

# Cardiac ventricular performance in the appropriate-for-gestational age and small-for-gestational age fetus: relation to regional cardiac non-uniformity and peripheral resistance

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**KEYWORDS:** Diastolic function, Fetal left cardiac ventricle, Ventricular remodeling

## ABSTRACT

**Objective** To investigate the relationship between parameters of diastolic function, loading conditions and remodeling of the left ventricle in the appropriate-for-gestational age and small-for-gestational age fetus.

**Methods** Two-dimensional echocardiographic left ventricular images were digitized in 24 appropriate-for-gestational age and 14 small-for-gestational age fetuses. The maximal short axis and long axis were measured. The left ventricular contour was divided into 12 segments. The changes in whole left ventricular cavity area were calculated for ventricular global area change assessment. The coefficient of variation for segmental fractional area change was calculated for the evaluation of left ventricular regional wall motion non-uniformity.

**Results** Mean left ventricular long axis/short axis ratio in the small-for-gestational age fetus ( $1.11 \pm 0.08$ ) was smaller ( $P < 0.01$ ) than in the appropriate-for-gestational age fetus ( $1.75 \pm 0.26$ ). Mean fractional area change in the small-for-gestational age fetus was larger ( $P < 0.01$ ) than in the appropriate-for-gestational age fetus ( $37.8 \pm 17.6\%$  vs.  $21.1 \pm 9.9\%$ ). Mean left ventricular global area change in the small-for-gestational age fetus was smaller ( $P < 0.05$ ) than in the appropriate-for-gestational age fetus ( $53.2 \pm 7.4\%$  vs.  $61.5 \pm 10.3\%$ ). Mean ventricular isovolumic relaxation time in the appropriate-for-gestational age fetus was shorter ( $P = 0.03$ ) than in the small-for-gestational age fetus ( $37 \pm 6$  ms vs.  $57 \pm 9$  ms). Mean transmitral E-wave/A-wave ratio in the small-for-gestational age fetus was smaller ( $P < 0.01$ ) than in the appropriate-for-gestational age fetus ( $0.69 \pm 0.08$  vs.  $0.80 \pm 0.08$ ). A negative correlation ( $P < 0.05$ ) was demonstrated between: (i) fractional area change and global area change in both small-for-gestational age ( $r = -0.62$ ) and appropriate-for-gestational age fetuses ( $r = -0.58$ ); (ii) umbil-

ical artery systolic/diastolic ratio and transmitral E-wave/A-wave ratio in both appropriate-for-gestational age ( $r = -0.58$ ) and small-for-gestational age ( $r = -0.60$ ) fetuses. A positive correlation existed between fractional area change and isovolumic relaxation time in the small-for-gestational age fetus ( $r = +0.72$ ;  $P < 0.01$ ).

**Conclusions** The changes in ventricular shape, wall motion, spatial non-uniformity and diastolic function in the small-for-gestational age fetus could be considered as adaptive changes, known as ventricular remodeling. It is proposed that the leading cause of ventricular remodeling in the small-for-gestational age fetus is chronic pressure overload due to increased placental vascular resistance.

## INTRODUCTION

Fetal echocardiographic studies utilizing two-dimensional (2D), M-mode and pulsed Doppler technology have become an important adjunct to the obstetric evaluation of high-risk pregnancies. Changes in Doppler cardiac and peripheral arterial flow velocity waveforms have been reported in small-for-gestational age (SGA) fetuses<sup>1,2</sup>. In the SGA fetus, reduced end-diastolic flow velocities in the fetal descending aorta and umbilical artery have been associated with increased peripheral vascular resistance<sup>3</sup>, and low peak systolic flow velocities have been demonstrated at the cardiac level, which may be the result of reduced volume flow (decreased preload), increased afterload or impaired contractility of the fetal myocardium<sup>2,4</sup>. Marked enhancement of the late diastolic (atrial) phase of ventricular filling has been observed in the SGA fetus, which was considered as indirect evidence of increased myocardial stiffness<sup>5</sup>.

