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BRIEF REPORT

Poor perinatal growth impairs baboon aortic windkessel function

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The ability of the aorta to buffer blood flow and provide diastolic perfusion (Windkessel function) is a determinant of cardiovascular health. We have reported cardiac dysfunction indicating downstream vascular abnormalities in young adult baboons who were intrauterine growth restricted (IUGR) at birth as a result of moderate maternal nutrient reduction. Using 3 T MRI, we examined IUGR offspring (eight male, eight female; 5.7 years; human equivalent 25 years) and age-matched controls (eight male, eight female; 5.6 years) to quantify distal descending aortic cross-section (AC) and distensibility (AD). ANOVA showed decreased IUGR AC/body surface area ($0.9 \pm 0.05\,cm^2/m^2$ *v.* $1.2 \pm 0.06\,cm^2/m^2$, M ± S.E.M., $P < 0.005$) and AD (1.7 ± 0.2 *v.* $4.0 \pm 0.5 \times 10^{-3}$/mmHg, $P < 0.005$) without sex difference or group-sex interaction, suggesting intrinsic vascular pathology and impaired development persisting in adulthood. Future studies should evaluate potential consequences of these changes on coronary perfusion, afterload and blood pressure.

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Key words: aorta, baboons, developmental programing, intrauterine growth restriction, maternal nutrient restriction

Introduction

The developmental origins of health and disease hypothesis postulates that reduced fetal growth programs offspring susceptibility to chronic later life conditions, including heart disease, stroke and hypertension. The Harvard Nurses' Health Study of 121,700 nurses showed that birth weight is negatively correlated with the incidence of coronary heart disease, stroke and total cardiovascular disease after adjusting for both age and body mass index.[1] The Health Professionals Follow-up study in 22,846 men concluded that low birth weight men were at higher risk for hypertension and diabetes, even after correcting for parental history and obesity.[2] We have reported cardiac dysfunction characteristic of increased afterload and vascular abnormalities in young adult intrauterine growth restricted (IUGR) male and female baboons without blood pressure changes.[3]

It is well recognized that the aorta is not a passive conduit. Aortic wall stretching and resultant excess flow accommodation in systole allows it to act as a blood reservoir. Its subsequent elastic recoil generates forward blood flow for continued diastolic perfusion of vital organs, termed the Windkessel function. The aorta thus significantly modulates left ventricular function, coronary blood flow and systemic arterial function. The aortic Windkessel function hinges upon its systolic buffering capacity and diastolic elastic potential, both strongly correlated with aortic size and distensibility.[4] Furthermore, aortic distensibility affects baroreceptor function[5] and is proposed as a marker of hypertensive risk. We hypothesize that IUGR reduces aortic cross-section (AC) and aortic distensibility (AD).

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Materials and methods

Ethical approval

All procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee and conducted in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Animal model

Baboons (*Papio hamadryas species*) were group housed and maintained with full social interaction and physical activity with access to individual feeding when required. Healthy non-pregnant female baboons of similar age, morphology (weight, body length, abdominal circumference, etc.) and phenotype to ensure homogeneity of the mothers in both groups were randomly assigned either to an *ad lib* monkey chow diet [controls (CTL)] during pregnancy and lactation or a globally reduced diet regimen consisting of 70% of feed eaten by CTL *ad lib* fed mothers [maternal nutrient reduction (MNR)] from 0.16 gestation (G) to end of lactation. Diet was Purina 5038 (Purina LabDiets, St Louis, MO, USA) containing 13% calories from fat, 18% calories from protein, 69% calories from carbohydrates, mineral and vitamin additives, and a metabolizable energy

