Maternal cardiovascular changes during pregnancy and postpartum in mice

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Received 23 July 2001; accepted in final form 9 November 2001.

Maternal cardiovascular changes during pregnancy and postpartum in mice. Am J Physiol Heart Circ Physiol 282: H918–H925, 2002; 10.1152/ajpheart.00641.2001.—Genetically altered mice may provide useful models for exploring cardiovascular regulation during pregnancy and postpartum if changes in mice mimic humans. We found in awake ICR (CD-1) mice at 17.5 days gestation that hematocrit was reduced 18%, and the pressor response to intravenous angiotensin II was reduced ~33%. Arterial pressure in awake mice was 12% lower in early pregnancy (3.5 days) than late pregnancy (17.5 days) and postpartum (3 and 17 days after delivery), whereas heart rate was 10–20% higher in the peripartum period (17.5 days gestation and 3 days postpartum). In late pregnancy, cardiac output under isoflurane anesthesia was 64% higher than in nonpregnant mice, due to a 37% increase in stroke volume and a 17% increase in heart rate. All changes P < 0.05. We conclude that, as in humans, mice exhibit hypotension in early pregnancy, and a blunted pressor response to angiotensin II, a decrease in hematocrit, and a marked increase in cardiac output in late pregnancy.

Cardiac output; blood pressure; angiotensin; hematocrit; heart rate; Doppler ultrasound; aortic blood velocity waveform

THERE ARE MARKED CHANGES in maternal cardiovascular function during pregnancy in humans and other species including a blunting of the pressor response to angiotensin II (1, 18, 34), an increase in plasma volume resulting in a decrease in hematocrit (20, 27), peripheral vasodilation associated with a marked increase in cardiac output (9, 10, 37, 38, 44), and transient hypotension (9, 10). The mechanisms that produce these changes are not fully understood. Improved understanding of cardiovascular adjustments during normal pregnancy is important because failure to make or to sustain these changes may result in impaired fetal growth and/or preeclampsia, the two most common and serious complications of human pregnancy.

Genetically altered mice are powerful tools for investigating the roles of genes and gene products in cardiovascular development and function. Such mice could be useful in determining the mechanisms responsible for cardiovascular changes during pregnancy provided that cardiovascular adjustments to pregnancy are similar in the two species, and that methods to assess physiological function in mice are adequate to detect them. Thus the objective of the current study was to measure changes in cardiovascular function during pregnancy in mice using noninvasive methods where possible. If noninvasive methods are adequate to detect changes, their use would facilitate future studies on valuable mutant mice in that mice would remain intact for further breeding and/or other studies, and such methods may prove feasible for use in high throughput screens.

We used, and further validated, a tail cuff system to measure heart rate and arterial pressure in awake mice (28), and used transcutaneous Doppler ultrasound to measure aortic blood velocities in anesthetized mice (25). Cardiac output and stroke volume were calculated from aortic blood velocity measurements and aortic luminal cross-sectional areas obtained from vascular casts. We further show that reliable aortic diameters can now be obtained using an ultrasound biomicroscope so that future measurements of cardiac output in mice can be made completely noninvasively.

METHODS

Experiments were approved by the Animal Care Committee of Mount Sinai Hospital and were conducted in accord with the guidelines of the Canadian Council on Animal Care. Breeding. Virgin female ICR (CD-1) mice (Harlan Sprague Dawley, Indianapolis, IN) at 6–8 wk of age either served as nonpregnant controls or were mated with an experienced male of the same strain. Groups were matched with respect to age and body weight when nonpregnant, and then studied in parallel so that measurement intervals for the nonpregnant group matched those of the pregnant and postpartum groups. Presence of a sperm plug was defined as day 0.5 of pregnancy. Pregnant mice were studied at day 3.5 of gestation (preimplantation) and at day 17.5 of gestation (1 day before normal-term delivery). Postpartum mice were studied at days 3 and 17 postpartum (presweaming). Mice were housed...
in pairs during delivery and postpartum. Litters were not weaned from the mothers until after the end of the study. Body weight was recorded on each study day.