Earlier, an increase in left ventricular (LV) isovolumic relaxation time was shown in the SGA fetus<sup>6</sup>. Left ventricular relaxation time and the rate of isovolumic relaxation are

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frequently used as indices of global LV function in the adult. Because these indices are determined by a variety of factors, such as ischemia<sup>7</sup>, inotropic state<sup>8</sup>, asynchrony<sup>9</sup> and loading conditions<sup>10</sup>, isovolumic relaxation time may reflect changes of these parameters. The role of these parameters in the regulation of diastolic function of the developing human heart is still undetermined.

Spatiotemporal uniformity of contraction and relaxation is now considered as one of the major determinants of ventricular function<sup>11</sup>. The role of LV regional non-uniformity in the development of diastolic abnormalities in the human adult heart has been demonstrated in the case of dilated cardiomyopathy and hypertensive diastolic dysfunction<sup>12,13</sup>. Both conditions are characterized by significant adaptive changes in LV form and function, reflecting cardiac remodeling. Recent investigations show that cardiac remodeling is a complex process resulting from an interaction between a mechanical factor (pressure or volume overload) that triggers adaptation, and numerous neurohormonal factors that are capable of modifying the cardiac phenotype and cardiomyocyte function<sup>14</sup>.

Significant changes in heart architecture, which may lead to regional modification of contractile uniformity, have been demonstrated as a result of chronic alterations in loading conditions in the chick embryo<sup>15</sup>. The adaptive changes in fetal cardiac structure and function as a result of changes in loading conditions are complex because of continuing myocyte proliferation, as well as structural and functional development.

The objective of the present study was to investigate the relationship between parameters of fetal ventricular diastolic function, ventricular loading conditions, fetal ventricular geometric and wall movement non-uniformity parameters, with the latter serving as indices of cardiac remodeling in both appropriate-for-gestational age (AGA) and SGA fetuses, with emphasis on the left ventricle.

## METHODS

Between 1 October 1997 and 1 March 1999, a total of 49 outpatients from the Department of the Mother and Child Institute, Yekaterinburg, consented to participate in the study. This selection was determined by willingness of the women to participate in the study and the availability of equipment. In each case, there was a singleton pregnancy. Pregnancy duration was determined from the last menstrual period and confirmed by sonographic measurement of the biparietal diameter between 14 and 18 weeks' gestation. Pregnancy was uneventful in 31 out of the 49 women. A satisfactory image of the LV endocardium was obtained in 24 of 31 (77.4%) women. Pregnancy duration in this subset at the time of the investigation was between 29 and 40 weeks (median, 35 weeks). Fetal upper-abdominal circumference was always between the 10th and 90th percentiles<sup>16</sup>. There were no structural abnormalities. All women in this subset delivered at term.

Small-for-gestational age, as expressed by an upper-abdominal circumference below the 5th percentile<sup>16</sup>, was diagnosed in the remaining 18 pregnancies. Umbilical artery

end-diastolic flow velocities were always reduced or absent. Satisfactory recordings of the LV endocardium were obtained in 14 women (77.7%). Pregnancy duration at the time of the recording was between 29 and 39 (median, 34) weeks. Pregnancy-induced hypertension (PIH), defined as a diastolic blood pressure of 90 mmHg or more, was present in 10 of 14 women; and pre-eclamptic toxemia, defined as PIH and proteinuria of 300 mg/L or more, existed in the remaining four women. There were no structural anomalies. Maternal age in both groups was 19–37 (median, 28) years. All women were non-smokers.

Two-dimensional, M-mode and pulsed Doppler fetal echocardiographic studies were performed using a combined curved-linear-array 2D real-time, pulsed Doppler, color Doppler and M-mode recording system (Panther 2002, Brul & Kjer, Copenhagen, Denmark) with a carrier frequency of 3.5 MHz. For Doppler studies, the high-pass filter was set at 100 Hz and the sample volume length was 2–3 mm.

