Hemodynamic and hormonal responses to hemorrhage in conscious rabbits at mid- and late gestation

Virgin L. Brooks, Rebecca R. Quesnell, Colleen M. Kane, and Lanny C. Keil. Hemodynamic and hormonal responses to hemorrhage in conscious rabbits at mid- and late gestation. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1082–R1090, 1998.—This study tests the hypothesis that conscious rabbits late in pregnancy (P), but not at midgestation (MP), are less able to maintain arterial pressure during hemorrhage. Blood volume (BV) was elevated (P < 0.05) by an average of 13 ± 4 (MP) and 35 ± 3% (P). Rabbits were bled in both the nonpregnant (NP) and P state at 2% of the initial BV per minute. The hemorrhage was stopped after arterial pressure decreased. In NP rabbits, arterial pressure was well maintained near control pressures of 70 ± 2 mmHg until 38 ± 2% of the initial BV was removed and then rapidly fell to reach a nadir at 35 ± 2 mmHg. In contrast, in P rabbits, basal arterial pressure was lower (61 ± 2 mmHg; P < 0.05) and gradually decreased to below control after 25% of the initial BV was removed. Moreover, the rapid hypotensive phase was triggered with a lower percent BV removal (33 ± 2% P < 0.05). Basal heart rate was higher during P (149 ± 5 vs. 189 ± 9 beats/min; P < 0.05), and reflex increases were delayed. The slope of the relationship between arterial pressure and vasopressin was not modified during P, although the line was shifted to a lower pressure (P < 0.05). Larger increases in plasma renin activity and ANG II concentration were produced during hemorrhage in P rabbits. In contrast, no differences in the changes in arterial pressure, heart rate, and vasopressin were found between NP and MP rabbits during hemorrhage, although increases in renin and ANG II were greater at MP (P < 0.05). In summary, although P conscious rabbits are less able to maintain blood pressure during hemorrhage, this change is not evident at MP. These data suggest that the factors that mediate the P-induced alterations in arterial pressure regulation are not operative until late in gestation.

arterial pressure; heart rate; vasopressin; renin; angiotensin II; baroreceptor reflex

NORMAL PREGNANCY is characterized by significant alterations in fluid and electrolyte homeostasis and blood pressure regulation. Blood volume and cardiac output increase by as much as 30–40%, and mean arterial pressure falls because of decreases in total peripheral resistance (28, 32). Not only does pregnancy alter the cardiovascular system at rest, but recent data document changes in cardiovascular homeostasis. For example, it has been shown in several species that pregnancy interferes with the normal ability to maintain arterial pressure during hemorrhage (7, 21, 33, 40). Moreover, women in late pregnancy are known to be more susceptible to orthostatic hypotension, with smaller increases in systemic vascular resistance or in plasma norepinephrine levels (1, 3, 11, 14). Because hemorrhage is a common occurrence during normal delivery, an understanding of the mechanism that mediates these inappropriate changes is essential for effective patient care.

In conscious, nonpregnant animals, the hemodynamic response to hemorrhage consists of two phases: an initial baroreflex-mediated nonhypotensive phase, followed by a rapid and profound hypotensive phase that is secondary to decreases in sympathetic activity (for review, see Ref. 37). It appears that, during pregnancy, the hypotensive phase is triggered with less blood loss (7, 33). Because blockade of the initial reflex increases in sympathetic activity, ANG II or vasopressin leads to premature hemorrhagic hypotension (26, 37), one explanation for the change during pregnancy may be that the baroreflex is not as effective. This explanation is supported by studies showing that reflex increases in heart rate, total peripheral resistance, sympathetic activity, vasopressin, and ACTH secretion are attenuated during late pregnancy (7–9, 18–20).

Although these studies demonstrate that arterial baroreflex function is blunted during late pregnancy in association with an inability to maintain arterial pressure during hemorrhage, the mechanism for these changes has not been identified. Pregnancy causes increases in numerous hormones and other alterations in the cardiovascular system that could mediate the change in baroreflex activity. To narrow the field of possibilities, we recently determined at which time during gestation the change in the baroreflex occurs. Our results demonstrated that baroreflex gain does not change significantly until the end of pregnancy in conscious rabbits (35). However, whether the cardiovascular responses to hemorrhage are also normal earlier in pregnancy has not been examined.

