Arterial baroreflex during pregnancy and renal sympathetic nerve activity during parturition in rabbits

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O’Hagan, Kathleen P., and Susan M. Casey. Arterial baroreflex during pregnancy and renal sympathetic nerve activity during parturition in rabbits. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1635–H1642, 1998.—The arterial baroreflex control of renal sympathetic nerve activity (RSNA) was evaluated in nine term pregnant (P) and 12 nonpregnant (NP) conscious New Zealand White rabbits. In an additional four P rabbits, the RSNA response to spontaneous parturition was measured. The blood pressure (BP)-RSNA relationship was generated by sequential inflations of aortic and vena caval perivascular occluders. Rest BP (P: 61 ± 2 vs. NP: 73 ± 2 mmHg) and the centering point of the baroreflex (P: 57 ± 2 vs. NP: 70 ± 2 mmHg) were lower (P < 0.05) in term pregnancy. Baroreflex range (P: 246 ± 14% vs. NP 263 ± 24% of rest RSNA) was not affected by pregnancy. However, maximal reflex gain was moderately depressed (−44%) in P rabbits (P: −15 ± 1 vs. NP: −27 ± 4% of rest RSNA/mmHg; P < 0.05) due to a significant reduction in the slope coefficient. Delivery of a fetus was associated with strong renal sympathoexcitation. Peak RSNA averaged 80 ± 37% of smoke-elicited RSNA or 1,221 ± 288% of rest RSNA (mean ± SD). These results suggest that, in contrast to rat pregnancy, depressed arterial baroreflex control of RSNA in rabbit pregnancy is due primarily to a reduction in maximal gain rather than a reduction in the maximal sympathetic response to hypotension.

METHODS

The experimental and animal care protocols were reviewed and approved by the Institutional Review Board for the Use and Care of Animals of Midwestern University. Female New Zealand White rabbits of breeding age (≥6 mo) were used for this study. The arterial baroreflex control of RSNA was studied in 9 rabbits during term pregnancy and in 12 nonpregnant rabbits. RSNA during parturition was obtained in an additional four pregnant rabbits. The nine pregnant rabbits utilized in the baroreflex study delivered their litters on days 30–32 of gestation, which is normal gestation time for a New Zealand White rabbit. Of a total of 62 pups delivered, 54 (87%) were live births, and all rabbits delivered live neonates. Neonates were killed upon discovery by an investigator with an intraperitoneal injection of pentobarbital sodium.
Surgical Preparation

General. Nonpregnant rabbits were anesthetized with Telazol (tiletamine hydrochloride and zolazepam hydrochloride; 15 mg/kg im; Elkins-Sinn, Cherry Hill, NJ) and xylazine (xylazine hydrochloride; 25 mg/kg im; Butler, Columbus, OH) and intubated with a cuffed endotracheal tube. To maintain a surgical plane of anesthesia, we mechanically ventilated the rabbits with 2.0% halothane in room air.

During pregnancy, rabbits were anesthetized with sodium thiopental (25 mg/kg iv; Pentothal, Abbott, North Chicago, IL) or thiamylal sodium (30 mg/kg iv; Bio-Tal, Boehringer Ingelheim, St. Joseph, MO), with supplements given as necessary. Surgical anesthesia was maintained with mechanical ventilation with halothane or isoflurane (2.5%) in room air. We switched to isoflurane to decrease the time required for the pregnant rabbits to regain the righting reflex postsurgery. In both pregnant and nonpregnant rabbits, buprenorphine hydrochloride (0.03 mg/kg; Reckitt & Colman, Richmond, VA) was given immediately and at 5–8 h postoperatively for pain management.

Technical note. A barbiturate was initially chosen over Telazol-xylazine for preanesthetic purposes in the pregnant animals due to adverse events that occurred in pilot work, which may have been due to use of Telazol alone (40 mg/kg im). Recently, we have found that the Telazol-xylazine regimen described above for the nonpregnant animals does not appear to increase the risk for early parturition or intrauterine death when administered to near-term pregnant rabbits.

