Full title: Persistence of cardiac remodeling in preadolescents with fetal growth restriction

First author's surname and short title: Sarvari. Cardiac remodeling in fetal growth restriction.

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ABSTRACT

Background: Fetal growth restriction (FGR) affects 5-10% of newborns and is associated with increased cardiovascular mortality in adulthood. We evaluated if prenatal cardiovascular changes previously demonstrated in FGR persist into preadolescence.

Methods and Results: A cohort study of 58 FGR (defined as birth weight below 10th centile) and 94 normally grown fetuses identified *in utero* and followed-up into preadolescence (8-12 years-old) by echocardiography and 3D shape computational analysis. Compared with controls, FGR preadolescents had a different cardiac shape, with more spherical and smaller hearts. Left ventricular ejection fraction was similar among groups, while FGR had decreased longitudinal motion (decreased mitral annular systolic peak velocities: controls median 0.11 m/s (interquartile range 0.09-0.12) *vs* FGR 0.09 m/s (0.09-0.10), $p<0.01$) and impaired relaxation (isovolumic relaxation time: controls 0.21 ms (0.12-0.35) *vs* FGR 0.35 ms (0.20-0.46), $p=0.04$). Global longitudinal strain was decreased (controls mean -22.4% (SD 1.37) *vs* FGR -21.5% (1.16), $p<0.001$) compensated by an increased circumferential strain and with a higher prevalence of post-systolic shortening in FGR as compared to controls. These differences persisted after adjustment for parental ethnicity and smoking, prenatal glucocorticoid administration, preeclampsia, gestational age at delivery, days in intensive care unit, gender, age and body surface area at evaluation.

Conclusions: This study provides evidence that cardiac remodeling induced by FGR persists until preadolescence with findings similar to those reported in their prenatal life and childhood. The findings support the hypothesis of primary cardiac programming in FGR for explaining the association between low birth weight and cardiovascular risk in adulthood.

Key words: echocardiography, remodeling, pregnancy, pediatrics, fetal programming, fetal growth restriction.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of mortality in adults. CVD usually undergoes a long subclinical phase with risk factors already present from early stages of life. Accumulating evidence from a large number of epidemiological(1) and animal studies(2) demonstrated a strong association between low birth weight and CVD and mortality in adulthood. The main cause of low birth weight is fetal growth restriction (FGR) defined as birth weight below the 10th centile and affecting 5-10% of all pregnancies. However, the mechanistic link between low birth weight and cardiovascular risk is not well understood. Previous studies have suggested that obesity, diabetes mellitus, hypertension and dyslipidemia secondary to FGR might explain the association between low birth weight and CVD(1). However, it has also been postulated that primary cardiovascular remodeling might also mediate this increased CVD and mortality in adults(3).

FGR is usually caused by placental insufficiency, and it is associated with sustained hypoxia, undernutrition and cardiac pressure/volume overload, which are thought to result in significant changes in fetal cardiac shape and function. Studies *in utero* have demonstrated that fetuses with FGR have more spherical hearts with reduced longitudinal motion and impaired relaxation(4-6) together with altered cord blood natriuretic peptides and troponin(4) concentrations. We previously demonstrated that cardiovascular remodeling persisted postnatally up to 5 years of age.(3) However, whether and how these findings persist into later stages of life is still unclear. Population studies in childhood(7) and adolescence(8) have shown positive correlation between birth weight, cardiac dimensions and left ventricular (LV) mass. Data from a Swedish cohort showed smaller ventricular and vascular dimensions with preserved cardiac mass and function in 19 young adults born with severe FGR.(9, 10) Finally, recent data from the Young Finns Study suggest subtle increases in heart size with normal sphericity indices, diastolic function and blood pressure in adults born small-for-gestational age at term.(11) These controversial results might reflect small sample sizes and differences in case mix, since a high proportion of these patients were identified after birth and consequently were mainly constitutionally small-for-gestational age cases (not truly growth restricted). Furthermore, evaluation of cardiac function was mainly performed by standard two-dimensional (2D) echocardiography. However, novel technologies such as deformation analysis and

computational analysis of three-dimensional (3D) left ventricular shape have enabled to reveal significant changes in cardiac structure and function in young adults born preterm.(12) These types of techniques have not been previously used assess cardiac geometry and function in FGR.

In this study, we aimed at assessing and characterizing cardiovascular remodeling into preadolescence by means of 2D and 3D echocardiography, LV shape analysis and speckle-tracking imaging in 58 FGR cases identified from prenatal life and 94 controls with appropriate fetal growth.

METHODS

Study Populations and Study Protocol

A prospective cohort study including 58 subjects with FGR and 94 normally grown fetuses identified *in utero* and followed up into preadolescence. FGR was defined by estimated fetal weight and birth weight below the 10th centile according to local standards. Controls were normally grown fetuses with birth weight above the 10th centile.(13) Exclusion criteria included congenital malformations/chromosomal defects, fetal infection or monochorionic pregnancies. The study protocol consisted of a medical examination, echocardiogram, blood pressure measurement and carotid ultrasound. It was approved by the local Ethics Committee and written parental consent was obtained for all study participants.