Table 1. *Baseline data measurements (mean ± S.E.M.)*

	CTL		IUGR		ANOVA
Baseline data	M ($n=8$)	F ($n=8$)	M ($n=8$)	F ($n=8$)	
Age	5.4 ± 0.5	5.7 ± 0.5	5.9 ± 0.4	5.5 ± 0.5	NS
Current weight (kg)	19.5 ± 2.4	13.9 ± 0.7	21.6 ± 1.5	13.4 ± 0.4	M > F***
Body surface area (m^2)	0.55 ± 0.05	0.44 ± 0.01	0.60 ± 0.03	0.44 ± 0.01	M > F***
Birth weight (kg)	0.93 ± 0.05	0.89 ± 0.04	0.82 ± 0.03	0.74 ± 0.05	CTL > IUGR**
Heart rate	111 ± 4.2	135 ± 4.6	112 ± 4.6	131 ± 4.2	F > M***
Blood pressure (mmHg)	M ($n=8$)	F ($n=8$)	M ($n=8$)	F ($n=7$)[a]	
Systolic	118 ± 5.7	116 ± 9.5	113 ± 6.7	119 ± 4.2	NS
Diastolic	68 ± 7.8	71 ± 9.2	63 ± 8.1	66 ± 4.9	NS
Mean arterial	85 ± 7.1	86 ± 9.2	80 ± 7.8	84 ± 3.8	NS
Pulse pressure	50 ± 4.2	52 ± 1.8	49 ± 3.5	53 ± 4.2	NS

CTL, control; IUGR, intrauterine growth restricted; NS, not significant.
[a]The blood pressure measurements could not be obtained in one female IUGR baboon.
**$P < 0.01$, ***$P < 0.005$.

content of 3.22 kcal/g. Offspring of MNR mothers were IUGR at term.[6] CTL and IUGR offspring were weaned to monkey chow at 9 months and moved to juvenile cages. Baseline data are shown in Table 1.

Blood pressure measurement and calculation

Blood pressure measurements were acquired with the Omron HBP-1300 professional sphygmomanometer in the left upper arm, using a small (17–22 cm) or a medium (22–32 cm) cuff as appropriate. Measurements were obtained upon intramuscular ketamine hydrochloride sedation induction (10–12 mg/kg) with the baboons in the supine position. Six measurements were obtained and averaged. Pulse pressure is defined as the difference between systolic and diastolic blood pressure. Mean arterial pressure was approximated by standard formula using systolic and diastolic blood pressures, MAP = 1/3 SBP + 2/3 DBP.

MRI

MRI was performed on two groups of baboons: IUGR (eight male, eight female, age = 5.7 ± 1.3 years; mean ± S.D.) and age-matched CTL baboons (eight male, eight female, age = 5.6 ± 1.3 years). To account for potential diurnal and prandial effects on vascular regulation, the studies were conducted during the same time of the day, in the morning (9 am to 11 am) after overnight fast. Anesthesia was induced with ketamine hydrochloride (10–12 mg/kg, i.m.) and maintained with isoflurane (0.8–1.0%, inh). Oral intubation was then performed followed by mechanical ventilation and physiologic monitoring.[3]

All studies were performed on a 3.0 Tesla MR scanner (TIM Trio, Siemens Healthcare, Malvern, PA, USA) with a six-channel anterior phased-array torso coil and corresponding posterior coil elements, resulting in an aggregate of 12 channels of data. Before each imaging session, a standard quality control phantom was scanned to ensure geometric accuracy, spatial resolution, and contrast were within acceptable limits. Breath-held, EKG-gated, steady-state free precession imaging sequence was used to acquire high temporal resolution cine images of the lower thorax with EKG gating (TR/TE 3.0/1.5 ms, 25 cardiac phases, matrix 144 × 192, FOV 188 × 250 mm^2). Segmentation of a single heart beat into 25 phases results in ~20 ms frames. A stack of 20–24 contiguous short-axis slices (2.5 mm thickness, no gap) was acquired at the level of the heart.

Image processing and analysis

The CMR[42] image analysis package (Circle Cardiovascular, Calgary, AB, Canada) was used for data analysis. To account for angulation of the aorta, axial slice images of the aorta were obtained and processed with 3D reconstruction via the CMR[42] multi-planar formatting module to ensure the axial slices are oriented perpendicular to the vascular long axis. The distal descending aortas at the level of the heart, above the diaphragm, were examined. Measurements of the aorta cross-sectional area were taken at the end-systolic and end-diastolic phases from the same axial slice level and averaged for further analysis. In addition, distensibility was calculated using the formula

$$\mathrm{AD} = \frac{\mathrm{Area}_{\mathrm{systole}} - \mathrm{Area}_{\mathrm{diastole}}}{\mathrm{Area}_{\mathrm{diastole}} \times \Delta \mathrm{P}}$$

where ΔP is approximated by using the left brachial pulse pressure. Duplicate measurements were made and averaged for use in the final analyses.