**Arterial pressure, heart rate, and hematocrit.** In the first series of animals, arterial pressure and heart rate of awake ICR mice were measured using an automated tail cuff system (BP-2000, Visitech Systems, Apex, NC) on gestational days 3.5 and 17.5, and days 3 and 17 postpartum (n = 14).

Nonpregnant mice were studied at equivalent intervals (n = 10). Mice were not “trained” in the apparatus before the study began because we found no evidence for a training effect in ICR mice when daily measurements were obtained over 5 days (see RESULTS). During measurements, mice were restrained in a dark chamber, in which the floor was heated to 38°C. Results from the first 10 inflation cycles were discarded, and the average obtained from the next 10 cycles was recorded. Mice were in the chamber for ~15 min. On each study day, blood pressure and heart rate were measured in the morning (9:00–10:30 AM) and in the afternoon (12:30–2:00 PM). There was no significant difference in arterial pressure among these time points, and although heart rate significantly decreased (from 661 ± 8 to 622 ± 7 beats/min), the change was small (~6%), so results were averaged to give one value for each study day.

Whole blood (~20 μl) was collected from the saphenous vein to measure hematocrit using a Hematology Analyzer (Acc-T Diff, Beckman Coulter, Toronto, ON, Canada). Two samples were collected 14 days apart from mice in the pregnant (n = 7), postpartum (n = 7), and nonpregnant groups (n = 9) after tail cuff measurements were completed on each study day.

**Pressor response to angiotensin II.** In the second series of animals, virgin females (n = 5) and 14.5 days pregnant ICR mice (n = 6) were anesthetized with isoflurane, and a catheter filled with heparinized saline was implanted in the jugular vein (1.6-mm outer diameter tubing with a flame-stretched tip; model PE-160 Intramedic; Becton Dickinson, Sparks, MD). The catheter was tunneled subcutaneously and exteriorized at the nape of the neck, and the tip was heat sealed. The catheter was flushed daily and mice were allowed 3 days for recovery. On the day of study, arterial blood pressure and heart rate were measured in awake mice by tail cuff (Visitech Systems) while 5% dextrose (control), then 0.03, 0.12, 0.48, and 1.92 ng·min⁻¹·g body wt⁻¹ of angiotensin II were infused for ~5 min each at 1 μl·min⁻¹·g body wt⁻¹ in sequence. Tail cuff measurements were obtained 3–5 min into each infusion interval (preliminary studies showed blood pressure stabilized within 1 min). After each dose, the tubing was flushed with 50 μl of 5% dextrose and blood pressure allowed to return to baseline (time ~30 min).

**Determination of blood velocity variables.** A third series of ICR mice were studied on days 3.5 and 17.5 of pregnancy (n = 9), days 3 and 17 postpartum (n = 7), or at equivalent time intervals in nonpregnant controls (n = 9). Mice were weighed then lightly anesthetized with 1–2% isoflurane in oxygen with the use of a face mask. Body temperature was measured with the use of a rectal probe and was maintained between 37 and 39°C using a heating pad and lamp. A 20-MHz transcutaneous pulsed Doppler system (model VF-1; Valpey Fisher, Hopkinton, MA) with a hand-held probe (Matec Instrument; Northborough, MA) was used to obtain blood velocity waveforms from the ascending thoracic aorta using published methods (25). The tip of the transducer was placed in the suprasternal notch, and the beam was directed in a caudal direction toward the heart with the range gate set at 4 mm. The waveform was recognized by its characteristic steep initial slope, more gradual convex downslope, and brief velocity reversal at the end of the ejection phase due to valve closure (e.g., Fig. 5). The angle of insonation was then adjusted to maximize peak velocity. Blood velocity waveforms collected over a 3-s time interval were saved and later analyzed (Doppler signal processing workstation; Indus Instruments, Houston, TX) to obtain heart rate, stroke distance (velocity envelope integrated over ejection time), mean blood velocity (velocity envelope averaged over the cardiac cycle), and the peak acceleration at the start of cardiac ejection. Measurements were averaged over 10 consecutive waveforms.

