Right atrial dimension/pressure relationship during volume expansion is unaltered by pregnancy in the rat

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Running head: atrial dimension during pregnancy

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ABSTRACT

Blood volume expands significantly during pregnancy, but afferent signals from cardiac receptors are reduced. In addition, during exogenous volume expansion, right atrial pressure 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 right atrial pressure (RAP) and dimension (RAD) in pregnant vs. virgin rats. Anesthetized animals were ventilated, and catheterized for measurement of arterial and right atrial pressure 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 (P=2.82±0.40; V=2.72±0.47mmHg). Basal RAD was significantly larger (4.36±0.66 vs. 3.36±0.48mm) in pregnant vs. virgin rats. In spite of increased basal atrial diameter in pregnant rats, the slope of the relationship between RAD and RAP during volume expansion was similar in the two groups. Results indicate that resting RAD is increased in rat pregnancy, 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.
INTRODUCTION

Plasma volume increases markedly during normal human and rat pregnancy (1, 3, 5, 12). This change occurs early in pregnancy and is maintained until 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. reported that the atrial natriuretic factor response to atrial balloon inflation was also reduced in pregnant rats (20). 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 concurrent with reduced atrial receptor afferent discharge during acute atrial volume expansion in pregnant compared with virgin rats (7). This finding suggested that during pregnancy exogenous volume expansion may, in fact, “overfill” the heart, a controversial hypothesis discussed by Schrier et al. (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 compared with nonpregnant rats. To our knowledge, this is the first report of atrial pressure/dimension relationships 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 the National Institutes of Health Guide of 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 Inactin (110 mg/kg ip), and supplemental anesthesia (10mg/kg iv) was administered as necessary to maintain a stable blood pressure and 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 PE50 catheter was inserted into the right atrium for measuring pressure.

Through a right parasternal incision, the thoracic cavity was opened and the right lung was gently retracted. The pericardium was dissected to expose the right atrium and ventricle. Two 1.0mm sonomicrometer crystals with a frequency of 64 MHz (Sonometrics, Inc., London, Ontario) were glued to the medial and lateral surfaces of the right atrium using 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 atrio-ventricular junction. Artificial ventilation was suspended during crystal placement (~ 5 sec.) to minimize interference from lung tissue. We found that in pregnant rats weighing 367±26gm, baseline atrial dimensions ranged from 3.3 – 5.5mm. In virgin rats weighing 257±20gm resting atrial dimension ranged from 2.9 – 4.1mm. The signal from the crystals was fed to a transceiver and computer interface (Sonometrics Inc, London, Ontario). After an optimum signal was obtained from the crystals, the lungs were re-expanded and the incision was covered using gauze. An equilibration period of approximately 30 minutes followed to stabilize all parameters.

Experimental procedures.

Plasma volume was determined before experimentation as described previously (2, 8) by intravenous injection of 100ul of Evans blue dye and subsequent spectrophotometric assessment of optical density (620nm) 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 minus the hematocrit. A post-infusion hematocrit measurement was also collected to verify volume expansion.

Right atrial dimension 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.
Right atrial and arterial blood pressures and right atrial dimension 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 since 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% per minute. Thus, absolute infusate volume was higher in pregnant (17.9±.63ml) compared with virgin (12.7±.35ml) rats.

Baseline measurements of all variables were averaged over 30 seconds, and then 12 data points were collected and averaged during the Dextran infusion for 5 seconds at the end of every minute. An additional data point was collected for 30 seconds one minute 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 in maximum and minimum dimension was considered to be the average right atrial dimension excursion at these time points.

Data acquisition and analysis

Blood pressure waveforms and dimension measurements were acquired on a computer (sampling rate of 800 Hz) and analyzed off-line using specially designed software (SonoVIEW, Sonometrics Inc., London, Ontario). 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. Data are reported as means ± S.E.M. and P<0.05 is considered significant.
RESULTS

Baseline RAP and RAD in pregnant and virgin rats are illustrated in Figure 1.

Right atrial pressure did not differ between groups, but RAD was significantly increased at rest in pregnant rats.

![Figure 1](image)

Figure 1. Baseline right atrial pressure (panel A) and right atrial dimension (Panel B) in pregnant (open bars) and virgin (closed bars) rats. *p<0.05 vs. virgin. Data are mean ± SEM

Baseline plasma volumes (P=20.2±0.6ml; V=13.9±0.4ml) and hematocrits (P=33±0.5%; V=42±0.8%) confirmed the significant plasma volume expansion of pregnancy. Post-infusion hematocrit measurements indicated significant hemodilution in both groups that was larger in the pregnant rats (P=25±1.6%; V=36±0.8%, p<0.05).

