ORIGINAL RESEARCH

The Preterm Heart in Childhood: Left Ventricular Structure, Geometry, and Function Assessed by Echocardiography in 6-Year-Old Survivors of Periviable Births

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***Background*—**Preterm birth has been associated with increased risk of cardiovascular morbidity in adult life. We evaluated whether preterm birth is associated with deviating cardiac structure and function before school start.

***Methods and Results*—**In total, 176 children aged 6 years and born extremely preterm (EXPT; gestational age of 22–26 weeks) and 134 children born at term (control [CTRL]) were studied. We used echocardiography to assess left heart dimensions, geometry, and functions. Recording and off-line analyses of echocardiographic images were performed by operators blinded to group belonging. Body size, blood pressure, and heart rate were also measured. Rates of family history of cardiovascular disease and sex distribution were similar in the EXPT and CTRL groups. Heart rate and systolic blood pressure did not differ, whereas diastolic blood pressure was slightly higher in EXPT than CTRL participants. After adjusting for body surface area, left ventricular length, width, and aortic valve annulus diameter were 3% to 5% smaller in EXPT than CTRL participants. Left ventricular longitudinal shortening and systolic tissue velocity were 7% to 11% lower, and transversal shortening fraction was 6% higher in EXPT than CTRL participants. The EXPT group also exhibited lower atrial emptying velocities than the CTRL group. Sex, fetal growth restriction, or a patent ductus arteriosus in the neonatal period did not contribute to cardiac dimensions or performance.

***Conclusions*—**Six-year-old children born extremely preterm exhibit a unique cardiac phenotype characterized by smaller left ventricles with altered systolic and diastolic functions than same-aged children born at term. **(*J Am Heart Assoc*. 2018;7: e007742. DOI: 10.1161/JAHA.117.007742.)**

Key Words: cardiovascular development • preterm birth • speckle tracking echocardiography • tissue Doppler imaging ultrasound

Preterm delivery (ie, >3 weeks too early) affects millions of women. As neonatal care advances and infant survival increases, there is an emerging interest in long-term outcomes. Following reports of adult hypertension,[1] stroke,[2] and increased cardiovascular mortality in adults who were born preterm,[3] concerns have been raised about the long-term cardiovascular health after preterm birth. Consequently, effects of preterm birth on cardiovascular development are important to explore and understand.

In the search for underlying mechanisms, studies of the heart in preterm children may be helpful. Given a relationship between lower gestational age and poorer cardiovascular fitness and health in adults,[3–6] the most vulnerable group would be survivors of extremely preterm birth. Two previous studies of

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Accompanying Tables S1 through S8 are available at http://jaha.ahajournals.org/content/7/2/e007742/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- On a group level, 6-year-old children born extremely preterm exhibit smaller left ventricles with altered functions compared with same-aged children born at term.

What Are the Clinical Implications?

- Survivors of extremely preterm birth should be assessed with echocardiography in childhood, and those detected with reductions in left ventricular size or function should be followed up in adulthood.

children[7] and adolescents[8] concluded that no or only minor cardiovascular effects were associated with extremely preterm birth. In contrast, more profound cardiac changes were reported in young adults, including left ventricular (LV) hypertrophy, altered ventricular shape, and reduced systolic and diastolic functions.[4] To some extent, these discrepancies in findings may reflect contributions from perinatal risk factors and exposures besides preterm birth, such as fetal growth restriction and neonatal morbidity. In addition, participants in 2 of these studies[4,8] were born between 1985 and 1991, and thus their outcomes may reflect selected survival and another, older type of care than the one used in more contemporary neonatal medicine. Finally, the selection of control group or normative reference data is critical for interpretation.

We assessed left heart dimensions, volumes, and functions in a large population-based cohort of 310 pre-school children. We hypothesized that extremely preterm birth is associated with altered development, including significant structural and functional changes of the heart that are detectable early in childhood. We also hypothesized that fetal and neonatal growth restriction as well as neonatal cardiovascular morbidity (eg, a significant patent ductus arteriosus [PDA]) may be in the casual pathway for adverse developmental trajectories of cardiac structure and function.

Methods

Individual data and study materials (images) will not be made available to other researchers for purposes of reproducing the results or replicating the procedures because the institutional review board and the informed consent of the parents only permit aggregated data to be publicly available or published. Analytic methods, however, are presented in this article to assist other researchers in reproducing the results or replicating the procedures.

Participants

EXPRESS (Extremely Preterm Infants in Sweden Study) is a prospective population-based cohort including all women residing in Sweden who delivered infants before 27 weeks of gestation from April 1, 2004, to March 31, 2007. Inclusion and exclusion criteria, perinatal characteristics, and data on survival, neonatal morbidity, neurodevelopmental outcomes at 30 months and 6.5 years of age, and vascular outcomes in childhood have been reported previously.[9–13]

All EXPRESS children were invited to a comprehensive follow-up at 6.5 years of age ±3 months. Among the regions of Sweden engaged, 3 (Umeå, Stockholm, Lund) conducted cardiovascular assessments in addition to neurodevelopmental testing. Of the 494 survivors in the EXPRESS cohort, 250 (51%) were from these regions. Using the Swedish Medical Birth Register, each child born extremely preterm (EXPT) was matched in 2010 to a pool of 10 healthy children born at term (control [CTRL]) and with same sex, date of birth, hospital, residency, and mothers' country of birth. Invitations were sent until 1 CTRL child for each EXPT child accepted participation. If all invited CTRL children declined and the list of eligible children was depleted, controls were listed as missing (4/138 [2.9%] in Umeå and Stockholm). Because of limited inclusion and unforeseen reduction in analysis capacity, only EXPT children could be investigated in Lund. In total, 176 (70% follow-up rate) EXPT and 134 CTRL children were assessed. Dropout analysis did not disclose any significant differences in gestational age, birth weight, or sex distribution between participants and those lost to follow-up.[13]

All parents and children invited to participate received oral and written information, and the parents or legal guardians of participating children signed informed consent. The study was approved by the Regional Ethics Review Board in Stockholm (no. 2010/520-31/2 and amendment no. 2011/376-32).

Clinical and Cardiac Assessments

Standardized operational procedures were used for all cardiac assessments, and all examiners were blinded to group assignments. Participants' medical histories and maternal smoking and parents' medical histories were obtained using a questionnaire. A family history of cardiovascular disease was defined as a history of myocardial infarction (29%), coronary intervention (14%), stroke (18%), pharmacological treatment of elevated blood lipids (25%), or hypertension (67%) in first-degree relatives of the parents. University education was defined as >12 years of formal education. A hemodynamically significant PDA was defined as a PDA in need of treatment (pharmacologically or surgically) in the neonatal period.