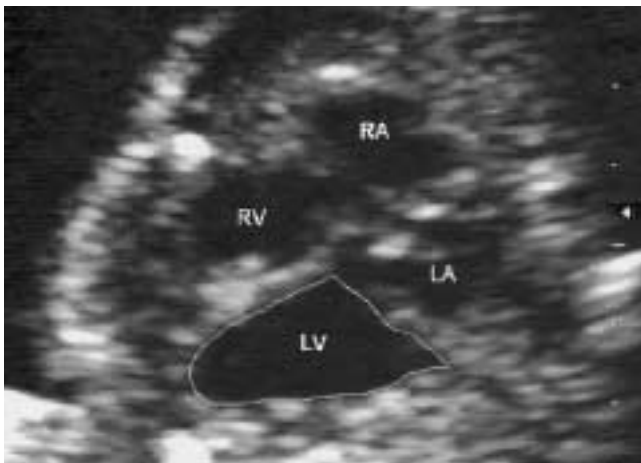
Standard cardiac long-axis, short-axis and apical four-chamber views were obtained. Four-chamber images were recorded during fetal apnea and absent fetal movements using VCR. Analysis of LV 2D images and M-mode recordings was performed offline using a framegrabber and personal computer.

Measurements of LV short-axis (transverse) diameter and long-axis (longitudinal) diameter (cm) were made in the four-chamber projection of the fetal heart. The maximal short-axis diameter of the LV chamber was measured immediately below the atrioventricular valve orifices from endocardium to endocardium. Measurements were made at end-diastole when the atrioventricular valve was closed but before the onset of systole. The maximal long-axis diameter of the LV was measured from the atrioventricular ring to the endocardium of the apex of the ventricle.

Assessment of LV remodeling was carried out from LV short-axis and long-axis measurements.

For the assessment of LV endocardium wall displacement and changes in LV segmental area during the cardiac cycle, offline analysis of 2D LV images was performed. For this purpose, the custom-made 'Dicor' software package was used<sup>17</sup>. Two-dimensional, four-chamber images were digitized using a framegrabber and stored in computer memory frame by frame during 2–3 cardiac cycles. The standard frame frequency was 25 frames per second. Since there were 12 frames per cardiac cycle, 25–30 frames were stored in the computer memory. The distance between calibration dots was digitized to provide 1 cm distance for computer analysis.

The endocardium boundary was tracked manually on the computer screen frame by frame (Figure 1). The delineation was started from the attachment of the mitral valve along the endocardial boundary in an anticlockwise fashion and completed at the opposite side of the atrioventricular valve (Figure 2); thus, both start and finish points were connected by a direct line. To avoid errors induced by mechanical displacement of the fetal heart as a result of maternal breathing or fetal movements, a floating axis reference system in the software was used<sup>18</sup>. For this purpose, end-diastolic and end-systolic LV silhouettes were matched along the ventricular long axis and cavity centers were superimposed. Then, each



**Figure 1** Example of left ventricular endocardium delineation in the appropriate-for-gestational age fetus at the end of diastole from a four-chamber view at 30 weeks of gestation. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium.