**Vascular casts for determination of luminal cross-sectional area.** At the end of the study, the animals were killed by exsanguination while still anesthetized. A fluid-filled catheter was inserted retrogradely into the descending thoracic aorta. A second catheter, which was connected to a pressure transducer, was placed in the ascending aorta via the left ventricle and was held in place with a tie at the root of the aorta. This catheter was used to monitor intravascular pressure during infusions via the first catheter. Fixative (3% paraformaldehyde-phosphate buffer) was infused retrogradely up the aorta for 10 min to fix the aorta, followed by liquid plastic (Batson’s No. 17 corrosion compound; Polysciences, Warrington, PA) that was infused until it had hardened. Intravascular pressure was maintained at 100 mmHg throughout the infusions using a constant pressure head (fixative) or by adjusting infusion rate (liquid plastic).

The cast was cut at the root of the aorta and proximal to the first aortic branch (brachiocephalic artery). The fixed aortic tissue was removed by gently sliding it off the cast. Ascending aortic diameter in the anterior-posterior plane was measured using a dissecting microscope and eyepiece graticule at the midpoint of each cast segment. Diameters were not obtained in 5 of the 25 experiments due to technical problems (bubbles or leaks).

Ascending aortic diameter during systole was later measured noninvasively in a separate group of five isoflurane-anesthetized, nonpregnant ICR mice using a newly developed and recently acquired ultrasound biomicroscope operating at 19 MHz (model VS40; VisualSonics, Toronto, Canada). This group was matched for body weight and age with the nonpregnant group that was cast as described above. If successful, such measurements would enable cardiac output to be determined noninvasively in future studies.

**Cardiac output and stroke volume.** The luminal cross-sectional area was calculated from ascending aortic diameter (area = π [diameter/2]²) measured from the vascular casts. Mean blood velocity and stroke distance were multiplied by luminal cross-sectional area to obtain cardiac output and stroke volume, respectively (25, 36). Because vessel area was measured from casts obtained at necropsy, these variables were calculated once at the last time point in each group.

**Validation of tail cuff measurements.** In a fourth series of animals, adult C57Bl/6J mice (Jackson Laboratories; Bar Harbor, ME) weighing 17–25 g were anesthetized with isoflurane, and a catheter (1.2 mm ID; Micro-Renathane 190; Braintree Scientific, Braintree, MA) with a flame-stretched tip was implanted in the carotid artery. The frequency response of the arterial catheter was maximized by minimizing the length of the flame-stretched tip and the catheter, and by flushing with 100% alcohol before filling with degassed heparinized saline (43). A second catheter (0.28 mm ID; Micro-Renathane 10) was implanted in the abdominal cavity to facilitate intraperitoneal injection of vasoactive agents. Catheters were filled with heparinized saline and were tunneled subcutaneously to exit between the scapulas. Catheters were heat sealed, mice were allowed to recover, and they were
studied the next day. Arterial pressures of awake mice were simultaneously recorded by tail cuff (Visitech Systems) and by attaching the carotid catheter to a chamber containing a catheter-tip pressure transducer (5-Fr; Millar, Houston, TX). Arterial pressure was measured under control conditions, after phenylephrine (1.5 mg/kg ip) to raise arterial pressure, and after nitroprusside (12.5 mg/kg ip) to lower arterial pressure. An average of six paired measurements were obtained per mouse (range 2–11). All catheters were “pop-tested” at the end of each experiment, and correction factors were calculated using published methods (30). Reported pressures were not corrected because correction changed values ≤2% due to the high natural frequency (50–125 Hz) and low damping coefficient of the catheter and recording system used for this study. The relationship between tail cuff and catheter measurements were assessed using correlation plots and by plotting the difference versus the average for pairs of measurements according to published methods (5).