Data were analyzed using GraphPad Prism 7. Grubbs' test (extreme Studentized deviate) was used to evaluate for statistical outliers. Normality of distribution was assessed by the d'Agostino-Pearson test. Two-way ANOVA analysis was used to evaluate the null hypotheses that there were no differences between the factors group and sex and no significant interactions. Correlation analysis between AC and birth weight was performed prior to and following normalization to body surface area (BSA).

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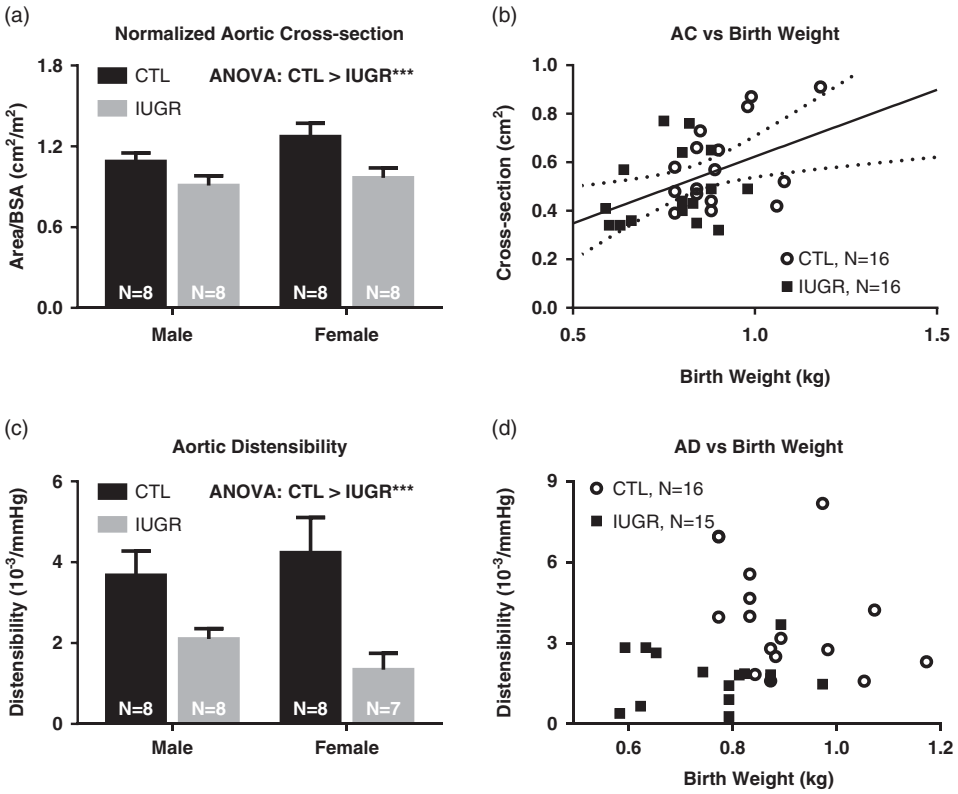

Fig. 1. Decreased aortic cross-section and distensibility with IUGR. (*a*) Lower AC/BSA was noted in IUGR (CTL *v.* IUGR, $1.2 \pm 0.06\,cm^2/m^2$ *v.* $0.9 \pm 0.05\,cm^2/m^2$, $P < 0.005$). No between sex difference or group–sex interaction was detected by ANOVA. (*b*) AC correlated positively with birth weight ($AC = 0.55 \times BW + 0.07$, $P = 0.01$, $R = 0.44$). Solid regression line is shown with dotted 95% confidence bands. (*c*) Decreased AD was seen in IUGR (4.0 ± 0.5 *v.* $1.7 \pm 0.2 \times 10^{-3}$/mmHg, $P < 0.005$). No between sex difference or group–sex interaction was detected by ANOVA. (*d*) No significant correlation was found between AD and birth weight, but group stratification was observed.

