA potentials were amplified by a preamplifier (∼1,000) and a low-noise differential amplifier (∼10–100) with use of a bandwidth of 100–3,000 Hz. The signal was full-wave rectified and averaged using a 100-ms moving time average. Artifacts in the renal SNA data associated with movement of the rabbit were identified at the time of occurrence by change in the audible signal and excessive burst amplitude and width. Artifacts were removed from the digitized data file before analysis. UtC was calculated as UtBF (in ml/min arterial BP (in mmHg). UtC = UtBF × arterial BP.

A three-way ANOVA with repeated measures (NCSS 2000, Kaysville, UT) was utilized to compare variables between the nonpregnant and pregnant groups over the three fixed exercise intensities. Hemodynamic and renal SNA values included in the statistical analysis (main effect of time) were
rest (2-min average) and the 1st and 5th min of exercise. Similarly, a three-way ANOVA with repeated measures was utilized to explore the recovery from exercise. Included in the statistical analysis were rest and the 1st and 5th min of recovery. Previous work in our laboratory has indicated that peak renal SNA values are typically recorded at the onset of exercise (32). A separate two-way ANOVA (group × exercise intensity) was applied to the renal SNA data collected over the first 20 s of exercise to explore the possibility that group differences would manifest at the onset of exercise. Resting hemodynamic values were analyzed with a two-way ANOVA (group × study protocol) with repeated measures. Significant ANOVA interactions or main effects were explored with the Tukey-Kramer multiple comparison procedure. Values are represented as means ± SE. Differences were considered statistically significant at $P < 0.05$.

**RESULTS**

The pregnant animals were significantly heavier than the nonpregnant animals (Table 1). In the nonpregnant group, plasma and blood volumes measured on the day of the exercise protocol were similar to values measured ~45 days earlier during the initial study. Pregnancy was associated with expansion of plasma (27 ± 4%) and blood (24 ± 4%) volumes on a per kilogram basis compared with prepregnant levels.

At the time of the initial study, which was at least 14 days after flowprobe implantation and when all animals were in the nonpregnant state, the two experimental groups demonstrated similar baseline hemodynamic values (Table 1). Term pregnancy (day 29) was associated with a decrease in BP (–Δ22 ± 2 mmHg) and increase in UtBF (Δ590 ± 140%) and UtC (Δ853 ± 202%) compared with prepregnant levels in the same animals. BP was lower on the day of the exercise protocol than at the initial study in the nonpregnant group, but the change was ~50% of the decline in BP in the pregnant rabbits (Table 1). HR was elevated on the day of the exercise protocol in both groups, which most likely reflects a heightened awareness on the part of the rabbits while unrestrained on the treadmill compared with sitting in the transport box. Renal SNA was measured only on the day of the exercise protocol and was similar, when expressed relative to maximum SNA elicited by the nasopharyngeal reflex, between the nonpregnant and pregnant groups.

### Table 1. Body weight, plasma and blood volume, and uterine circulatory and renal SNA values in pregnant and nonpregnant rabbits