**Statistical analysis.** Results are reported as means ± SE. Change in arterial pressure relative to the baseline before each dose of angiotensin II was calculated, and the effect of pregnancy on the pressure change was determined using a two-way repeated-measures ANOVA (SigmaStat; SPSS, Chicago, IL). Arterial pressure, heart rate, hematocrit and blood velocity variables were tested for significant changes over time and among groups using a two-way repeated-measures ANOVA, followed by a Student-Newman-Keuls multiple comparison posttest (SigmaStat). Differences in cardiac output, stroke volume, and thoracic aortic diameter among groups were tested for significance using a one-way ANOVA, followed by a Student-Newman-Keuls multiple comparison posttest. P < 0.05 was considered statistically significant.

**RESULTS**

**Arterial pressure, heart rate, and hematocrit.** ICR mice studied while awake with the use of the tail cuff system had arterial pressures in late pregnancy (115 ± 2 mmHg) and postpartum similar to those of the control group (111 ± 3 mmHg averaged over the four study days), whereas arterial pressure was significantly reduced at 3.5 days gestation (102 ± 4 mmHg) compared with the same group studied later in gestation or postpartum (Fig. 1). Heart rate also tended to be reduced in early gestation (575 ± 12 beats/min) and then increased significantly to high levels in late gestation (692 ± 10 beats/min) and 3 days postpartum (697 ± 18 beats/min) before decreasing to levels similar to the nonpregnant group (632 ± 18 beats/min averaged over the four study days) by 17 days postpartum (627 ± 12 beats/min). Hematocrit significantly decreased by 18% during gestation falling from 48 ± 2% at 3.5 days to 39 ± 2% at 17.5 days (Fig. 2). There were no significant changes over time in arterial pressure, heart rate, or hematocrit in the nonpregnant control group (Figs. 1 and 2). Body weight increased by 101% between gestation falling from 48 ± 2% at 3.5 days to 39 ± 2% at 17.5 days (Fig. 2). There were no significant changes over time in arterial pressure, heart rate, or hematocrit in the nonpregnant control group (Figs. 1 and 2). Body weight increased by 101% between gestational days 3.5 (28.1 ± 0.5 g) and 17.5 (56.6 ± 1 g), but only 11% in nonpregnant mice over the same time interval (27.7 ± 0.8 to 30.7 ± 0.7 g).

Study mice were not “trained” in the tail cuff system because we found in a preliminary study using eight nonpregnant ICR mice that there was no significant change over 5 days of daily recording in arterial pressure (107 ± 4 on day 1 vs. 119 ± 5 mmHg on day 5; P = 0.1 by paired t-test) and heart rate (590 ± 18 on day 1 vs. 578 ± 26 beats/min on day 5; P = 0.3) nor did the mean time to obtain a measurement or the number of successful inflation trials significantly change with time. In this preliminary study, the mean coefficient of variation for repeated measurements of arterial pressure and heart rate were both 10%. In the blood pressure study itself, the coefficient of variation among the four repeated trials in the nonpregnant group was 8% for blood pressure and 6% for heart rate.

We found that arterial pressure measured in nonpregnant mice using the tail cuff system underestimated systolic pressure measured simultaneously using an implanted carotid arterial catheter, whereas it closely approximated mean arterial pressure over a wide range of pressures (Fig. 3). Tail cuff pressures were highly correlated with mean arterial pressure (Pearson r = 0.89; P < 0.0001) but were slightly higher (by 2.5 mmHg on average) (Fig. 3). The standard deviation of differences in mean arterial pressures and tail cuff pressures was 7.4 mmHg.

**Angiotensin II pressor response.** Arterial pressures of awake ICR mice were measured using the tail cuff
system before and during angiotensin II infusions into chronically implanted jugular vein catheters. The pressor response was significantly reduced by 33% at 17.5 days gestation relative to nonpregnant controls (P < 0.007; Fig. 4). Baseline arterial pressures (99 ± 2 pregnant vs. 104 ± 2 mmHg nonpregnant) and baseline heart rates did not significantly differ among the groups although heart rate tended to be higher in the pregnant (690 ± 17 beats/min) than nonpregnant (633 ± 37 beats/min) mice.