At arrival, height, weight, and head and waist circumferences were measured, and body mass index and body surface area (BSA) were calculated.[14] A validated oscillometric device, the Omron HEM 907 (Omron Healthcare), was used to measure heart rate and systolic and diastolic blood pressures.

The same experienced cardiac sonographer at each center investigated all participants. The equipment setup included the Acuson SC2000 (Siemens Medical Solutions) with a multifrequency 8- to 3-MHz vector wide-view array transducer in Stockholm and the Philips iE33 (Philips Health Care) with a multifrequency phased array transducer in Lund and Umeå. A complete echocardiographic assessment was performed to exclude structural heart defects and significant pulmonary hypertension, defined as tricuspid regurgitation >2.8 m/s. Off-line image analyses were performed by 2 operators: one (L.A.M.) for recordings from Umeå and Stockholm and the other (O.B.) for recordings from Lund. Two platforms were used for postprocessing the 2-dimensional and strain data (Syngo Dynamics Work Place and SC2000 Work Place; Siemens Medical Solutions). Both operators were blinded to group assignments.

Left Heart Dimensions and Volumes

Cardiac dimensions and volumes were determined according to standards and guidelines of the American Society of Echocardiography.[15,16] Longitudinal maximal length of the left atria in end systole and of the left ventricle in end diastole and the corresponding perpendicular maximal width of the left atrium and the width of the left ventricle (shown as LV_{width}) were determined from an apical 4-chamber view.

Interventricular septum thickness (shown as IVS_d) and LV posterior wall thickness (shown as PW_d) were measured in end-diastole using M-mode in a parasternal long-axis view. LV relative wall thickness was calculated: $(IVS_d+PW_d)/LV_{width}$. The aortic valve (AoV) annulus diameter was measured in systole from 2-dimensional images in parasternal long-axis view. Dimensions are reported in millimeters.

LV mass (LVM) was calculated using the Devreux formula.[17] Left atrial and ventricular sphericity indexes were calculated by dividing cavity length by cavity width.

Stroke volume (shown as SV) was calculated using LV outflow tract velocity time integral (shown as $LVOT_{VTI}$) and AoV annulus diameter: $SV=\pi\times AoV\ annulus^2/4\times LVOT_{VTI}$. Cardiac output was calculated as SV×heart rate/min.

LV Systolic and Diastolic Functions

Systolic function was evaluated by MAPSE (mitral annular plane systolic excursion, mm; longitudinal shortening) and shortening fraction (transversal shortening) of the left ventricle. The left ventricular outflow tract blood velocity time integral was measured with pulsed waved Doppler. Tissue Doppler imaging (pulsed Doppler) was used to measure global systolic myocardial velocity (s′), as determined at the base of the mitral annulus, that is, in the annular septal and lateral walls (apical 4-chamber view).

Diastolic function was assessed by early (E) and late (A) transmitral velocities of the left atrium, measured with pulsed wave Doppler with the cursor close to mitral leaflet tips still in atrium. Tissue Doppler imaging was also used to measure early (e′) and late (a′) myocardial velocities (in cm/s) and systolic ejection time (shown as ET; in milliseconds), isovolumic contraction time (shown as IVCT; in milliseconds), and isovolumic relaxation time (shown as IVRT; in milliseconds). As an estimate of left atrial filling pressure, the ratio of transmitral early velocity to tissue Doppler early diastolic mitral annular velocity was used. Myocardial performance index was calculated according the following formula: IVCT+IVRT/ET.

Finally, and determined at 1 site only (Stockholm; n=167), longitudinal myocardial deformation of the left ventricle during systole was assessed using 2-dimensional speckle tracking echocardiography (STE). Acquisition of STE data was performed at 70 to 90 frames per second using a velocity vector imaging software (VVI v3.0; Siemens Acuson Medical Solutions). The LV endocardial border was manually traced to obtain global longitudinal peak systolic strain (percentage), strain rate (1/s), and endocardial velocity (in cm/s). In addition to global longitudinal values, STE outcome variables were also determined at basal septal and basal lateral segments of the left ventricle.

The mean success rate for cardiac outcome measurements was 85%, and it varied between 79% (for the ratio of transmitral early velocity to tissue Doppler early diastolic mitral annular velocity) to 93% (for posterior wall thickness).

Statistical Analyses

Results are reported as means and standard deviations or numbers (proportions and percentages). Based on visual inspection of data distributions, on summary statistics of the software (providing information on means and standard deviations and on medians and quantiles) and given skewness >-1 but <1, we assumed all outcome variables to be approximately normally distributed.

To compare groups, the Student *t* test or χ^2 test was used. Adjusted differences in means in cardiac dimensions and volumes and their 95% confidence intervals were calculated using multiple linear regression including group (EXPT or CTRL), BSA, and site as independent variables. Cardiac functional outcome variables were adjusted only for site. To elucidate any sex differences, we stratified our analyses by sex and tested for group differences (EXPT versus CTRL) among girls and boys.

After comparing EXPT and CTRL data, we tested whether gestational age (22–24 versus 25–26 weeks), small size for gestational age (SGA) at birth (defined as birth weight ≥2 SD below the mean for a Swedish reference for normal fetal growth versus appropriate birth weight[18]), SGA at 36 weeks

(defined as a weight at 36 weeks of postmenstrual age of ≥2 SD below the mean reference value), and treatment for PDA (yes or no) in the neonatal period were associated with cardiac outcome in EXPT children. All PDA analyses included gestational age as an independent variable.

The study was powered to detect effect sizes ≥0.3 SD. Given multiple comparisons—even though several outcome variables were interlinked—we decided to consider a *P* value <0.01 as statistically significant.

Results

Cohort Characteristics

Maternal age and rates of family history of cardiovascular disease were similar in both groups, whereas the proportion of university-educated mothers was lower in the EXPT group than in the CTRL group. Weight, height, body mass index, and BSA were lower in the EXPT group than in the CTRL group. Heart rate and systolic blood pressure were similar, whereas diastolic blood pressure was slightly higher in EXPT versus CTRL children (Table 1).

Left Heart Dimensions, Volumes, and Geometry

In unadjusted analyses, left atrial systolic (LAs) dimensions, left ventricular diastolic (LVd) dimensions, and AoV annulus diameter were smaller in EXPT participants than in CTRL participants. The proportion of EXPT children with LV length <10th percentile in the CTRL group was 51%. The unadjusted sphericity index was also lower in the EXPT group than in the CTRL group. After adjusting for BSA and site, 3 dimension differences remained statistically significant: LV length and width and AoV annulus diameter were 3% to 5% (corresponding to 0.3–0.8 SD) smaller in EXPT participants than in CTRL participants, whereas stroke volume and cardiac output did not differ significantly between groups (Table 2).

