■ ORIGINAL ARTICLE

Longitudinal assessment of cardiac function in extremely low birth weight children at 7 and 11 years of age: implications for adult medicine

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A B S T R A C T

Background: The long-term impact of extreme prematurity on cardiac structure and function has not been fully evaluated**.**

Aims: The aim of the study was to assess cardiac condition at 11 years of age in a local cohort of extremely low birth weight (ELBW) children born between 2002 and 2004 and to compare it to a previous study in the same group at 7 years of age.

Methods: Sixty-four children with ELBW (median birth weight of 890 g) and 36 children born at full term underwent echocardiography and physical examination.

Results: M-mode echocardiography parameters, expressed as z-scores for body surface area (mean [SD]), showed significant differences in left ventricular end-diastolic dimension (–1.01 [0.91] vs 0.35 [0.71]; P <0.001), left ventricular end-systolic dimension (–0.29 [0.92] vs 0.57 [0.65]; P <0.001), aorta dimension (0.63 [1.14] vs 1.63 [1.30]; P <0.001), and left atrial dimension (–1.75 [0.97] vs –0.01 [0.86]; P <0.001) between the study group and controls at 11 years of age. Fractional shortening (FS) and ejection fraction (EF) were higher in the ELBW children than in their full-term counterparts (33.6 [5.5] vs 30.8 [4.34]; P = 0.009 and 0.63 [0.07] vs 0.58 [0.06]; P = 0.005, respectively) at a mean age of 11 years.

Conclusions: The ELBW children had smaller hearts than full-term controls at both 7 and 11 years of age. The FS and EF were elevated in the group of 11-year-old ELBW children. We observed comparable progress in cardiac growth (approximately 20%) in premature and full-term children over a 4-year study period.

Key words: cardiac index, extremely low birth weight, left ventricular hypertrophy, preterm infants, stroke volume

INTRODUCTION

Continuous improvements in perinatal medical services and neonatal intensive care have resulted in an increasing number of surviving extremely low birth weight (ELBW) infants. This particular patient population suffers the highest risk of early and late complications of prematurity. There are a growing number of studies evaluating the long-term side effects of perinatal disorders. Since some published reports show increased cardiovascular mortality in adults who were born preterm [1, 2], a number of researchers have investigated the impact of extreme prematurity on cardiac structure and function during extended periods of time.

The aim of this study was to identify any potential late cardiac complications in a group of 11-year-old children whose birth weight was less than 1000 g and who had already undergone similar examinations at the age of 6–7 years (results published previously in *Neonatology* in 2013 [3]). In particular, the results of the echocardiographic investigations were compared. The results made it possible to perform a detailed evaluation of cardiac functional and structural variability together with an assessment of overall cardiac development. It was hypothesized that cardiac lesions in the ELBW group occurred mostly in the perinatal period. The general heart development of the ELBW children and their healthy counterparts was comparable during their preschool and early school years.

METHODS

Patients

A cross-sectional observational study was conducted in the Outpatient Pediatric Department of the University

WHAT'S NEW?
Extremely low birth weight children had smaller hearts than full-term controls at both 7 and 11 years of age. The observation that the heart growth rate during preschool age and school age in extremely premature infants is comparable to that in full-term controls suggests that the most critical cardiac lesions occurred in early postnatal life. Despite their normal heart development during school age, preterm infants require repeated monitoring to diagnose possible cardiac complications later in life.

Children's Hospital in Krakow, Poland, between December 30, 2013, and April 30, 2015. The study cohort comprised ELBW survivors recruited at birth and term control participants enrolled in the study at 6–7 years of age.

During the study period, 169 newborns with birth weights <1000 g were born alive in the southeast district of Poland (Malopolska Region). All these children were hospitalized in one of 3 tertiary-care neonatal intensive care units in southeastern Poland. Ninety-one infants were discharged home, and they were further monitored on an outpatient basis. Eighty-one children took part in the follow-up assessment at 6–7 years of age. The control group for the study included forty age- and gender-matched children with birth weights >2500 g who were recruited at a single general practitioner's office between 2009 and 2010. Details on the methodology and results of the follow-up performed at 6–7 years of age have already been published [3].