**Blood velocity and cardiac output.** Sample aortic blood velocity waveforms recorded in isoflurane-anesthetized ICR mice in the pregnant and nonpregnant groups are shown in Fig. 5. There were significant increases between days 3.5 and 17.5 of gestation in heart rate (+11%), mean blood velocity (+27%), peak acceleration (+47%), and peak systolic blood velocity (+20%). Stroke distance (+16%) did not change significantly over this interval (Fig. 6). Between days 3 and 17 postpartum, there was a significant decrease in mean blood velocity (+15%), but other variables did not change significantly although they tended to continue toward control nonpregnant values over this interval (Fig. 6). There were no significant changes in the nonpregnant group during the 2-wk period between recording sessions. The coefficient of variation between the two measurements in the nonpregnant group was 8% for heart rate, 9–10% for mean blood velocity, peak velocity, and stroke distance, and 19% for peak acceleration.

Cardiac output in late gestation (38 ± 3 ml/min at 17.5 days) was significantly higher than that of nonpregnant controls (25 ± 2 ml/min) and 17-day postpartum mice (25 ± 4 ml/min) (Fig. 7). This was primarily due to a significant 37% increase in stroke volume from 46 ± 4 μl in the nonpregnant group to 63 ± 3 μl in late pregnancy. Stroke volume significantly decreased postpartum (48 ± 7 μl) (Fig. 7). A smaller but significant increase in heart rate (+17%) also contributed to the increase in cardiac output in late pregnancy (Fig. 7).

The average body weight of the intact, living mouse was 32 ± 1 g in the nonpregnant group (at x + 14 days), 59 ± 5 g at 17.5 days gestation in the pregnant group (84% higher), and 39 ± 2 g at 17 days after delivery in the postpartum group. At these same time points, ascending aortic diameter was 13% higher on average in the late pregnant group (1.53 ± 0.05 mm) than in the nonpregnant control group (1.35 ± 0.06 mm) and the postpartum group (1.40 ± 0.07 mm) but differences were not statistically significant. Ascending aortic diameters were measured in a similar group of nonpregnant mice using an ultrasound biomicroscope (systolic diameter = 1.41 ± 0.02 mm; n = 5). Similar diameters were obtained by both techniques but diameters were obtained in all mice using ultrasound, whereas casts failed in 5 of 25 experiments. Furthermore, the ultrasound method was noninvasive and highly reproducible (coefficient of variation of repeated measurements was <3%). By late pregnancy, cardiac output expressed per kilogram total body weight (641 ± 48 ml·min⁻¹·kg⁻¹; n = 7) did not differ significantly from the nonpregnant (735 ± 46 ml·min⁻¹·kg⁻¹; n = 8) or postpartum (681 ± 100 ml·min⁻¹·kg⁻¹; n = 5) values.

**DISCUSSION**

We have shown that, as in humans, ICR mice are hypotensive in early pregnancy, and they have elevated heart rates, reduced hematocrit, and reduced sensitivity to intravenous angiotensin II in late pregnancy. These alterations in blood pressure and heart rate were detectable in awake mice using an automated tail cuff system. We also showed that an augmentation in cardiac function during pregnancy could be detected noninvasively in isoflurane-anesthetized mice.
mice using a 20-MHz transcutaneous Doppler ultrasound system. Evidence for augmented function includes significant increases in heart rate, and in mean velocity, peak velocity, and peak acceleration of blood flow velocity in the ascending aorta. Although the augmentation in cardiac output and stroke volume was determined using aortic cast diameters in the current study, we also showed that noninvasive measurements of aortic diameter can be reliably obtained using high frequency ultrasound imaging. Thus cardiac output and stroke volume could also be determined completely noninvasively in future studies. Thus cardiovascular changes similar to those occurring in human pregnancy are detectable by noninvasive means in mice.