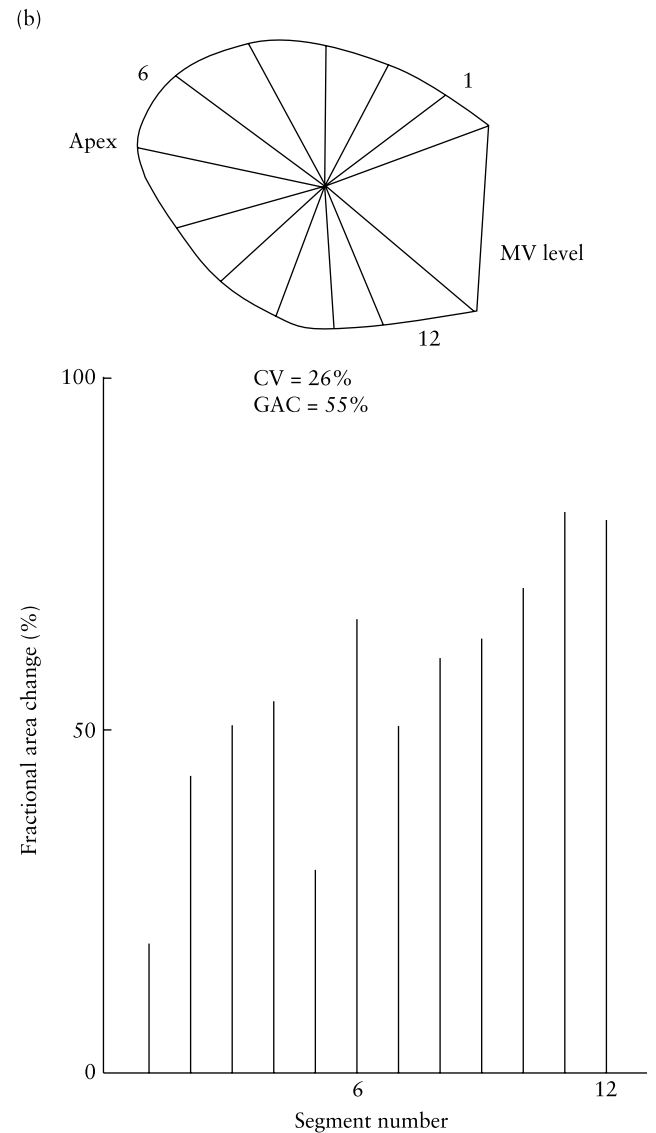
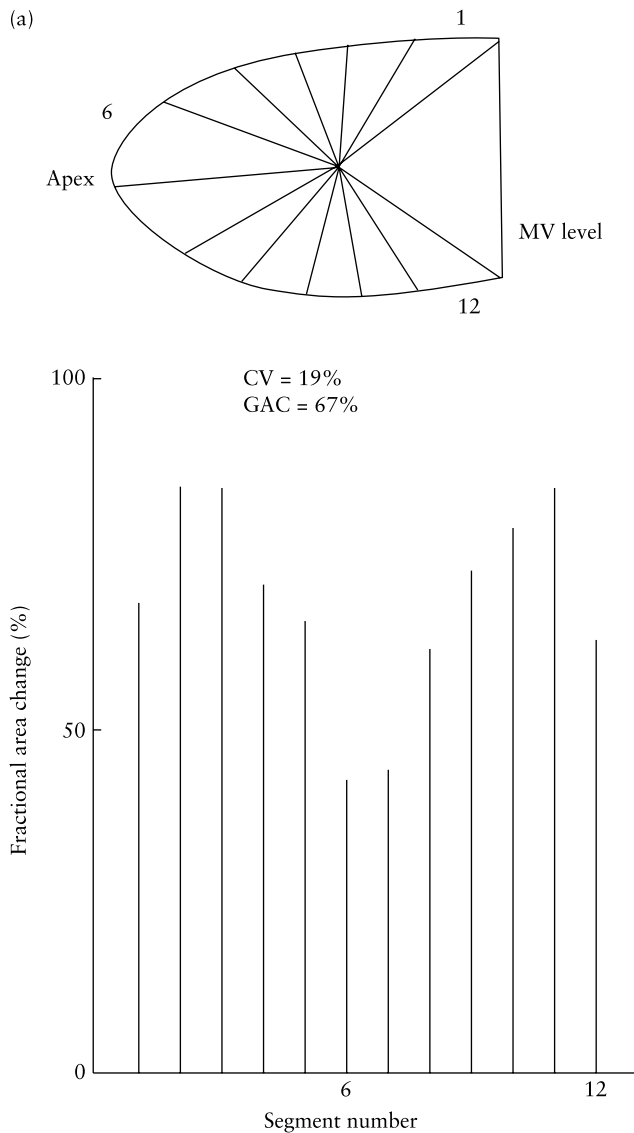
ventricular contour was divided into 12 segments by radii connecting the endocardial boundary and the center of the cavity. Each segment has an equal central angle. The 12 segment areas thus obtained were designated as areas 1–12 in anticlockwise fashion. The following parameters were determined:

- (i) LV end-diastolic cavity area (EDA), defined as the largest area and LV end-systolic area (ESA), defined as the smallest area determined from the sequence of LV contour areas;
- (ii) LV global area change (GAC) was calculated as:

$$GAC (\%) = (EDA - ESA) / EDA \times 100\%$$

This parameter was used for the assessment of the contractile function of the entire LV ventricle.

