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Association of Birth Weight with Cardiovascular Parameters in Adult Rats During Baseline and Stressed Conditions

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ABSTRACT: Low birth weight (LBW) due to intrauterine growth restriction (IUGR) in humans is associated with increased blood pressure (BP) in adulthood. In Western countries, IUGR is based on uteroplacental dysfunction. We used an animal model of uteroplacental dysfunction to evaluate this correlation. We hypothesize that IUGR increases baseline BP and alters the BP response to acute stress, which may explain BP differences in previous studies using stressful methods to obtain BP. IUGR was induced by bilateral uterine artery ligation in pregnant Wistar rats according to a modified method of Wigglesworth. BP was measured in the offspring using telemetry, allowing for unstressed measurements in conscious animals. Cardiovascular data were obtained at the age of 12 wk during baseline and acute olfactory stress induced by an ammonia gauze. Rats born after IUGR had a lower birth weight *versus* controls and did not completely catch up in weight. At baseline, systolic BP (SBP), mean arterial pressure (MAP), and pulse pressure (PP) were elevated in IUGR rats *versus* controls, by 8, 6, and 5 mm Hg, respectively. There was a strong negative correlation between birth weight and SBP and between birth weight and PP. During acute stress, there was a tendency to reach a higher peak in SBP and to need a longer period to recover in IUGR animals. We conclude that IUGR is associated with increased baseline BP. **(*Pediatr Res* 59: 126–130, 2006)**

IUGR leads to LBW, which is linked to an increased risk of various chronic diseases in adulthood (1–4). Numerous studies have described the association between LBW and hypertension (for review, see Huxley *et al.* (5)). The pathways that may lead to a rise in BP are not fully understood (6–18).

Several previous authors have studied BP in growth-restricted animals (19). In these studies, BP is commonly measured indirectly using the tail-cuff method. This method entails restraining and preheating the animal, which leads to increased BP, heart rate (HR), and plasma levels of epinephrine and norepinephrine (20). In fact, restraints on laboratory animals have been used as a stressor (21). Results obtained from these studies should therefore be interpreted with caution. The described raised BP in IUGR animals might reflect a different stress response rather than a raised baseline BP.

BP can be measured both directly as in a nonstressed manner by telemetry (20). Previously, only two reports using telemetry have addressed the effect of IUGR on BP in rats. Tonkiss *et al.* (22) found a small rise in baseline diastolic BP (DBP) but not in SBP in IUGR rats. They also described a marked difference in the response to acute stress with a greater increase in DBP and SBP in IUGR rats. Jansson and Lambert (23) found no evidence for BP elevation after IUGR. In these studies, different models for IUGR were used. For a review of currently applied IUGR models, see Holemans *et al.* (19). Tonkiss *et al.* (24) applied an IUGR model based on prenatal protein restriction, which might not be representative of the human situation. In Western countries, the leading cause of IUGR is uteroplacental insufficiency. Therefore, an animal model using reduced uteroplacental blood flow will be the most appropriate model to study the effect of IUGR. Jansson and Lambert (23) used an IUGR model based on unilateral uterine artery ligation.

To evaluate the raised BP in human IUGR, we studied BP by telemetry in an IUGR rat model based on bilateral ligation of the uterine arteries. The pups are classified as IUGR if their birth weight is 2 SD below the mean weight of control pups, which is consistent with the human situation. Age-matched controls are obtained from sham-operated dams.

Second, we were interested in the stress response of IUGR animals. We hypothesized that an altered stress response might be reflected by an augmented rise in cardiovascular parameters during stress and a prolonged period of recovery. Various odors, including predator odor and ammonia, are well-known stressors for the rat and lead to a cortisol release and BP increase (22,25). We used ammonia as a stressor as it is a naturally occurring stressor, being present in rat secretions (26). Furthermore, it is easy to administer and remove.

MATERIALS AND METHODS

Timed pregnant Wistar rats were obtained from Harlan CPB (Horst, The Netherlands). Animals were housed individually in plastic cages with wood chips as bedding in the Clinical Animal Laboratory of the VU University Medical Center. A 12:12-h light-dark cycle was maintained (light on at 06:00 h) in the room, at constant temperature (22 ± 1°C) and relative humidity. Rats had free access to tap water and were fed a standard rodent chow (ssniff R/M-H, Bio Services, Schaijk, The Netherlands). All experiments were in

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Abbreviations: BP, blood pressure; **CTRL,** control; **DBP,** diastolic blood pressure; **HR,** heart rate; **IUGR,** intrauterine growth restriction; **LBW,** low birth weight; **MAP,** mean arterial pressure; **PP,** pulse pressure; **SBP,** systolic blood pressure; **SLA,** spontaneous locomotor action

accordance with the approval obtained from the Animal Welfare Committee (DEC) of the VU University Medical Center, Amsterdam.

