



UT Health
San Antonio



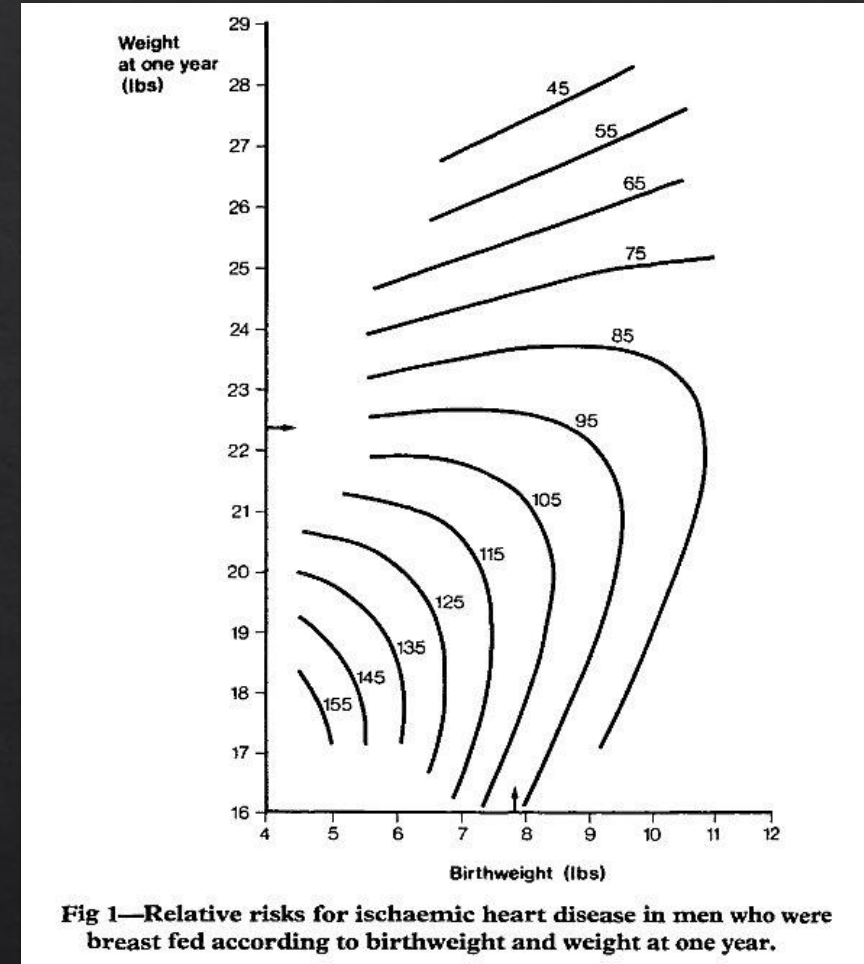
Fetal Origins of Late Life Disease and Function: Cardiovascular Dysfunction Induced by Developmental Programming

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David Barker's Hypothesis

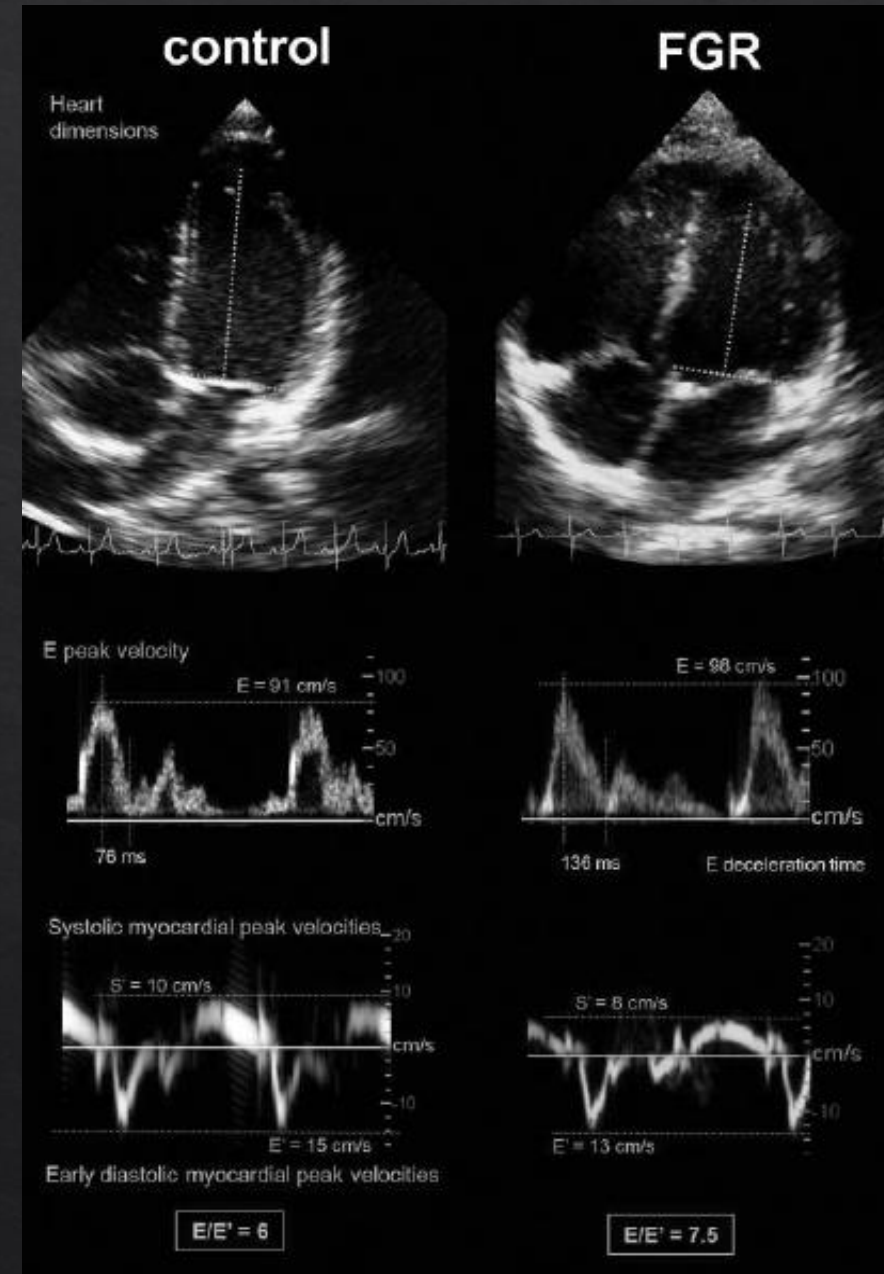
- Examined cardiovascular mortality in men born in Hertfordshire, England, and found that deaths from ischemic heart disease were more common in men who had been small at birth.
- The new model of degenerative disease that is developing will include programming by the environment in fetal and infant life.