Echocardiography

Each individual underwent a comprehensive echocardiogram using a Vivid E9 (General Electric Healthcare) with a 2.5 MHz (M5S) and an active matrix 4D volume phased array transducer (4V-D). Standard echocardiographic views were obtained with the patient in left lateral decubitus position and images were analyzed offline with commercially available software (EchoPac, General Electric Healthcare, version 108.1.6). *Cardiac dimensions* were measured according to the recommendations of the American Society of Echocardiography(15), and 2D sphericity indices were calculated as base-to-apex length/basal diameter. Relative wall thickness was calculated as (posterior LV wall thickness*2)/end-diastolic LV cavity diameter. LV volumes were estimated from 3D datasets by intrinsic automated border detection in the 4D autoLVQ. RV end-diastolic and end-systolic areas were calculated by planimetry from 2D 4-chamber view. Left and right atrial areas were measured at maximum distension. *Systolic function* was assessed by LV cardiac output ejection fraction measured by conventional 2D echocardiogram and also estimated from the 3D datasets Mitral and tricuspid longitudinal ring displacements were assessed by M-mode and real time tissue Doppler from an apical 4-chamber view. . LV and RV strain were obtained from 2D speckle-tracking offline analysis (2D strain, EchoPac, General Electric, Milwakee, USA). When post systolic shortening was present, the post systolic index (PSI) was calculated as the average of (peak post systolic strain-peak systolic

strain)/ peak systolic strain*100 in 18 longitudinal LV segments. The presence of post-systolic shortening was also assessed by M-mode from a parasternal long-axis view defined as late inward motion (after aortic valve closure) of the LV septum/posterior wall in M-mode. *Diastolic function* was assessed by E/A ratio, tissue Doppler early diastolic (e′) peak myocardial velocities and isovolumic relaxation times.

Left ventricular shape analysis

From the segmentation of the LV from the 3D datasets, the endocardial surfaces in end-diastole (represented by 362 vertices with known point correspondences) were extracted. The analysis of the shape variability between the groups was carried out using Principal Component Analysis (PCA) applied to the end-diastolic meshes.

Vascular Assessment

Systolic and diastolic blood pressures were normalized into Z-scores based on international standards for children.(16) Right and left carotid arteries were scanned according to a standardized protocol(17) with a 13-MHz linear-array transducer using a Vivid q (General Electric Healthcare, Horten, Norway) ultrasound system. Carotid intima-media thickness (IMT) measurements were performed offline based on a trace method (EchoPAC, General Electric Healthcare, version 108.1.x).

Statistical Analysis

Stata 14.0 (StataCorp. LP, College Station, TX) was used for statistical analysis. Study groups were described using mean ± SD, median (interquartile range) or frequencies and compared by Student's t-test, Wilcoxon-MannWhitney and chi-square tests as appropriate. Umbilical and middle cerebral arteries were normalized into z-scores(18) according to gestational age at scan. Cardiac and vascular comparisons between the study and control groups were adjusted for parental ethnicity and smoking, prenatal glucocorticoid administration, preeclampsia, gestational age at delivery, days in intensive care unit, gender, age and body surface area at evaluation by linear, quantile or logistic regression analysis. The analysis of the shape variability between the groups was carried out using

PCA applied to the end-diastolic meshes. Using the elbow rule, the dimensionality of the shape space was reduced to 20 dimensions and the differences in shape variation along the first 20 principal components were analyzed using two-sided t-test. A subanalysis subdividing the population according to prematurity was also performed for all cardiovascular results (Supplemental data). Reproducibility for 2D-strain analysis was performed in 10 subjects and results are shown in the supplemental data. All reported P-values are 2-sided.

RESULTS

Baseline, perinatal and follow-up characteristics

Baseline and perinatal characteristics are shown in Table 1. The study groups were similar in terms of parental characteristics. As expected, FGR cases showed worse feto-placental Doppler, higher prevalence of preeclampsia, lower gestational age at delivery, Apgar score and umbilical artery pH, and longer stay in the neonatal intensive care unit as compared to controls. According to the study design, the prevalence of spontaneous prematurity was higher in the control group, while most preterm deliveries in the FGR group were medically induced due to severe growth restriction or placental insufficiency.

Characteristics at the time of the present study are shown in Table 2. The age range was 8 to 12 years. At the time of evaluation, FGR cases showed lower height, weight and body surface area, with similar results for body mass index as compared to control subjects. Pubertal state and sedentary activities were similar among groups. All subjects were asymptomatic, and none of them used medication at the time of the cardiovascular evaluation. There were no patients with pulmonary hypertension or chronic lung disease with the exception of asthma (controls: 3% vs FGR 5%, p=0.62).