The present study had two purposes. First, anesthetized pregnant rabbits have been shown to have less tolerance for hemorrhage (21), but whether the same is true in conscious rabbits is not known. Because anesthesia markedly blunts baroreflex activity (37, 43), it is important to establish whether conscious, pregnant rabbits exhibit the same response. Therefore experiments were performed to test the hypothesis that late-pregnant conscious rabbits are less able to maintain arterial pressure during hemorrhage. Second, it was hypothesized that blood pressure maintenance during hemorrhage is normal in conscious rabbits at midgestation, since baroreflex function is normal. These hypotheses were addressed by examining the hemodynamic and hormonal responses to hemorrhage in conscious rabbits before pregnancy and at either midgestation or the end of pregnancy.
METHODS

Surgical preparation. Female (n = 16) New Zealand White rabbits weighing between 3.2 and 4.2 kg (nonpregnant) were used for these experiments. The rabbits were obtained when 14–15 wk old and allowed a 1-wk acclimatization period. Surgery was then performed to implant nonocclusive abdominal and vena caval catheters as previously described (17). Briefly, the animals were initially anesthetized (1 ml/kg im) with a cocktail containing 5:2:5:1 of ketamine (100 mg/ml), xylazine (20 mg/ml), and acepromazine (10 mg/ml), and a surgical plane of anesthesia was maintained with 1:10 ketamine 0.9% NaCl solution administered intravenously as needed. A midline abdominal incision was made and indwelling polyethylene catheters with Silastic tips were implanted in the abdominal aorta and vena cava. The catheters were tunneled from the abdominal cavity subcutaneously and were exteriorized at the nape of the neck. The tip of one of the vena caval catheters was advanced from its abdominal introduc- tor to the thoracic inferior vena cava. This catheter was used to measure central venous pressure. The rabbits were given penicillin G procaine (60,000 U im) on the day before and the day after the surgery. The animals were given buprenorphine (Buprenex, 0.15 im) 2–3 h after surgery (when sternal) and received an analgesic (50 mg acetaminophen) by mouth three times per day for 3–4 days after surgery. The neck incision was treated with topical nitrofurazone antibacterial dressing for 1 wk after surgery. Catheters were flushed immediately after surgery and then three times weekly, using sterile 0.9% NaCl, and filled with heparin (1,000 U/ml) to maintain patency.

Animals were allowed at least 2 wk for recovery from surgery. During this time the rabbits were transitioned from a high-fiber diet (Ralston Purina 5326) to a high-protein diet (Ralston Purina 5321), increasing 10% high protein/day for 10 days. The female rabbits were then maintained on 150 g/day of the high-protein diet (0.25% sodium and 16.2% protein) to enhance breeding efficiency. All animals were allowed free access to distilled water. During recovery, the rabbits were also trained to rest quietly in a specially designed opaque Plexiglas box that was used to restrain the rabbits during experiments. Room temperature was kept between 64 and 68°F, and a 16-h light cycle was maintained for optimal breeding.

Hemorrhage protocol. Two separate groups of rabbits were studied: six rabbits were hemorrhaged before and after 4 wk of pregnancy, and five rabbits were studied before and after 2 wk of gestation. After the nonpregnant hemorrhage, the animals were bled with noninstrumented proven male breeder rabbits, and this was considered day 1 of pregnancy. The pregnancy of all rabbits studied at 2 wk of gestation was confirmed by palpation by the veterinary staff at Oregon Health Sciences University before the experiment was performed.

Blood volume increases significantly during pregnancy. Therefore, to produce equivalent hemorrhages in the rabbits when they were pregnant and nonpregnant, the animals were bled as a function of their initial blood volume. Blood volume was estimated in several pregnant and nonpregnant rabbits by measuring the volume of distribution of technetium-labeled erythrocytes (2). The purpose of the repeated measurements was to determine whether blood volume was consistent between animals as a function of body weight. If blood volume did not vary significantly between animals, it could then be estimated from the body weight rather than from using the indicator-dilution technique.