*Barker DJP, et al. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989; ii:577-80.

Studies in People

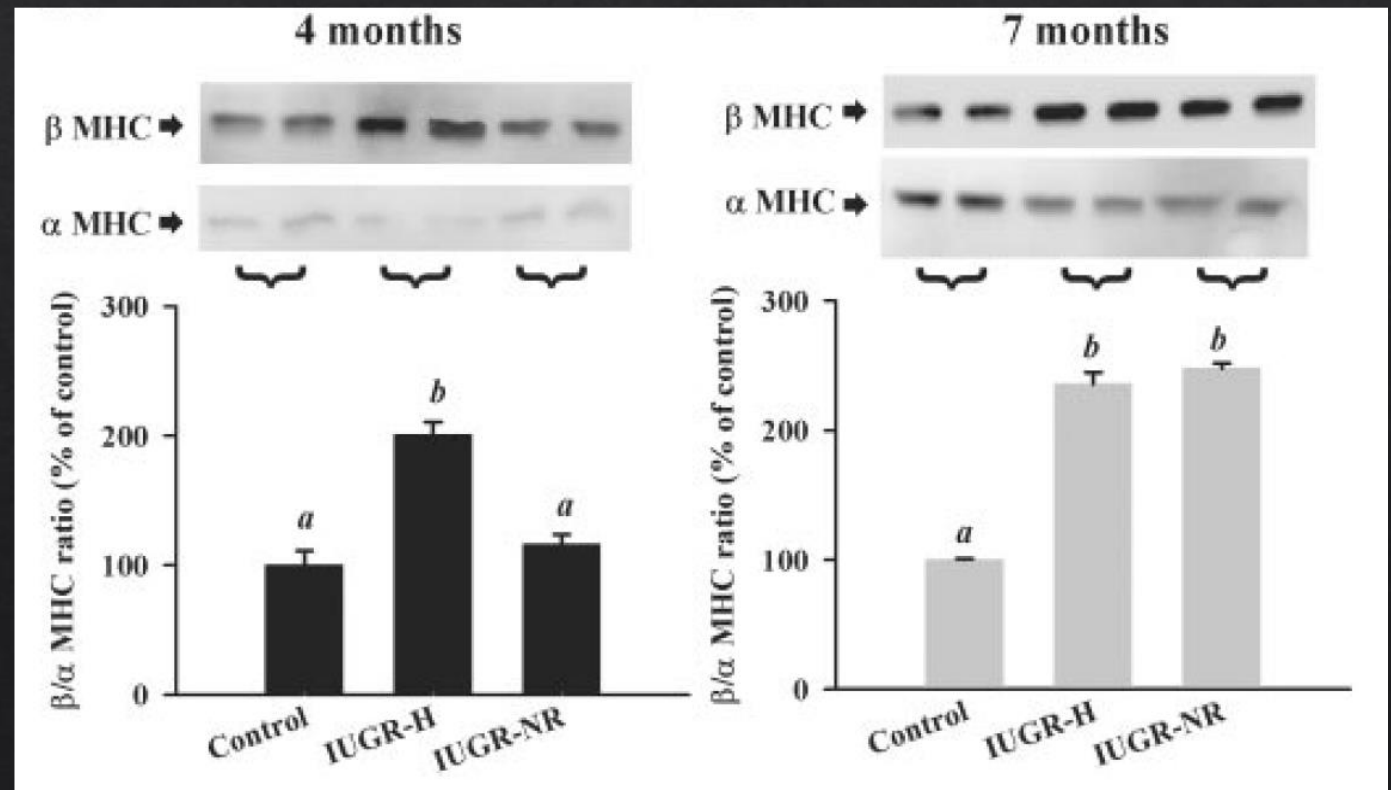
- ◆ Crispi et al. studied 80 subjects with FGR and compared them with 120 normally grown fetuses.
- ◆ Fetal growth restriction (FGR) failure to achieve full in utero growth potential because of genetic or environmental factors.
- ◆ Found reduced stroke volume associated with subclinical longitudinal systolic dysfunction and diastolic changes.