Data are presented as mean ± S.E.M. In bar graphs, the number of animals used in final analysis is indicated as *n*. Asterisks denote significance, $P < 0.05$ for all tests.

Normalization

The cross-section measurements were evaluated with reference to BSA, estimated using weight based models previously described for baboons.[7] For females:

$$BSA = 0.078 \times weight^{0.664}$$

and in males,

$$BSA = 0.083 \times weight^{0.639}$$

where weight is measured in kg, and the calculated BSA has unit of m^2.

Results

Blood pressure

Blood pressure data are shown in Table 1. There was no difference detected in systolic blood pressure, diastolic blood pressure, mean arterial blood pressure or pulse pressure between the groups or the sexes. No group–sex interaction was detected.

Aortic cross-section

Before normalization to BSA, ANOVA revealed no group ($P = 0.07$) or sex ($P = 0.14$) difference and no group–sex interaction ($P = 0.38$) in AC. After normalization to BSA, group difference ($P = 0.004$) was seen without sex difference ($P = 0.13$) or group–sex interaction ($P = 0.42$) with lower AC/BSA in IUGR ($1.2 \pm 0.06\,cm^2/m^2$ *v.* $0.9 \pm 0.05\,cm^2/m^2$, M ± S.E.M., Fig. 1a).

Linear regression revealed a positive correlation between AC and birth weight ($AC = 0.55$, $BW + 0.07$, $P = 0.01$, $R = 0.44$, Fig. 1b). The within-group correlation was not different between groups ($P = 0.39$). After normalization to BSA, the overall correlation was not significant ($P = 0.13$).

Aortic distensibility

ANOVA revealed group as a significant factor in AD ($P = 0.0008$) without sex difference ($P = 0.87$) or group–sex interaction ($P = 0.27$), with lower AD in IUGR (4.0 ± 0.5 *v.* $1.7 \pm 0.2 \times 10^{-3}$/mmHg, Fig. 1c).

Linear regression between AD and birth weight of the IUGR and CTL animals revealed no significant correlation combined ($P = 0.41$, Fig. 1d) or individually ($P_{CTL} = 0.20$, $P_{IUGR} = 0.83$).

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Discussion

The developmental programming hypothesis states that gene–environment interactions and epigenetic changes during perinatal development have long-term impacts upon the life-course health trajectory of the offspring.[8] We examined aortic structure in a cohort of baboons in which we have established left ventricular deficits in IUGR compared with contemporaneous controls.[3] We uncovered persistent distal thoracic aorta abnormalities in young adult IUGR males and females – decreased lumen size and functional aorta impairment indicated by decreased distensibility.

The clinical literature on the relationship between aortic elasticity and prenatal growth reports mixed findings. Increased aortic stiffness has been noted in very low birth weight premature infants,[9] small-for-gestational-age newborns,[10] and IUGR children.[11] A few studies detected a similar trend of increase in aortic stiffness that did not reach significance.[12,13] Some studies failed to demonstrate any correlation.[14] We suspect the disparate findings in the literature arose from the use of birth weight as a direct marker of intrauterine growth. Birth weight distribution in healthy neonates indicates low birth weight can result from a normal pregnancy. In our model, overlap of birth weight suggests birth weight alone is an insufficient measure of prenatal health. In placental insufficiency induced IUGR fetal sheep, aortic stiffness was increased with altered collagen-to-elastin ratio,[15] signifying the detected viscoelastic changes of poor prenatal growth have biomechanical basis at the molecular level. We hypothesize from the lack of correlation between birth weight and AD in this study that the presence of a prenatal insult, not the extent of IUGR or birth weight *per se*, determines abnormal matrix deposition and the resultant aortic mechanical property. Disruption of elastin content was previously noted in hypoxia induced IUGR fetal sheep[16] and uterine artery ligation induced IUGR fetal and adult guinea pigs.[17] An early study on the rat aorta revealed elastin deposition is largely limited to the prenatal and early postnatal period, and the concentration of elastin decreases thereafter.[18] Our findings are the first to indicate that functional changes in a developmentally programmed primate model of IUGR persist into adulthood. In the context of the Windkessel function, decreased aortic distensibility with IUGR is important because the elastic recoil of the aorta provides the bulk of the contractile force of diastolic perfusion of the systemic circulation, including the coronary arteries.

