Right atrial dimension-pressure relation during volume expansion is unaltered by pregnancy in the rat

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Hines, Tina, Sarang S. Abhyankar, and Jessica M. Veeh. Right atrial dimension-pressure relation during volume expansion is unaltered by pregnancy in the rat. Am J Physiol Heart Circ Physiol 288: H116–H120, 2005. First published September 16, 2004; doi:10.1152/ajpheart.00551.2004.—Blood volume expands significantly during pregnancy, but afferent signals from cardiac receptors are reduced. In addition, during exogenous volume expansion, right atrial pressure (RAP) increases more for equivalent volumes in pregnant animals, implying reduced atrial compliance. To examine possible gestational alterations in atrial dimension during volume expansion, we compared the effects of volume expansion on RAP and right atrial dimension (RAD) in pregnant vs. virgin rats. Anesthetized animals were ventilated and catheterized for measurement of arterial pressure and RAP and for drug infusion. Through a parasternal incision, ultrasonic crystals were glued to the medial and lateral surfaces of the right atrium for measurement of RAD. Plasma volume and hematocrit were determined before experimentation. RAP, RAD, and arterial pressure were recorded at baseline and during progressive volume expansion (6% dextran, 60% of initial blood volume). Baseline RAP was similar in the two groups: 2.82 ± 0.40 and 2.72 ± 0.47 mm Hg in pregnant and virgin rats, respectively. Basal RAD was significantly larger in pregnant than in virgin rats: 4.36 ± 0.66 vs. 3.36 ± 0.48 mm. Despite increased basal RAD in pregnant rats, the slope of the RAD-RAP relation during volume expansion was similar in the two groups. Results indicate that resting RAD is increased in pregnant rats and that the change in dimension during volume loads is similar to that in virgin rats. Thus, during pregnancy, the right atrium appears to accommodate the increased blood volume, and reduced afferent signaling most likely is due to mechanisms other than mechanical alterations of the atrium by expanded volume.

PLASMA VOLUME INCREASES MARKEDLY during normal human and rat pregnancy (1, 3, 5, 12). This change occurs early in pregnancy and is maintained until full-term gestation. In the nonpregnant female, volume increases of the magnitude seen in pregnancy would be rapidly returned to baseline by reflex neural and humoral pathways. The sensitivity of these volume regulatory mechanisms is significantly attenuated in pregnant animals and humans, however, such that the normal hypervolemia of pregnancy is maintained (4, 7, 8, 10, 19).

Evidence in pregnant rats suggests that one mechanism for attenuated reflex volume regulation may be reduced afferent signals from mechanoreceptors in the right atrium. We have found that pregnancy reduces overall atrial mechanoreceptor discharge frequency by elimination or desensitization of receptors with high-frequency discharge (7). Zhang et al. (20) reported that the atrial natriuretic factor response to atrial balloon inflation was also reduced in pregnant rats. Further, c-fos expression in the hypothalamus was significantly reduced after atrial stimulation in pregnant animals (4). Thus there appears to be a reduction in the sensitivity of mechanosensitive receptors that arise from the right atrium to inform the brain about volume status in pregnant rats. Consistent with this concept was the measurement of significantly larger changes in right atrial pressure (RAP) concurrent with reduced atrial receptor afferent discharge during acute atrial volume expansion in pregnant than in virgin rats (7). This finding suggested that, during pregnancy, exogenous volume expansion may, in fact, “overfill” the heart, a controversial hypothesis discussed by Schrier and Durr (17). If, indeed, there were overfilling of the right atrium during acute expansion, then the dimension of the chamber would increase less during this stimulus. This could explain attenuated atrial receptor discharge frequency, atrial natriuretic factor release, and central neural activation in response to atrial stretch in pregnant rats. A smaller increase in atrial dimension for a given increase in volume could also contribute to the greater pressure increase during exogenous volume increase in the pregnant animals reported previously (7). Thus, in the present study, we directly measured right atrial dimension (RAD) during volume expansion and hypothesized that the increase in atrial dimension for a given increase in atrial pressure would be less in pregnant than in nonpregnant rats. To our knowledge, this is the first report of atrial pressure-dimension relations during pregnancy.