Cardiac morphometry and function

Echocardiographic results of the study populations are shown in Table 3 and Figures 1-2. FGR cases presented shorter, wider and more spherical ventricles as compared to controls. LV myocardial wall thicknesses and atrial dimensions were similar in the study groups. While LV ejection fraction and 2D cardiac output were similar among groups, 3D analysis revealed a significant decrease cardiac output in the FGR cases as compared to controls. FGR cases showed a reduced mitral longitudinal motion by tissue Doppler. RV fractional area change and tricuspid longitudinal motion were similar in FGR and controls. LV and RV global longitudinal strain was significantly decreased while LV circumferential strain was increased in FGR as compared to controls. FGR cases also showed a higher prevalence of post-systolic shortening as measured by M-mode and 2D speckle-tracking. While post-systolic shortening was sometimes present in controls, it was mostly confined to the basal septum whereas in FGR, it was more prevalent in the basal lateral wall resulting in a higher

PSI in FGR. FGR cases presented signs of diastolic dysfunction with prolonged LV and RV isovolumic relaxation times.

Left ventricular shape analysis

Principal component analysis revealed that the first 4 PC accounted for 95.3% of the variance in LV size and geometry within the study population (Figure 3): PC 1 representing changes in overall ventricular size; PC 2 and 3 representing changes of the position of the apex with respect to the mitral valve; and PC 4 corresponding to the change in LV sphericity, manifested mostly as regional changes in septal geometry. While changes in apex orientation were not statistically significant, we observed significant differences between groups in the first and fourth PC with p-values of <0.001 and 0.042, respectively, corresponding to a smaller and more spherical LV in FGR individuals as compared to controls. PC 5 (related to apical sphericity) and 6 (lateral sphericity) added only 1.7% more explanatory power and were not different.

Vascular Assessment

There was a non-significant trend to higher blood pressure values in FGR as compared to controls (Table 4). Results on carotid mean IMT were similar among the study groups.

DISCUSSION

This study demonstrates for the first time the persistence of cardiac remodeling into preadolescence in FGR cases. Preadolescents with FGR showed non-hypertrophic smaller and more spherical ventricles with reduced longitudinal motion and deformation as well as impaired relaxation. These findings were confirmed by both 2D and 3D echocardiography. We have previously postulated that this type of cardiac remodeling is most likely the result of changes in cardiac development, induced by sustained *in utero* pressure/volume overload, hypoxia and undernutrition secondary to placental insufficiency.(3) While in postnatal conditions the resulting increased wall stress on the myocardial fibers should trigger a compensating hypertrophic response, intrauterine remodeling seems different, likely due to plasticity of the myocardium together with sustained hypoxia and undernutrition leading to persistent shape changes rather than hypertrophy. Under these circumstances, the FGR heart might respond by an increase in the local radius of curvature, which consequently leads to a more spherical shape and a switch from longitudinal to circumferential function. A more globular ventricle, with possibly an altered fiber architecture induced by the wall stress, may not be as efficient as a normally developed heart. The shape alteration might not have an important influence on the wall stresses at rest, but believe it would alter the response to a pressure challenge. The results of the present study are in line with previous studies demonstrating more globular hearts with impaired longitudinal motion and relaxation in FGR fetuses,(5, 19) infants (20) and children.(3) Our data is also partially in agreement with recent reports in late childhood,(7, 21) adolescence(8) and youth,(9, 10) suggesting smaller cardiovascular dimensions and mass with preserved cardiac function (assessed by 2D and Doppler) in FGR. These previous studies on adolescents and young FGR cases did not evaluated ventricular shape. We believe that the use of 3D shape analysis and the large sample size of cases identified prenatally has enabled us to further demonstrate changes in ventricular sphericity and myocardial dysfunction in FGR.

Our study also provides evidence of decreased LV longitudinal deformation compensated by an increased circumferential strain. These results are consistent with previous data in infancy demonstrating reduced longitudinal deformation,(22) and in early childhood showing reduced longitudinal motion and increased myocardial thickening in FGR.(23) Finally, we could also

demonstrate a higher prevalence of post-systolic shortening in FGR, reflecting regional differences in myocardial deformation.(24) Interestingly, in FGR, post-systolic shortening was found in both the LV basal septal as well as in the LV basal lateral wall. The presence of post-systolic shortening in the basal septum has also been described *in utero* in 57% of FGR cases in relation to poor perinatal outcome and can be found in some normal adults and is related to pressure overload resulting in higher wall stress in the septum, being the flattest structure.(19, 25) However, post-systolic shortening in the lateral wall is likely due to the sphericity change in the LV where a more curved septum would have reduced wall stresses as compared to the lateral wall in the presence of normal blood pressure (Figure 3). The presence of post-systolic deformation can also explain the LV strain gradient from base to apex reported in FGR infants.(22)

