

Pregnancy: Its Effects on Blood Pressure, Heart Rate and Sympatho-Adrenal Activity in Spontaneously Hypertensive Rats<sup>1</sup> (40180)RICHARD McCARTY<sup>2</sup> AND IRWIN J. KOPIN*Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014*

Pregnancy is associated with major adjustments to the cardiovascular system. Characteristic changes that occur during the course of a normal pregnancy are increases in plasma volume, cardiac output, and heart rate and decreases in stroke volume and peripheral vascular resistance (1, 2). Women with mild essential hypertension generally tolerate pregnancy without major complications; however, there is an increased risk of maternal and perinatal mortality in patients with chronic essential hypertension (2, 3).

Alterations during pregnancy of preexisting hypertension have been evaluated in several experimental animal systems. Reductions in arterial pressure have been reported for term-pregnant spontaneously hypertensive rats (4) and in rats made hypertensive by bilateral renal encapsulation (5) or constriction of blood flow through the renal artery (6). Other studies have failed to observe systematic changes in blood pressure during pregnancy in deoxycorticosterone-saline (DOCA-salt) hypertensive rats (7, 8).

In the present study, we have compared blood pressure, heart rate, and plasma catecholamine levels in nonpregnant and term-pregnant spontaneously hypertensive and Wistar-Kyoto normotensive rats. Blood pressure and heart rate were measured directly in halothane-anesthetized rats via a catheter placed in the ventral caudal artery. This system is less stressful and affords more accurate measurements than indirect tail plethysmography (9).

**Methods.** Stroke-prone hypertensive (SP-SHR), spontaneously hypertensive (SHR), and Wistar-Kyoto normotensive (WKY) female rats were obtained at 10-11 weeks of age from the Veterinary Resources Branch, National Institutes of Health. In our labora-

tory, female rats were housed 4 per cage under a 12-h light-dark cycle with food and water available *ad libitum*. After 1 week, females were mated by placing one male rat of the same strain and approximate age in a cage with four females. The male was removed after two days.

Females were examined at  $20 \pm 1$  days after mating (i.e. days 19-21 of gestation). For each strain, an equal number of pregnant and nonpregnant females from the same cage were selected and studied on one occasion only. Each female was weighed then anesthetized with halothane (4% in O<sub>2</sub>). During surgery, anesthesia was maintained with a 2% mixture of halothane in O<sub>2</sub>. An incision was made through the ventral surface of the tail and the caudal artery was dissected free. A PE 50 catheter was inserted into the artery and secured with several sutures. The tubing was filled with 0.9% saline that contained 500 U heparin per ml. Patency of the catheter was maintained by flushing with 0.5 ml of the saline solution. The catheter was attached to a Statham pressure transducer, and mean arterial pressure (MBP, mm Hg) and heart rate (HR, beats/min) were recorded on a multichannel Grass polygraph. A blood sample was then collected in an iced heparinized tube. After centrifugation at 5,000 rpm for 10 minutes, plasma was removed and stored at  $-20^{\circ}$  until assayed for norepinephrine (NE) and epinephrine (EPI) by a sensitive radioenzymatic method (10, 11). In a pilot study with nonpregnant female rats, it was determined that halothane anesthesia did not significantly alter MBP, HR, or plasma NE and EPI (R. McCarty, unpublished observations).

**Results.** Of 48 females (of each strain) that were mated, 12 SP-SHR and 11 SHR rats were pregnant when examined at 20 days gestation. In contrast, 15 of 32 WKY females were pregnant when mated in a similar manner. The pregnancy success rate for hypertensive females (SP-SHR and SHR strains) was

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significantly lower than for WKY females ( $\chi^2 = 4.2$ ,  $P < 0.05$ ).

The effects of pregnancy on body weight, MBP, and HR of hypertensive and normotensive females are summarized in Table I. Pregnant females of each strain weighed significantly more than age-matched controls ( $P < 0.01$ ). In addition, pregnancy was associated with a significant increase in basal heart rate as measured at 20 days gestation ( $P < 0.05$ ). There were no differences between pregnant and non-pregnant females of either strain with respect to MBP ( $P > 0.05$ ). There was, however, a tendency for MBP to increase in pregnant SP-SHR females and to decrease in pregnant WKY females. The MBPs of SP-SHR and SHR females were significantly higher than normotensive WKY females ( $P < 0.01$ ).