Exogenous intravenous volume expansion resulted in equivalent increases in RAP and RAD in both groups (Figure 2). As shown, baseline RAD was larger in pregnant rats and increased similarly to virgin rats during volume expansion. The slopes of these relationships did not differ between groups (P = 0.21±0.02; V = 0.22±0.01 mm/mmHg).
Figure 2. Right atrial dimension/pressure relationships during progressive 60% volume expansion in pregnant (open circles) and virgin (closed circles) rats. Data are mean ± SEM.

Because baseline RAD was larger in pregnant rats, we also plotted the change in RAD as a function of the change in RAP (Figure 3). The slope of this correlation was somewhat lower in pregnant rats (0.21±0.03mm/mmHg), but not statistically different (p=0.39) from that in virgin animals (0.24±0.02mm/mmHg). There is a suggestion of slightly higher atrial pressures at equivalent atrial dimensions in pregnant animals at the higher levels of volume expansion.
Figure 3. Changes in right atrial dimension and pressure and slopes of the dimension/pressure relationship during a progressive 60% volume expansion in pregnant (open circles) and virgin (closed circles) rats. Data are mean ± SEM.

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 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 are seen in Figure 4.

Figure 4. Right atrial pressure/dimension loops at baseline in a pregnant and a virgin rat. Note the larger dimension and slight larger dimension excursion during one cardiac cycle in the pregnant animal.

Although the mean right atrial dimension/pressure relationships (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 right atrial maximum and minimum dimensions were plotted to determine possible group differences in pulsatile excursion of the atrial wall during volume expansion (Figure 5). Although maximum – minimum difference in atrial dimension (atrial excursion) excursion was slightly larger 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 compared with virgin rats, and the effects of exogenous volume expansion on MAP differed significantly between groups (Figure 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).
Figure 6. Mean arterial pressure in pregnant (open circles) and virgin (closed circles) rats during a progressive 60% volume expansion. *p<0.05 pregnant vs. virgin. Data are mean ± SEM.
DISCUSSION

This study has provided new findings about right atrial dimension 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 term pregnant compared with 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 relationships as an indirect index of compliance, we have demonstrated that in response to a rather marked cumulative exogenous volume expansion, the right atrium in pregnant rats is no less compliant than in nonpregnant animals. This observation indicates that smaller increases in atrial dimension during exogenous volume expansion most likely do not contribute to the blunted reflex effects or blunted afferent cardiac mechanoreceptor firing that have been reported.

There are very few reports of right atrial dimension during pregnancy. Left atrial dimension has been measured and increases approximately 16%, peaking at 28 weeks of pregnancy in humans. A further increase in dimension occurs in first few days postpartum (15, 16). We showed a 26% increase in right atrial dimension at term pregnancy in rats in which the maximum plasma volume increase is slightly higher than humans. Thus, it appears that both left and right atrial dimensions 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 made by Kaufman et al. In that study unstressed right atrial volume was found to be 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 relationships as an index of compliance. The similar change in dimension for a change in pressure in pregnant compared with virgin rats would seem consistent with previous findings related to atrial compliance.

Based on our report of reduced high frequency firing in cardiac mechanoreceptors receptors in pregnant rats, both 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, using equivalent volumes in pregnant and virgin rats, evoked larger changes in RAP in pregnant animals. Thus, there was the suggestion of reduced compliance in this group. Compared to the Dextran infusion technique used in the current study, the acute volume expansion technique used previously (7) involved a more rapid rate of infusion, and averaging of RAP over shorter time periods. This difference in infusion rate and measurement periods and 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 current findings indicate that the right atrial dimension/pressure relationship 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
to accommodate the volume
load may be slightly reduced. This possibility will require further validation. Still,
mechanisms responsible for gestational alterations in volume-sensitive atrial
mechanoreceptors receptors remain to be defined. Preliminary studies by Sims and
Kaufman showed that the progesterone metabolite 3alpha-OH-DHP in virgin rats
attenuated high frequency discharge in atrial receptors (18). 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 right atrial
dimension 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 right atrial pressure. In addition the similar increase in atrial
dimension/pressure relationships in pregnant compared with 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 blunted
atrial stretch receptor reflexes that have been reported in pregnant females.
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REFERENCES