Implantation of chronic perivascular aortic and vena caval occluders. To manipulate BP for evaluation of the arterial baroreflex, perivascular occluders were implanted on the thoracic descending aorta and on the thoracic inferior vena cava in separate surgeries. The occluders were fabricated in the laboratory. At least 10 days separated the implantation of the aortic and vena caval occluders. A left thoracotomy was performed at the third intercostal space for placement of the aortic occluder. The vena caval occluder was implanted through a right thoracotomy at the fourth intercostal space. For both procedures, the occluder tubing exited the thorax through an adjacent intercostal space, and the free end of the appliance was secured in a subcutaneous pouch. In the nonpregnant group of rabbits, 6–49 (median = 20) days separated the second thoracotomy surgery and the renal nerve implant surgery. For rabbits selected for the pregnant group, 34–76 (median = 41) days separated the second thoracotomy surgery and the renal nerve implant surgery.

Implantation of renal nerve recording electrodes. In nonpregnant and pregnant rabbits, chronic recording electrodes were implanted on the left renal nerves. This surgery was performed in pregnant rabbits on day 26 of gestation. Gestation in the rabbit is ~30 days. Via a retroperitoneal approach, the left kidney was exposed, and one or two renal nerves were dissected away from the renal artery. The recording electrodes were two 30-cm lengths of Teflon-coated multistranded stainless steel wire (0.009-in. diameter, 316L557/44T; Medwire, Mt. Vernon, NY). One end of each electrode was stripped and curled into a J-shaped hook. The renal nerves were placed in the hooks and suspended above the renal artery. The bare end of a third length of wire was embedded in perirenal fat to serve as a ground. The entire nerve-electrode-ground complex was then embedded in silicone gel (Silgel 604; Wacker Chemie). The three electrode leads were secured to muscle at the incision site, routed subcutaneously to the dorsal aspect of the neck, and externalized. Small gold pins were cramped onto the exposed ends of the leads. The leads were wrapped in a strip of cloth adhesive tape for protection, wound into a small bundle, and secured to the skin for storage. Rabbits were studied on the second day postsurgery. This time corresponded to day 28 of gestation (term pregnancy) in the pregnant rabbits.

Experimental Procedures

Instrumentation. On the day of the experiment, the rabbit was placed in a wooden box (15 × 40 cm) with a wire mesh floor and a lid with a grid that allowed instrumentation leads and catheters to exit the box. The skin overlying the central ear artery and marginal vein was anesthetized with topical EMLA cream (2.5% lidocaine and 2.5% prilocaine; Astra, Westborough, MA). Arterial 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 or via a cut down under an additional local anesthetic block with 2% lidocaine hydrochloride. 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. The free ends of the aortic and vena caval occluders were retrieved from their respective subcutaneous pouches under a local anesthetic block (2% lidocaine). Extension tubing connected the occluders to saline-filled 1-ml glass syringes.

Nasopharyngeal reflex. After instrumentation, the nasopharyngeal reflex was assessed. In rabbits, activation of the nasopharyngeal reflex with cigarette smoke produces a dramatic increase in RSNA (11). We have operationally defined the RSNA response to the nasopharyngeal reflex as the "maximum" RSNA that can be elicited by physiological means in a conscious rabbit, because increases in RSNA elicited by other physiological stimuli, such as hypotension (11) and severe hypoxemia (27), fail short of the level achieved during activation of the nasopharyngeal reflex.

To elicit the nasopharyngeal reflex, cigarette smoke containing 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 RSNA were averaged. The nasopharyngeal reflex was elicited at the start of the experiment. The average smoke-elicited RSNA value was operationally defined as maximum RSNA. Minimum or baseline RSNA was obtained at the end of the day's experiment after suppression of postganglionic activity by intravenous infusion of trimethaphan camyslate (5 mg/kg Arfonad; Roche Laboratories, Nutley, NJ). This voltage was subsequently subtracted from all RSNA measurements. RSNA recorded during the experiment was then expressed in the following two ways: first, as a percentage of the smoke-elicited maximum activity and second, as a percentage of absolute RSNA at rest (% of rest).