<table>
<thead>
<tr>
<th></th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
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<tbody>
<tr>
<td>Body weight, kg</td>
<td>3.6 ± 0.1 (n = 12)</td>
<td>3.7 ± 0.1 (n = 17)</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>3.7 ± 0.1 (n = 12)</td>
<td>4.1 ± 0.1† (n = 17)</td>
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<tr>
<td>Plasma volume, ml/kg</td>
<td>42 ± 2 (n = 11)</td>
<td>40 ± 1 (n = 17)</td>
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<tr>
<td>Exercise protocol</td>
<td>41 ± 2 (n = 11)</td>
<td>52 ± 2 (n = 15)†</td>
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<tr>
<td>Blood volume, ml/kg</td>
<td>60 ± 3 (n = 11)</td>
<td>58 ± 2 (n = 17)</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>57 ± 2 (n = 11)</td>
<td>72 ± 3 (n = 15)†</td>
</tr>
<tr>
<td>Arterial BP, mmHg</td>
<td>51 ± 2 (n = 12)†</td>
<td>58 ± 2 (n = 16)†</td>
</tr>
<tr>
<td>Initial study</td>
<td>81 ± 2 (n = 10)</td>
<td>80 ± 2 (n = 16)</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>71 ± 2 (n = 12)*</td>
<td>59 ± 2 (n = 16)†</td>
</tr>
<tr>
<td>Heart Rate, beats/min</td>
<td>214 ± 10 (n = 10)</td>
<td>215 ± 6 (n = 17)</td>
</tr>
<tr>
<td>Initial study</td>
<td>257 ± 13 (n = 12)*</td>
<td>279 ± 5 (n = 16)*</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>1.2 ± 0.4 (n = 6)</td>
<td>2.5 ± 0.4 (n = 9)</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>1.9 ± 0.3 (n = 8)</td>
<td>13 ± 3 (n = 10)†</td>
</tr>
<tr>
<td>UtBF, ml/min</td>
<td>1.5 ± 0.5 (n = 6)</td>
<td>2.9 ± 0.5 (n = 9)</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>2.8 ± 0.5 (n = 8)</td>
<td>22 ± 5 (n = 10)†</td>
</tr>
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<td>Renal SNA, %maximal</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Initial study</td>
<td>13 ± 3 (n = 6)</td>
<td>13 ± 1 (n = 9)‡</td>
</tr>
<tr>
<td>Exercise protocol</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Values are means ± SE. Initial body weights and blood volume measurements were taken no earlier than 14 days after the first surgery and before breeding. For the initial study, measurements were taken for 10 min after 1 h of rest in the transport box. For the measurements on the day the exercise protocol was performed, the values were a 2-min average taken while the animal was sitting unrestrained on the treadmill. Not applicable: animals were not instrumented with renal nerve recording electrodes for the initial study. Renal sympathetic nerve activity (SNA) and uterine artery blood flow (UtBF) measurements were not made concurrently in every animal. UtC, uterine artery conductance; BP, blood pressure. *$P < 0.05$, initial study vs. exercise protocol; †$P < 0.05$, nonpregnant vs. pregnant.

**UtBF Response to the Nasopharyngeal Reflex**

The UtBF response to activation of the nasopharyngeal reflex was measured in seven pregnant and eight nonpregnant rabbits. Activation of the nasopharyngeal reflex resulted in profound uterine artery constriction in the nonpregnant rabbits as indicated by a 92 ± 3% decrease in UtBF to 0.15 ± 0.06 ml/min. The corresponding decrease in UtC was 94 ± 2%. A similar response occurred in the pregnant rabbits: UtBF decreased 85 ± 4% to 2 ± 0.5 ml/min with a corresponding 87 ± 3% decrease in UtC. There were no differences in the relative decreases in UtBF ($P = 0.12$) or UtC ($P = 0.16$) between the nonpregnant and pregnant rabbits.

**BP and HR Responses to Graded Exercise**

BP in the pregnant group ($n = 17$) was lower than in the nonpregnant group ($n = 12$) at rest and during exercise and recovery, regardless of the exercise intensity (Fig. 1). The pressor responses over time and exercise intensities were similar in both groups.

The average HR just before the three exercise trials was significantly higher in the pregnant group (277 ± 4 vs. 249 ± 5 beats/min). At the onset of exercise, HR increased abruptly in both groups and continued to move upward during the 5 min of exercise in both groups (Fig. 1). In our laboratory, the observed upper limit for exercise HR in rabbits is 400 beats/min. At the 5th min of exercise, HR was significantly greater in the pregnant (333 ± 4 beats/min; 83% of maximum) than nonpregnant group (318 ± 7 beats/min; 79% of maximum) at the lowest exercise intensity but was similar between groups during the two higher intensity runs [346–350 beats/min at 10 m/min, 7% grade (86–87% of maximum), and 355 (89% of maximum) at 10 m/min, 11% grade]. For both groups, HR increased significantly when the intensity increased from 7 m/min, 0%
grade to 10 m/min, 7% grade (Fig. 1). However, when stratified by group, the HR response to the increase in grade from 7 to 11% did not reach statistical significance. This raises the possibility that the increase in grade from 7 to 11% did not result in a consistent increase in oxygen consumption across rabbits. In retrospect, we did observe that rabbits responded to the increase in grade with fewer but more powerful (and thus longer) hops. The rabbits that employed this strategy may have experienced a lower oxygen cost of movement than rabbits that did not, resulting in a variable HR response to the highest exercise workload.