Studies in Animals

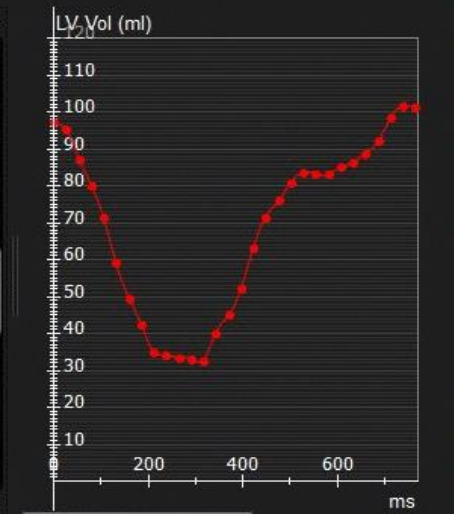
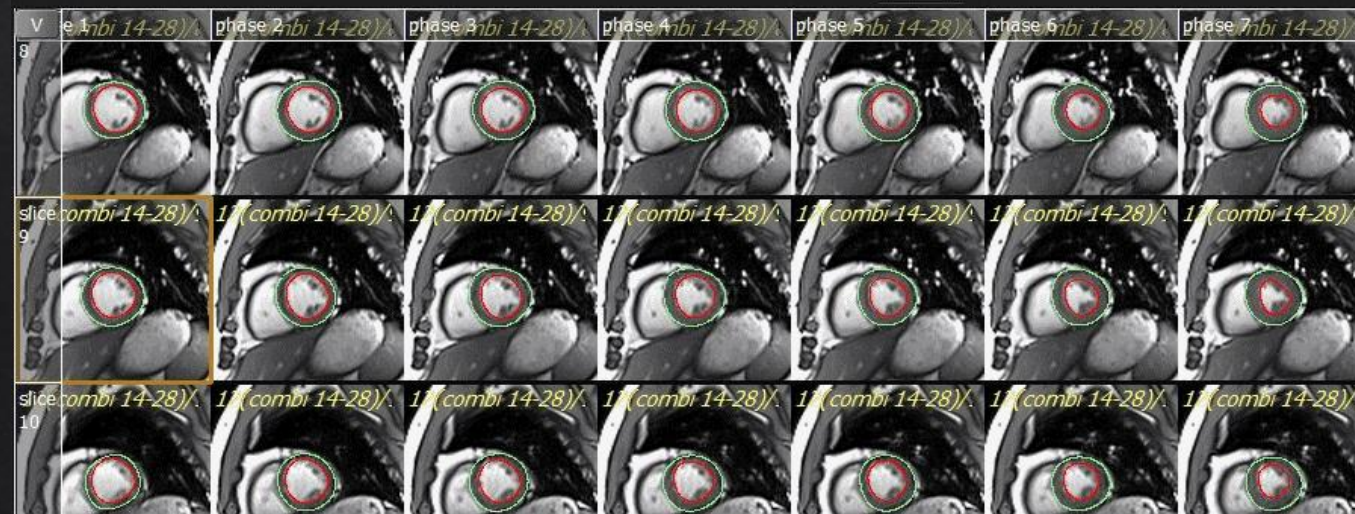
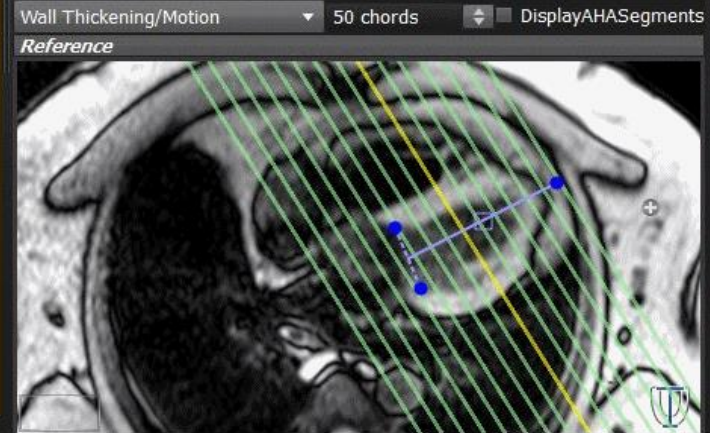
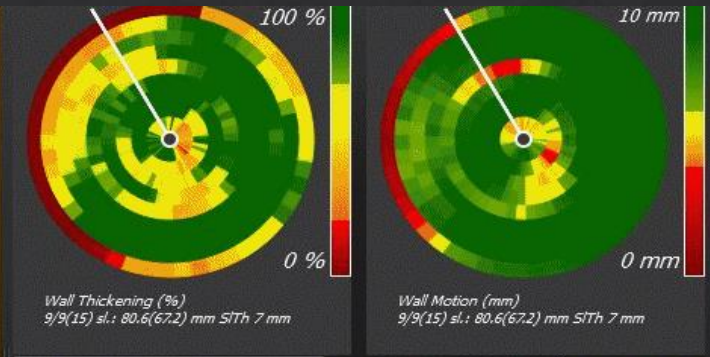
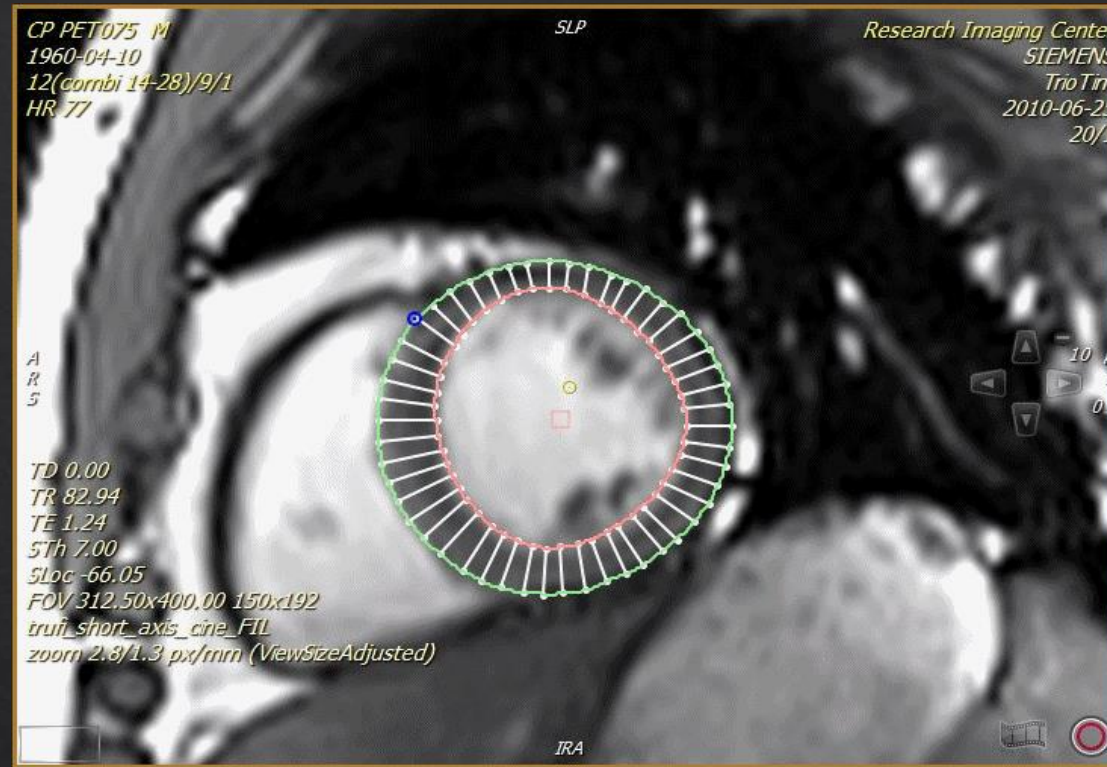
◆ Sprague-Dawley rats were randomized on day 15 of pregnancy to hypoxia (IUGR-H, 12% oxygen), nutrient restriction (IUGR-NR, 40% of control diet) or control (room air) groups.