Regarding vasculature, the present study could not demonstrate the persistence of significant changes in vascular structure and function in FGR preadolescents, although a non-significant trend to higher blood pressure values could be observed in FGR cases. While most studies agree that blood pressure and intima-media thickness are consistently increased in neonates and children with FGR(3, 26, 27), literature on vascular structure and function in FGR adolescents and young adults is controversial. Large population studies seem to confirm a significant inverse correlation between low birth weight and blood pressure in people of all ages.(27-29) However, the fact that this association has been reported to be of little magnitude (an increase of 1-4 mmHg) could explain the non-significant results of the present study and other previous reports with relatively low sample sizes.(11, 30) Regarding vascular wall thickness, there is no data from large population studies, but recent cohort studies have reported normal(31) or increased IMT(32) in adolescents and young adults with FGR. These inconsistencies could be explained by differences in populations and FGR definition or by the strong impact of postnatal environmental factors (mainly variations in the dietary consumption of omega-3) on IMT that could enforce the effect of prenatal factors on vascular structure.

This study has some strengths and limitations that merit commenting on. The present study represents a follow-up of a well-characterized cohort of FGR identified in fetal life. Modern prenatal ultrasonographic information has demonstrated to improve the definition of truly intrauterine growth restricted cases.(33) The cardiac assessment of this population was comprehensively conducted

including 2D and 3D echocardiography together with LV shape analysis and deformation imaging. However, we acknowledge the lack on studies validating 3D calculations invasively: The changes reported here are subclinical with most cardiovascular measurements lying within normal ranges.. Despite these differences being recognized as potential cardiovascular risk factors, their long-term persistence and association with adult cardiovascular disease remains to be proven. Recent data from the Young Finns Study suggest that only subtle cardiac size increases with preserved function are present in FGR adults.(11) However, this study exclusively used standard 2D echocardiography including cases born at term (usually mild FGR cases) with no information about prenatal Doppler. These facts might have limited their potential capability to detect subtle cardiac structural and functional changes. Therefore, we believe that future studies are warranted to further assess the persistence of cardiac remodeling and dysfunction in older subjects who suffered FGR.

Additionally, we acknowledge that our study was not designed to assess the effect of other prenatal, neonatal and postnatal factors on cardiovascular function. However, all cardiovascular results were adjusted by several potential confounders such as parental ethnicity and smoking, prenatal glucocorticoids, preeclampsia, gestational age at delivery, days in intensive care unit, gender, age and body surface area. As prematurity has recently been demonstrated to be a strong determinant of cardiovascular structure and function in adulthood,(12) we further analyzed the cardiovascular results taking into account prematurity (see Supplemental data). While preterm FGR cases (also presenting more severe placental insufficiency) showed the most prominent cardiac remodeling, echocardiographic changes were also significant in mild FGR born at term. 3D shape analysis also revealed that prematurity only had an influence in the first shape PC (size), but not on the other components (sphericity and apex rotation) associated to FGR (see Supplementary data). In addition, the pattern of remodeling here shown for FGR with non-hypertrophic spherical ventricles differs from the increased cardiac mass reported in adults born preterm,(12) also suggesting an independent effect of FGR on cardiac structure and function. We also acknowledge that future studies might reveal non-obvious confounders not considered in the design and analysis of this study that might have affected the present results. Finally, the potential interaction between metabolic and cardiac programming in the risk of cardiovascular disease remains to be elucidated.

In conclusion, this study demonstrates for the first time the persistence of cardiac remodeling in FGR at preadolescent age. These findings are consistent with the hypothesis of primary cardiac programming in FGR for explaining their increased cardiovascular risk in adulthood. From a clinical perspective, the existence of fetal cardiac remodeling in FGR provides important opportunities to improve cardiovascular health in a relevant proportion of the general population, as FGR affects 7-10% of it. The importance of early identification and the impact of interventions in pediatric risk factors for cardiovascular disease are now well recognized. Recent reports have demonstrated the beneficial effect of postnatal diet (mainly breastfeeding and dietary intake of omega-3)(33, 36) on cardiovascular remodeling among FGR individuals. Given the high prevalence of FGR, lifestyle policies could have a high impact in public health by potentially improving the long-term cardiovascular health of these children.

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FIGURE LEGENDS

Figure 1. Echocardiographic images in a control and a fetal growth restricted (FGR) subject. Top: Two-dimensional apical 4-chamber views at end diastole illustrating more spherical cardiac shape in FGR. Middle: Mitral longitudinal motion by M-mode demonstrating reduced mitral annular plane systolic excursion (MAPSE) in FGR. Bottom: Tissue Doppler spectrum illustrating lower mitral systolic (s') and early diastolic (e') myocardial peak velocities in FGR.

Figure 2. Longitudinal 2D speckle-tracking echocardiographic studies in a control subject and a fetal growth restricted (FGR) subject, illustrating reduced global longitudinal strain (GLS) and presence of post-systolic shortening (PSS, yellow arrow) in the basal lateral segment of the left ventricle in FGR.