Table 1. Cohort Characteristics

	EXPT (n=176)	CTRL (n=134)	*P* Value
Maternal data			
Age, y, mean (range)	31.4 (18–46)	31.8 (21–43)	0.47
Family history of CVD	128 (74)	102 (77)	0.65
University education	82 (47)	84 (63)	0.004
Pregnancy data			
Maternal smoking	9 (5)	2 (1)	0.09
Preeclampsia	16 (10)	0	NA
Multiple birth	29 (17)	0	NA
Neonatal data			
Gestational age, wk, mean (SD); range	24.9 (1.0); 22–26	39.4 (1.2); 37–41	NA
Boys	98 (55)	79 (60)	0.53
Birth weight, g, mean (SD); range	788 (169); 348–1161	3591 (461); 2430–4315	NA
SGA at birth	27 (16)	0	NA
SGA at 36 wk of postmenstrual age	76/161 (47)	–	NA
PDA	104 (61)	0	NA
6.5-y follow-up, mean (SD)			
Age, mo	80.8 (2.3)	81.1 (2.0)	0.23
Weight, kg	20.6 (3.6)	24.3 (3.9)	<0.001
Height, cm	118.1 (5.6)	123.1 (5.0)	<0.001
BMI, kg/m^2	14.7 (1.6)	16.0 (2.0)	<0.001
BSA, m^2	0.82 (0.09)	0.91 (0.09)	<0.001
HR, beats/min	88 (13)	85 (9)	0.016
SBP, mm Hg	98 (8)	97 (8)	0.38
DBP, mm Hg	57 (6)	55 (6)	0.005

Data are n (%) if not indicated otherwise. BMI, body mass index; BSA, body surface area; CTRL, control (born at term); CVD, cardiovascular disease; DBP, diastolic blood pressure; EXPT, extremely preterm; HR, heart rate; PDA, patent ductus arteriosus; SBP, systolic blood pressure; SGA, small for gestational age.

Table 2. Left Heart Dimensions, Volumes, and Wall Thickness in 6.5-Year-Old EXPT and CTRL Children

	EXPT (n=157)*	CTRL (n=133)*	*P* Value	Adjusted Differences in Means (95% CI)†	*P* Value
LA dimensions					
LA_s length	34.7 (5.8)	39.3 (4.8)	<0.001	−0.20 (−1.4 to 0.9)	0.72
LA_s width	27.2 (3.1)	29.5 (3.3)	<0.001	−0.7 (−1.5 to 0.1)	0.10
LA sphericity index	1.28 (0.20)	1.34 (0.19)	0.009	0.02 (−0.03 to 0.07)	0.38
LV dimensions					
LV_d length	54.6 (4.3)	58.6 (3.9)	<0.001	−1.9 (−2.8 to −0.9)	<0.001
LV_d width	35.6 (3.2)	37.3 (3.2)	<0.001	−1.0 (−1.8 to −0.3)	0.009
LV sphericity index	1.54 (0.17)	1.59 (0.16)	0.03	−0.01 (−0.05 to 0.03)	0.62
AoV annulus diameter	13.9 (1.1)	15.5 (1.0)	<0.001	−0.8 (−1.0 to −0.6)	<0.001
Volumes					
SV, mL	15.8 (2.7)	17.6 (2.9)	<0.001	−0.8 (−1.5 to −0.02)	0.05
CO, L/min	1.37 (0.24)	1.47 (0.22)	0.001	−0.03 (−0.10 to 0.04)	0.36
Wall thickness					
IVS_d	5.6 (0.9)	6.1 (0.8)	<0.001	−0.1 (−0.3 to 0.1)	0.36
PW_d	5.4 (0.8)	5.6 (0.7)	0.004	0.1 (−0.1 to 0.3)	0.50
Relative WT	0.31 (0.04)	0.31 (0.04)	0.98	0.01 (−0.002 to 0.02)	0.09
LVM, g‡	48.5 (11.4)	59.3 (11.1)	<0.001	−3.0 (−5.4 to −0.4)	0.01

Data are shown as mean (SD) and expressed in millimeters if not indicated otherwise. AoV indicates aortic valve; CI, confidence interval; CO, cardiac output; CTRL, control (born at term); EXPT, extremely preterm; IVS_d, interventricular septum thickness; LA, left atrium; LAs, left atrium in systole; LV, left ventricle; LVd, left ventricle in diastole; LVM, left ventricular mass; PW_d, posterior wall thickness; SV, stroke volume; WT, wall thickness.

*Crude values.

†Adjusted for body surface area (m^2) and site.

‡LVM calculated according to Devereux.[17]

LV Wall Thickness and Mass

Before adjusting for BSA, interventricular septum thickness and LV posterior wall were significantly thinner in EXPT than CTRL participants, whereas the relative wall thickness —taking size of the LV cavity into account—did not differ between groups. After adjusting for BSA and site, there were no remaining group differences in LV wall thickness. LVM was, with borderline statistical significance (*P*=0.014), lower in the EXPT group than in the CTRL group (Table 2).

LV Systolic and Diastolic Function

LV longitudinal shortening (ie, MAPSE) was 7% lower, systolic myocardial velocity at the lateral ventricular base was 11% lower, and shortening fraction was 6% higher in the EXPT group than in the CTRL group. The proportion of EXPT participants with MAPSE <10th percentile in the CTRL group was 27%, systolic myocardial velocity at the lateral ventricular base <10th percentile was 26%, and shortening fraction >90th percentile was 15%. Myocardial performance index and systolic myocardial velocity of the septal wall did not differ between groups (Table 3).

Septal measurements showed no group differences in diastolic function except for shorter isovolumic contraction time in EXPT than CTRL participants. Tissue Doppler imaging measurements at the LV lateral wall showed lower diastolic myocardial velocities and higher ratios of transmitral early velocity to tissue Doppler early diastolic mitral annular velocity, indicating a stiffer left ventricle in EXPT than CTRL participants (Table 3).

Endocardial deformation determined by STE did not reveal any significant group differences in global or basal longitudinal strain, strain rate, or peak velocity (Table 4).

We found no difference in LV size or function that was significantly related to maternal university education, except for 6.4% higher LVM in children who had a mother with university education than in children of mothers without a university education (*P*=0.002). Including maternity university education in the model for LVM marginally diminished the adjusted difference in LVM means between the EXPT and CTRL groups, from −3.0 to −2.5 g (*P*=0.04).