◆ Fetal substrate restriction during development resulted in pathological ultrastructural changes in LV cardiac tissue.



Cardiac MRI

MRI was performed on a 3.0 T scanner using a 12-channel phased-array coil and parallel imaging to produce cine images of cardiac motion in multiple breath-holds (>20 s/ea.) with ECG triggering.

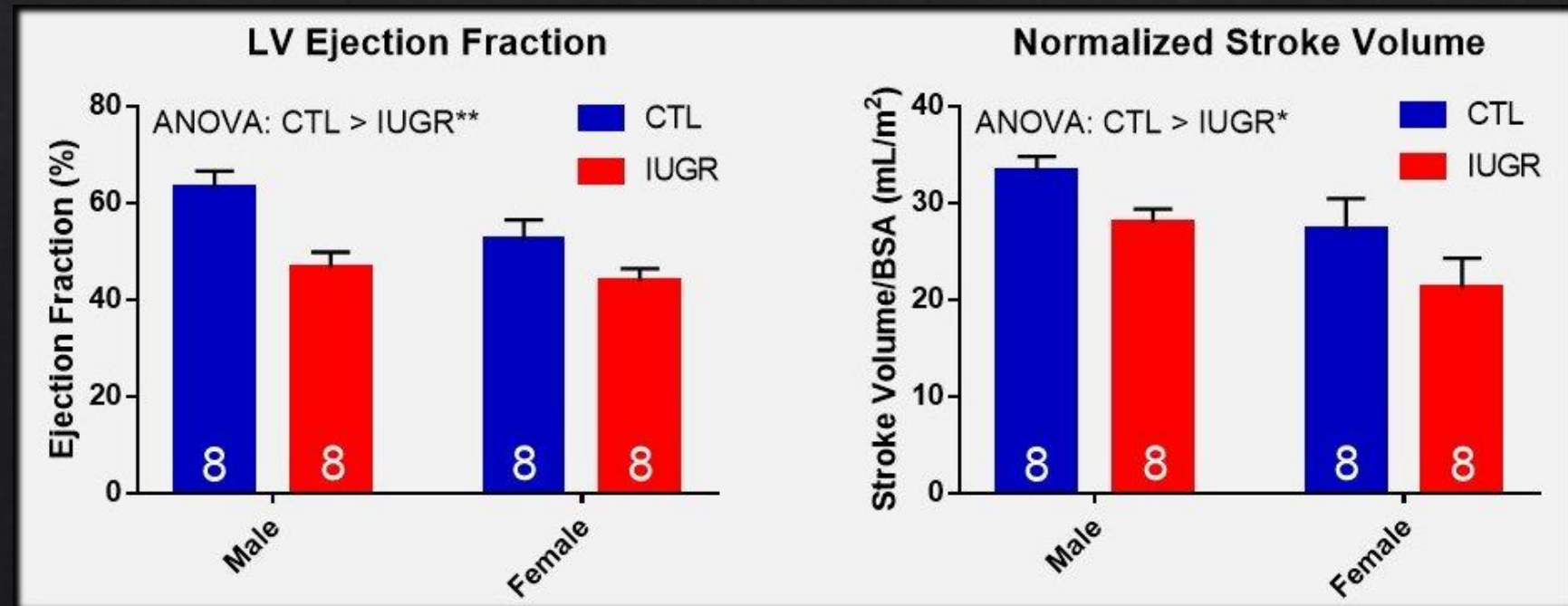


Baboon IUGR Model

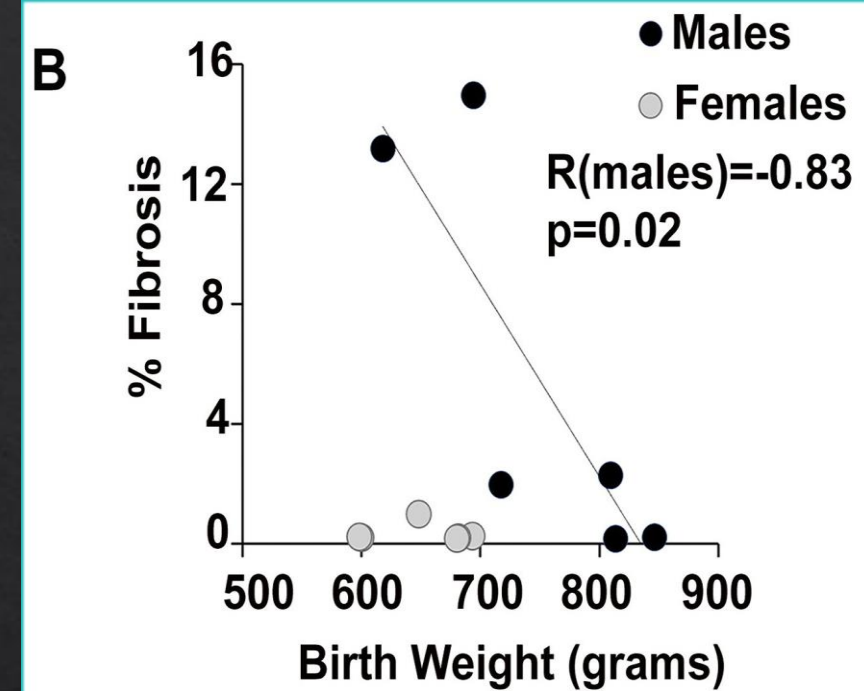
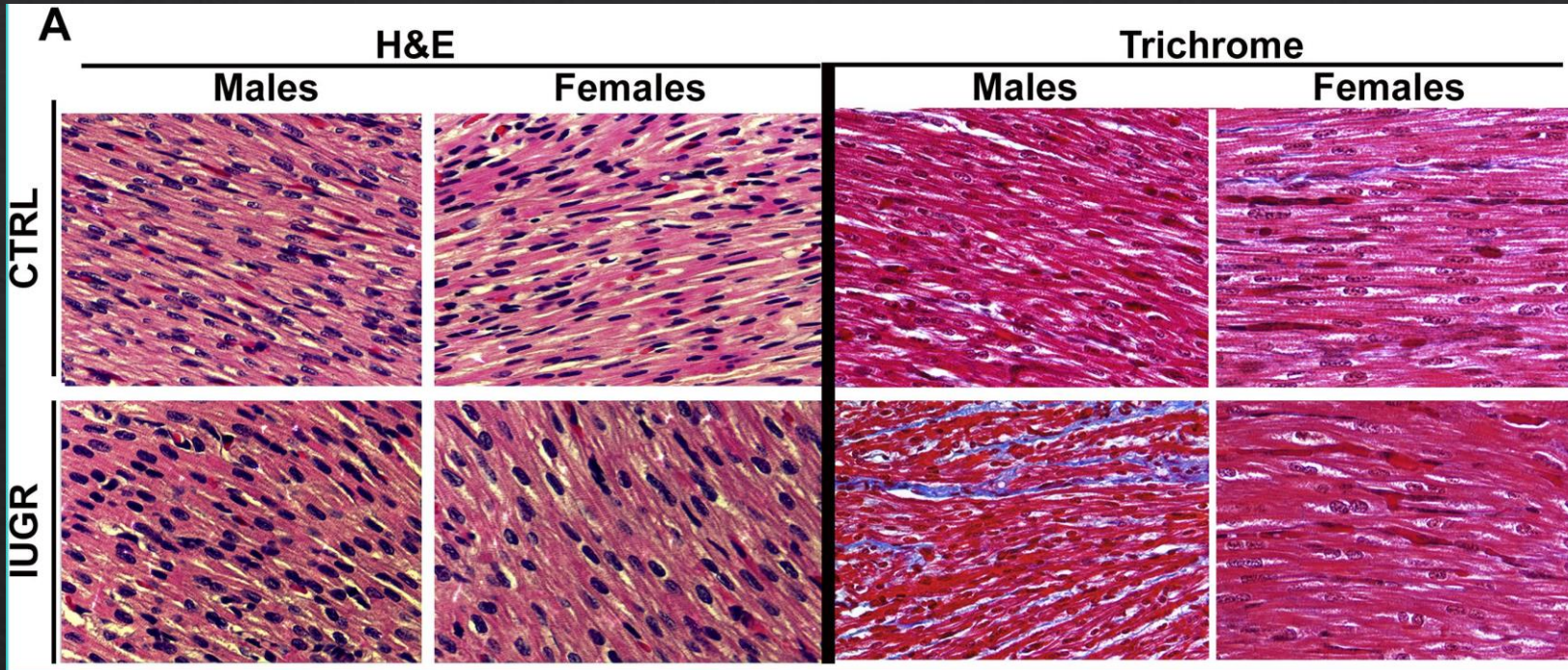
Male and female baboons received a 30% global reduction in food during fetal life and until weaning that resulted in a 12 - 14% reduction in birth weight.