Figure 3. Cardiac shape variability within controls and fetal growth restricted (FGR) cases. **A**: Comparison of the different shape modes between FGR and controls, demonstrating the first and fourth principal components (PC) to be significantly different. **B**: Contribution of each shape component to explain the variability in the whole population showing that the first 6 PC explain over 97% of variability. **C**: Illustration of the interpretation of the first 4 PC of variation resulting from the principal component analysis. The shapes correspond to long axis and short axis views (seen from the mitral valve) with the red segment indicating the septum. In all the cases, the mean shape is at coordinate 0. The green and purple asterisks represent the mean shapes of the FGR and control populations within ±2 standard deviations (STD). The shaded overlays show an overlay of the extreme at the other side of the range.

Table 1. Baseline and perinatal characteristics of the study groups.

	Controls (n=96)	**FGR** (n=58)	P-value
Maternal characteristics			
Age, years	43.5 ± 4.59	42.6 ± 3.98	0.21
Non-caucasian ethnicity, %	5.21	12.3	0.11
Low socioeconomical status, %	33.3	45.6	0.26
Smoking, %	31.2	36.8	0.48
Prenatal feto-placental ultrasound			
Umbilical artery pulsatility index, z-score	-0.17 (-0.15-0.8)	4.49 (0.76-6.11)	<0.001
Middle cerebral artery pulsatility index, z-score	-0.18 (-1.21-0.75)	-1.84 (-2.66- -0.88)	0.01
Pregnancy complications			
Preeclampsia, %	2.08	24.1	<0.001
Gestational diabetes, %	4.35	8.77	0.27
Spontaneous preterm delivery or rupture of membranes, %	28.1	3.45	<0.001
Use of steroids in pregnancy, %	29	50	0.01
Perinatal data			
Birth weight, g	3190 (2315-3575)	1560 (1022-2540)	<0.001
Birth weight percentile	54.5 (34-81)	0 (0-2)	<0.001
Gestational age at delivery, weeks	38.4 (34.3-40)	34.3 (31.5-39.2)	0.01
Preterm delivery, %	34.4	60.3	0.002
Umbilical artery cord pH	7.30 (7.24-7.35)	7.24 (7.17-7.27)	<0.001
Major neonatal morbidity*, %	9.78	18.5	0.13
Days in neonatal intensive care unit	0 (0-5.5)	17.5 (3-90)	<0.001

Data expressed as mean±SD, median (interquartile range) or %.

Right column shows P-values for Student's t-test, Wilcoxon-MannWhitney or chi-square tests as appropriate.

FGR indicates fetal growth restriction.

*Major neonatal morbidity defined by the presence of bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy, persistent ductus arteriosus or sepsis.

Table 2. Anthropometric characteristics of the study groups at follow-up.

	Controls (n=96)	**FGR** (n=58)	P-value
Age, years	11.4 (9.03-12.3)	10.1 (8.64-11.1)	<0.001
Male gender, %	48.9	39.7	0.26
Height, cm	144 ± 12.8	139 ± 11.2	0.01
Weight, g	39.6 ± 9.90	36.2 ± 9.88	0.04
Body mass index, kg/m^2	18.8 (16.7-20.6)	18.2 (16.5-20.2)	0.54
Body surface area, m^2	1.25 ± 0.20	1.17 ± 0.20	0.03
Prepubertal state*, %	36.5	46.5	0.21
PAC-Physical activity score†	3.28 (2.80-3.62)	3.33 (2.77-3.87)	0.32

Data expressed as mean±SD, median (interquartile range) or %.

Right column shows P-values for Student's t-test, Wilcoxon-MannWhitney and chi-square tests as appropriate.

FGR indicates fetal growth restriction.

*Prepubertal state according to Tanner scale.

†Physical activity score according to PAC (Physical Activity Questionnaire for Older Children).

Table 3. Echocardiographic results of the study groups.

	Controls (n=96)	**FGR** (n=58)	adjusted p- value*
Left ventricular morphometry			
Base-to-apex length, mm	68.6 ± 6.47	64.1 ± 6.12	0.003
Basal diameter, mm	33.6 ± 2.98	34.5 ± 3.44	0.003
Sphericity index	2.05 ± 0.16	1.86 ± 0.16	<0.001
Relative wall thickness	0.36 ± 0.04	0.37 ± 0.05	0.55
Right ventricular morphometry			
Base-to-apex length, mm	65.1 ± 6.40	61.4 ± 6.42	0.01
Basal diameter, mm	30.3 ± 3.95	30.2 ± 3.44	0.32
Sphericity index	2.13 (2.01-2.26)	1.99 (1.88-2.18)	0.006
Atrial morphometry			
Lelft atrial area, cm^2	11.3 ± 2.38	10.7 ± 2.53	0.80
Right atrial area, cm^2	9.55 (8.6-11.5)	8.75 (7.6-10)	0.80
Systolic function			
Heart rate, bpm	81.3 ± 12.5	82.3 ± 8.68	0.57
LV cardiac output, L/min	3.67 ± 0.81	3.55 ± 0.81	0.83
LV ejection fraction, %	58.0 (56.1-60.4)	57.9 (56.6-61.7)	0.56
RV fractional area change, %	43.1 ± 5.37	43 ± 5.59	0.90
Mitral ring displacement, mm	15.8 ± 1.85	14.8 ± 1.80	0.07
Tricuspid ring displacement, mm	23.7 ± 2.37	22.9 ± 2.88	0.70
Mitral s', m/s	0.11 (0.09-0.12)	0.09 (0.09-0.10)	0.01
Tricuspid s', m/s	0.14 ± 0.01	0.13 ± 0.01	0.39
LV global longitudinal strain, %	-22.4 ± 1.37	-21.5 ± 1.16	<0.001
LV global circumferential strain, %	-22.6 ± 2.65	-24.2 ± 2.55	0.004
RV global longitudinal strain, %	-29.4 ± 3.47	-27.6 ± 3.45	0.005