Significance of Sex

There were no sex differences in dimensions, volumes, or wall thicknesses with 1 exception: LV width did not differ between

Table 3. Left Heart Function in 6.5-Year-Old EXPT and CTRL Children

	EXPT (n=157)*	CTRL (n=130)*	*P* Value	Adjusted Differences in Means (95% CI)†	*P* Value
Systolic function					
MAPSE, mm	12.4 (1.9)	13.3 (1.7)	<0.001	−0.9 (−1.4 to −0.4)	<0.001
Shortening fraction	0.36 (0.04)	0.34 (0.06)	<0.001	0.02 (0.009–0.03)	0.001
Septal					
TDI s′, cm/s	6.7 (1.0)	6.6 (0.7)	0.50	−0.1 (−0.4 to 0.1)	0.30
MPI'	0.44 (0.07)	0.45 (0.07)	0.16	−0.01 (−0.03 to 0.009)	0.26
Lateral					
TDI s′, cm/s	8.3 (1.4)	9.1 (1.4)	<0.001	−1.0 (−1.4 to −0.6)	<0.001
MPI'	0.43 (0.06)	0.42 (0.07)	0.18	0.009 (−0.009 to 0.03)	0.34
Diastolic function					
Mitral valve E, cm/s	90.7 (13.1)	88.1 (12.1)	0.08	0.8 (−2.3 to 3.9)	0.62
Mitral valve A, cm/s	47.5 (11.1)	45.9 (8.6)	0.17	0.8 (−1.7 to 3.3)	0.52
Septal					
Mitral e′, cm/s	12.4 (1.4)	12.1 (1.3)	0.11	0.1 (−0.3 to 0.5)	0.58
Mitral a′, cm/s	4.6 (1.3)	4.4 (0.9)	0.30	−0.06 (−0.4 to 0.2)	0.72
E/e′	7.4 (1.3)	7.3 (1.1)	0.59	0.04 (−0.3 to 0.4)	0.83
IVCT, ms	60 (12)	65 (13)	0.0008	−4.5 (−7.8 to −1.2)	0.008
IVRT, ms	57 (10)	56 (8)	0.65	−0.7 (−2.9 to 1.6)	0.57
Lateral					
Mitral e′, cm/s	16.5 (2.4)	17.8 (2.5)	<0.001	−1.6 (−2.3 to −0.9)	<0.001
Mitral a′, cm/s	5.2 (1.4)	5.2 (1.1)	0.94	−0.5 (−0.8 to −0.2)	0.003
E/e′	5.7 (1.2)	5.0 (1.0)	<0.001	0.6 (0.3 to 0.9)	<0.001
IVCT, ms	61 (12)	63 (13)	0.17	−1.8 (−5.2 to 1.7)	0.31
IVRT, ms	57 (11)	53 (9)	0.007	1.8 (−0.8 to 4.6)	0.18

Data are shown as mean (SD). CI indicates confidence interval; CTRL, control (born at term); E/e′, transmitral early diastolic velocity indexed to mitral annular early diastolic velocity; EXPT, extremely preterm; IVCT, mitral annular isovolumic contraction time, IVRT, mitral annular isovolumic relaxation time; MAPSE, mitral annular plane systolic excursion; mitral a′, mitral annular late diastolic velocity; mitral e′, mitral annular early diastolic velocity; mitral valve A, transmitral valve late diastolic velocity; mitral valve E, transmitral valve early diastolic velocity; MPI', tissue Doppler imaging–derived myocardial performance index; TDI s′, tissue Doppler imaging–derived mitral annular systolic ejection velocity.

*Crude values.

†Adjusted for site.

EXPT girls and CTRL girls, whereas it was smaller in EXPT boys than in CTRL boys (P=0.01 for interaction; Tables S1 and S2). In addition, differences between the EXPT and CTRL groups in systolic or diastolic heart functions remained after stratifying by sex (data not shown).

Perinatal Risk Factors and the Preterm Heart

Stroke volume was 7% and MAPSE was 8% lower in EXPT children born at 22 to 24 weeks of gestation than in those born at 25 to 26 weeks of gestation. There were no other associations with gestational age at birth. Cardiac outcome in EXPT children born with SGA did not differ from those born with appropriate size for gestational age, and infants remaining or having SGA at 36 weeks of postmenstrual age did not end up with a different cardiac phenotype than that observed in those who were of appropriate size for gestational age at 36 weeks of postmenstrual age (data not shown). Similarly, there were no outcome differences between EXPT children who were treated for a PDA in the neonatal period and those who were not (Tables S3 through S8).

Discussion

Our results highlight 3 major cardiac differences between children born EXPT and those born at term: (1) The left ventricle and its outlet were significantly smaller, (2) LV contraction was more concentric (as opposed to a longitudinal, piston-like pumping pattern), and (3) the diastolic filling pattern indicated a stiffer LV wall in EXPT than CTRL children. The absence of associations with poor fetal or neonatal

Table 4. Global Longitudinal Strain, Strain Rate, and Velocity of the Left Ventricle Assessed by STE in 6.5-Year-Old EXPT and CTRL Children

Left Ventricle	EXPT (n=82)	CTRL (n=85)	Differences in Means (95% CI)	*P* Value
Deformation in systole				
Strain, %	−20.4 (3.8)	−20.0 (3.4)	−0.4 (−1.5 to 0.7)	0.50
Strain rate, 1/s	−1.34 (0.35)	−1.31 (0.25)	0.04 (−0.1 to 0.06)	0.44
Peak velocity, cm/s	2.9 (0.6)	3.1 (0.7)	−0.2 (−0.4 to 0.04)	0.12
Septal peak velocity cm/s	5.0 (0.9)	5.2 (0.9)	−0.2 (−0.5 to 0.06)	0.12
Lateral peak velocity cm/s	4.6 (1.3)	5.2 (1.4)	−0.5 (−1.0 to −0.08)	0.02

Assessments at one site only. Values are presented as unadjusted means (SD) and differences in means (95% CI). CI indicates confidence interval; CTRL, control (born at term); EXPT, extremely preterm.

growth or to a PDA in the neonatal period, as well as the finding of the smallest cardiac volumes and most deviating LV contraction patterns in those with the shortest gestations, provide support for the assumption of a causal relationship between EXPT birth and adverse cardiovascular development.