Experimental groups. IUGR was induced by bilateral ligation of the uterine arteries on d 17 of gestation according to a modified method of Wigglesworth (27), under general anesthesia using ketamine HCl (75 mg/kg i.p.) and xylazine (5 mg/kg i.p.). Control animals (CTRL) were obtained from sham-operated dams that underwent the same procedure except for the actual ligation. At d 21–22 of gestation, the pups were born. IUGR was defined as a weight on d 2 (day of birth was defined as d 1) below 5.3 g, corresponding to −2 SD of the mean of CTRL pups. Litters were reduced to nine to 10 pups. IUGR and CTRL pups were cross-fostered by a recipient mother that had had the same surgery as the natural mother and was matched for the day of delivery. Animals were weaned at d 28 and housed two per cage. Body weight was measured at regular intervals. Because surgery is known to influence body weight (28), only preimplantation weight data are used.

Telemetry. At the age of 11 wk, eight IUGR (born from eight different mothers) and eight CTRL (born from four different mothers) males were selected. Animals were ranked according to their body weight, and the highest and lowest ranked animals were excluded. Animals were anesthetized with ketamine HCl (75 mg/kg i.p.) and xylazine (5 mg/kg i.p.), shaved, and cleaned with chlorhexidine. Telemetry transmitters (TA11PA-C40, Data Sciences International, St. Paul, MN; body:transmitter size ratio = 27:1 to 43:1 [28]) were implanted according to standard procedure (29). Briefly, a midline abdominal incision was made, and the aorta was exposed. The catheter of the transmitter was inserted into the abdominal aorta and guided upstream. Tissue adhesive was used to secure the catheter and obtain hemostasis. The transmitter was placed in the abdominal cavity and sutured to the abdominal musculature.

Data acquisition. Animals were allowed to recover at least 1 wk after surgery. This has been shown to be sufficient (28) and was confirmed in our study group, where body weight returned to the preoperative value within 3 d after surgery. The Dataquest ART 2.1 Silver telemetry system (Data Sciences International) with RPC-1 receivers was used for telemetric measurement of SBP (mm Hg), MAP (mm Hg), DBP (mm Hg), HR (beats/min), and spontaneous locomotor action (SLA) in the animal house. SLA is detected by the system as a change in received signal strength and expressed as counts per minute, with every count representing a movement of the rat of 1.5 to 2 cm.

The Dataquest ART Acquisition software was used to sample all animals during the same period. Baseline sampling was performed every 6 min, setting segment duration at 30 s. In this mode, the average of a 30-s segment is stored as a single value every 6 min. Data were exported from the Dataquest ART Analysis software (Data Sciences International) to Microsoft Excel 2000 (Microsoft Corporation, Seattle, WA). PP (mm Hg) was calculated as the difference between SBP and DBP. If PP fell below 20 mm Hg, the BP measurements were considered to be unreliable, but HR was used unless PP fell below 10 mm Hg. Baseline cardiovascular measurements were obtained from18:00 until 06:00 h to exclude the influence of the presence of people. Data from two consecutive dark periods were averaged and are presented.

Stress test. When studying the effect of acute stress on BP and HR, continuous sampling (storing one value every 2 s) was performed during the light phase. Sampling started with a reference period of 15–20 min. Following the reference sampling, acute olfactory stress was induced by hanging a 5 × 5-cm gauze with 2 mL ammonia from the wire top of the cage for 5 min. Care was taken to prevent ammonia from touching or dripping on the interior of the cage. The maximum value during stress in HR and SBP was recorded as well as the period to reach this maximum. Values were included only when the value directly before and after the maximum were within a 10% range of the maximum value. Sampling was continued for 45 min to measure recovery from stress. Values from the recovery period were averaged over a 30-s segment. Recovery was defined as a parameter being 100% or less of the reference value during at least two consecutive 30-s segments.

Statistics. Values are presented as means (± SD) unless stated otherwise. Differences between groups were analyzed with analysis of variance (ANOVA). Correlations between variables were estimated by calculating the Pearson correlation coefficient using SPSS (version 11, SPSS Inc., Chicago, IL) as statistical analysis system. A $p < 0.05$ was considered to be statistically significant (two tailed).