The segmental end-diastolic, end-systolic areas and fractional area change (FAC) were calculated for each of the 12 segments by the same method as the global parameters;



**Figure 2** Example of left ventricle (LV) contour segmental division and method of evaluation of LV wall motion in an (a) appropriate-for-gestational age and (b) small-for-gestational age fetus at 29 weeks' gestation. Upper: LV contours obtained as a result of endocardium delineation. Lower: graphs representing LV fractional area change (FAC) during the cardiac cycle in different segments. CV, coefficient of variation for segmental FAC; GAC, LV global area change; MV, mitral valve.

(iii) The coefficient of variation (CV) for segmental FAC was calculated for the evaluation of the LV regional wall motion non-uniformity by:

$$CV = (SD/MA) \times 100\%$$

where SD = standard deviation of segmental FAC and MA = mean value of segmental area change.

Fetal heart rate (bpm) was calculated from the time difference between aortic valve closure in two consecutive cardiac cycles in M-mode.

Simultaneous M-mode registration of aortic valve and left atrial wall movement allows determination of left isovolumic relaxation time (ms) by establishing the time interval between aortic valve closure and the onset of passive atrial filling.

Maximum Doppler flow velocity waveforms at mitral valve were obtained from the four-chamber view. The Doppler sample volume (2–3 mm) was placed immediately distal to mitral valve. The angle between the Doppler cursor and assumed flow direction was always kept below 10°. The ratio between peak velocity of E-wave (cm/s) and peak velocity of A-wave (cm/s) or E/A ratio was calculated.

Umbilical artery Doppler flow velocity waveforms were recorded from a free-floating loop of the umbilical cord for calculation of the systolic/diastolic (S/D) ratio as a measure of downstream impedance.

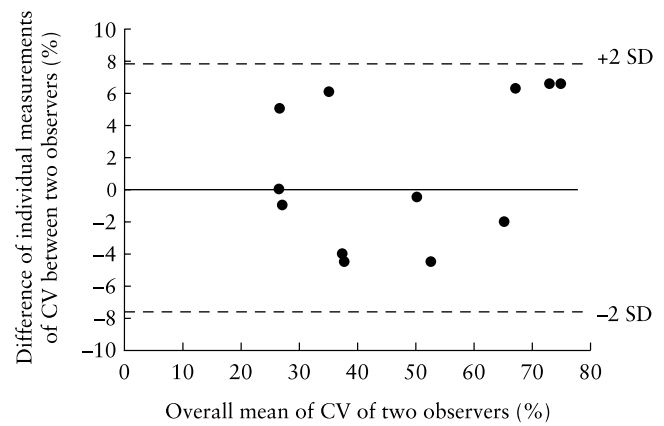
### Intra- and interobserver reliability assessment

Intra-observer reproducibility was established for FAC by repeating the analysis of one selected cycle 10 times (K.M.) in six AGA fetuses. Selected cardiac cycles were recorded on hard disc and analyzed in random order. The CV of segmental FAC was obtained for each cardiac cycle in each fetus. Intra-observer reproducibility was determined by calculating the intraclass correlation coefficient between repeated CVs for each fetus.

To assess interobserver agreement, recordings and delineations of 2D images from two investigators (K.M. and P.T.) were compared in six AGA and six SGA fetuses. Each observer performed measurements twice for calculation of CV in each AGA and SGA fetus and in the same cardiac cycle, resulting in four CV values for FAC for the same cardiac cycle. Reliability was estimated graphically<sup>19</sup>. In order to assess interobserver agreement graphically, the difference between the mean CV for each of two observers was plotted against the mean of all four CVs from the two observers for each fetus<sup>19</sup>. Limits of agreement, defined as twice the SD of the differences between observers, were calculated (Figure 3). Assuming that these differences follow a normal distribution and satisfy good interobserver reproducibility, 95% of the differences will lie between these limits.