On the day of the experiment, the rabbits were placed in the Plexiglas box and allowed 30–45 min to equilibrate. Arterial pressure and heart rate were measured continuously via the aortic catheter by using a Statham pressure transducer, a Grass tachometer, and a Grass polygraph. Central venous pressure was measured via a vena caval catheter using a second transducer. The second venous catheter was attached to sterile tubing that was threaded through a peristaltic pump and connected to a sterile plastic bag. After injection of 1 ml heparin (1,000 U/ml iv), baseline hemodynamic measurements were made, and a control venous blood sample was collected (4.5 ml). The hemorrhage was then begun by withdrawing venous blood into the sterile bag at a rate of 2% of the initial total blood volume per minute. The hemorrhage was continued in the nonpregnant and 2-wk pregnant rabbits until arterial pressure abruptly fell below 40 mmHg and was then stopped. When the rabbits were studied at 4 wk of gestation, they were bled for the same length of time (or percent blood volume) as when they were nonpregnant.

To determine whether pregnancy alters hormonal responses (vasopressin, ANG II, and renin) to hemorrhage, venous blood samples (3 ml) were collected after 5, 10, and 15 min of hemorrhage (10, 20, and 30% initial blood volume loss) and again just after the hemorrhage was stopped. These samples were considered part of the hemorrhage. After the hemorrhage was terminated, a 15-min period was allowed for stabilization of plasma hormone levels, and a final blood sample was collected (4.5 ml). The shed blood was then returned to the rabbit by reversing the direction of the pump.

Hormonal analyses. All blood samples were collected into iced plastic tubes containing heparin or EDTA. Immediately after completion of the experiment, the blood was centrifuged at 4°C, and plasma was stored at −20 or −80°C until assayed. Vasopressin and ANG II concentrations were measured by RIA from extracted plasma as previously described (5, 8). Plasma renin activity is the amount of ANG I produced in 1 ml of plasma incubated at 37°C for 1 h. Plasma ANG I was measured by RIA using an antibody generously provided by Dr. Ian Reid and a previously published procedure (38). Between-assay variability for the plasma renin activity procedure is 14.5% (n = 15). Plasma protein concentration was quantified using a refractometer (Hitachi).

Data and statistical analysis. For most figures, ~30-s averages of arterial pressure, heart rate, and central venous pressure were obtained from the polygraph recordings every 2.5 min beginning with the start of the hemorrhage. In Fig. 2, however, arterial pressure measurements were quantified from the continuous pressure tracing every 0.5 min beginning with the lowest pressure point or pressure nadir. Between-group differences in the hemodynamic and hormonal responses to hemorrhage were determined using two-way ANOVA for repeated measures (randomized block) and the post hoc Tukey-Kramer procedure (29, 42). Vasopressin and renin activity values were subjected to logarithmic transformation before ANOVA. Differences in the slope of relationships between plasma vasopressin concentration or plasma renin activity were determined using analysis of covariance (42). If no difference in slope was detected, analysis of covariance was used to determine whether there was a change in the position or intercept of the lines. Finally, between-group differences in blood volume were assessed using a paired or Student's t-test (42). All statistics were performed using GB-STAT (Dynamic Microsystems, Silver Spring, MD).
RESULTS

Effect of pregnancy on blood volume. Measurements of blood volume were extremely consistent both within and between nonpregnant rabbits, especially when normalized to body weight. In 13 nonpregnant rabbits, blood volume averaged 183 ± 6.3 ml or 48.9 ± 0.3 ml/kg. As expected, after 4 wk of pregnancy (n = 8), blood volume was higher (P < 0.001; 243 ± 5 ml or 53.0 ± 1.2 ml/kg), but the measurements were more variable than in nonpregnant animals. As a result, in some nonpregnant rabbits blood volume was estimated by assuming a value of 49 ml/kg, but blood volume was directly quantified in all pregnant rabbits the day before the hemorrhage experiment using the indicator-dilution technique.

Effect of 4 wk of pregnancy on hemodynamic responses to hemorrhage. In two of the six rabbits studied, the nonpregnant blood volume was estimated from body weight, rather than from the volume of distribution of technetium-labeled erythrocytes. As before, blood volume was increased (P < 0.0001) by 35.4 ± 2.6% in pregnant rabbits (245 ± 5 ml) compared with nonpregnant (182 ± 5 ml). Blood volume was also larger when normalized to body weight (54.3 ± 1.4 vs. 49.5 ± 0.1 ml/kg; P < 0.05).