Children,[7] adolescents,[8] and young adults born very preterm[4] have previously been reported to exhibit a reduction in cardiac size similar to that in our study (ie, short left ventricles with smaller internal diameters). Adults who were born preterm were also reported to have higher LVM than those born at term.[4] The higher LVM in adults could be attributed to higher blood pressures in adults who were born preterm than in those born at term,[4] whereas blood pressure differences in our cohort were small or nonexistent. Infants,[19] children,[7] and adolescents[8] born preterm have—as in our cohort—been found to exhibit similar or even lower LVM than peers born at term, also in the presence of elevated blood pressure.[8–20]Taken together, these findings indicate that LV hypertrophy of the preterm heart may be a late phenomenon emerging after childhood and adolescence. Consistent with lower LVM, we previously found a smaller left main coronary artery in EXPT children than in CTRL children.[13]

Global longitudinal systolic strain or strain rate of the left ventricle did not differ between groups. In contrast, previous STE studies in infants[19] and adults[4] have demonstrated reduced strain, strain rate, and myocardial velocity in preterm offspring. We estimated strain with echocardiography, which differs from results obtained with magnetic resonance used in adult studies.[4] In addition, global strain may mask regional reductions in myocardial deformation such as those found at the free wall of the left ventricle (but not in the interventricular septum) in 6-month-old infants born EXPT.[19]

The underlying mechanisms for adverse cardiac development following preterm birth are still largely unknown. In an animal model of preterm birth—delivering healthy pregnant sheep before they reached full-term gestation—cardiomyocyte hypertrophy and collagen deposition were observed in the offspring as early as 9 weeks after term-equivalent age.[21] In human studies, altered myocardial function seems to precede structural changes and has been reported weeks and months after preterm birth.[19,22,23] These observations suggest that the triggering events are birth related.

In fetal life, half of the combined cardiac output is distributed via the aorta to the placenta. Accordingly, placental needs and blood flow drive aortic growth, especially in the third trimester. If the birth-related termination of the placental circulation occurs well before term, aortic size will be superfluous and its growth will decelerate.[24] Whether this adaptation to preterm circulatory conditions could play a role in the postnatal development of the preterm heart remains to be clarified. We note that the AoV annulus diameter was ≈1 SD narrower in EXPT than CTRL participants after adjusting for current body size.

Children born as SGA did not differ in left heart structure and function from those born as appropriate size for gestational age. Our findings are similar those reported in a smaller cohort of 5-year-old children.[25] Many participants suffered from postnatal growth restriction in infancy, and this has been explained by suboptimal neonatal nutrition. Although feeding the preterm infant with formula[26] and intralipids[27] have been linked to poorer adult cardiovascular physiology, we found no association between poor neonatal growth and LV structure and function at 6 years of age.

PDA is a common complication after EXPT birth. Studies in infancy have not shown an association between PDA and lasting effects on cardiac structure and function,[28] and such observations seem to be confirmed by our follow-up study.

The strengths of this study include the population-based and prospective design, including infants from both tertiary and nontertiary centers in Sweden. This ensures high generalizability. EXPRESS also represents a cohort with comparatively high (78%) survival of periviable births, reducing potential effect modifications from early death as a competing outcome. Gestational age was estimated by early ultrasound

in almost all pregnancies, limiting misclassification. Maternal smoking in pregnancy was rare, excluding this factor as a possible confounder. The follow-up time was 6 years, and the study consisted of a sufficiently large number of children to allow for subgroup and risk factor analyses. The control group was large and carefully chosen, and we refrained from comparing EXPT data with recently published normative values because of their small numbers (n=17–24)[29,30] and potential selection bias (reference children had been referred for evaluation of heart murmurs or a family history of heart disease).[29,30] Blinding of those performing the measurements and analyses was used to minimize observer bias. Dropout analysis did not indicate any response bias.

Our study also has limitations. Residual confounding may have occurred as the populations of women who delivered EXPT and their infants may have been different in terms of genetic or other characteristics than those delivering at term. The EXPRESS database does not contain information on PDA diagnostics; accordingly, we could not compare our follow-up data with neonatal echocardiographs. We report only data for the left side of the heart, leaving out the right heart and the pulmonary circulation; however, no participant had pulmonary hypertension, suggesting that there was no significant left–right ventricle interaction driven by increased right ventricular load. Measurements were performed under resting conditions and do not reflect the myocardial flow reserve. Stroke volume measurements by standard 2-dimensional echo techniques may be subject to error. Blood sampling for lipid profiling, inflammatory status, or other biomarkers was not performed. Small numbers in some of the subgroup analyses may limit conclusions about statistically insignificant differences.

From a clinical perspective, we note that the group differences reported in this article in terms of LV size and function are in the same range and direction as those observed in children with a family history of hypertrophic cardiomyopathy.[31] In those at risk (ie, those with a known mutation causing hypertrophic cardiomyopathy or history of familial hypertrophic cardiomyopathy), the LV wall thickness appears to be similar to or thinner than average before it becomes hypertrophic,[31] indicating that the pathophysiological process may involve cardiac changes in childhood that are subtle and difficult to interpret. Accordingly, although the majority will not constitute a clinical problem for the pediatric cardiologist at 6 years of age, we think that children born EXPT should be assessed with echocardiography before starting school, and those detected with reductions in LV size or function should be included in a follow-up program.

In conclusion, 6-year-old children born EXPT exhibit significantly smaller left hearts featuring signs of deviating systolic and diastolic functions, also in the absence of arterial hypertension. This cardiac phenotype of children born EXPT is likely to reflect adverse early cardiovascular development of the preterm heart and may be part of the explanation of why the first adult generation of EXPT survivors experiences increased cardiovascular morbidity and mortality.

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Disclosures

None.

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Supplemental Material

Table S1. Cardiac dimensions and volumes in 6½-year-old girls born extremely preterm (EXPT) or at term (CTRL).

	Girls EXPT* (n=69)	Girls CTRL* (n=52)	p-value	Adjusted† differences in means (95% CI)	p-value
LA dimensions					
LA_s length	33.8(5.1)	38.0(4.0)	<0.001	-0.5(-2.0;1.0)	0.54
LA_s width	27.0(3.2)	28.6(2.8)	0.006	-0.4(-1.5;0.8)	0.55
LA sphericity index	1.26(0.19)	1.34(0.17)	0.03	0.0007(-0.07;0.07)	0.98
LV dimensions					
LV_d length	54.7(4.1)	58.6(4.2)	<0.001	-1.9(-3.4;-0.4)	0.02
LV_d width	35.4(3.2)	36.0(2.7)	0.30	-0.3(-1.4;0.7)	0.59
LV sphericity index	1.55(0.16)	1.64(0.16)	0.004	-0.04(-0.11;0.02)	0.21
AoV annulus	13.7(1.0)	15.0(0.9)	<0.001	-0.6(-1.0;-0.3)	<0.001
Volumes					
SV, ml	15.3(2.2)	17.3(2.7)	<0.001	-1.4(-2.4;-0.3)	0.01
CO, l/min	1.36(0.22)	1.47(0.22)	0.02	-0.06(-0.2;0.04)	0.22
Wall thickness					
IVS_d	5.5(0.9)	5.9(0.9)	0.005	-0.2(-0.5;0.2)	0.35
PW_d	5.3(0.7)	5.5(0.7)	0.11	-0.1(-0.4;0.2)	0.44
Relative WT	0.31(0.04)	0.31(0.04)	0.88	0.0(-0.02;0.02)	1.00
LVM‡ g	46.4(8.6)	54.9(10.1)	<0.001	-3.7(-7.0;-0.4)	0.03

Data are mean (SD) and expressed in millimeters if not indicated otherwise. *Unadjusted values.