### Statistical analysis

Data are expressed as mean ± SD. Analysis was performed using the paired *t*-test. *P* < 0.05 was considered statistically significant. Regression coefficients were obtained using a simple linear model.



**Figure 3** Differences between the individual means of coefficient of variation (CV) of two observers plotted against the overall means of both observers.

## RESULTS

Intraclass coefficients changed from 0.69 to 0.88 (mean  $0.80 \pm 0.05$ ) in six series of repeated (10 times) LV contour assessments by one observer (K.M.). Values above 0.75 show an acceptable level of concordance<sup>20</sup>.

Graphical evaluation of interclass reproducibility revealed that all values for differences between two observers lie within the area defined as twice the SD of these differences, demonstrating an acceptable interobserver reliability (Figure 3).

Differences between SGA and AGA fetuses for fetal heart rate, umbilical artery S/D ratio, isovolumic relaxation time, transmitral E/A ratio, LV short and long axis, LV GAC and LV segmental area changes are given in Tables 1 and 2. In the AGA fetus, LV short/long axis ratio was larger ( $1.75 \pm 0.26$ ; *P* < 0.01) than in SGA fetus ( $1.11 \pm 0.08$ ).

There was a significant decrease in FAC in 10 out of 12 basal segments in the SGA fetus (Table 2). As a result, the mean coefficient of variation for FAC in the SGA fetus was larger (*P* < 0.01) than in the AGA fetus ( $37.8 \pm 17.6\%$  vs.  $21.1 \pm 9.9\%$ ).

**Table 1** Mean ± SD values for the different cardiac parameters in AGA and SGA fetuses

Parameter	AGA (n = 24) Mean ± SD	SGA (n = 14) Mean ± SD	P
FHR (bpm)	146 ± 12	142 ± 8	NS
UA S/D ratio	2.31 ± 0.33	3.45 ± 0.75	<i>P</i> < 0.01
LV IVRT (ms)	37 ± 6	57 ± 9	<i>P</i> < 0.05
Transmitral E/A ratio	0.80 ± 0.08	0.69 ± 0.08	<i>P</i> < 0.01
LV long axis (cm)	2.38 ± 0.33	1.91 ± 0.23	<i>P</i> < 0.05
LV short axis (cm)	1.36 ± 0.23	1.72 ± 0.27	<i>P</i> < 0.05
LV long/short axis ratio	1.75 ± 0.26	1.11 ± 0.08	<i>P</i> < 0.01
LV GAC (%)	61.5 ± 10.3	53.2 ± 7.4	<i>P</i> < 0.05
LV CV FAC (%)	21.1 ± 9.9	37.8 ± 17.6	<i>P</i> < 0.01

SD, standard deviation; AGA, appropriate-for-gestational age; SGA, small-for-gestational age; UA S/D, umbilical artery systolic/diastolic ratio; IVRT, isovolumic relaxation time; LV, left ventricular; GAC, global area change; CV FAC, coefficient of variation for fractional area change; NS, not significant.