Figures 1 and 2 summarize the changes in arterial pressure and heart rate during hemorrhage in nonpregnant and 4-wk pregnant rabbits. When the rabbits were bled 2% of blood volume per minute in the nonpregnant state, arterial pressure was well-maintained until it rapidly decreased below 40 mmHg after a loss of 37.7 ± 1.5% of the initial blood volume. Pressure fell to a nadir at 35 ± 2 mmHg 20.0 ± 1.0 min after beginning the hemorrhage. In contrast, when the rabbits were pregnant, basal arterial pressure was lower (P < 0.05; Table 1) and did not exhibit the normal maintenance phase during the beginning of hemorrhage. Instead, pressure tended to fall soon after the beginning of hemorrhage and became significantly below control after 25% of the initial blood volume was removed. A second difference was that the initiation of the rapid hypotensive phase occurred with less blood loss when the rabbits were pregnant (37.7 ± 1.5%, nonpregnant; 32.5 ± 1.5%, pregnant; P < 0.05) and that the pressure nadir occurred sooner (16.8 ± 1.0 min after starting the hemorrhage; P < 0.01). Moreover, when the data were aligned to the nadir in pressure in each rabbit (Fig. 2), it was apparent that the arterial pressure nadir was higher during pregnancy (42 ± 2 mmHg; P < 0.05) and that the pressure fall when the rabbits were pregnant (13 ± 4 mmHg) was less (P < 0.05) than when they were not pregnant (31 ± 5 mmHg).

The changes in heart rate during hemorrhage were also different in late-pregnant rabbits (Fig. 1). Basal heart rate was higher (Table 1; P < 0.05), and the initiation of a significant reflex tachycardia was delayed, despite the tendency for pressure to decrease with less blood loss in the pregnant animals. On the other hand, although central venous pressure was

<table>
<thead>
<tr>
<th></th>
<th>Arterial Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>Central Venous Pressure, cmH2O</th>
<th>Hematocrit, %</th>
<th>Protein, g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>71 ± 2</td>
<td>161 ± 8</td>
<td>31.7 ± 1.0</td>
<td>37.2 ± 1.4</td>
<td>4.3 ± 0.3</td>
</tr>
<tr>
<td>2 wk P</td>
<td>71 ± 2</td>
<td>166 ± 11</td>
<td>40.0 ± 1.2</td>
<td>37.0 ± 1.4</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>NP</td>
<td>70 ± 3</td>
<td>154 ± 6</td>
<td>38.0 ± 0.8</td>
<td>40.7 ± 0.8</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>4 wk P</td>
<td>61 ± 2*</td>
<td>188 ± 9*</td>
<td>6.6 ± 0.8*</td>
<td>36.5 ± 0.7*</td>
<td>4.1 ± 0.1*</td>
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</table>

Values are means ± SE. NP, nonpregnant; 2 wk P, 2 wk pregnant; 4 wk P, 4 wk pregnant. *P < 0.05, P vs. NP.
initially higher in the pregnant rabbits (Table 1), hemorrhage produced similar decreases in both groups. Lowest levels were achieved after the hemorrhage was stopped (1.9 ± 0.4 cmH2O, nonpregnant; 4.6 ± 0.7 cmH2O, pregnant; P < 0.05). Plasma protein concentration and hematocrit were lower during late pregnancy (Table 1). Both protein and hematocrit decreased significantly (P < 0.05) during hemorrhage, but the decreases were not different between groups (data not shown).