IUGR resulted in diminished aortic cross-section. The role of IUGR in reducing aortic size has been noted in small-for-gestational-age children.[12,13] Species differences may exist as IUGR induced by hypoxia in chick embryos[19] and hyperthermia in fetal sheep[20] reduce aortic cross-section, but aortic size is unaffected by maternal nutrient restriction or hypoxia induced IUGR in rats.[21,22] Our results suggest in a primate model that IUGR, induced by 30% reduced maternal nutrition, decreases offspring aortic cross-section. Concurrent decrease in vessel size and distensibility is important because reduction in size further diminishes aortic buffering capacity. With aortic narrowing, flow velocity and luminal pressure increase if flow volume is maintained, potentially leading to self-propagating flow-mediated arterial wall stiffening.[23]

One of the major questions related to developmental programming is the extent to which programmed outcomes persist through life. Human aorta stiffness increases with age, with one human study reporting that age-related aortic stiffness increase proceeds in a sex dependent manner.[24] In future studies we propose to determine whether these programming effects in the aorta increase, decrease or remain unchanged with aging across the life-course. Thus, we could not perform a necropsy to obtain tissues to test the molecular and cellular mechanisms involved. While studies in other models have provided a potential mechanism for our observed changes, it remains to be established whether comparable cellular processes occur in primates given the differences between monotocous precocial species including primates and polytocous altricial rodents. Understanding species similarities and differences aids evaluation of key mechanisms. On a few occasions, we have assessed blood pressure in IUGR and control animals and found no group differences in systolic, diastolic and pulse pressures.[3] It is unusual for animals with decreased distensibility to exhibit no change in pulse pressure, a known consequence of impaired aortic function.[4,23] Although fetal exposure to high doses of steroids leads to hypertension in later life, we have shown that hypertension is not exhibited in exposed sheep by 5 months of age.[25] We note that a large human systematic review by Huxley *et al.* concluded that negative correlation between birth weight and systolic blood pressure, although present, is both subtle (2 mmHg/kg birth weight) and attenuated in adolescence,[26] whereas other animal models have reported much more drastic increases in arterial blood pressure.[27–29] We hypothesize that as with many other responses to developmental challenges, compensatory processes occur to normalize anticipated blood pressure increases and that additional stressors, such as aging, are needed for abnormalities to emerge in our animals, which are in early young adulthood (human equivalent 20–25 years). In addition, we note that the extent of our nutrient reduction is both milder compared with some other global nutrient reduction models (30 *v.* 50%) and continues into lactation, where catch-up growth may be blunted. Combined, these factors may result in a smaller degree of blood pressure increase that is currently below our detection threshold. Alternatively, it is possible that the lack of difference may originate from the use of anesthesia and supine positioning of the animals during the measurements. Finally, we acknowledge that distensibility is only one facet of 'arterial stiffness' and, as measured in this study, reflects more on the aorta's elastic property rather than compliance, which carries a different mechanical significance.[30] We further note that our AD measurements are calculated based on using brachial pulse pressure instead of more invasively obtained and more accurate aortic pulse pressure, meant to examine the

differences in physiology between IUGR and control animals instead of providing highly accurate measures of AD. Differences in measurement methodologies used in published studies likely contribute to the divergent results seen regarding arterial stiffness.

In summary, we report decreased AD and size secondary to IUGR, suggesting IUGR causes long-term impairment of aortic Windkessel function. Reduction in normalized aortic cross-section indicates that elements of poor structural growth persist into adulthood. Importantly, decreased distensibility similar to that observed with advanced aging is seen, suggesting elevated afterload, blood pressure dysregulation and altered flow require study. Disruption of aortic function by IUGR is important because coronary perfusion occurs predominantly during diastole and heightened incidence of ischemic heart disease has been repeatedly associated with IUGR. Together, our results suggest IUGR-related vascular changes contribute to the known cardiac dysfunction outcomes from poor prenatal growth and warrant further study.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the Association for Assessment and Accreditation of Laboratory Animal Care International and has been approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee.

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