MATERIALS AND METHODS

Virgin female Sprague-Dawley rats (Charles River Laboratory, Wilmington, MA) were mated or served as age-matched controls (n = 9 in each group). Day 1 of pregnancy was determined by the presence of sperm in the vaginal smear, and experiments were conducted on gestational day 20 (rat pregnancy = 22 days). Animals were maintained on a 12:12-h light-dark cycle and were fed standard rat chow during the gestational period. All procedures and protocols were in accordance with the National Institutes of Health Guide for the Care and Use of Animals and were approved by the Institutional Animal Care and Use Committee of the University of Missouri Kansas City.

Surgical procedures. Rats were anesthetized with thiobutabarbital (Inactin, 110 mg/kg ip), and supplemental anesthesia (10 mg/kg iv) was administered as necessary to maintain a stable blood pressure and the absence of reflex withdrawal to hindpaw pinch. Catheters were inserted into the right femoral artery and vein for measurement of arterial pressure and dextran infusion, respectively. The trachea was cannulated, and animals were artificially ventilated with oxygen-enriched room air. The right jugular vein was exposed, and a polyethylene-50 catheter was inserted into the right atrium for pressure measurement. Through a right parasternal incision, the thoracic cavity was opened, and the right lung was gently retracted. The pericardium was

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dissected to expose the right atrium and ventricle. Two 1.0-mm sonomicrometer crystals with a frequency of 64 MHz (Sonometrics, London, ON, Canada) were glued to the medial and lateral surfaces of the right atrium with cyanoacrylate adhesive (Vetbond, 3M Animal Care Products, St. Paul, MN). The medial crystal was positioned as far medial on the atrium as possible under the atrial appendage. The lateral crystal was placed at the lower border of the atrium near the atroventricular junction. Artificial ventilation was suspended during crystal placement (~5 s) to minimize interference from lung tissue. We found that, in pregnant rats weighing 367 ± 26 g, baseline atrial dimensions were 3.3–5.5 mm. In virgin rats weighing 257 ± 20 g, resting atrial dimension was 2.9–4.1 mm. The signal from the crystals was fed to a transceiver and computer interface (Sonometrics). After an optimum signal was obtained from the crystals, the lungs were reexpanded, and the incision was covered with gauze. An equilibration period of ~30 min followed to stabilize all parameters.

Experimental procedures. Plasma volume was determined before experimentation as described previously (2, 8) by intravenous injection of 100 μl of Evans blue dye and subsequent spectrophotometric assessment of optical density (620 nm) in an arterial plasma sample. Plasma volume was calculated from a standard curve constructed with known concentrations of blue dye, and blood volume was calculated by dividing the plasma volume by 1 – hematocrit. A postinfusion hematocrit measurement was also collected to verify volume expansion.

RAP was determined from the transit time of an ultrasonic wave between the sonomicrometer crystals. The sonomicrometer was calibrated internally by the factory for dimension accuracy. Arterial and atrial blood pressure signals were fed to the same computer interface and calibrated at the beginning of each experiment using a mercury manometer.

RAP, arterial blood pressure, and RAD were measured during progressive intravenous volume expansion with 6% dextran to 60% of initial blood volume. Initial blood volume was used to standardize the magnitude of volume expansion in the two groups, because resting intravascular volume in the 20-day pregnant rat is already significantly expanded, and administration of equivalent volumes would have represented a smaller stimulus in the pregnant animals. Dextran was infused at a rate designed to increase the blood volume cumulatively at 5%/min. Thus absolute infusate volume was higher in pregnant than in virgin rats: 17.9 ± 0.63 vs. 12.7 ± 0.35 ml.

Baseline measurements of all variables were averaged over 30 s, and then 12 data points were collected and averaged during the dextran infusion for 5 s at the end of every minute. An additional data point was collected for 30 s at 1 min after the infusion (total of 14 measurement periods).