†Differences in means adjusted to body surface area (m^2) and site. ‡LVM calculated according to Devereux[1].

AoV annulus=Aorta valve annulus diameter, CO=cardiac output, IVS=interventricular septum, LA=left atrium, LV=left ventricle, LVM=left ventricular mass, PW=posterior wall, Sphericity index= length/width. SV=stroke volume, WT=wall thickness.

Table S2. Cardiac dimensions and volumes in 6½-year-old boys born extremely preterm (EXPT) and at term (CTRL).

	Boys EXPT* (n=86)	Boys CTRL* (n=77)	p-value	Adjusted† differences in means (95% CI)	p-value
LA dimensions					
LA_s length	35.5(6.3)	40.2(5.0)	<0.001	-0.05(-1.7;1.6)	0.95
LA_s width	27.4(3.0)	30.0(3.5)	<0.001	-1.0(-2.1;0.2)	0.09
LA sphericity index	1.30(0.21)	1.35(0.21)	0.12	0.04(-0.03;0.1)	0.28
LV dimensions					
LV_d length	54.6(4.4)	58.7(3.8)	<0.001	-1.7(-3.0;-0.4)	0.008
LV_d width	35.6(3.3)	38.1(3.4)	<0.001	-1.6(-2.6;-0.5)	0.003
LV sphericity index	1.54(0.17)	1.55(0.14)	0.66	0.02(-0.04;0.07)	0.56
AoV annulus	14.1(1.1)	15.8(1.0)	<0.001	-1.0(-1.3;-0.06)	<0.001
Volumes					
SV, ml	16.1(3.0)	17.8(3.1)	0.0008	-0.3(-1.4;0.7)	0.53
CO, l/min	1.38(0.26)	1.47(0.24)	0.03	-0.009(-1.0;0.08)	0.85
Wall thickness					
IVS_d	5.6(0.9)	6.2(0.7)	<0.001	-0.04(-0.3;0.2)	0.69
PW_d	5.5(0.8)	5.7(0.7)	0.02	0.2(-0.05;0.4)	0.13
Relative WT	0.31(0.04)	0.31(0.04)	0.78	0.02(0.004;0.03)	0.014
LVM‡ g	50.1(12.8)	62.3(10.8)	<0.001	-2.6(-5.8;0.6)	0.11

Data are mean (SD) and expressed in millimeters if not indicated otherwise.

*Unadjusted values.

†Mean difference adjusted to body surface area (m^2) and site.

‡LVM calculated according to Devereux[1]

AoV annulus=Aorta valve annulus diameter, CO=cardiac output, IVS=interventricular septum, LA=left atrium, LV=left ventricle, LVM=left ventricular mass, PW=posterior wall, Sphericity index=length/width. SV=stroke volume, WT=wall thickness.

Table S3. Cardiac dimensions and volumes in 6½-year-old children born extremely preterm stratified by gestational age in weeks.

	GA 22-24 wks* (n=40)	GA 25-26 wks* (n=105)	p-value	Adjusted† differences in means (95% CI)	p-value
LA dimensions					
LA_s length	32.8(5.1)	35.3(5.8)	0.017	0.6(-0.9;2.1)	0.40
LA_s width	26.1(2.5)	27.6(3.2)	0.007	0.7(-0.3;1.8)	0.17
LA sphericity index	1.26(0.18)	1.29(0.21)	0.52	-0.007(-0.07;0.06)	0.82
LV dimensions					
LV_d length	53.9(4.1)	54.9(4.4)	0.22	-0.3(-1.7;1.01)	0.63
LV_d width	34.8(3.3)	35.8(3.2)	0.09	0.5(-0.4;1.5)	0.28
LV sphericity index	1.56(0.16)	1.54(0.18)	0.58	-0.03(-0.09;0.02)	0.27
AoV annulus	13.5(1.1)	14.0(1.0)	0.003	0.3(0.005;0.60)	0.05
Volumes					
SV, ml	14.6(2.3)	16.1(2.4)	0.001	1.2(0.3;2.1)	0.01
CO, l/min	1.28(0.28)	1.40(0.22)	0.009	0.1(0.008;0.02)	0.03
Wall thickness					
IVS_d	5.4(1.0)	5.6(0.8)	0.27	-0.08(-0.4;0.2)	0.59
PW_d	5.3(0.7)	5.4(0.8)	0.88	-0.2(-0.4;0.08)	0.18
Relative WT	0.32(0.05)	0.30(0.04)	0.14	-0.02(-0.03;-0.002)	0.03
LVM‡, g	43.9(7.7)	49.9(11.9)	0.003	1.1(-2.0;4.2)	0.48

Data are mean (SD) and expressed in millimeters if not indicated otherwise.

*Unadjusted values.

†Mean difference adjusted to body surface area (m^2) and site.

‡LVM calculated according to Devereux[1]

AoV annulus=Aorta valve annulus diameter, CO=cardiac output, IVS=interventricular septum, LA=left atrium, LV=left ventricle, LVM=left ventricular mass, PW=posterior wall, Sphericity index=length/width. SV=stroke volume, WT=wall thickness.

Table S4. Left heart systolic and diastolic function in 6½-year-old children born extremely preterm stratified by gestational age in weeks.