Renal SNA Response to Exercise

Renal SNA was measured during dynamic exercise in nine pregnant animals and six nonpregnant animals. Pregnancy did not affect the pattern of the renal SNA response to exercise (Fig. 2). Renal SNA increased abruptly at the onset of exercise and was maintained at an elevated level for the duration of the 5-min exercise period at all exercise intensities. At the cessation of exercise, renal SNA decreased immediately in both groups and returned to resting levels within the 1st min of recovery.

Exercise Intensity and the Renal SNA Response

In the nonpregnant group, the renal SNA response to exercise increased when intensity increased from 7 m/min, 0% grade to 10 m/min, 7% grade ($P < 0.05$), but there was no further increase when the treadmill grade was increased to 11% (Fig. 2). A similar pattern occurred in the pregnant group (Fig. 2).

Expression of the renal SNA data as a percent change from rest also demonstrated a significant increase in renal SNA when exercise intensity increased from the 7 m/min, 0% grade (nonpregnant +38 ± 11%, pregnant +96 ± 21%) to the 10 m/min, 7% grade (nonpregnant +143 ± 56%, pregnant +165 ± 34%) with no further change when the grade increased to 11% (nonpregnant +102 ± 17%, pregnant +205 ± 34%).

Pregnancy Status and the Magnitude of the Renal SNA Response

Inspection of the renal SNA data in 10-s intervals during the 1st min of exercise revealed that peak levels...
of renal SNA were typically achieved at the onset of exercise (Fig. 2). However, a two-way ANOVA that explored the effect of group and exercise intensity on renal SNA (expressed relative to the smoke-elicited maximum and resting activity) averaged over the first 20 s of exercise indicated neither a main effect of group nor an interaction between group and exercise intensity. Averaged over groups, there was a small but significant decline in renal SNA from the 1st to 5th min (+163 ± 16 vs. 131 ± 15% from rest, *P < 0.01), but renal SNA still remained elevated over resting levels.

The results of the three-way ANOVA (group, pregnancy status, and time) indicated that there was no interaction between exercise intensity and pregnancy status for renal SNA expressed relative to maximum activity. When averaged over the three exercise trials, there was no difference in the steady-state (5 min) renal SNA in the nonpregnant (22 ± 2% of maximum) and pregnant rabbits (24 ± 1% of maximum, *P = 0.41).

One concern with the use of fixed exercise intensities to evoke renal SNA responses is that the relative workloads may have been greater for the pregnant than nonpregnant rabbits. In a subanalysis of the data during steady-state exercise, we limited the data to renal SNA measured at HR greater than 78% of maximum, the lowest value measured in the pregnant group, and repeated the one-way ANOVA. The renal SNA response was again similar in the nonpregnant (23 ± 2% of maximum) and pregnant groups (24 ± 1% of maximum).

Similar analyses were applied to the renal SNA data expressed relative to resting activity. Again, there was no interaction between the exercise intensity and pregnancy status for renal SNA expressed relative to resting activity (*P = 0.17). However, when averaged over the three exercise trials, there was a significant difference between the steady-state (5 min) change in renal SNA in the nonpregnant rabbits (+94 ± 22% from rest) and pregnant rabbits (+155 ± 19% from rest, *P = 0.045). When the data were limited to renal SNA measured at a HR greater than 78% of maximum to match relative exercise intensities between the groups, the difference persisted: nonpregnant 84 ± 23% vs. pregnant 155 ± 19% from rest, *P = 0.03.