	MALE CTL	FEMALE CTL	MALE IUGR	FEMALE IUGR	ANOVA
Number	8	8	8	8	-
Age (yr)	5.4 ± 0.5	5.7 ± 0.5	5.9 ± 0.4	5.5 ± 0.5	NS
Weight (kg)	19.5 ± 2.4	13.9 ± 0.7	21.6 ± 0.7	13.4 ± 0.7	M > F***
BSA (m ²)	0.55 ± 0.04	0.44 ± 0.02	0.60 ± 0.02	0.44 ± 0.01	M > F***

LV FUNCTION: No Sex Differences



Baboon Fetal Heart Tissue

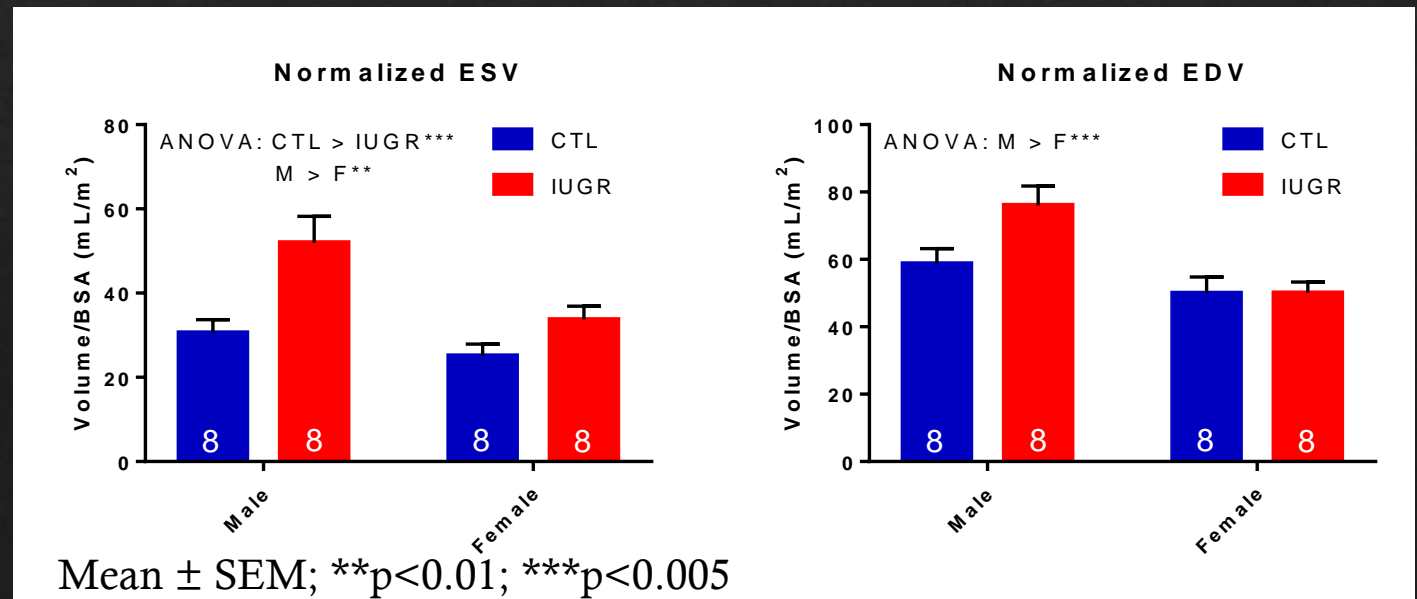
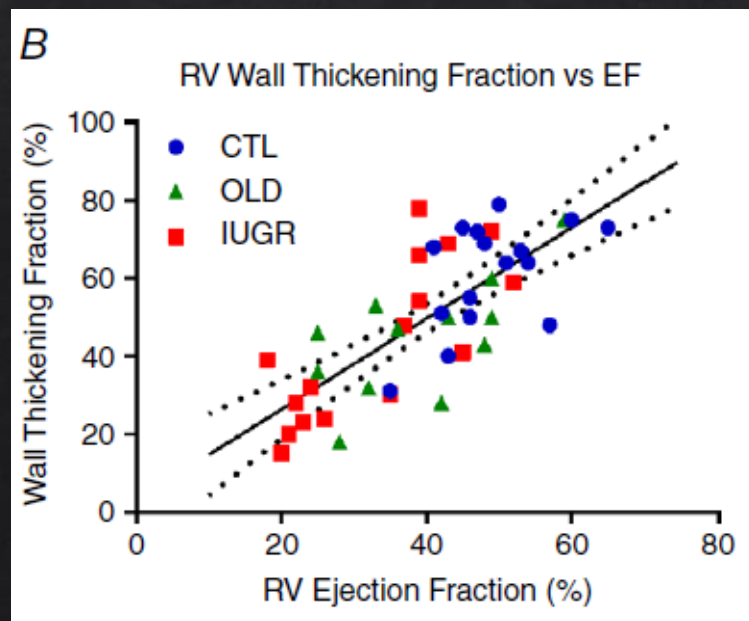
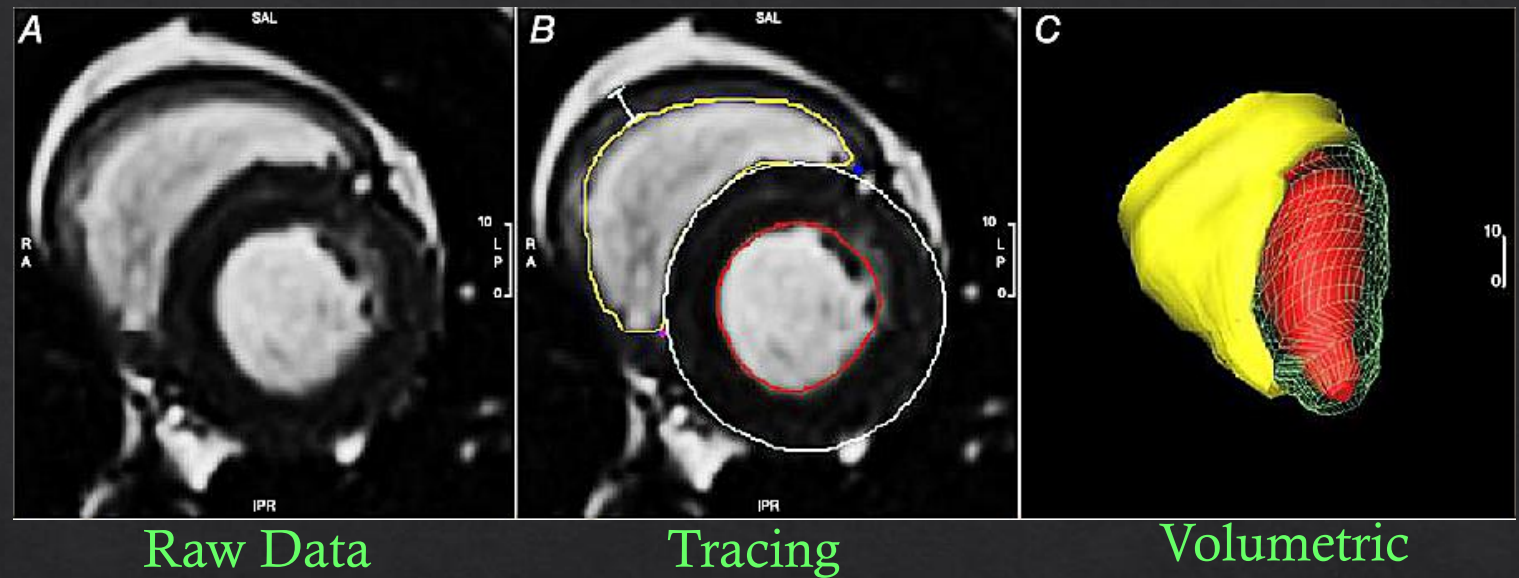
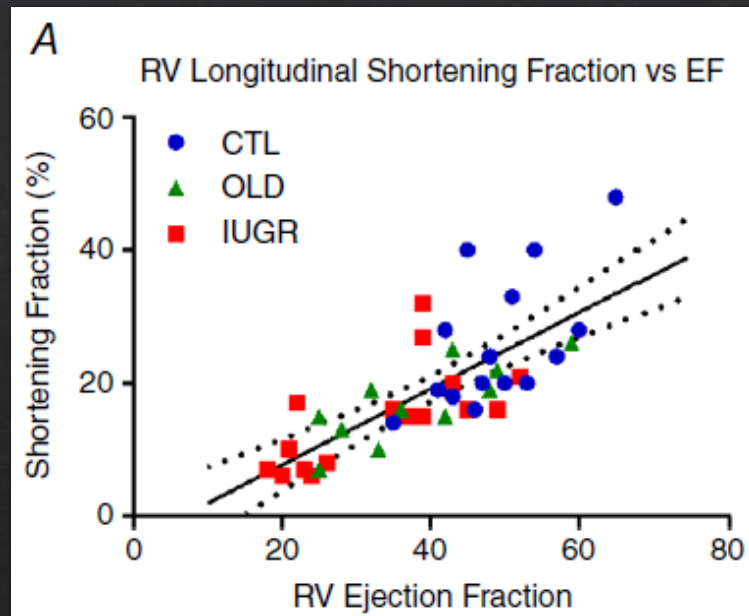