**Table 2** Mean  $\pm$  SD values of LV global area change and LV segmental area changes in AGA and SGA fetuses

Parameter	AGA (n = 24) Mean $\pm$ SD	SGA (n = 14) Mean $\pm$ SD	P
LV GAC (%)	61.5 $\pm$ 10.3	53.2 $\pm$ 7.4	$P < 0.05$
LV FAC segment 1 (%)	64.8 $\pm$ 8.0	39.7 $\pm$ 8.4	$P < 0.01$
LV FAC segment 2 (%)	68.4 $\pm$ 11.0	49.8 $\pm$ 6.2	$P < 0.01$
LV FAC segment 3 (%)	69.1 $\pm$ 11.1	48.6 $\pm$ 6.0	$P < 0.01$
LV FAC segment 4 (%)	53.2 $\pm$ 8.4	55.8 $\pm$ 9.0	NS
LV FAC segment 5 (%)	42.4 $\pm$ 8.1	66.4 $\pm$ 7.2	$P < 0.01$
LV FAC segment 6 (%)	46.8 $\pm$ 7.6	69.5 $\pm$ 10.7	$P < 0.01$
LV FAC segment 7 (%)	47.6 $\pm$ 11.4	55.1 $\pm$ 8.5	NS
LV FAC segment 8 (%)	64.6 $\pm$ 10.2	47.2 $\pm$ 4.3	$P < 0.01$
LV FAC segment 9 (%)	70.3 $\pm$ 13.2	51.8 $\pm$ 7.6	$P < 0.01$
LV FAC segment 10 (%)	70.1 $\pm$ 12.4	50.6 $\pm$ 6.5	$P < 0.01$
LV FAC segment 11 (%)	71.6 $\pm$ 12.3	50.8 $\pm$ 5.7	$P < 0.01$
LV FAC segment 12 (%)	70.1 $\pm$ 9.5	53.6 $\pm$ 9.1	$P < 0.01$

SD, standard deviation; AGA, appropriate-for-gestational age; SGA, small-for-gestational age; LV, left ventricular; GAC, global area change; FAC, fractional area change; NS, not significant.

A negative correlation was demonstrated between CV and GAC in both SGA ( $r = -0.62$ ;  $P < 0.05$ ) and AGA fetuses ( $r = -0.58$ ;  $P < 0.05$ ).

A typical example of the evaluation of LV endocardial wall motion and changes in CV and FAC during the cardiac cycle in AGA and SGA fetuses is shown in Figure 2. A significant positive correlation existed between isovolumic relaxation time and CV for FAC in the SGA fetus ( $r = +0.72$ ;  $P < 0.01$ ). A significant negative correlation was demonstrated between umbilical artery S/D and transmitral E/A ratio both in the AGA ( $r = -0.58$ ;  $P < 0.05$ ) and SGA ( $r = -0.60$ ;  $P < 0.05$ ) fetus.

## DISCUSSION

In the present study, the relationship between the parameters of diastolic function, loading conditions and remodeling of the left ventricle of AGA and SGA fetuses was investigated.

The following observations were made in the SGA fetus: (i) a significant change in LV long axis/short axis ratio; (ii) an increase in LV spatial non-uniformity of contraction and a significant decrease in LV GAC; (iii) a positive correlation between the degree of LV non-uniformity as expressed by CVs of segmental FAC and isovolumic relaxation time (M-mode). Moreover, a negative correlation was found between CV of segmental FAC and LV global area change as well as between umbilical artery S/D ratio and transmitral E/A ratio in both AGA and SGA fetuses.

Intrauterine growth restriction (IUGR) secondary to utero-placental insufficiency is characterized by significant changes in peripheral vascular resistance, which influences LV afterload; chronic hypoxemia, which may impair myocardial contractility; and polycythemia, which may alter blood viscosity and ventricular filling<sup>5</sup>. As a consequence, growth-restricted fetuses demonstrate impaired ventricular filling properties with lower E/A ratio at the level of the atrioventricular valves<sup>5,21</sup> and increased LV isovolumic relaxation time<sup>6</sup>.

In addition to loading and inactivation, regional non-uniformity has been recognized as a major determinant of relaxation in the heart<sup>11,22,23</sup>. Changes in regional non-uniformity in space and time affect LV relaxation and impair diastolic function in coronary artery disease<sup>24</sup>. This may result in hypertrophic cardiomyopathy<sup>12</sup> in the mature human heart.

Although impaired fetal global LV diastolic function is well-recognized in IUGR, the precise mechanisms of this abnormality have not been fully studied because of the difficulty in obtaining non-invasive measurements of local diastolic function and possible non-uniformity.