Sympatho-adrenal activity was assessed in anesthetized pregnant and control females by measurement of circulating levels of NE and EPI. Mean circulating levels of catecholamines in blood obtained from rats anesthetized with halothane ranged from 821 to 1000 pg/ml for NE and 854–1100 pg/ml for EPI. There were no differences in plasma NE and EPI between pregnant and control females of either strain ( $P > 0.05$ ). In addition, levels of plasma catecholamines were similar for hypertensive and normotensive rats.

**Discussion.** Results of this study indicate that SP-SHR and SHR females had lower pregnancy success rates than WKY females after an initial two-day exposure to a male rat of the same strain and age. Similar observations have been reported by Douglas and Langford (7) for female rats made hypertensive by administration of DOCA and saline drinking water.

The increases in heart rate of term-pregnant rats in the present study parallel the findings reported for human patients during

the course of a normal pregnancy (1, 2). The absence of attendant increases in plasma catecholamines suggests that diminished vagal activity rather than enhanced sympathetic tone, was responsible for the increase in heart rates. No differences were noted in the blood pressure of pregnant and control rats of either strain. The latter finding is in disagreement with a recent report on the antihypertensive effect of pregnancy in SHR and WKY rats (4). This study by Aoi *et al.* (4) utilized 8- to 10-month old female rats of unspecified parity that had higher initial blood pressures as measured by an indirect method that requires pre-heating and restraint. Such measurements were repeated daily through delivery and two days postpartum. A significant decrease in blood pressure of WKY and SHR females was observed during the last three days of gestation, with a return to normal values after delivery. The differences in ages of the animals, the stage of development of blood pressure elevation, or the method of measurement of blood pressure may account for the discrepancy of the results of Aoi *et al.* (4) and those in the present study. The indirect measurement of B.P. requires heating the animals to produce vasodilation in the tail blood vessels. SHR animals are more sensitive to heat (12), and if pregnancy further enhances this sensitivity, excess vasodilation could have resulted in a more marked decrease in B.P. in these animals than in WKY controls.

The measurement of circulating levels of NE and EPI provides an accurate assessment of the activity of the sympathetic nerves and the adrenal medulla, respectively (13–15). In the present study no differences in plasma catecholamines were noted between pregnant and nonpregnant rats of the same strain or between females of different strains. Similarly, urinary excretion of NE and EPI re-

TABLE I. EFFECTS OF PREGNANCY ON BODY WEIGHT (g), MEAN ARTERIAL PRESSURE (mm Hg), AND HEART RATE (BEATS/MIN) OF HYPERTENSIVE AND NORMOTENSIVE FEMALE RATS, VALUES ARE EXPRESSED AS MEAN  $\pm$  SEM.

	SP-SHR		SHR		WKY	
	Control	Pregnant	Control	Pregnant	Control	Pregnant
Sample size	13	13	11	11	15	15
Body weight	178 $\pm$ 3	208 $\pm$ 4**	182 $\pm$ 3	213 $\pm$ 3**	191 $\pm$ 4	239 $\pm$ 5**
Mean arterial pressure	127 $\pm$ 5	139 $\pm$ 3	126 $\pm$ 5	124 $\pm$ 6	102 $\pm$ 2	95 $\pm$ 3
Heart rate	314 $\pm$ 10	348 $\pm$ 11*	324 $\pm$ 8	379 $\pm$ 9**	297 $\pm$ 8	383 $\pm$ 5**

\*  $P < 0.05$ ; \*\*  $P < 0.01$  (two-tailed "t" test).

mains within normal limits in humans during the course of pregnancy, with increases in both substances on day 1 post-partum (16, 17). An elevation in circulating NE and EPI during delivery could result in increased uterine contractions and decreased blood flow to the fetus (18).

Additional studies of the course of pregnancy in SHR rats may provide a valuable animal model for the detection and treatment of complications that are known to occur during pregnancy in patients with chronic hypertension (2, 3, 19).

*Summary.* Blood pressure, heart rate and plasma catecholamine levels were compared in non-pregnant and term-pregnant SP-SHR, SHR, and WKY female rats. Rats were anesthetized with halothane and the ventral caudal artery was cannulated. The pregnancy success rate for hypertensive females (SP-SHR and SHR) was significantly lower than for WKY females ( $P < 0.01$ ). Pregnancy was associated with an increase in heart rate for females of each strain ( $P < 0.05$ ). No differences were observed between pregnant and control females of the three strains with regard to blood pressure or levels of circulating catecholamines. These findings indicate that pregnancy is not attended by further increases in blood pressure or sympatho-adrenal activity in SP-SHR, SHR, or WKY females. Additional studies of SHR females may provide an experimental model for the evaluation and treatment of complications arising during pregnancy in patients with chronic hypertension.

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