Taken together, these results indicate that pregnancy does not impair the ability to raise renal SNA at the initiation of exercise or during steady-state dynamic exercise.

**Uterine Hemodynamic Responses to Exercise**

UtBF was measured in 11 pregnant animals and 8 nonpregnant animals. UtBF was elevated at rest, during exercise, and through recovery in the pregnant animals (Fig. 3). There was no significant main effect of exercise intensity on the UtBF response. In both groups, the qualitative response to exercise was similar, such that UtBF decreased rapidly at the onset of exercise and remained at an attenuated level through the 5 min of exercise. However, the relative (%) decrease in UtBF in response to exercise was lower in the pregnant compared with the nonpregnant rabbits (Fig. 4). When averaged over exercise intensity, UtBF in the nonpregnant rabbits decreased 48 ± 4% at 5 min of exercise compared with a decrease of 16 ± 4% (*P < 0.01 vs. nonpregnant) in the pregnant animals. Thus the...
relative decrease in UtBF with exercise was significantly attenuated at term pregnancy (Fig. 4). UtC was calculated as UtBF/BP. As with UtBF, UtC was elevated in pregnancy (23 ± 3 vs. 3 ± 0.4 ml·min⁻¹·mmHg⁻¹ × 10⁻²), and there was no main effect of exercise intensity on the UtC response. Although absolute UtC decreased in both groups in response to exercise, the relative (%) decrease in UtC from resting values was attenuated in the pregnant rabbits. The average decrease in UtC at the 5th min of exercise was −27 ± 4% in the pregnant rabbits compared with −54 ± 4% in the nonpregnant rabbits (P < 0.05).

At the cessation of exercise, UtBF (Fig. 3) and UtC rapidly returned toward resting levels over the 1st min of recovery. At 5 min postexercise, UtBF and UtC were similar to resting levels. There was no significant effect of exercise intensity on the recovery response.

DISCUSSION

In this study, chronically instrumented rabbits were utilized to evaluate the impact of term pregnancy on the renal SNA and uterine hemodynamic responses to moderate to heavy dynamic exercise. Continuous measurements of blood flow in a uterine artery and of renal SNA were obtained in nonpregnant and pregnant rabbits. The major findings of this study were 1) pregnancy did not affect the pattern of the renal SNA response to exercise; 2) pregnancy did not impair the ability to raise renal SNA in response to exercise; 3) the rise in renal SNA was related to exercise intensity; and 4) pregnancy was associated with an attenuated uterine artery constrictor response to exercise. We also observed that over the moderate to heavy exercise workloads utilized in this study, there was no significant relationship between exercise intensity and the uterine artery constrictor response in either the nonpregnant or pregnant states.

There are limited data on the impact of pregnancy on neural control of the circulation during dynamic exercise. In the rabbit, as in other species, the cardiovascular adjustments to dynamic exercise include decreases in vascular conductance in visceral circulations such as the renal and splanchnic circulations (15). This vascular response is principally mediated by increases in sympathetic nerve activity (15, 30, 36). There is indirect evidence that sympathetic modulation of HR during submaximal exercise is reduced during human pregnancy (2). However, the maximal HR response to exercise has been reported as unchanged (16) or reduced by 4 beats/min (24) in human pregnancy, indicating that the ability to maximally raise cardiac SNA during exercise is probably unaffected.

At rest, pregnancy is associated with normal plasma catecholamine levels (2, 5), although SNA to leg muscle is elevated (13). Direct measurements of muscle SNA or regional norepinephrine spillover during exercise have not been reported in pregnant women. Bonen et al. (5) and Avery et al. (2) measured circulating catecholamines, an indirect measure of sympathoadrenal activation, in late pregnant women during cycle ergometry. Plasma epinephrine was reduced during pregnancy at moderate exercise (below the ventilatory threshold) in both studies. Bonen et al. (5) but not Avery et al. (2) reported depressed plasma norepinephrine responses at moderate exercise, while plasma norepinephrine and epinephrine were both reduced during exercise above the ventilatory threshold, compared with the postpartum state (2).