	GW22-24* (n=41)	GW 25-26* (n=109)	p-value	Adjusted† differences in means (95% CI)	p-value
Systolic function					
MAPSE, mm	11.7(1.9)	12.8(1.8)	0.002	1.1(0.4;1.7)	0.002
Shortening fraction	0.37(0.05)	0.36(0.04)	0.75	-0.001(-0.02;0.02)	0.88
Septal					
TDI s', cm/s	6.4(0.8)	6.8(1.1)	0.04	0.4(0.08;0.8)	0.02
MPI'	0.44(0.08)	0.44(0.07)	0.55	0.009(-0.02;0.04)	0.56
Lateral					
TDI s', cm/s	8.0(1.8)	8.4(1.3)	0.15	0.4(-0.1;1.0)	0.12
MPI'	0.45(0.07)	0.42(0.06)	0.07	-0.02(-0.05;0.003)	0.08
Diastolic function					
MV E, cm/s	90.2(13.2)	91.0(13.0)	0.76	1.0(-3.4;5.5)	0.64
MV A, cm/s	46.0(11.2)	47.8(10.9)	0.34	2.0(-1.9;5.9)	0.31
Septal					
Mitral e', cm/s	12.5(1.4)	12.4(1.5)	0.69	-0.09(-0.6;0.4)	0.75
Mitral a', cm/s	4.6(1.7)	4.6(1.2)	0.81	0.09(-0.4;0.6)	0.72
E/e'	7.3(1.3)	7.5(1.2)	0.33	0.2(-0.3;0.7)	0.37
ivct, ms	60(13)	60(12)	0.91	-0.04(-5.0;4.3)	0.88
ivrt, ms	56(9)	58(10)	0.38	1.9(-1.7;5.5)	0.30
Lateral					
Mitral e', cm/s	16.2(2.7)	16.7(2.2)	0.35	0.5(-0.4;1.4)	0.30
Mitral a', cm/s	5.2(1.4)	5.3(1.4)	0.71	0.2(-0.3;0.6)	0.49
E/e'	5.8(1.5)	5.6(1.1)	0.58	-0.1(-0.6;0.4)	0.58
ivct , ms	64(14)	60(11)	0.09	-4.1(-8.9;0.7)	0.09
ivrt , ms	56(10)	57(11)	0.71	1.1(-3.1;5.3)	0.61

*Unadjusted mean (SD) values.

[†]Mean difference adjusted for site.

E/e'= transmitral early diastolic velocity indexed to mitral annular early diastolic velocity,

ivct= mitral annular isovolumic contraction time, ivrt= mitral annular isovolumic relaxation time,

MAPSE= Mitral annular plane systolic excursion, Mitral valve E=transmitral valve early diastolic velocity, Mitral e'= mitral annular early diastolic velocity, Mitral a'= mitral annular late diastolic velocity, TDI=Tissue Doppler Imaging, TDI s'=mitral annular systolic ejection velocity in, MPI'= TDI derived myocardial performance index.

Table S5. Cardiac dimensions and volumes in 6½-year-old children born extremely preterm stratified by small for gestational age (SGA) or appropriate for gestational age (AGA) at birth.

	SGA* (n=22)	AGA* (n=123)	p-value	Adjusted† differences in means (95% CI)	p-value
LA dimensions					
LA_s length	31.8(4.6)	35.1(5.7)	0.010	-0.6(-2.5;1.3)	0.52
LA_s width	25.7(3.2)	27.4(3.0)	0.016	-0.7(-2.07;0.6)	0.27
LA sphericity index	1.25(0.19)	1.29(0.20)	0.40	0.02(-0.07;0.10)	0.69
LV dimensions					
LV_d length	52.5(4.3)	54.9(4.2)	0.015	-1.4(-3.1;0.3)	0.10
LV_d width	35.7(3.2)	35.5(3.2)	0.81	0.07(-1.2;1.3)	0.91
LV sphericity index	1.48(0.18)	1.56(0.17)	0.06	-0.04(-0.1;0.03)	0.24
AoV annulus	13.5(1.05)	13.9(1.07)	0.10	0.009(-0.03;0.05)	0.62
Volumes					
SV, ml	15.5(2.2)	15.6(2.5)	0.81	0.2(-1.0;1.46)	0.68
CO, l/min	1.40(0.22)	1.36(0.24)	0.60	0.06(-0.06;0.2)	0.34
Wall thickness					
IVS_d	5.4(1.0)	5.6(0.9)	0.41	0.05(-0.3;0.4)	0.78
PW_d	5.2(0.8)	5.4(0.8)	0.20	-0.06(-0.4;0.2)	0.69
Relative WT	0.30(0.04)	0.31(0.04)	0.69	-0.0004(-0.02;0.02)	0.97
LVM‡ g	44.9(13.4)	48.8(10.6)	0.12	0.3(-3.4;3.9)	0.89

Data are mean (SD) and expressed in millimeters if not indicated otherwise.

*Unadjusted values.

† Difference in means adjusted to body surface area (m^2) and site.

‡LVM calculated according to Devereux[1]

AoV annulus=Aorta valve annulus diameter, CO=cardiac output, IVS=interventricular septum, LA=left atrium, LV=left ventricle, LVM=left ventricular mass, PW=posterior wall, Sphericity index=length/width. SV=stroke volume, WT=wall thickness.

Table S6. Left heart systolic and diastolic function in 6½-year-old children born extremely preterm stratified by small for gestational age (SGA) and appropriate for gestational age (AGA) at birth.

	SGA* (n=26)	AGA* (n=139)	p-value	Adjusted† differences in means (95% CI)	p-value
Systolic function					
MAPSE, mm	12.2(2.2)	12.5(1.8)	0.42	-0.4(-1.2;0.5)	0.37
Shortening fraction	0.37(0.04)	0.36(0.05)	0.41	0.005(-0.02;0.02)	0.63
Septal					
TDI s', cm/s	6.4(0.8)	6.7(1.0)	0.31	-0.5(-1.0;0.001)	0.05
MPI'	0.46(0.06)	0.44(0.07)	0.29	0.02(-0.02;0.06)	0.26
Lateral					
TDI s', cm/s	8.3(1.4)	8.3(1.5)	0.96	-0.2(-0.9;0.5)	0.60
MPI'	0.46(0.06)	0.42(0.06)	0.05	0.03(-0.004;0.06)	0.08
Diastolic function					
MV E, cm/s	95.5(16.0)	89.9(12.3)	0.06	4.4(-1.3;10.1)	0.13
MV A, cm/s	47.6(10.5)	47.2(11.1)	0.89	-0.1(-5.2;4.9)	0.96
Septal					
Mitral e', cm/s	12.3(1.3)	12.4(1.5)	0.73	-0.3(-1.0;0.4)	0.40
Mitral a', cm/s	4.4(1.0)	4.6(1.4)	0.56	-0.4(-1.0;0.2)	0.23
E/e'	8.0(1.7)	7.3(1.2)	0.038	0.6(-0.02;1.2)	0.06
ivct , ms	63(12)	59(12)	0.23	4.5(-1.6;10.6)	0.15
ivrt , ms	60(7)	57(10)	0.22	1.6(-3.1;6.4)	0.50
Lateral					
Mitral e', cm/s	17.0(2.4)	16.5(2.4)	0.41	0.2(-0.9;1.4)	0.69
Mitral a', cm/s	5.8(1.8)	5.1(1.3)	0.06	0.2(-0.4;0.8)	0.46
E/e'	5.9(1.7)	5.6(1.1)	0.35	0.3(-0.4;0.9)	0.38
ivct , ms	65(11)	60(12)	0.17	4.8(-1.4;11.1)	0.13
ivrt , ms	59(13)	56(11)	0.26	1.4(-4.1;6.9)	0.62

*Unadjusted values.