RESULTS

Figure 1 shows body weight of the IUGR and CTRL rats from birth to the age of 11 wk. By definition, the IUGR rats had a lower birth weight (4.3 ± 0.7 g) than CTRL rats (6.3 ± 0.4 g) ($F = 35.1$, $p < 0.001$). IUGR rats showed no complete catch-up growth and had a persistent significantly lower body weight. At the age of 11 wk, body weight was 310 ± 31 g *versus* 369 ± 15 g in controls ($F = 23.0$, $p < 0.001$).

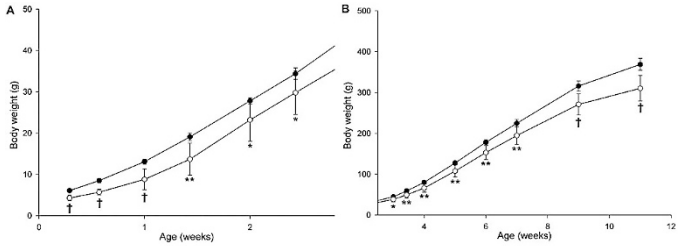

Figure 1. Body weight from d 2 until d 21 (*A*) and d 21 until d 78 (*B*) in male IUGR (○; $n = 8$) and CTRL (●; $n = 8$) rats. *$p < 0.05$, **$p < 0.01$, †$p < 0.001$.

Baseline BP values are presented in Table 1. BP measurements were not reliable in two IUGR rats because of poor signals and were excluded from all BP analyses. Compared with the CTRL rats, IUGR rats had significantly higher mean SBP, MAP, and PP. Birth weight showed a strong negative correlation with SBP (r = 0.712, $p = 0.004$) and PP (r = 0.633, $p = 0.015$) as depicted in Fig. 2. The correlation between birth weight and DBP did not reach significance ($r = 0.298$, $p = 0.30$).

Before the stress test, daytime cardiovascular measurements found similar differences in SBP values (138 *versus* 130 mm Hg, $F = 20.3$, $p = 0.001$, Fig. 3 *B*) and MAP (121 *versus* 114 mm Hg, $F = 13.0$, $p = 0.004$) but not in PP between IUGR and CTRL rats.

The cardiovascular stress response is depicted in Figure 3. Acute stress made HR increase gradually and reach a plateau after 5 min (Fig. 3*A*). SBP and DBP increased instantly to remain at a plateau for the duration of the stress (Fig. 3*B* and *C*). During acute stress, SBP did not differ significantly between groups (154 *versus* 149 mm Hg). Cardiovascular parameters during stress are presented in Table 2.

DISCUSSION

This study shows a difference in cardiovascular parameters between IUGR and CTRL rats at the age of 12 wk under basal conditions in a rat model of IUGR induced by maternal bilateral uterine artery ligation. Also, a tendency to an altered response to acute olfactory stress was noted.

This is the first study to apply telemetric measurement of cardiovascular data in an animal model of IUGR induced by

Table 1. *Baseline cardiovascular data*

	CTRL ($n = 8$)	IUGR ($n = 6$)
HR (beats/min)	380 ± 14	377 ± 11
SLA (counts/min)	5.2 ± 1.9	6.2 ± 1.3
DBP (mm Hg)	94 ± 3	98 ± 7
MAP (mm Hg)	108 ± 4	114 ± 5*
SBP (mm Hg)	124 ± 4	132 ± 4†
PP (mm Hg)	29 ± 3	34 ± 4*

Mean data ± SD are presented for IUGR and CTRL male rats at the age of 12 wk.

* $p < 0.05$ *versus* CTRL.

† $p < 0.005$ *versus* CTRL.