In the current study, we directly measured sympathetic nerve activity to a regional vascular bed, the kidney, in term pregnant rabbits. The qualitative character of the renal SNA response was similar in pregnant and nonpregnant animals: renal SNA increased abruptly at the onset of exercise and was maintained at an elevated level through the 5-min exercise duration. In contrast to our hypothesis, the magnitude of the renal SNA response to graded exercise was not attenuated at term pregnancy, whether the values were expressed relative to the smoke-elicited maximum or relative to resting activity. We reiterate that the absolute sympathetic activity cannot be compared across animals using whole nerve recordings (see METHODS). Thus it is not possible to determine whether our observation that relative renal SNA (as expressed as a % of maximal SNA) was unaffected by pregnancy translates as a similar absolute sympathetic outflow during exercise. A conservative interpretation of these data is that term pregnancy does not impair the ability to raise renal SNA in response to exercise.

Renal blood flow and conductance decrease during dynamic exercise in nonpregnant rabbits (30), and renal vasoconstriction is largely attenuated with renal denervation or α-adrenoceptor antagonism. Renal blood flow has not been measured during exercise in pregnant rabbits, so it is unknown whether the relationship between the renal SNA and renal vasoconstrictor responses to exercise is altered at term pregnancy. Renal blood flow decreases during exercise in pregnant rats (20), and the rise in renal vascular resistance may be increased in pregnant rats (10). In sheep, mild exercise has minor effects on renal blood flow, and this response is not altered with pregnancy (3, 4).

There is evidence in rats and rabbits that normal pregnancy is associated with an attenuated ability to reflexively raise SNA in response to hypotension or a reduced sensitivity of the BP:renal SNA relationship (25, 33, 34). As with renal SNA, the sensitivity of the baroreflex control of HR is depressed in late pregnant rabbits (35). Although strong evidence supports an attenuation of arterial baroreflex control of sympathetic outflow, the results from the current study indicate that term pregnancy is not associated with a global attenuation of the ability to raise renal SNA in response to physiological stress. As discussed above, our results indicate that term pregnancy does not impair the ability to raise renal SNA at either the initiation of exercise or during short-term steady-state exercise. Furthermore, we found that pregnancy did not affect the ability to raise renal SNA in response to
stimulation of the nasopharyngeal reflex via inhalation of cigarette smoke (see Quantification of renal SNA).

**Uterine Vasoconstrictor Response to Exercise**

The UtBF response to dynamic exercise has not been reported for nonpregnant women. These data are scarce in animal models as well. Dowell and Kauer (10) utilized microspheres to measure regional blood flows during treadmill exercise in nonpregnant rats. Uterine blood flow was not altered, although uterine vascular resistance increased 25% during steady-state submaximal exercise. In the present study, we documented that in the nonpregnant rabbit, UtBF decreases 48% and UtC decreases 54% with moderately heavy exercise. Similar to the mesenteric and renal circulations (8, 15, 30), UtBF and UtC decreased rapidly at the onset of treadmill exercise. The uterine circulation is innervated by sympathetic adrenergic nerves (37, 40). Sympathetic stimulation or \(\alpha\)-adrenergic agonists cause uterine artery constriction (7, 17, 19, 21, 37). Thus, if the uterine circulation is similar to other visceral beds, it is likely that this initial uterine vasoconstriction reflects the exercise-induced activation of sympathetic nerves and that at least in part, the vasoconstriction is mediated via \(\alpha\)-adrenergic receptors.

In the nonpregnant rabbits, uterine vasoconstriction was maintained through 5 min of exercise. The net vascular response to steady-state dynamic exercise will reflect the integration of endothelial, neural, and circulating hormonal factors on vascular smooth muscle. It is likely that sympathetic nerve activity is still elevated to the uterine circulation during steady-state exercise, as has been documented for the renal circulation during exercise (Ref. 32 and current study).