Effect of 2 wk of pregnancy on hemodynamic responses to hemorrhage. Figure 3 illustrates the changes in arterial pressure and heart rate in rabbits studied in both the nonpregnant state and after 2 wk of gestation (n = 5). In all rabbits after 2 wk of pregnancy, blood volume was increased by an average of 13 ± 4%, from 178 ± 7 to 201 ± 15 ml (P = 0.057). When the rabbits were hemorrhaged before pregnancy, arterial pressure was again well maintained for a period and then rapidly decreased. The changes in arterial pressure were similar when the rabbits were bled after 2 wk of gestation (Fig. 3). Indeed, the percent blood volume loss required to decrease arterial pressure below 40 mmHg was not different between groups (38.4 ± 2.1%, nonpregnant; 40.0 ± 2.3%, pregnant). The pressure nadir also occurred at similar times after the beginning of hemorrhage (19.7 ± 1.1 min, nonpregnant; 20.6 ± 1.1 min, pregnant). Moreover, the pressure nadir (33.2 ± 1.8 mmHg, nonpregnant; 32.6 ± 3.4 mmHg, pregnant) and arterial pressure at the end of the 15-min recovery period (52.4 ± 2.6 mmHg, nonpregnant; 53.6 ± 3.2 mmHg, pregnant) were not different between groups. Heart rate increased significantly after 20% blood volume removal, and this increase was similar in rabbits studied before pregnancy as at 2 wk of gestation (Fig. 3).

Central venous pressure, hematocrit, and plasma protein concentration decreased during hemorrhage when the rabbits were nonpregnant and 2-wk pregnant (P < 0.05; data not shown). However, neither the control values (Table 1) nor the hemorrhage-induced decreases in hematocrit or protein were different between groups.

Effects of pregnancy on hormonal responses to hemorrhage. Hemorrhage increased plasma vasopressin concentration in all groups (Table 2). At the end of pregnancy, vasopressin was elevated after loss of 30% of the initial blood volume. However, in nonpregnant rabbits and rabbits at midgestation, a significant increase did not occur until arterial pressure fell. To determine whether the more rapid increase in vasopressin in the late-pregnant rabbits was due to the larger falls in arterial pressure, plasma vasopressin was correlated to arterial pressure (Fig. 4). In Fig. 4, the results obtained during the pressure fall were not included, because pressure was rapidly decreasing when the blood sample was collected. When vasopressin was plotted on a logarithmic scale, it was linearly related to the fall in

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**Table 2. Vasopressin and plasma renin activity during hemorrhage**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>PF</th>
<th>PF + 15 min</th>
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</thead>
<tbody>
<tr>
<td><strong>Plasma vasopressin concentration, pg/ml</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NP</td>
<td>0.9 ± 0.4</td>
<td>1.3 ± 0.5</td>
<td>0.8 ± 0.4</td>
<td>6.5 ± 4.7</td>
<td>42.9 ± 11.0*</td>
<td>37.7 ± 3.8*</td>
</tr>
<tr>
<td>2 wk P</td>
<td>2.1 ± 0.7</td>
<td>1.0 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>2.3 ± 1.1</td>
<td>27.4 ± 21.4*</td>
<td>32.5 ± 10.7*</td>
</tr>
<tr>
<td>NP</td>
<td>3.0 ± 0.7</td>
<td>2.1 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>4.3 ± 1.6</td>
<td>31.6 ± 13.3*</td>
<td>44.4 ± 10.6*</td>
</tr>
<tr>
<td>4 wk P</td>
<td>2.6 ± 0.1</td>
<td>2.6 ± 0.6</td>
<td>3.7 ± 1.5*</td>
<td>18.4 ± 8.4†</td>
<td>53.5 ± 11.5*</td>
<td>47.0 ± 13.8*</td>
</tr>
<tr>
<td><strong>Plasma renin activity, ng ANG I·ml⁻¹·h⁻¹</strong></td>
<td></td>
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</tr>
<tr>
<td>NP</td>
<td>2.4 ± 0.4</td>
<td>2.8 ± 0.4</td>
<td>4.5 ± 0.9</td>
<td>6.8 ± 1.5*</td>
<td>16.0 ± 4.6*</td>
<td>18.9 ± 6.5*</td>
</tr>
<tr>
<td>2 wk P</td>
<td>4.5 ± 0.8†</td>
<td>4.9 ± 1.1†</td>
<td>6.5 ± 0.7†</td>
<td>9.3 ± 0.9†</td>
<td>21.9 ± 1.7†</td>
<td>30.4 ± 5.7†</td>
</tr>
<tr>
<td>NP</td>
<td>1.4 ± 0.6</td>
<td>1.6 ± 0.5</td>
<td>5.2 ± 1.9</td>
<td>4.8 ± 1.9*</td>
<td>6.6 ± 1.3*</td>
<td>12.1 ± 3.9*</td>
</tr>
<tr>
<td>4 wk P</td>
<td>7.12 ± 2.1†</td>
<td>10.5 ± 2.6†</td>
<td>15.2 ± 3.5†</td>
<td>27.3 ± 7.1†</td>
<td>37.8 ± 12.8†</td>
<td>31.9 ± 9.3†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Percentages are of initial blood volume removed; PF, pressure fall, time at which arterial pressure is rapidly decreasing; PF + 15, 15 min after stopping hemorrhage. *P < 0.01, compared with control within group. †P < 0.05, P vs. NP.
arterial pressure; however, there was no difference in the slopes between groups. Nevertheless, the line relating vasopressin to pressure was shifted to a lower arterial pressure level in late-pregnant rabbits \((P < 0.05)\). In contrast, there was no difference in the vasopressin-pressure relationships in nonpregnant and 2-wk pregnant rabbits (Fig. 4).