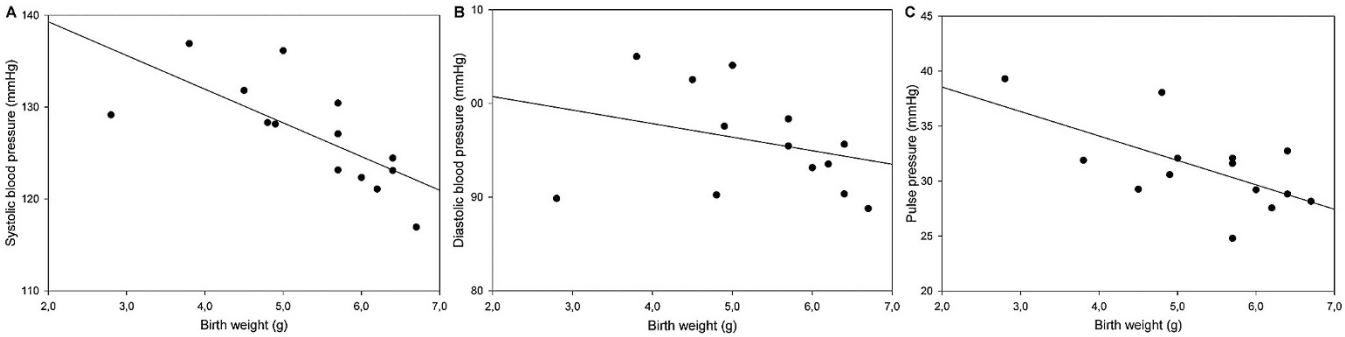

Figure 2. Correlation between birth weight and SBP (r = 0.712; $p = 0.004$) (*A*), birth weight and DBP ($r = 0.298$; $p = 0.30$) (*B*), and birth weight and PP ($r = 0.633$; $p = 0.015$) (*C*) in 12-wk-old male rats ($n = 14$).

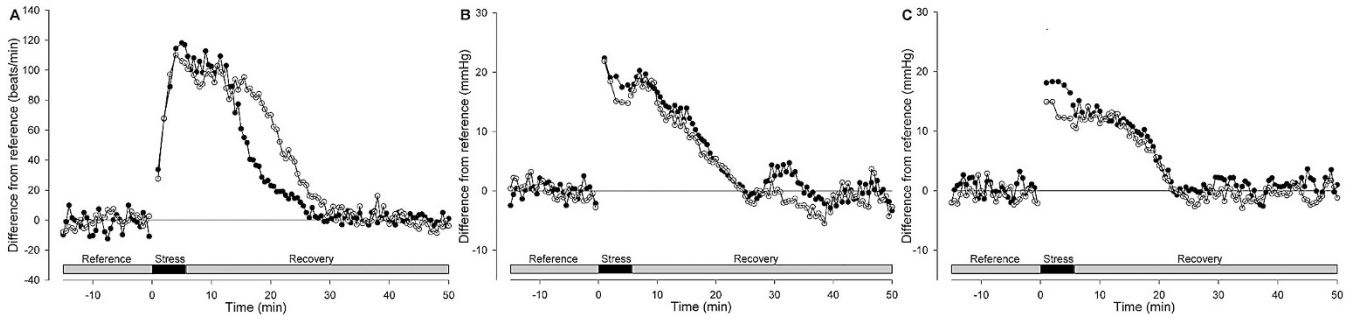

Figure 3. HR (*A*), SBP (*B*), and DBP (*C*) during reference period, acute olfactory stress, and recovery in 12-wk-old male IUGR (○) and CTRL (●) rats.

Table 2. *Cardiovascular data during stress test*

	CTRL ($n = 8$)	IUGR ($n = 6$)	p*
HR reference (beats/min)	316 ± 9	322 ± 12	
SBP reference (mm Hg)	130 ± 3	138 ± 4	$p = 0.001$
MAP reference (mm Hg)	114 ± 3	121 ± 3	$p = 0.004$
DBP reference (mm Hg)	102 ± 3	106 ± 6	
PP reference (mm Hg)	28 ± 2	32 ± 6	
HR max† (beats/min)	467 ± 23	476 ± 15	
SBP max† (mm Hg)	186 ± 16	201 ± 11	$p = 0.058$
HR time max‡ (s)	266 ± 16	247 ± 28	
SBP time max‡ (s)	24 ± 15	17 ± 14	
HR recovery (min)	22.9 ± 5.4	30.6 ± 9.3	$p = 0.076$
SBP recovery (min)	19.6 ± 4.5	19.5 ± 6.2	

Mean data ± SD are presented for IUGR and CTRL male rats at the age of 12 wk.

* IUGR *versus* CTRL.

† Max, maximum value during acute stress.

‡ Time max, time until maximum value was reached during acute stress.

bilateral ligation of the uterine arteries in the pregnant rat. This method is more laborious than others, but closely resembles the human situation of uteroplacental insufficiency, so conclusions derived from this animal model may be more relevant.