Presence of post-systolic shortening[†], %	19.5	33.3	0.04
Post-systolic index[‡]	0.66 (0.33-1.02)	1.47 (0.97-1.97)	<0.001
Diastolic function			
Mitral E/A ratio	1.91 ± 0.40	2.07 ± 0.40	0.07
Mitral e', m/s	0.21 ± 0.03	0.20 ± 0.03	0.84
LV isovolumic relaxation time, s	0.50 (0.40-0.59)	0.54 (0.45-0.62)	0.04
Tricuspid E/A ratio	2.04 ± 0.36	1.95 ± 0.31	0.56
Tricuspid e', m/s	0.17 ± 0.03	0.16 ± 0.03	0.14
RV isovolumic relaxation time, s	0.21 (0.12-0.35)	0.35 (0.20-0.46)	0.004
Left ventricular 3D echocardiography			
End-diastolic volume from 3D echo, mL	84.0±18.2	75.5±17.9	0.67
Cardiac output from 3D echo, L/min	3.50 (3.10-4)	3.20 (2.80-3.90)	0.049
Ejection fraction from 3D echo, %	56.8 ± 2.90	57.5 ± 3.95	0.91

Data expressed as mean ± SD, median (interquartile range) or %.

*P-values for regression analysis adjusted by parental ethnicity and smoking, prenatal glucocorticoid administration, preeclampsia, gestational age at delivery, days in intensive care unit, gender, age and body surface area at evaluation.[†] by M-mode. [‡]by 2D speckle-tracking.

FGR indicates fetal growth restriction. LV indicates left ventricular. RV indicates right ventricular. 2D indicates two-dimensional. 3D indicates three-dimensional. E indicates early diastolic inflow. A indicates atrial inflow. s' indicates myocardial peak velocity in systole. e' indicates myocardial peak velocity in early diastole.

Table 4. Vascular results of the study groups.

	Controls (n=96)	**FGR** (n=58)	adjusted p-value*
Systolic blood pressure, mmHg	107 ± 1.14	109 ± 1.51	0.31
Systolic blood pressure, z-scores	0.29 ± 1.10	0.67 ± 1.01	0.14
Diastolic blood pressure, mmHg	61.9 ± 8.01	63.6 ± 9.20	0.41
Diastolic blood pressure, z-scores	-0.02 (-0.39 – 0.41)	0.19 (-0.17 – 0.53)	0.41
Carotid intima-media thickness, mm	0.45 ± 0.04	0.45 ± 0.03	0.81

Data expressed as mean±SD or median (interquartile range).

*P-values for regression analysis adjusted by parental ethnicity and smoking, prenatal glucocorticoid administration, preeclampsia, gestational age at delivery, days in intensive care unit, gender, age and body surface area at evaluation.

FGR indicates fetal growth restriction.

Figure 1.