To measure the magnitude of the atrial dimension excursion at baseline and during volume expansion, values for maximum and minimum atrial dimensions during the cardiac cycle were acquired and averaged from the dimension waveform during the 14 measurement periods. The difference between maximum and minimum dimension was considered to be the average RAD excursion at these time points.

Data acquisition and analysis. Blood pressure waveforms and dimension measurements were acquired on a computer (sampling rate = 800 Hz) and analyzed offline using specially designed software (SonoVIEW, Sonometrics). Changes in RAP, RAD, and atrial dimension excursion across time were analyzed between and within groups by repeated-measures analysis of variance. Correlations between RAP and RAD and changes in these variables were analyzed using linear regression. Values are means ± SE. P < 0.05 was considered significant.

RESULTS

Baseline RAP and RAD in pregnant and virgin rats are illustrated in Fig. 1. RAP did not differ between groups, but RAD was significantly increased at rest in pregnant rats. Baseline plasma volumes (20.2 ± 0.6 and 13.9 ± 0.4 ml in pregnant and virgin rats, respectively) and hematocrits (33 ± 0.5 and 42 ± 0.8%, respectively) confirmed the significant plasma volume expansion of pregnancy. Postinfusion hematocrit measurements indicated significant hemodilution in both groups that was larger in the pregnant rats: 25 ± 1.6 vs. 36 ± 0.8% (P < 0.05).

Exogenous intravenous volume expansion resulted in equivalent increases in RAP and RAD in both groups (Fig. 2). Baseline RAD was larger in pregnant rats and increased similar to that in virgin rats during volume expansion. The slopes of these relations did not differ between groups: 0.21 ± 0.02 and 0.22 ± 0.01 mm/mmHg in pregnant and virgin rats, respectively.

Because baseline RAD was larger in pregnant rats, we also plotted the change in RAD as a function of the change in RAP (Fig. 3). The slope of this correlation was somewhat lower in pregnant rats (0.21 ± 0.03 mm/mmHg) but not statistically different (P = 0.39) from that in virgin animals (0.24 ± 0.02 mm/mmHg). There is a suggestion of slightly higher atrial pressures at equivalent atrial dimensions in pregnant animals at the higher levels of volume expansion.

The atrial pressure-dimension loop derived from an x-y plot of pressure and dimension waveforms is described as a figure of eight, with an “A loop” during systole defining the highest

![Fig. 1. Baseline right atrial pressure (RAP, A) and right atrial dimension (RAD, B) in pregnant (open bars) and virgin (solid bars) rats. *P < 0.05 vs. virgin. Values are means ± SE.](http://ajpheart.physiology.org/)
atrial pressure and minimum dimension and a “V loop” during diastole defining the maximum atrial dimension during filling (14). An example of these loops from a pregnant and a virgin rat is shown in Fig. 4.

Although the mean RAD-RAP relations (slopes) were equivalent in pregnant and virgin rats, the average change in dimension, or pulsatile excursion, during the cardiac cycle may have differed between groups. Thus average maximum and minimum RAD were plotted to determine possible group differences in pulsatile excursion of the atrial wall during volume expansion (Fig. 5). Although the maximum-minimum difference in atrial dimension (atrial excursion) was slightly greater in pregnant rats across the period of volume expansion, the dimension excursion was quite small in both groups and did not differ statistically between groups (P = 0.08).

Baseline mean arterial pressure (MAP) was lower in pregnant than in virgin rats, and the effects of exogenous volume expansion on MAP differed significantly between groups (Fig. 6). The reflex sympathoinhibitory effect of volume expansion was associated with a progressive decrease in MAP in virgin rats. In pregnant animals, the reflex depressor response was significantly attenuated, as has been reported previously (6, 8, 9). The larger hemodilution measured after dextran infusion in pregnant rats also suggested a blunted reflex diuresis in this group, consistent with work by Kaufman and Deng (10).