Generation of baroreflex curves. The BP-RSNA relationship was generated by sequential inflations of the vena caval and aortic occluders. Inflation of the vena caval occluder decreased BP, whereas inflation of the aortic occluder increased BP. Before data collection, two to three sets (aortic + caval) of ramp inflations were performed and discarded, as a previous study by Bell et al. (3) showed that the first two sets of ramp inflations in an experimental session result in an exaggerated reflex response. A 30-s rest period preceded a slow, manual ramp inflation of the occluder at a target rate of 2–3 mmHg/s. At least 2 min separated the aortic and vena caval occluder inflations to allow return of BP, HR, and RSNA to basal values. Three to four sets of occluder inflations were completed in a sequential manner in each animal.

RSNA during parturition. We emphasize that the experimental design was not prospective in nature and that data collection occurred when the opportunity was presented. We
were not able to record on tape all of the fetal deliveries that occurred in a single animal, so that the number of analyzed responses per animal (2–8) is lower than the actual number of fetuses delivered (6–13/animal). The four pregnant rabbits represented in this data set were chronically instrumented and acutely prepared on the day of the experiment, as described above. Two rabbits (rabbits 2 and 3) delivered 30–45 min after the nasopharyngeal reflex was elicited, one (rabbit 1) delivered during generation of the baroreflex ramps, and one (rabbit 4) was not initially exposed to smoke but delivered before beginning the baroreflex testing. The nasopharyngeal reflex was elicited in this rabbit after parturition had ended. Baseline noise was assessed during ganglionic block, as described above. We were able to tape nearly artifact-free hemodynamic and RSNA responses to the delivery of at least two fetuses in each rabbit. Artifacts in the raw BP and RSNA data were removed before the data were analyzed. All rabbits but rabbit 4 delivered a live litter. The neonates were killed immediately with an intraperitoneal injection of pentobarbital sodium. Intrauterine death of the fetuses of rabbit 4 was likely due to a bout of postoperative hypoxemia experienced by the dam. Review of surgical records revealed no unusual events that could account for early parturition in the remaining three rabbits.

Data Analysis

RSNA potentials were amplified by a preamplifier (×1,000) and a low-noise differential amplifier (×10–100) with the use of a bandwidth of 100–3,000 Hz. The signal was full-wave rectified and averaged using a 100-ms moving time averager. Arterial BP, HR, and averaged RSNA signals were simultaneously stored on magnetic tape using a Vetter data recorder and were written to paper on a Grass polygraph. Data were analyzed off-line using custom-written software on a Hewlett-Packard 360 workstation. Artifacts in the RSNA 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 that occurred during data collection other than during ramp occluder inflations were removed from the digitized data file before analysis. Data from ramp occluder inflations, which contained movement artifacts, were discarded, and the ramp inflation was repeated.

Baroreflex control of RSNA during pregnancy. Resting BP, HR, and RSNA for each baroreflex curve were derived from the average of the two 30-s periods preceding the ramp inflations. The data from one set of aortic and vena caval ramp inflations were combined into a single data file for determination of a BP-RSNA baroreflex curve. Using iterative least-squares regression, we fit BP-RSNA data with the following four-parameter sigmoid logistic function (19):

$$RSNA = A/[1 + \exp(B(BP - C))] + D,$$

where A is the range between the upper and lower plateaus, B is the range-independent slope coefficient, C is the BP at the midpoint of the RSNA range ($BP_{50}$), and D is the lower plateau. The upper plateau is equal to A + D. The gain of the BP-RSNA baroreflex curve at $BP_{50}$ (maximum gain) was calculated as $-B \times A/A$. For statistical analysis, parameters from replicate baroreflex curves in each rabbit were averaged to yield a single value for each curve parameter. Comparisons between responses of the pregnant and nonpregnant groups were completed with a two-tailed unpaired t-test (NCSS 6.0). In the case of unequal variance between groups, the Aspin-Welch Unequal Variance test was utilized. Values are represented as means ± SE. Differences were considered statistically significant at P < 0.05.