Basal plasma renin activity was elevated in the rabbits at both 2 and 4 wk of pregnancy (Table 2). Plasma renin activity increased in nonpregnant and 2-wk pregnant rabbits after a 20% hemorrhage but increased after only 10% of the initial blood volume was removed in the late-pregnant rabbits. Moreover, the levels of renin activity achieved throughout the hemorrhage were higher during mid- and late gestation. Figure 5 illustrates that the higher activities in the 4-wk pregnant rabbits can be largely explained by an increase in slope of the relationship between arterial pressure and plasma renin activity \((P < 0.001)\). After 2 wk of pregnancy, the slope was not significantly increased \((P = 0.15)\); however, there was a significant shift in the curve to the right \((P < 0.001)\). Similar changes were observed in plasma ANG II concentration. Plasma ANG II concentration was elevated in the rabbits at the end of gestation \((P < 0.05)\) but not at midgestation (Fig. 6). Plasma ANG II was increased at the end of hemorrhage in all rabbits, but the response in 4-wk pregnant rabbits was greater.

**DISCUSSION**

The major new findings of this study are the following. 1) Conscious rabbits in late pregnancy exhibit a reduced ability to maintain arterial pressure and increase heart rate during the initial nonhypotensive
phase of hemorrhage. 2) Arterial pressure maintenance during hemorrhage is normal in conscious rabbits at midgestation. 3) Hypotension-induced increases in plasma vasopressin concentration are normal, but reset to a lower pressure, during late pregnancy in the rabbit. 4) Basal and stimulated increases in plasma renin activity are enhanced in rabbits at both mid- and late gestation.

Pregnancy-induced changes in the hemodynamic responses to hemorrhage have been previously studied in conscious dogs, goats, and sheep and anesthetized rabbits. Two studies restricted their focus to the posthemorrhagic hypotensive period. Humphreys and Jelsma (21, 22) demonstrated that increases in total peripheral resistance and hindlimb resistances were less in anesthetized pregnant rabbits after a rapid 10% hypotensive hemorrhage. Moreover, the differences in resistance between pregnant and nonpregnant rabbits were eliminated by arterial baroreceptor denervation, and these authors (21, 22) suggested that baroreflex function was subnormal during gestation. However, anesthesia markedly blunts baroreflex function and attenuates or eliminates the initial sympathoexcitatory phase of hemorrhage (37, 43); so it is difficult to compare these results with those performed in conscious animals. Olsson et al. (33), on the other hand, reported that the decreases in arterial pressure and subsequent recovery were similar after hemorrhage but that the hypotensive phase was triggered with less blood removal in conscious pregnant goats. Two studies examined both the nonhypotensive and hypotensive phases. In pregnant dogs, arterial pressure was well maintained for a period, but the sympathoinhibitory, hypotensive phase was observed with smaller bled volumes as in goats (7). Finally, in pregnant sheep, arterial pressure progressively decreased during hemorrhage in contrast to the near maintenance of pressure observed in nonpregnant animals (40). A similar pattern was observed in the present study: a progressive decrease in arterial pressure was followed by a rapid fall, which was evoked with removal of a smaller percentage of the initial blood volume. Thus pregnancy appears to hinder arterial pressure maintenance during the early phase of hemorrhage in conscious rabbits as in other species.