**DISCUSSION**

This study has reported new findings about RAD and the changes in dimension during a volume load in pregnant rats. First, we have shown that resting RAD is increased, whereas...
baseline RAP is equivalent, in full-term pregnant and virgin rats. Thus the increase in atrial dimension during pregnancy appears to accommodate the marked gestational increase in blood volume without increasing atrial pressure. Second, using atrial dimension-pressure relations as an indirect index of compliance, we have demonstrated that, in response to a rather marked cumulative exogenous volume expansion, the right atrium is no less compliant in pregnant than in nonpregnant animals. This observation indicates that smaller increases in atrial dimension during exogenous volume expansion most likely do not contribute to the blunt reflex effects and blunt atrial mechanoreceptor firing that have been reported.

There are very few reports of RAD during pregnancy. Left atrial dimension has been measured and increases ~16%, peaking at 28 wk of pregnancy in humans. A further increase in dimension occurs in the first few days postpartum (15, 16). We showed a 26% increase in RAD at full-term pregnancy in rats, in which the maximum plasma volume increase is slightly higher than in humans. Thus it appears that left atrial dimension and RAD increase to accommodate the increased volume load during gestation.

The finding that resting RAD is increased in late-pregnant rats appears to conflict with atrial volume measurements of Kaufman and Deng (10). In their study, unstressed right atrial volume was similar in isolated atria from pregnant and virgin rats (10). Right atrial wall thickness has not been measured in the pregnant rat, and a thicker wall could contribute to differential findings. In addition, it is conceivable that measurements in vitro may not reflect measurements of the dynamic atrium in the whole animal. This same study found no gestational difference in right atrial compliance in vitro. We did not directly measure compliance in the present study but considered changes in atrial dimension to be reflective of changes in infused volume and used atrial dimension-pressure relations as an index of compliance. The similar change in dimension for a change in pressure in pregnant and virgin rats would seem consistent with previous findings related to atrial compliance (10).

On the basis of our report of reduced high-frequency firing in cardiac mechanoreceptors in pregnant rats, at baseline and during stimulation (7), we had hypothesized a smaller increase in atrial dimension during volume expansion in pregnant animals. In our previous study, cardiac mechanoreceptors were stimulated by acute bolus saline injections into the right atrium. This stimulus, for which equivalent volumes were used in pregnant and virgin rats, evoked larger changes in RAP in pregnant animals. Thus there was the suggestion of reduced compliance in this group. The acute volume expansion technique used previously (7) involved a more rapid rate of infusion and averaging of RAP over shorter time periods than the dextran infusion technique used in the present study. This difference in infusion rate and measurement periods may have contributed to the larger maximum changes in RAP we observed. In response to a marked exogenous intravenous volume load infused at a slower rate, however, the present findings indicate that the RAD-RAP relation is not altered during rat pregnancy. The slight reduction in the slope when change in dimension was plotted as a function of change in pressure in pregnant rats could suggest that, at the highest levels of volume-induced pressure change, the ability of the atrium to accommodate the volume load may be slightly reduced. This possibility will require further validation. However, mechanisms responsible for gestational alterations in volume-sensitive atrial mechanoreceptors remain to be defined. Preliminary studies by Sims and Kaufman (18) showed that the progesterone metabolite 3α-hydroxydihydroprogesterone in virgin rats attenuated high-frequency discharge in atrial receptors. This same metabolite has been found to significantly affect central nervous responses to atrial receptor stimulation (11) and to arterial baroreceptor activation during pregnancy (11, 13). Additional studies are needed to confirm the role of this humoral modulator in altered volume regulation during pregnancy.

In summary, this study has demonstrated for the first time that RAD is increased at baseline in the pregnant rat. The increased dimension is adequate to accommodate the marked plasma volume expansion of pregnancy without an increase in RAP. In addition, the similar increase in atrial dimension-pressure relations in pregnant and virgin rats during a substantial exogenous volume expansion indicates that the ability of the right atrium to accommodate an additional volume load without marked changes in pressure is not impaired in the pregnant animal. We conclude that a smaller increase in atrial dimension during exogenous volume expansion does not explain the attenuation of afferent cardiac receptor discharge observed during pregnancy, nor is it likely to contribute to blunt atrial stretch receptor reflexes, which have been reported in pregnant females.

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GRANTS

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