RSNA during parturition. The ear artery BP and RSNA responses associated with delivery of a fetus were analyzed in 2-s intervals. The peak pressor and RSNA responses were then identified. Resting levels of BP and RSNA were obtained from data files recorded before the onset of parturition. After correction for baseline noise, RSNA was expressed as a percentage of the 2-s interval with the highest RSNA value recorded during the nasopharyngeal reflex as well as a percentage of rest RSNA. Peak responses for replicate deliveries were averaged to yield a single value per animal. Comparisons of rest to peak BP and RSNA values were completed with a paired t-test, and comparisons of resting data between the parturient and pregnant rabbits were completed with an unpaired t-test.

RESULTS

Baroreflex Control of RSNA During Pregnancy

The pregnant rabbits (4.04 ± 0.11 kg) were heavier than the nonpregnant rabbits (3.62 ± 0.10 kg; P < 0.05). Term pregnancy was associated with a lower resting BP compared with the nonpregnant rabbits (P < 0.001; Table 1). HR and rest RSNA were similar between the pregnant and nonpregnant rabbits.

A representative curve fit for one set of aortic and vena caval ramp inflations in a pregnant rabbit is illustrated in Fig. 1. The mean baroreflex curves for the pregnant and nonpregnant groups are plotted in Fig. 2, where RSNA is expressed as a percentage of the smoke-elicited maximum RSNA in Fig. 2, top, and is expressed as a percentage of rest RSNA in Fig. 2, bottom. As expected from the pregnancy-associated decrease in rest BP, the centering point ($BP_{50}$) of the baroreflex curve during term pregnancy was shifted to a lower pressure (P < 0.05; Table 1). In the nonpregnant rabbits, progressive reduction in arterial pressure raised RSNA to 32 ± 4% of the smoke-elicited maximum, whereas a progressive increase in arterial pressure suppressed RSNA to 3 ± 1% of maximum. Compared with RSNA at rest, nonpregnant rabbits were capable of raising RSNA to 263 ± 24% and suppressing RSNA to 25 ± 4% of rest RSNA in response to changes in arterial pressure. Neither the upper nor lower plateau of the baroreflex curve was affected during term pregnancy, whether expressed as a percentage of smoke-elicited maximum RSNA or as a percentage of rest RSNA.

The slope coefficient in the pregnant group was 41% lower than was observed in the nonpregnant rabbits (P < 0.01; Table 1). As a result, the maximum gain (gain at $BP_{50}$) of the baroreflex control of RSNA in the pregnant group was depressed relative to the nonpregnant group (P < 0.01). The decrease in maximum gain was evident whether RSNA was expressed as a percentage of the smoke-elicited maximum (~$31\%$) or as a percentage of rest RSNA (~$44\%$ relative to the nonpregnant group).

RSNA During Parturition

We observed that delivery of a fetus was associated with a "straining" type of behavior, marked by a mild arching of the spine, abdominal muscle contraction, and occasionally a slight grunting noise. These behav-
ior signs were associated with Valsalva-like swings in BP and in large increases in RSNA. We operationally define a “contraction” as the period associated with the concurrent pressor and excitatory RSNA responses (Fig. 3). Three examples from two rabbits of the pressor and RSNA responses associated with delivery are presented in Fig. 3. Figure 3, B and C, illustrates two different patterns of pressor and RSNA responses leading to delivery of a fetus. In Fig. 3B (rabbit 1), two major contractions of sudden onset are separated by a 20-s period of quiescence, with delivery associated with the second contraction. In contrast, Fig. 3C (rabbit 3) illustrates a series of contractions resulting in progressive increases in BP and RSNA, which peak at the time of delivery.

At rest in these four pregnant rabbits, the average BP was 57 ± 3 mmHg, the HR was 240 ± 17 beats/min, and RSNA was 7 ± 1% of the smoke-elicited maximum. Rest BP and HR were not different from values observed in the baroreflex pregnant group (Table 1). Rest RSNA was not compared, as maximum RSNA was calculated differently in the two groups. Peak BP

Table 1. Blood pressure, heart rate, and RSNA at rest and baroreflex curve parameters in pregnant and nonpregnant rabbits