During pregnancy, heart rate increased 20% when measured in awake ICR mice using the tail cuff system and by 11% when measured in isoflurane-anesthetized mice using Doppler ultrasound. These results are consistent with the 17% increase in heart rate observed in late pregnancy in awake C57Bl6 mice measured with the use of an implanted radiotelemetry system (7) and the 23% higher heart rates observed in midpregnancy in ICR mice anesthetized with ketamine and xylazine (17). Thus mice increase heart rate in late pregnancy to a similar extent as in humans (~16–27%) (10, 37) and rats (10–15%) (20, 38). Possible mechanisms responsible for increased heart rate during pregnancy include a direct chronotropic effect of Relaxin on the heart (42) and/or an increase in cardiac sympathetic activity, given that pregnancy increases cardiac norepinephrine turnover in rats (11).

Unlike heart rate, changes in blood pressure during pregnancy are small and more variable in timing across species. We observed a transient reduction (~13 mmHg) in arterial pressure at 3.5 days gestation (i.e., before implantation) in ICR mice. In awake C57Bl6 mice (7, 26) and in anesthetized ICR mice (17), arterial pressure was transiently reduced in midgestation (~9–13 days), an age not included in the current study. Whether arterial pressure was reduced at 3.5 days gestation in mice was not reported in these prior studies. In humans, arterial blood pressure was reduced (~6 to ~16 mmHg) at the earliest time point of measurement during pregnancy, ~6–8 wk of gestation (9, 10). Arterial pressure then returned to nonpregnant levels by late pregnancy as we (current study) and others (7) have found in mice. Arterial pressure in pregnant rats, on the other hand, decreases only late in gestation (34). Mechanisms causing arterial pressure to decrease transiently during pregnancy in any species are not fully understood. In human pregnancy, an early decrease in arterial pressure likely results from the marked peripheral vasodilation that is believed to be the earliest cardiovascular change during pregnancy (15). Arterial pressure may then recover as cardiac output and blood volume rise later in gestation (15).

The current study is the first to report on whether cardiac output changes during pregnancy in mice. The increase in cardiac output that we observed by late pregnancy in mice (+64%) appeared to be somewhat larger than the 37–53% increase in cardiac output observed in human (44) and rat pregnancy (20, 38). This may have been due to the larger percent increase in maternal body weight during pregnancy in ICR mice in the current study (84–101%) compared with in-
Increases of ~20% in humans (9, 10) and ~35% in rats (14, 38). When cardiac output in late pregnancy is expressed per unit body weight or surface area, it is still significantly elevated by 20–22% in human pregnancy (19, 32) and by 28% in rat pregnancy (20), but we did not find this to be the case in mice. In mice, the increase in cardiac output by late pregnancy was only sufficient to compensate for the increase in weight. Possibly the increase in cardiac output would have been more marked had we studied mice in second or later pregnancies as observed in humans (10).

The current study is the first to report on whether peak acceleration and peak aortic blood velocity are altered during pregnancy in mice. Increases in cardiac output, peak acceleration and peak aortic blood velocity observed in the current study all point to an augmented cardiac performance during pregnancy in mice. Augmented function is likely secondary to a combination of increased cardiac preload, decreased afterload, and increased heart chamber size (due to growth). Whether there is an increase in cardiac contractility during pregnancy in humans is controversial (19, 21, 32). In rats, in vitro measures of cardiac contractility are slightly elevated during pregnancy (6). Both increased preload due to plasma volume expansion (16, 19, 41, 46) and an estrogen-induced enlargement in ventricular size (22) likely contribute to increased left ventricular end-diastolic volume (8, 19, 21, 37) that would also tend to increase stroke volume. Also,
plasma volume expansion likely occurs in mice in that, as in humans (27) and rats (20), we observed a significant decrease in hematocrit during pregnancy. In humans, the decrease in hematocrit is due to the dilutional effect of a greater increase in plasma volume than in red blood cell volume during pregnancy (27). Cardiac afterload decreases during pregnancy in humans and rats due to increases in aortic distensibility and left ventricular and/or aortic diameters (24, 39, 45) and decreased end-systolic blood pressure (19, 32). Increased preload or decreased afterload increase peak aortic blood velocity and peak aortic acceleration in nonpregnant humans (4). Thus pregnancy-related changes in loading conditions may explain the augmentation in peak aortic velocity and acceleration that we observed in mice, and that are also observed in human (23) and rat (38) pregnancy. Increased cardiac contractility could also be involved (38). Whether caused by changes in loading conditions or contractility, increases in cardiac output, peak velocity, and peak acceleration nevertheless indicate a significant augmentation in cardiac function occurs during pregnancy in mice as in other species.