The explanation for the deleterious effects of pregnancy on blood pressure regulation during the nonhypotensive segment of hemorrhage has not been directly investigated, but there is indirect evidence to suggest that inadequate baroreflex-induced sympathoexcitation is the cause. First, reflex increases in heart rate and sympathetic activity are reduced during late pregnancy (6, 8, 9, 18, 24). Second, after acute or chronic blockade of the sympathetic nervous system or arterial baroreceptor denervation in nonpregnant animals, hemorrhage causes a progressive decrease in pressure (37), similar to the pattern observed in the present study and in pregnant sheep (40). Importantly, in rabbits, the initial nonhypotensive phase is mediated almost entirely by increased sympathetic activity rather than the actions of other pressor systems (37). On the other hand, dogs rely more on ANG II and vasopressin during the nonhypotensive phase compared with other species (37), and prehypotensive pressure maintenance was normal during pregnancy in this species. Third, chronic adrenergic ablation with 6-hydroxydopamine in pregnant sheep does not worsen the response to hemorrhage (40).

Another potential explanation for the decrease in arterial pressure below control with less blood loss in pregnant rabbits is that the rate of fluid shift into the vasculature during hemorrhage is less. Hematocrit and plasma protein concentration were measured to estimate the rate of fluid uptake. Because the percent decreases in protein and hematocrit were the same between groups, it appears that reduced blood volume restitution cannot be the cause for the faster pressure falls during pregnancy. This conclusion agrees with a previous study in rabbits (41), although the pregnant animals were studied at midgestation in that report.

In nonpregnant rabbits and other species, the sharp fall in pressure that signifies the beginning of the hypotensive phase is mediated by withdrawal of sympathetic tone (37). Next, pressure begins to return toward control levels, and this recovery is mediated by increases in ANG II and vasopressin (37). In the present study, the magnitude of posthemorrhagic hypotension was smaller when the rabbits were pregnant. One explanation for this difference could be that the fall in sympathetic activity was less, because reflex sympathoexcitation was reduced during the nonhypotensive phase. Alternatively, the increases or actions of ANG II and/or vasopressin could be greater. We found that increases in these hormones were normal or greater than normal when the rabbits were pregnant. However, because sensitivity of vascular smooth muscle may be less during pregnancy (12, 16, 31), it is not clear whether the more rapid recovery is due to enhanced vasoconstriction induced by these peptides.

In conscious rabbits at the end of gestation, plasma vasopressin concentration increased with a smaller degree of blood loss. This more rapid rise was apparently due to the more rapid falls in arterial pressure, since the slope of the relationship between vasopressin and pressure was not different between groups. However, the baroreflex curve was shifted to a lower pressure level in the late-pregnant rabbits, suggesting that reflex regulation of vasopressin is reset. This finding agrees with a previous study utilizing nitroprusside infusion as a means to activate the baroreceptor reflex (23). Other studies have investigated whether baroreflex control of vasopressin secretion is altered in late pregnancy. In rats, volume depletion due to subcutaneous polyethylene glycol administration produces similar increases in vasopressin in pregnant and nonpregnant animals (4, 25), although Olsson et al. (33) reported enhanced plasma vasopressin levels after hemorrhagic hypotension in pregnant goats. However, in these studies, the changes in vasopressin were not related to changes in pressure. On the other hand, the slope of the relationship between arterial pressure and vasopressin is reduced in pregnant dogs (7, 8). The explanation for these between-species differences is not clear. Neverthe-
less, it is worth noting that reflex regulation of vasopres-
sin release during hemorrhage is different in dogs
compared with other species, in that significant in-
creases in vasopressin occur before the hypotensive
phase (37).

It is well established that the renin-angiotensin
system is activated during pregnancy (39). The present
results confirm this and further show that hypotension-
induced increases in renin and ANG II are enhanced at
late pregnancy, in agreement with earlier studies (7, 8,
15). A new observation is that this sensitization of
reflex release of renin is also present at midgestation.
Because the rabbit uterus and/or placenta produces
increased quantities of renin during pregnancy (13), it
might seem possible that the excess renin originates
from that site. However, reduction of uterine perfusion
pressure due to inflation of an occluder does not lead to
increased plasma renin activity, although inactive re-
in concentration increases (27). Instead, it appears
that the renal baroreceptor becomes more sensitive to
decreases in renal perfusion pressure during preg-
nancy (15).