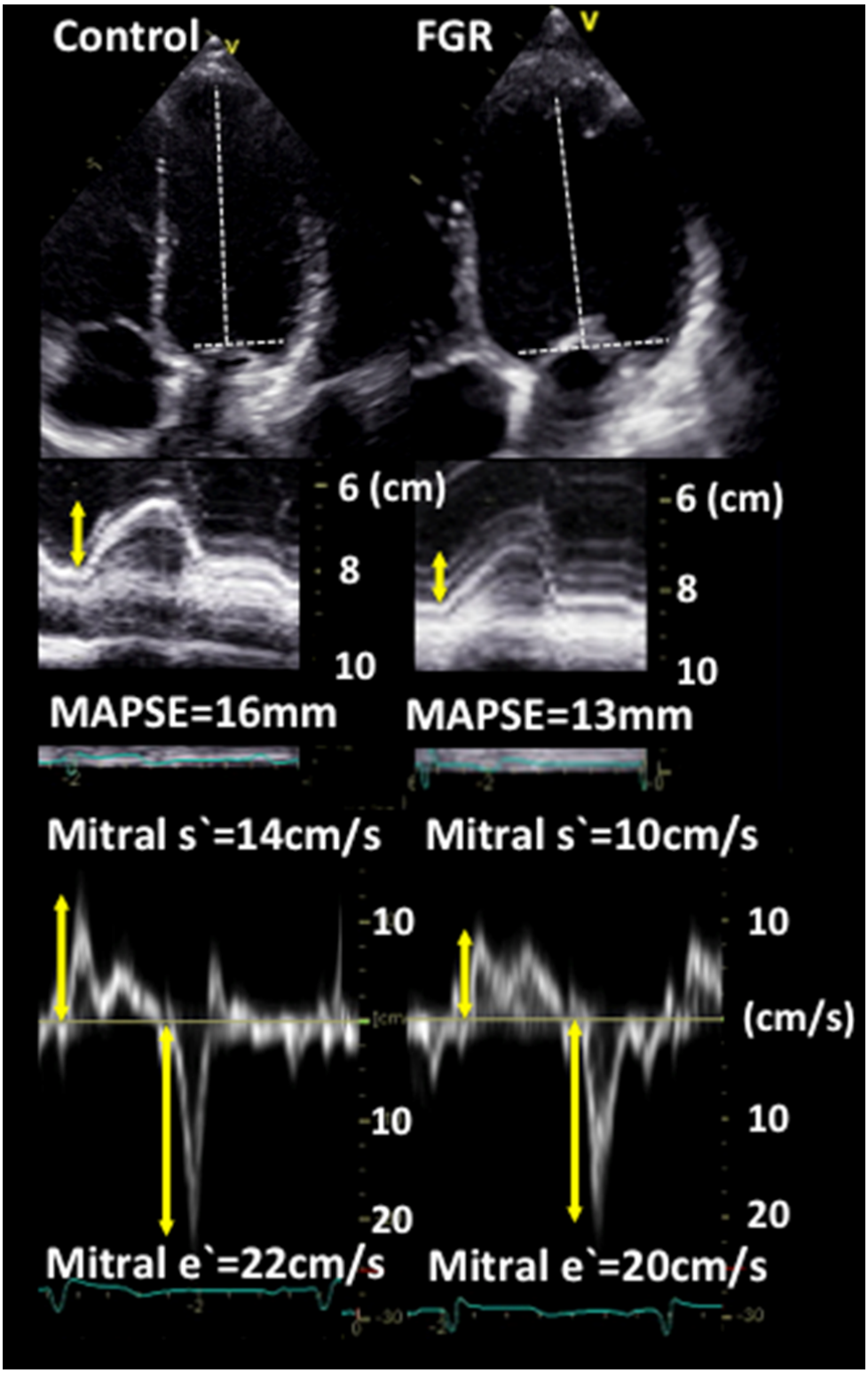

Control
FGR
6 (cm)
8
10
6 (cm)
8
10
MAPSE=16mm
MAPSE=13mm
Mitral s`=14cm/s
Mitral s`=10cm/s
10
10
(cm/s)
10
10
20
20
Mitral e`=22cm/s
Mitral e`=20cm/s

Figure 2.