It has been clearly documented in animals such as the sheep (23), rat (10), goat (18), and in rabbits (current study) that uteroplacental blood flow decreases during moderate to heavy dynamic exercise. The results are more variable in pregnant women, but this is likely related to difficulties in imaging the uterine vasculature that restrict measurements to brief pauses in the exercise or immediately postexercise (11, 14, 27, 29). As seen in our data (Fig. 3) and in that of Lotgering et al. (23), uteroplacental blood flow and conductance rapidly return toward resting levels upon the cessation of movement, indicating that the studies in pregnant women may underestimate the degree of uterine artery constriction.

Based on available evidence, the UtBF response to exercise appears similar among the pregnant sheep, goat, and rabbit. In sheep, rat, and goat (10, 18, 23), the relative reductions in uteroplacental flow with submaximal exercise have not exceeded 30% (sheep = −13% with moderate exercise; goat = −11% with mild exercise; rat = −26% with moderate exercise). Our data in rabbits (−16 ± 4% averaged over moderate-heavy exercise) are consistent with these values.

A question that has been largely unaddressed is whether pregnancy alters the pattern or magnitude of the uterine vasoconstrictor response to exercise. In the current study, we were able to address both issues with the use of a nonpregnant control group and continuous measurements of UtBF. Inspection of Fig. 3 shows that qualitatively, the UtBF and UtC responses to dynamic exercise are similar in pregnant and nonpregnant rabbits in that UtBF and UtC decrease at the onset of exercise, remain below resting levels for the 5-min exercise period, and return to near resting levels within the 1st min postexercise. In the pregnant goat (18) and sheep (23), uterine artery flow was measured with electromagnetic flowprobes over 10 min of exercise. Similar measurements have not been reported for nonpregnant sheep or goats. In the pregnant sheep, UtBF exhibited a slow, downward drift when exercise increased from 10 to 40 min (23). It is unknown whether the duration of exercise affects the UtBF response in the rabbit.

In the rabbit, pregnancy did attenuate the magnitude of the uterine artery constrictor response to dynamic exercise, as assessed by the relative change (%) in UtBF and UtC in the nonpregnant and pregnant groups. Dowell and Kauer (10) measured organ blood flow with radioactive microspheres in pregnant and nonpregnant rats at rest and during steady-state exercise. In contrast to the rabbit data, uterine flow did not change with exercise in the nonpregnant state in the rat (calculated from their Fig. 1), while uterine vascular resistance increased −25% (10). At term pregnancy, the uterine vasoconstrictor response in the rat was enhanced, as uterine blood flow decreased −29% and uterine vascular resistance increased −50%. There are no exercise data available in the nonpregnant state for either sheep or goats, so it is unknown whether attenuation of the uterine vasoconstrictor response occurs with pregnancy in these species.

A mechanism that may contribute to the attenuation of the uterine artery constrictor response to exercise in the pregnant rabbit is reduced sympathetic control of the uterine vasculature. Pregnancy is associated with a decreased density of tissue catecholaminergic content or innervation of the myometrium and vasculature as identified by histochemical methods (21, 37), although perivascular nerves were clearly identified in the pregnant uterus by Zuspan et al. (40). In anesthetized animals, the degree of uterine vasoconstriction in response to nerve stimulation was reduced in pregnant dogs (37) but not in postpartum rats (19). Similar functional studies have not yet been performed in rabbits. However, strong activation of the nasopharyngeal reflex in the pregnant rabbits in this study substantially reduced UtBF and UtC to the pregnant uterus (−85–87%), which implies that residual perivascular uterine sympathetic innervation is present and is capable of being reflexively activated in the pregnant rabbit.

Reduced \(\alpha\)-adrenoceptor control of the uterine vasculature with pregnancy is another putative mechanism that could result in an attenuated vasoconstrictor response to exercise. The sensitivity of the pregnant uterine vasculature to \(\alpha_1\)-adrenoceptor agonists has been reported as decreased (17) and increased (7).
In term pregnant rabbits, the attenuated uterine artery constrictor response to moderate to heavy exercise may be a protective mechanism for the pregnant rabbit. As discussed by Gilbert et al. (12), the uterus in the term pregnant rabbit has a relatively high oxygen extraction (60–74% compared with 24% in the sheep) at rest, and arterial oxygen content in the rabbit is lower at term than at midgestation. With a limited ability to increase oxygen extraction, defense of UtBF during exercise becomes an important strategy in maintaining adequate oxygen delivery to the fetuses.