Fetal growth restriction has been associated with raised afterload<sup>1,2</sup>, although conflicting data exist regarding LV afterload in the SGA fetus. Hypoxemia and hypercarbia can cause fetal cerebral vasodilatation, which may result in a selective decrease in LV afterload, increase in LV output and proportional decrease in right ventricular output, as has been proposed previously<sup>4</sup>. Alternatively, measurement of blood flow in the fetal aortic isthmus allows assessment of the equilibrium between the downstream impedance of the two vascular systems perfused in parallel fashion by the two cardiac ventricles<sup>25</sup>. This means that afterload for the right and left ventricles should be the same. Consequently, the cause of circulatory redistribution between left and right heart in the SGA fetus should be the change in venous return (or preload) and not afterload. In this case, the left ventricle is both volume and pressure overloaded. We speculate that, as a consequence of this combined (pressure and volume) overload, geometrical remodeling of the left ventricle takes place, decreasing the long axis/short axis ratio and rendering the left ventricle shape more round. The observed increase in cardiac short-axis dimension in fetuses with IUGR has been demonstrated previously<sup>26</sup>. We speculate that the leading cause of ventricular remodeling in the SGA fetus is pressure overload as a result of increased placental vascular resistance.

The decrease in contractile activity of basal segments of the left ventricle, as well as the decrease in global area change, increase in isovolumic relaxation time and spatial non-uniformity of contraction, accompany geometrical remodeling of the left ventricle. We propose that the decrease in contractile activity of the basal segments is a result of the stretching of these segments and limitation of segmental movement by the rigid valvular ring. Such changes could produce a significant increase in non-uniformity of the ventricular wall contraction and increase in CV of segmental fractional area change. The decrease in LV GAC in the SGA fetus may be a result of LV pressure overload, remodeling and moderate dilation. Thus, the decrease in GAC as a result of LV remodeling should parallel the increase in segmental non-uniformity which is confirmed by the observed negative correlation between LV GAC and CV of segmental FAC. We cannot explain the finding of a similar relationship for the AGA fetus, although such a relationship has been demonstrated in the adult.

According to studies in experimental dogs, an acute increase in LV peak systolic and end-diastolic pressure by brief clamping of the aorta, augments LV asynchrony and induces prolongation of LV isovolumic relaxation<sup>27</sup>. Acute volume loading in the anesthetized dog prolongs the rate

of LV isovolumic pressure fall but does not alter LV asynchrony<sup>28</sup>. We speculate that the observed relationship between CV of segmental FAC and isovolumic relaxation time in the SGA fetus is a result of LV pressure overload.

In an earlier study in the SGA fetus, we demonstrated a correlation between S/D ratio in the umbilical artery and isovolumic relaxation time, indicating that an increase in LV afterload leads to an increase in LV diastolic pressure gradient during diastole, confirming LV pressure overload<sup>6</sup>.

In the present study, we demonstrated a significant negative correlation between umbilical artery S/D ratio and transmitral E/A ratio in both AGA and SGA fetuses, which confirms that LV filling is under strict control of ventricular afterload and LV diastolic pressure. The presence of a significant negative correlation between umbilical artery S/D ratio and transmitral E/A ratio in SGA fetuses shows that there is no selective decrease in LV afterload in the growth-restricted fetus, which means that the left ventricle is really subject to pressure overload.

We speculate that prolongation of LV isovolumic relaxation and changes in transmitral E/A ratio could be paralleled by LV remodeling, a decrease in GAC during contraction and an increase in LV non-uniformity. All these changes could be the result of a significant increase in peripheral resistance or LV afterload. The influence of chronic hypoxemia on fetal heart remodeling and diastolic function still remains unclear. It was shown that chronic fetal placental embolization and hypoxemia cause significant hypertension and myocardial hypertrophy in fetal sheep<sup>29</sup>. The present study shows that chronic increase in LV afterload can cause adaptive events which are associated with fetal heart remodeling. Since there is some epidemiological evidence that a small birth weight is a significant predictor for the development of arterial hypertension and death from coronary artery disease in adults<sup>30</sup>, it would be important to determine whether fetal hypertension and cardiovascular remodeling associated with chronic placental damage persists in later life.

In conclusion, we propose that changes in SGA fetal LV shape, wall motion, spatial non-uniformity and diastolic function reflect ventricular remodeling due to chronic pressure overload associated with increased placental vascular resistance.

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