Our values of cardiac output, stroke volume, and heart rate in nonpregnant ICR mice (23 ml/min, 46 μl, and 498 beats/min, respectively) were higher than a previous study on anesthetized mice using similar methods [i.e., 16 ml/min, 35 μl, 459 beats/min (mouse strain not specified)] (25). Possibly the light isoflurane anesthesia that we used had less cardiodepressive effects than the pentobarbital anesthetic used in the other study (25). In support of this view, a recent echo cardiographic study showed that light isoflurane anesthesia decreased heart rate slightly (−3%) but did not alter the fractional area change of the left ventricle during systole compared with conscious mice and thus appeared to have only modest cardiodepressive effects (40). Indeed, cardiac output in our anesthetized mice were more similar to that of conscious wild-type mice measured using echocardiography [i.e., 21 ml/min in a 129/Ola and C57Bl/6J hybrid (48), and 32 ml/min in 129 SvEv/Tac (47)]. Our values in anesthetized mice were higher than when cardiac output was measured using the microsphere technique in awake, chronically catheterized mice [16 ml/min, 25 μl, 653 beats/min (3)]. In this case, the difference may be due to the mouse strain studied (C3H/HeJ), prior surgery, and the short recovery interval (4 h), increased output impedance caused by the ventricular catheter, and/or the simultaneous blood withdrawal used to calibrate the measurement.

The current study is the first to report on whether the pressor response to angiotensin II changes during pregnancy in mice. The pressor response to intravenous angiotensin II infusion was blunted by −39% in mice near term in the current study, which is similar to the 20–40% blunting observed in chronically instrumented rats near term (29, 31, 34) but apparently less than the −50–60% blunting observed near term in human pregnancy (2, 18). Whether the blunted pressor response in mice was due to alterations in systemic vascular resistance or cardiac output was not determined in the current study. However, in other species [e.g., guinea pig, sheep (13, 33)], pregnancy specifically attenuates the angiotensin-induced increase in systemic vascular resistance, whereas decreases in cardiac output are similar to those of nonpregnant animals. In rats, the pregnancy-induced blunting of the pressor response to angiotensin is not mediated by estrogen or progesterone (12, 34), and persists after ovarectomy (1) so does not appear to be mediated by other ovarian hormones either (e.g., Relaxin). Ganglionic blockade blunts the response so it appears to be partially mediated by the autonomic nervous system (35). However, the effect can be abolished by competitive inhibitors of nitric oxide synthases (29, 31, 31, 31), suggesting that augmented nitric oxide production during pregnancy plays a central role in the blunted response to angiotensin II at least in rats.

In summary, mice, like humans, exhibit hypotension in early pregnancy, and a blunted pressor response to angiotensin II, a decrease in hematocrit, and a marked increase in cardiac output in late pregnancy. With the exception of the angiotensin II response that requires implanted catheters, other changes can be detected using noninvasive means. Thus results suggest that genetically modified mice will provide useful new models for better defining the mechanisms mediating normal cardiovascular changes during pregnancy and postpartum.

This work was supported by operating grants from the Canadian Institutes of Health Research (formerly Medical Research Council of Canada). B. L. Langille and S. L. Adamson were Career Investigators of the Heart and Stroke Foundation of Ontario and A. Y. H Wong received a Bernard Ludwig Fellowship in Obstetrics and Gynecology from the Samuel Lunenfeld Research Institute at Mount Sinai Hospital. Funding for the ultrasound biomicroscope was gratefully received from the Richard Ivey Foundation.

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