Histology of fetal hearts from male and female CTRL and IUGR baboons on day 165 of gestation.

A. H&E and Trichrome staining

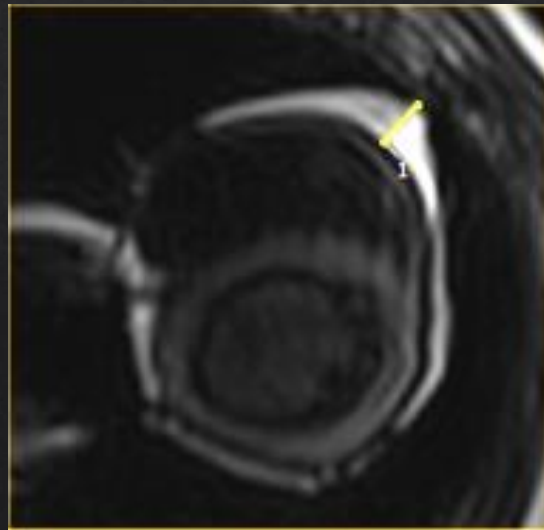
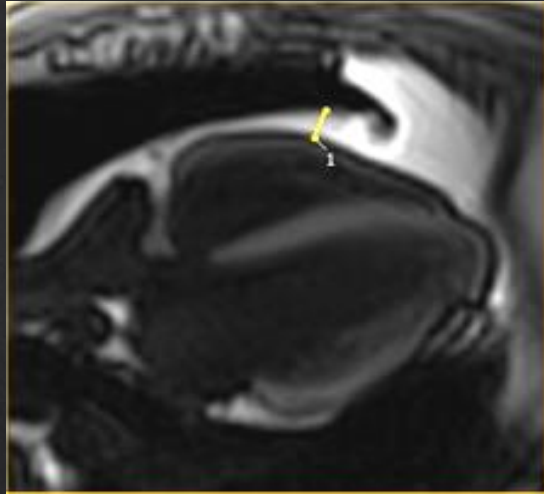
B. Correlation fibrosis and birth weight (n = 6 per group)