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant (n = 9)</th>
<th>Nonpregnant (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest B P, mmHg</td>
<td>61 ± 2*</td>
<td>73 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>268 ± 8</td>
<td>257 ± 10</td>
<td></td>
</tr>
<tr>
<td>RSNA, % of smoke-elicited maximum</td>
<td>14 ± 1</td>
<td>13 ± 2</td>
<td></td>
</tr>
<tr>
<td>RSNA, % of upper plateau</td>
<td>39 ± 2</td>
<td>38 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

Baroreflex curve parameters

RSNA expressed as % of smoke-elicited maximum

A RSNA range, % of maximum         35 ± 3       32 ± 4
B Slope coefficient               −0.242 ± 0.015* −0.412 ± 0.046 <0.01
C BP50, mmHg                      57 ± 2*       70 ± 2       <0.001
D Lower plateau, % of maximum     3 ± 1        3 ± 1
A + D Upper plateau, % of maximum | 38 ± 4       35 ± 3
Maximum gain, %/mmHg              −2.04 ± 0.16* −2.97 ± 0.22 <0.01

RSNA expressed as a % of rest RSNA

A RSNA range, %                    246 ± 14      263 ± 24
B Lower plateau, %                19 ± 3        25 ± 4
A + D Upper plateau, %             265 ± 13      288 ± 24
Maximum gain, %/mmHg              −15 ± 1       −27 ± 4 <0.01

Values are means ± SE; n, no. of rabbits. BP, blood pressure; HR, heart rate; RSNA, renal sympathetic nerve activity; BP50, BP at midpoint of RSNA range. Maximum gain is the first derivative of the logistic function at BP50. A–D represent parameters of the sigmoid logistic function. Values of parameters B and C are not affected by the manner in which RSNA is expressed. *P < 0.05 pregnant vs. nonpregnant.
during delivery was 91 ± 10 mmHg (mean ± SD), which corresponded to an average rise in BP of 34 ± 6 mmHg.

The peak RSNA responses associated with delivery of a fetus for each pregnant rabbit are presented in Fig. 4. A single sympathoexcitatory response ranged from 29 to 135% of the smoke-elicited maximum, with an average group RSNA response of 80 ± 37% of the smoke-elicited maximum (mean ± SD). Two of the four rabbits had peak RSNA responses to parturition that exceeded the peak RSNA response to smoke-induced stimulation of the nasopharyngeal reflex (Fig. 3, A and C, and Fig. 4). The rabbit with the lowest mean RSNA (expressed as a percentage of the smoke-elicited maximum) response during parturition delivered nonviable fetuses. When expressed as a percentage of rest RSNA, the sympathoexcitatory responses ranged from 361 to 1,967% with a mean RSNA response of 1,221 ± 288% of rest RSNA (mean ± SD).

**DISCUSSION**

This investigation evaluated the arterial baroreflex control of RSNA during term pregnancy and the RSNA response to parturition in conscious rabbits. The two major findings were as follows: 1) the sensitivity of the RSNA baroreflex was moderately depressed in term pregnancy, which was primarily due to a decrease in the slope coefficient or "curvature" (14, 19) of the sigmoid BP-RSNA relationship rather than a decreased RSNA range; and 2) a strong renal sympathoexcitation occurred at the time of delivery in conscious gravid rabbits.

The use of a multifiber recording of RSNA precludes direct comparison of the absolute level of sympathetic nerve activity between animals. With this caveat in
mind, our results in rabbits suggest that sympathetic drive to the kidney at rest is not greatly altered during term pregnancy. Resting RSNA, whether expressed relative to RSNA elicited by the nasopharyngeal reflex or to the maximal RSNA elicited by hypotension (upper plateau of the baroreflex curve), was similar in the nonpregnant and pregnant rabbits. In contrast, Masilamani and Heesch (23) found that resting RSNA measured as impulses per second (+Δ73%) or expressed relative to RSNA at the upper plateau (+Δ59%) was higher in term pregnant, conscious rats than in nonpregnant rats. Recently, Schobel and colleagues (30) used peroneal nerve microneurography to quantitate the level of sympathetic nerve activity to skeletal muscle blood vessels in third-trimester pregnant women. They found that muscle sympathetic nerve activity at rest was similar in age-matched nonpregnant women and normotensive pregnant women. Earlier studies have reported plasma norepinephrine and epinephrine levels in the third trimester as similar to (21) or less than (18) the level of catecholamines observed in nonpregnant women. It is not known if renal sympathetic drive is elevated in normal human pregnancy.