Most studies use the indirect and stress-inducing tail-cuff method, which has serious flaws. Stress can be avoided by measuring BP during anesthesia, which allows for a direct intraarterial BP monitoring, but these results may only show the effect of the anesthesia rather than the true changes in BP. Telemetry is the most reliable method for measuring BP in conscious and freely moving animals. However, it is an invasive method and may therefore influence the results. To minimize these influences, transmitters were implanted at a time that the body:transmitter size ratio was in an acceptable range (28). Also, animals were allowed to recover for at least 1 week before measurements started. This has been shown to suffice for rats (28) and was confirmed in our study by the return of body weight to presurgical levels within 3 d after implantation. Furthermore, many factors can induce stress in rodents, like sounds, odors, and activities, which influences measurements (30). In our laboratory, the time when most stimuli can be avoided is during the night, when staff is not present regularly and sounds are reduced to a minimum (M.F. Schreuder, unpublished observations). For these reasons, our data reflect basal BP values. We found a significant correlation between birth weight and baseline SBP. In humans, a higher body weight is associated with a higher BP (31). Huxley *et al.* (32) suggested that the regression coefficient should not be adjusted for current size since adjustment might produce an association even if birth weight and current BP are uncorrelated. Therefore, only an unadjusted regression is presented which shows a negative correlation.

In this study, PP was increased after IUGR and an inverse relationship between birth weight and PP was found. A rise in PP is primarily due to an increased arterial stiffness and is an independent predictor of cardiovascular disease risk in humans (33). IUGR is linked with a increased large artery stiffness, and a negative correlation with birth weight has been described (34). Future research using the described animal model is necessary to study the underlying factors that determine the altered arterial elasticity.

We noted no significant elevation in DBP and no association between birth weight and DBP. One possible interpretation of these data together with the increase in SBP and PP is

that IUGR does not influence BP *per se*, but programs arterial stiffness only. However, the relatively small number of animals can also explain the absence of significance.

Jansson and Lambert (23) were the first to study the effect of uteroplacental insufficiency on BP using telemetry in a large group of rats and found no association between birth weight and BP after IUGR. Differences in experimental design may account for this. First, different rat strains were used (Wistar *versus* Sprague-Dawley), which could influence the effect of IUGR on BP since BP does differ between strains (35). Second, the ligation was performed on different days during pregnancy (d 18 *versus* d 17). The timing of insults during fetal life is known to influence the effects of these insults on BP (36). Third, ligation of the uterine artery may induce hypertension in the mother, which makes the hemodynamic situation in the contralateral unoperated uterine horn different from the hemodynamics in the uterine horns from an unoperated dam (37). Since this can influence BP in the CTRL animals, a difference with IUGR rats can be smaller and therefore more difficult to be found. Using a moderate sound stress (7-mm Hg rise in MAP), Jansson and Lambert found no relation between birth weight and the change in cardiovascular parameters. We used a more severe stressor and found no significant difference in change in BP either, even though there was a tendency to an altered stress response.

During baseline conditions, we found an increase of 8 mm Hg in SBP. Most studies using the tail-cuff method have found a much higher difference in BP between controls and IUGR animals (38,39). These data are more in line with the increase of 15 mm Hg that we found during acute stress. In our opinion, this underlines the known stressed effect of the tail-cuff method. The time to reach maximum values of HR and SBP, and the time to return to reference values were not significantly different between groups. However, we hypothesize that the trend seen in 12-wk-old rats is indicative of an altered stress response after IUGR. More information on cardiovascular data later in life is needed, both under basal as well as stressed conditions.

Some studies have described a difference in BP between sexes in various models of hypertension. After IUGR, BP is affected more in male than female rats (40). As Jansson and Lambert (23) found no difference in BP after IUGR, we selected male rats as they are more likely than females to show a difference in BP.

A negative association between birth weight and BP has been confirmed in several different animal species, including the guinea pig (41), pig (42), and sheep (43). As these associations are present in several animal models after only a short period of IUGR, BP should be checked in children after IUGR to prevent secondary damage due to a raised BP. A possible explanation for the association between LBW and a higher BP is a reduction in the number of nephrons, which has been shown after IUGR (6–12,44) and may be due to an increased renal apoptosis (13). To compensate for the reduced filtration surface, hypertrophy and hyperfiltration occur, leading to raised glomerular blood pressure and SBP and finally proteinuria and end-stage renal disease (14–17). A relationship between low nephron number and raised BP has been confirmed in patients with "essential" hypertension: compared with individuals with normal BP, patients with hypertension had less glomeruli at autopsy (18).

In conclusion, telemetric assessment of cardiovascular parameters revealed an increase in SBP, MAP, and PP under baseline conditions in 12-wk-old male rats after IUGR. We showed a strong and significant negative relationship between birth weight and SBP and between birth weight and PP.

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