The relative UtBF response to exercise in pregnant sheep (23) and goats (18) was intensity dependent. In this study, we did not observe a significant relationship between absolute exercise intensity and the UtBF or treadmill exercise, V̇O₂ max in the rabbit. In a study by Avery et al. (2), we observed a significant relationship between exercise intensity and the uterine artery constrictor response to exercise in the nonpregnant rabbit. In this study, we did not observe a significant relationship between absolute exercise intensity and the UtBF or V̇O₂ max in the rabbit. However, we did observe a significant relationship between absolute exercise intensity and the uterine artery constrictor response to exercise in the nonpregnant rabbit.

Limitations

We utilized a discontinuous graded exercise protocol using fixed (absolute) workloads for the nonpregnant and pregnant groups. Comparison of physiological responses to exercise using fixed workloads to group the data is most accurate when the exercise intensities represent similar relative workloads among individuals. For that reason, using absolute workload as the grouping variable in this study has potential limitations. First, the increase in grade from 7 to 11% did not elicit a consistent increase in HR in either the pregnant or nonpregnant rabbits. We believe that a change in gait at the higher grade may have lowered the oxygen cost of movement in some rabbits. Second, it is unknown to what extent pregnancy affected the oxygen cost of movement or maximal oxygen consumption (V̇O₂ max) in the rabbit, although we believe this effect to be small. In pregnant women undergoing maximal treadmill exercise, V̇O₂ max (expressed as l/min), maximal HR, and maximal power output are unaffected (24). Whether efficiency is altered in submaximal weight-bearing exercise in pregnant women is not settled, with increases, decreases, and no change in efficiency observed (39). Weight gain, which is a factor that could decrease exercise efficiency with pregnancy, averaged ~11% in the rabbits. However, this relative increase in body weight is small relative to pregnant women who gain the recommended 11.5–16 kg (in a 57-kg woman, the increase in weight is 20–28%).

For these reasons, we evaluated the HR range over which data were measured in the nonpregnant and pregnant rabbits. The HR range was greater in the nonpregnant rabbits. We thus performed a subanalysis, limiting the data in the ANOVA from the nonpregnant group to the HR range observed in the pregnant group. This adjustment did not affect the results: with moderate to heavy exercise, the relative decreases in UtBF and UtC were blunted and the ability to raise renal SNA was not impaired in the pregnant rabbits.

In conclusion, term pregnancy in rabbits did not impair the ability to raise sympathetic activity to a regional vascular bed, the kidney, during short-term moderate to heavy exercise. The uterine artery constrictor response to exercise was attenuated at term pregnancy. These results suggest that under normal conditions, the pregnant uterine circulation bed in the rabbit may be relatively protected from exercise-related redistribution of blood flow.

Perspectives

Physical activity is a common stressor. That uteroplacental blood flow decreases during dynamic exercise in normal pregnancy is supported by studies in animals and women. There is limited evidence that in pregnancies complicated by superimposed hypertensive conditions, such as preeclampsia and pregnancy-induced hypertension, exercise may result in exaggerated reductions in uteroplacental flow (14). Our observations in exercising rabbits suggest that in normal pregnancy, the exercise-related redistribution of blood flow away from the uterus is blunted compared with the nonpregnant condition. A greater understanding of the contributions of endothelial, neural, and hormonal mechanisms in mediating the attenuated uterine vascular response to exercise in normal pregnancy may provide insight into abnormal circulatory responses to physical activity in preeclampsia and other hypertensive pregnancy conditions.

DISCLOSURES

This study was supported by National Heart, Lung, and Blood Institute Grant HL-61368-01 and Midwestern University.

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