[†] Differences in means adjusted for site.

E/e'= transmitral early diastolic velocity indexed to mitral annular early diastolic velocity, ivct= mitral annular isovolumic contraction time, ivrt= mitral annular isovolumic relaxation time, MAPSE= Mitral annular plane systolic excursion, Mitral valve E=transmitral valve early diastolic velocity, Mitral e'= mitral annular early diastolic velocity, Mitral a'= mitral annular late diastolic velocity, TDI=Tissue Doppler Imaging, TDI s'=mitral annular systolic ejection velocity in, MPI'= TDI derived myocardial performance index.

Table S7. Cardiac dimensions and volumes in 6½-year-old children born extremely preterm (EXPT) stratified by presence of hemodynamically significant PDA in the neonatal period.

	PDA* (n=90)	No PDA* (n=58)	p-value	Adjusted† differences in means (95% CI)	p-value
LA dimensions					
LA_s length	34.7(5.8)	34.7(5.8)	0.98	1.0(-0.4;2.4)	0.16
LA_s width	27.0(3.1)	27.6(3.2)	0.21	-0.4(-1.4;0.6)	0.41
LA sphericity index	1.29(0.2)	1.26(0.2)	0.33	0.06(-0.003;0.1)	0.06
LV dimensions					
LV_d length	54.2(4.1)	55.2(4.6)	0.18	0.02(-1.3;1.3)	0.98
LV_d width	35.4(3.1)	35.8(3.4)	0.42	-0.01(-0.9;0.9)	0.98
LV sphericity index	1.54(0.2)	1.55(0.2)	0.62	-0.002(-0.06;0.06)	0.95
AoV annulus	13.8(1.0)	14.0(1.1)	0.20	0.05(-0.2;0.3)	0.72
Volumes					
SV, ml	15.5(2.8)	16.1(2.1)	0.18	-0.06(-1.0;0.8)	0.89
CO, l/min	1.38(0.3)	1.35(0.2)	0.50	0.07(-0.2;0.2)	0.13
Wall thickness					
IVS_d	5.5(0.9)	5.6(0.9)	0.22	-0.01(-0.3;0.3)	0.94
PW_d	5.3(0.8)	5.5(0.7)	0.17	-0.2(-0.4;0.1)	0.24
Relative WT	0.31(0.05)	0.31(0.04)	0.90	0.006(-0.009;0.02)	0.43
LVM‡, g	46.3(9.3)	51.4(13.1)	0.006	-2.8(-5.7;-0.03)	0.05

Data are mean (SD) and expressed in millimeters if not indicated otherwise.

*Unadjusted values.

† Differences in means adjusted to body surface area (m^2) , gestational age in weeks, and site.

‡LVM calculated according to Devereux[1]

AoV annulus=Aorta valve annulus diameter, CO=cardiac output, IVS=interventricular septum, LA=left atrium, LV=left ventricle, LVM=left ventricular mass, PW=posterior wall, Sphericity index=length/width. SV=stroke volume, WT=wall thickness.

Table S8. Left heart systolic and diastolic function in 6½-year-old children born extremely preterm stratified by stratified by presence of hemodynamically significant PDA.

	PDA* (n=91)	PDA* (n=59)	p-value	Adjusted† differences in means (95% CI)	p-value
Systolic function					
MAPSE, mm	12.3(1.9)	12.8(1.8)	0.14	-0.3(-0.9;0.4)	0.40
Shortening fraction	0.36(0.04)	0.37(0.04)	0.09	-0.01(-0.03;0.0008)	0.06
Septal					
TDI s', cm/s	6.7(1.1)	6.6(0.8)	0.36	0.3(-0.05;0.6)	0.09
MPI'	0.43(0.06)	0.44(0.07)	0.40	-0.01(-0.03;0.01)	0.40
Lateral					
TDI s', cm/s	8.3(1.5)	8.2(1.3)	0.71	0.2(-0.4;0.7)	0.49
MPI'	0.45(0.07)	0.44(0.06)	0.42	0.01(-0.04;0.01)	0.31
Diastolic function					
MV E, cm/s	89.3(12.5)	93.1(13.5)	0.08	-4.6(-9.0;-0.3)	0.04
MV A, cm/s	47.5(10.4)	47.0(12.1)	0.78	0.5(-3.4;4.3)	0.81
Septal					
Mitral e', cm/s	12.3(1.4)	12.6(1.4)	0.14	-0.4(-0.9;0.1)	0.13
Mitral a', cm/s	4.6(1.2)	4.5(1.6)	0.80	0.1(-0.4;0.6)	0.61
E/e'	7.4(1.2)	7.5(1.4)	0.51	-0.1(-0.6;0.3)	0.56
ivct, ms	60(14)	59(10)	0.51	1.3(-3.3;5.9)	0.58
ivrt, ms	56(10)	58(10)	0.29	-1.5(-5.0;2.0)	0.40
Lateral					
Mitral e', cm/s	16.3(2.3)	16.9(2.5)	0.19	-0.6(-1.4;0.3)	0.20
Mitral a', cm/s	5.3(1.5)	5.1(1.3)	0.52	0.2(-0.2;0.7)	0.26
E/e'	5.6(1.2)	5.7(1.4)	0.66	-0.1(-0.6;0.4)	0.68
ivct, ms	60(12)	62(12)	0.34	-3.2(-7.9;1.4)	0.17
ivrt, ms	55(11)	59(11)	0.07	-3.3(-7.3;0.7)	0.10

*Unadjusted values.

[†] Differences in means adjusted for gestation age in weeks & site.

E/e'= transmitral early diastolic velocity indexed to mitral annular early diastolic velocity, ivct= mitral annular isovolumic contraction time, ivrt= mitral annular isovolumic relaxation time, MAPSE= Mitral annular plane systolic excursion, Mitral valve E=transmitral valve early diastolic velocity, Mitral e'= mitral annular early diastolic velocity, Mitral a'= mitral annular late diastolic velocity, TDI=Tissue Doppler Imaging, TDI s'=mitral annular systolic ejection velocity in, MPI'= TDI derived myocardial performance index.

Supplemental Reference:

1. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986;57:450-458.