IUGR Baboon Right Ventricular (RV) Systolic Function

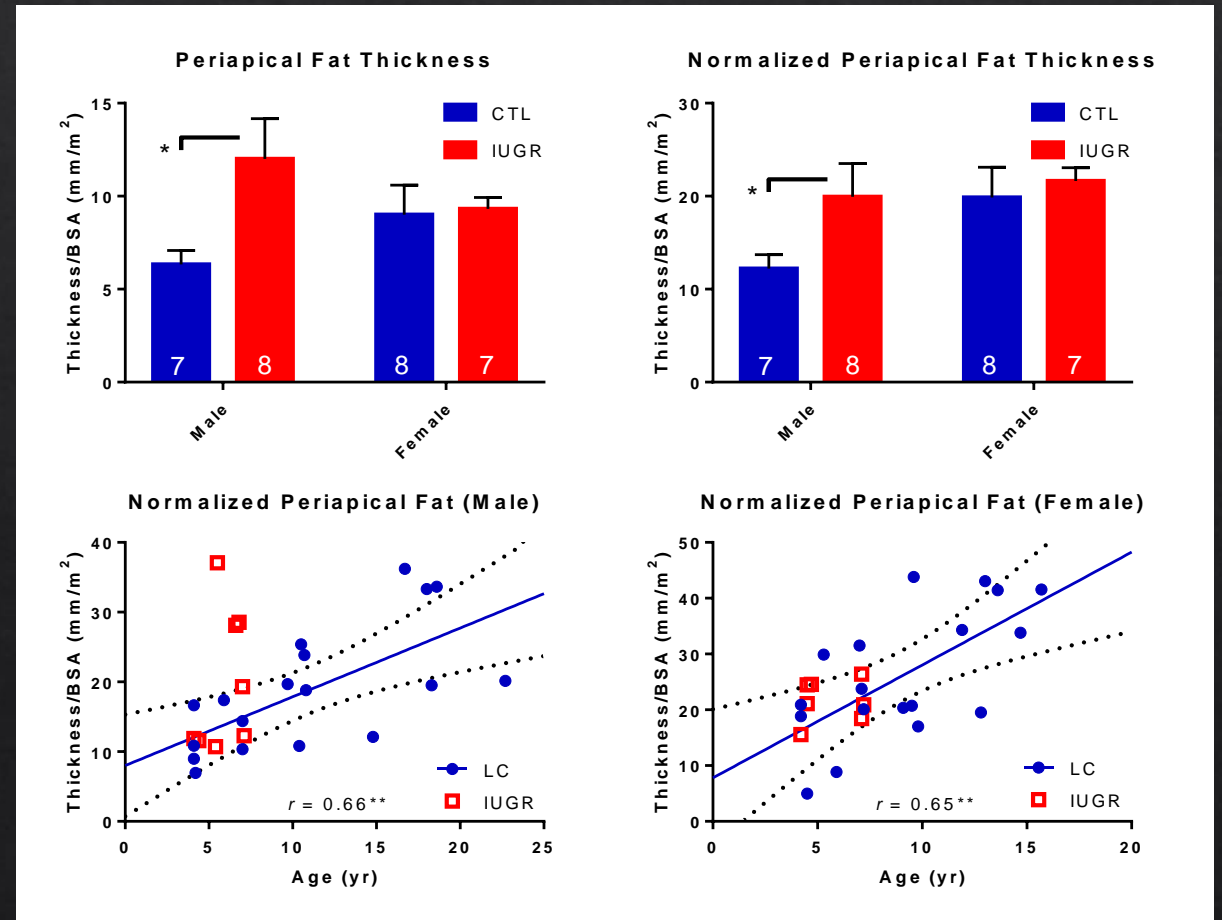


Pericardial Adiposity

Thickness of the pericardial fat layer was measured in a mid-ventricular short axis view.



Normalized pericardial fat thickness was increased in male IUGR baboons vs. CTL ($p=0.04$) but not females ($p = 0.32$).



Major Gaps

- ◆ Deploy more fetal and early imaging to develop a quantitative definition of IUGR in humans that is not exclusively dependent on fetal size.
- ◆ Explore relationships between imaging biomarkers, histological, RNAseq, lipidomic, metabolic, physiological, behavioral, and other data.
- ◆ Better understand the role of mitochondrial dynamics on adaptive capacity in programming.
- ◆ What kind of therapies can we develop?

Future directions

- ◆ Employ ^1H -MRS, 4D-Flow, Diffusion MRI methods and do them *in utero*
- ◆ Epigenetic clock (DNA methylation)
- ◆ Evaluate cardiac function under pharmacological stress conditions (i.e. adenosine or dobutamine)
- ◆ Expand to other developmental models, e.g. maternal obesity & diabetic pregnancy
- ◆ Develop machine learning approaches

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