Myocardial Function and Remodeling in a Baboon Model of Intrauterine Growth Restriction

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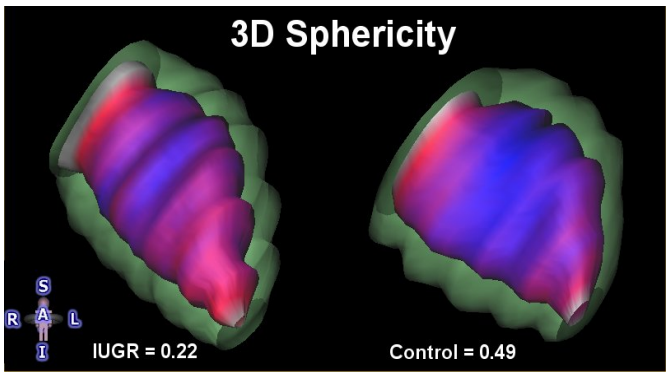
Target audience – MR researchers and clinical investigators interested in quantitative assessment of cardiac abnormalities and environmental factors that influence heart disease.

Purpose – The Developmental Programming Hypothesis states that responses to challenges during critical developmental time windows alter growth with persistent effects on phenotype. Intrauterine growth restriction (IUGR) affects 4-8% of babies in developed countries and as many as 6 to 30% in developing countries. Human epidemiological and controlled animal studies in non-primate species, rodents and sheep show that unwanted effects of poor maternal nutrition on development may persist and predispose to later-life cardiovascular diseases (CVD), as well as metabolic syndrome and obesity. MicroRNA studies in IUGR males revelaed seven of 15 differentially expressed miRNAs (mir-19a, mir-23b, mir-27b, mir-99b, mir-143, mir-181a, and mir-378-3p), which have been linked to CVD. The current investigation was undertaken to determine if similar indications of remodeling could be found by MRI in a baboon model of IUGR in which maternal caloric intake was restricted to 70% of normal. Ultrasound imaging studies in human children with a history of fetal growth restriction suggest that an important imaging biomarker for cardiac programming may be the amount of geometric remodeling occurring in the left ventricle. (1) One measure of myocardial deformation is the sphericity, which is defined as ratio of the LV volume to the volume of a sphere having the diameter of the LV long axis. (2) In this study cardiac MRI was used to measure LV cardiac function the 3D sphericity index to determine if subclinical myocardial remodeling is associated with fetal programming.

Methods – Magnetic resonance imaging (MRI) was used to quantify phenotypic expressions of epigenetic variation in nine male baboons, consisting of five age-matched controls (CTR) and four with restricted growth (RG). All studies were performed on a 3.0 Telsa MR scanner (TIM Trio, Siemens Healthcare, Malvern, PA) with a six-channel anterior phased-array torso coil and corresponding posterior coil elements resulting in an aggregate of up to 12 channels of data using electrocardiographically (ECG) gated steady-state free precession (SSFP) imaging sequences. Briefly, multiple contiguous short-axis slabs, oriented perpendicular to the long-axis of the ventricles were obtained during brief (12-24 s) periods of breath-holding. Frequency scout images were performed prior to SSFP imaging to remediate off-resonance artifacts inherent to SSFP imaging by adjusting the synthesizer frequency. Cardiac morphology and function were evaluated after initial anatomical gradient echo scout images were obtained. High temporal resolution cine imaging with a retrospective gating was performed, using the balanced SSFP sequence (typical parameters: TR/TE = 3.0/1.5 ms, 25-30 cardiac phases, matrix 144×192, FOV 188×250 mm^2, in plane resolution 1.3×1.3 mm^2). A stack of 24-30 contiguous short-axis slices (slice thickness 2.5 mm, no gap) were acquired serially during repetitive breath-holds at end expiration. Cardiac MRI analysis was performed using the CMR^{42} image analysis package (Circle Cardiovascular, Calgary, AB).The ventricular function analysis determined left ventricular (LV) volumes, LV function and mass (using the area-length method). LV volumetry was also performed by semi-automatic subendocardial contour detection. End diastolic volume and end systolic volume were determined from the areas of the endocardial regions of interest (ROI). In the tracing convention used, the papillary muscles were included as part of LV cavity volume. Left ventricular volume was calculated and displayed for each phase. The smallest volume was assumed to be at end-systole and the largest volume is assumed to represent end-diastole. Ejection fraction (EF) was computed as EF= (EDV- ESV)/EDV. Left ventricular epicardial borders were also traced on the end-diastolic images with LV mass computed as the myocardial volume (i.e., epicardial - endocardial volumes) multiplied by myocardial density (1.05 g/ml). In addition to volumetric measurements, percent wall thickening and wall motion (thickening or thinning, in mm) were also determined by cardiac segment.

Baboons	Control	Growth Restricted
N (all male)	5	4
Age (yrs)	4.4± 0.4	4.9± 0.7
Weight (kg)	15± 1.6	18.1± 2.3
BSA (m^2)	0.47± 0.03	0.53± 0.04
EDV (cm^3)	23.6± 3.4	31.3± 9.3
SV (cm^3)	12.4± 2.2	13.8± 4.2
HR (bpm)	92.6± 4.3	97.5± 8.2
CO (cm^3)	1149.4± 193.2	1315.8± 398.6

Results – Myocardial mass (MM) normalized for body surface area (BSA), was lower in (79.9±13.5 g-mm^{-2}) RG animals compared to age-matched CTR (84.0±4.44 g-mm^{-2}). End-systolic volume (ESV) normalized to BSA, was higher in RG animals (32.99±13.36 mm^2) compared to age-matched male (23.28±5.84 mm^2) CTR. Ejection fraction (EF) was lower in male (44.5±11.8%) RG animals compared to CTR (53.4±6.35%). The effect sizes measured suggest that these differences could become significant with a large N and older subjects (Cohen's d = 0.99 for ESV/BSA and 0.98 for EF.) The age correlations in this group of RG males were MM/BSA: slope = 16.4/yr, r = 0.85), ESV/BSA slope = 18/yr, r=0.95 and EF slope = -12.8/yr, r = -0.75. A significant difference was found between the 3D sphericity index (3DSI-CONT = 0.372±0.079, 3DSI-RG = 0.260±0.027, p =0.03), in male animals suggesting that remodeling is occurring in the RG animals. Shaded, three-dimensional color renderings from MRI data of the left ventricles of two male baboons are depicted in an anterior aspect and displayed in the Figure (right) along with three-dimensional sphericity indexes (3DSI). The left rendering is from an RG animal with 3DSI = 0.22 and the rendering on the right is from a control animal with 3DSI = 0.49.



Discussion – The sphericity results suggest that significant myocardial remodeling takes place in even young baboons that have experienced IUGR. There are several potential causes for these interesting observations including hypertension, myocardial remodeling and aortic arch stiffness. These results demonstrate that MRI can be a robust method for longitudinal studies of subclinical cardiac dysfunction and left ventricular remodeling in the setting of IUGR.

Conclusion – We speculate that volume and/or pressure overloading of the RG heart produces subclinical alterations in cardiac function, which may lead to abnormal wall stresses during myocardial fiber development, triggering a compensating LV remodeling response. We expect that measurable functional, as well as morphological, abnormalities will become more evident in the IUGR baboons with age.

References – (1) Crispi F et al. *Circulation* 121:2427-2436, 2010. (2) Mannaerts HF et al. *Eur Heart J.* 25:680, 2004.