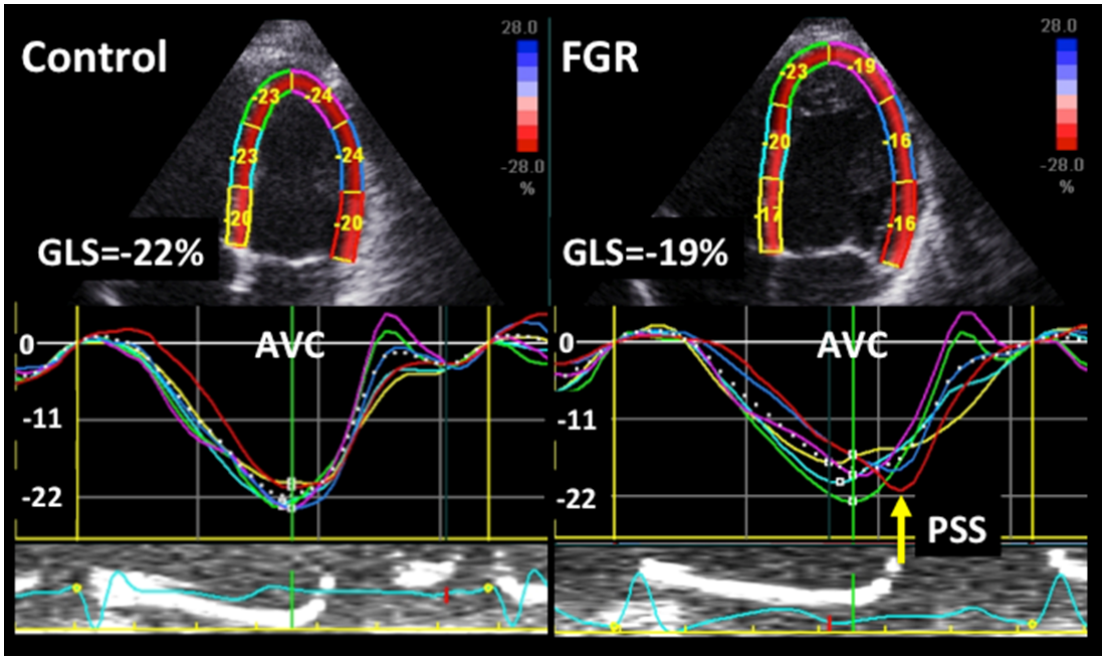
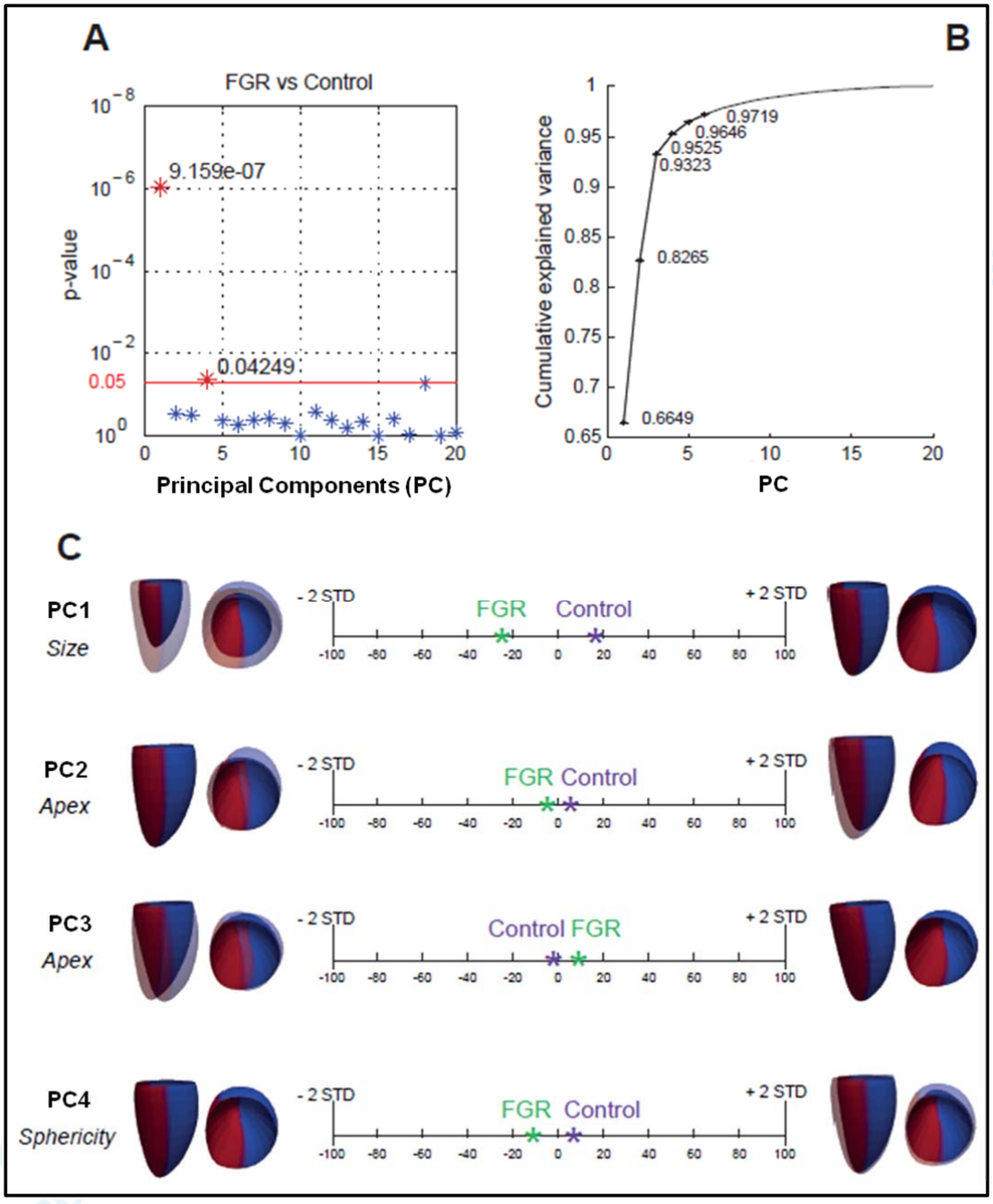

Control
28.0
-28.0
%
-23
-24
-23
-24
-20
-20
GLS=-22%
0
AVC
-11
-22
FGR
28.0
-28.0
%
-23
-19
-20
-16
-17
-16
GLS=-19%
0
AVC
-11
-22
PSS

Figure 3.


A
FGR vs Control
p-value
9.159e-07
0.04249
0.05
Principal Components (PC)
B
Cumulative explained variance
0.9719
0.9646
0.9525
0.9323
0.8265
0.6649
PC
C
PC1
Size
PC2
Apex
PC3
Apex
PC4
Sphericity
- 2 STD
+ 2 STD
FGR
Control