A significant gestational hypotension has been reported previously in term pregnant conscious rabbits (6, 26), although Quesnell and Brooks (29) recently reported only a slight resting hypotension at term in the rabbit. Rabbit (26) as well as rat (15, 23) pregnancies differ from human pregnancy in that the peak gestational decline in BP occurs near term as opposed to the rabbit. The recent observation (10) that maternal gain of the BP-RSNA relationship was depressed by ~30% in the pregnant rabbits, which is similar to the reduction in maximal gain observed in the present study. Although the contributions of baroreflex range and slope coefficient to the reduction in maximal gain were not explicitly evaluated, it does not appear that baroreflex range was substantially altered in the pregnant rabbits.

Masilamani and Heesch (23) evaluated the arterial baroreflex control of RSNA in conscious rats using graded intravenous infusions of phenylephrine and nitroprusside. RSNA responses were normalized to resting RSNA. In contrast to pregnant rabbits, the maximal RSNA response to hypotension was significantly depressed, and the slope coefficient was slightly higher in the pregnant rats. As a result, there was a trend for a lower maximal gain (~Δ28%) in the pregnant rats. The reduced sympathetic reserve (maximum – resting RSNA) exhibited by the pregnant rats could be due to an increase in resting RSNA, a reduction in the absolute maximal neural activity elicited by hypotension, or a combination of factors. With the limitations of multifiber nerve recordings in mind, the absolute RSNA data (impulses/s) suggest an elevation of resting RSNA with little alteration in maximal absolute RSNA at term pregnancy in the rat (23).

The position of resting RSNA on the baroreflex curve becomes an important issue in the comparison of the arterial baroreflex function in pregnant rats and rabbits. When RSNA is normalized to the maximal RSNA response to hypotension, resting RSNA in pregnant rats was 78 ± 9% of the maximal RSNA, whereas in our pregnant rabbits, resting RSNA was 39 ± 2% of maximal RSNA. The pregnant rats demonstrated a reduction in sympathetic reserve (maximum – resting RSNA), as resting RSNA is near the saturation point on the baroreflex curve. The recent observation (10) that pregnant rats have fewer Fos-positive nuclei in the rostral ventrolateral medulla in response to hydralazine-induced hypotension supports the concept of a gestation-related attenuation in sympathetic activation. Pregnant rabbits, on the other hand, operate...
under resting conditions near the point of maximal gain on the BP-RSNA relationship and appear to have a normal sympathetic reserve. However, pregnant rabbits should demonstrate a reduced buffering ability because maximal gain (i.e., slope coefficient) is moderately depressed. It is unknown whether the attenuated ability to raise RSNA in response to hypotension in rat pregnancy can be generalized to other physiological stimuli for renal sympathetic stimulation, such as hypoxemia, parturition, or activation of the nasopharyngeal reflex.

Cardiovascular regulation during hemorrhage in rabbits is strongly dependent on intact neural autonomic mechanisms (20), and the renal vasoconstrictor response is largely under the control of arterial baroreceptors (8). In addition to depressed arterial baroreflex control of RSNA, term pregnant rabbits also exhibit a reduced arterial baroreflex control of HR (4, 6, 29) due to a large decrease (approximately −70%) in maximal gain. The depressed baroreflex control of sympathetic activity and HR likely contribute to the reduced ability of term pregnant rabbits to maintain BP during hemorrhage (16). Altered BP regulation during hemorrhage has also been reported for term pregnant goats (28) and dogs (5).

The influence of normal human pregnancy on the cardiac and sympathetic baroreflexes is not fully understood. There is indirect evidence supporting a depressed cardiac baroreflex early but not late in human pregnancy (12). Theoretically, a depression in maximal gain of arterial baroreflexes would increase BP lability, which could lead to reduced orthostatic tolerance during activities of daily living. Syncopal symptoms are reported with greater frequency in the first trimester compared with the third, and the progressive increase in blood volume associated with pregnancy has been invoked as the mechanism responsible for the increased hemodynamic stability (reviewed in Ref. 12). Thus the impact of gestation-associated alterations in central arterial baroreflex control may be magnified in pregnancies complicated by impaired blood volume expansion, such as pregnancy-induced hypertension (1).