Although it is clear that animals in late pregnancy
display a lessened ability to tolerate hypovolic chal-
lenges, to our knowledge, the combined nonhypotensive
and hypotensive responses to hemorrhage earlier in
pregnancy have not been investigated before. The
present results indicate that the responses are normal
in rabbits. The different degrees of arterial pressure
maintenance during hemorrhage in rabbits at mid- and
late gestation correlate with a similar difference in
baroreflex control of heart rate. baroreflex gain de-
creases during pregnancy to reach a minimum just
before delivery but is not different from nonpregnant at
midgestation (Fig. 7; Ref. 35). Importantly, the de-
creased gain appears to be due to a central defect in the
regulation of sympathetic outflow (6). This correlation
suggests two conclusions. First, these data further
support the hypothesis that a malfunction of baroreflex
control of sympathetic activity is the explanation for
the problems with hemorrhage during pregnancy. Sec-
ond, it appears that the factors that mediate the
changes in the baroreflex and responses to hemorrhage
appear late in pregnancy, at least in the rabbit.

In summary, the present study demonstrates that
late-pregnant, conscious rabbits are less able to main-
tain arterial pressure during the early phases of hemor-
rhage than other species. It is likely that this change is
due to an attenuation of reflex increases in sympathetic
outflow. The mechanism for the blunted baroreflex
function is not known; however, the fact that this
change is not present at midgestation suggests that the
factors responsible become operative near the end of
pregnancy.

Perspectives

The mechanism by which pregnancy leads to blunted
baroreflex function has received recent attention. Hee-
sch and Rogers (18) have hypothesized that increases
in the progesterone metabolite 3-hydroxydihydroproges-
terone (3-OHDP) contribute to the blunted sympatho-
excitatory responses observed during pregnancy, by
acting at central γ-aminobutyric acid type A receptors.
Their hypothesis has been supported by studies in
anesthetized and conscious rats showing that infusion
of 3-OHDP qualitatively and rapidly mimics some
effects of pregnancy; i.e., maximal gain and maximal
reflex-induced renal sympathetic nerve activity are
reduced (18, 30). However, the results of the present
study would appear to conflict with this hypothesis. We
have found that maximal gain of baroreflex control of
heart rate progressively decreases throughout gesta-
tion to reach a minimum just before delivery (Fig. 7).
Because progesterone and its metabolites increase very
early during pregnancy (10), this finding suggests that
these steroids cannot be the sole mediator. This conclu-
sion is supported by recent studies of Pecins-Thompson
and Keller-Wood (34) and Roesch and Keller-Wood (36)
showing that acute and chronic progesterone infusion
(with and without estrogen) does not decrease the slope
of the relationship between arterial pressure and heart
rate in ewes.

One potential explanation for these divergent conclu-
sions is that Heesch and Rogers (18) studied renal
sympathetic nerves, whereas others have investigated
baroreflex control of heart rate, which is regulated
through changes in both the sympathetic and parasymp-
thetic nervous systems. However, we have found that
the reduced gain of baroreflex control of heart rate
during late pregnancy is due to a change in sympa-
thetic control of the heart (6). Moreover, in the present
study, the cardiovascular response to hemorrhage was
normal at midgestation. Because it is known that
arterial pressure support during the nonhypotensive
phase of hemorrhage is mediated almost exclusively by
activation of the sympathetic nervous system in rabbits
(37), this finding suggests that regulation of sympa-
thetic outflow is normal at midgestation, a time when
progesterone and its metabolites are maximal. There-
fore either the mechanism that mediates the blunted
baroreflex function is different between species or
steroids, such as 3-OHDP, act in concert with other

![Fig. 7. Weekly changes in maximal gain of baroreflex control of heart
rate during pregnancy. Gain was inversely correlated to gestational
age (P = 0.001; r = −0.52; n = 34). Data from Ref. 35.](image)
factors that become operative late in gestation to decrease function of the baroreflex.

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