The mechanisms responsible for altered arterial baroreflex control of RSNA and HR during normal pregnancy are not clear. A strong candidate mechanism is the rise in sex steroids associated with pregnancy. Estrogen supplementation in nonpregnant rabbits does not attenuate the baroreflex control of RSNA (6). In contrast, intravenous infusion of a progesterone metabolite into nonpregnant rats produced, within 15 min, alterations in the arterial baroreflex control of RSNA that mimicked the pregnancy-associated reduction in maximal sympathoexcitation (23). In the rabbit, peak levels of plasma progesterone occur at days 12–15 during gestation and are only 50% of peak levels at day 27 of gestation (7). The progesterone-to-estradiol-17β ratio is similar on day 12 and day 27. Quesnell and Brooks (29) observed that the arterial baroreflex control of HR is unchanged at midgestation (approximately day 14) in the rabbit but is depressed at days 28–30. The lack of a temporal association between peak plasma progesterone levels, the progesterone-to-estradiol-17β ratio, and onset of alterations in baroreflex function weakens the argument for a putative causal relationship between progesterone and arterial baroreflex function in the pregnant rabbit. Additionally, progesterone in the rat appears to reduce the sympathetic reserve, whereas neither the ability to raise HR (4, 29) nor RSNA above resting levels is greatly affected in rabbit pregnancy.

RSNA response to parturition. Spontaneous parturition in the rabbit was associated with a strong activation of sympathetic drive to the kidney. Generally, parturition (+Δ1221 ± 144% from resting RSNA, mean ± SE) appears to be a more potent stimulus for RSNA in rabbits than either severe hypotension (263 ± 24%) or hypoxemia in the nonpregnant state (+Δ161 ± 44%; see Ref. 27). Parturition is a physiological stimulus that rivals activation of the nasopharyngeal reflex as an excitatory stimulus for RSNA. Indeed, two of the four rabbits studied exhibited peak RSNA responses to parturition that exceeded the peak RSNA response to nasopharyngeal stimulation with cigarette smoke.

Sympathoadrenal activation occurs in women undergoing active labor, culminating in vaginal delivery (17, 21, 25, 31). Plasma norepinephrine and epinephrine reach peak levels at the time of vaginal delivery or immediately afterward (21, 25). Sympathoadrenal activation is probably due to labor effort as well as maternal anxiety and pain (17, 31). In the parturient rabbits, sympathetic activation was closely associated in time with maternal labor effort, as indicated by simultaneous appearance of large and sustained RSNA bursting and the Valsalva-like swings in BP (Fig. 3). It is unknown to what extent maternal pain contributed to the degree of sympathetic activation in the rabbit. Maternal effort or pain might be related to fetal pup weight. However, we did not see an obvious association between average pup weight and RSNA response during parturition. The rabbit with the smallest average litter weight (rabbit 3, 24 g/pup vs. a high litter weight of 32.2 g/pup for rabbit 2) had the highest average RSNA response to parturition (RSNA expressed as percentage of smoke-elicited maximum; Fig. 4). A low pup weight also does not explain why the rabbit that delivered a nonviable litter (rabbit 4; 29.4 g/pup) had the lowest RSNA response to parturition.

In summary, term pregnancy in the conscious rabbit was associated with moderate depression in the arterial baroreflex control of RSNA, which was manifested as a decrease in maximal reflex gain. Unlike the rat, pregnancy in the rabbit did not appear to attenuate the maximal RSNA response to acute hypotension. A gestational reduction in the arterial baroreflex control of RSNA and HR (29) could contribute to a decreased ability to maintain adequate BP during acute perturbations in cardiovascular homeostasis, such as hemorrhage (8, 16). Finally, parturition in rabbits was associated with a strong activation of sympathetic drive to the kidney that far exceeded RSNA responses to the...
physiological stimuli severe hypoxemia (27) and hypotension.

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REFERENCES