All the participants of the study at 6–7 years of age were invited to the present follow-up at 10–11 years of age. Ultimately, 64 (79%) children from the study group and 36 (90%) children from the control group returned for the second follow-up assessment (Figure 1).

The study was approved by the Jagiellonian University Bioethical Committee and adheres to the tenets of the Declaration of Helsinki. The parents and caregivers signed informed consent before the children were included in the study.

Follow-up at 10–11 years of age
All the study participants underwent physical examinations, height and weight measurements, and standard two-dimensional echocardiography tests. The parents completed questionnaires on their children's demographic data and health status. The whole procedure was completed during a single visit to the Pediatric Outpatient Department of the University Children's Hospital of Krakow.

Echocardiography
The same echocardiographic analyses, as in a previously published study, were performed using the same ultrasound device — the Philips EnVisor HD (Philips, Amsterdam, The Netherlands) with a 2- to 4-MHz transducer and simultaneous heart rate (HR) measurement [3]. The measurements were performed twice by the same echocardiographers as in the previous study. Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), interventricular septal thickness at end diastole (IVSd) and end systole (IVSs), left ventricular posterior wall thickness at end diastole (LVPWd) and
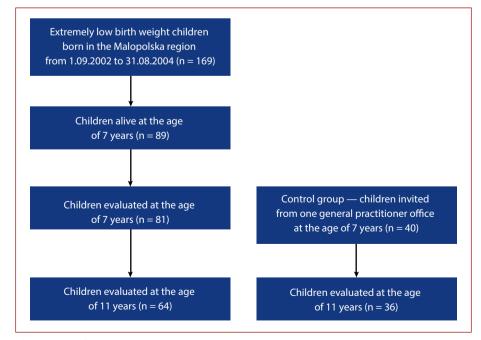

Figure 1. Protocol of the study — flow diagram

end systole (LVPWs), right ventricular end-diastolic dimension (RVDD), and left atrial dimension (LAD) were measured using 2-dimensional guided M-mode echocardiography with the parasternal shortaxis view at the midpapillary level.

Diameters and thickness were corrected for body surface area (BSA), and normal ranges were assessed according to values published by Kampmann et al. [4].

When the z-scores of RVDD, LVEDD, and the LAD were >2, right ventricle (RV), left ventricle (LV), or left atrium (LA) enlargement was diagnosed.

The following parameters were calculated from M-mode measurements: LV volumes at end diastole (EDV) and end systole (ESV) according to the method described by Tortoledo et al. [5] and ejection fraction (EF), fractional shortening (FS), and stroke volume (SV).

Left ventricular mass (LVM) was calculated according to the formula described by Devereux et al. [6]. The LVM z-score for height was calculated using the method described by Foster et al. [7]. The LVM index (LVMI) was obtained by dividing LVM by height$^{2.7}$ to normalize and linearize the relationship between LVM and height [8]. Left ventricular hypertrophy (LVH) was based on the reference values published by Diaz et al. [9]. For the purpose of this study, HR was evaluated. Original data were converted into z-scores.

Moreover, the cardiac index was calculated. The cardiac index was the normalized value of cardiac output calculated for BSA.

Outcome variables

The primary outcome variable was the identification of a cardiac complication. Cardiac complications were diagnosed if at least one of the following abnormalities was detected: (1) LVH; (2) systolic dysfunction, defined as abnormal EF and/or FS; and (3) RV, LV or LA enlargement. The secondary outcome variables included absolute and relative values of LVEDD, LVESD, IVSd, IVSs, LVPWd, LVPWs, RVDD, LAD, EF, FS, LVM, LVMI, and cardiac index.

Statistical analysis

The groups were compared using Student's t-test, the Mann–Whitney U test, the χ^2 test, or Fisher's exact test, as appropriate. The Shapiro-Wilk test was used to check the normality of the distribution of quantitative variables. Based on the obtained results, the hypothesis of normal distribution in the case of variables such as birth weight, gestational age, and age at evaluation was rejected. For the remaining variables, parametric tests were used in the further part of the analysis. The analysis of HR rates utilized an ANOVA of HR adjusted for BSA. The comparison of selected echocardiographic measurements between children aged 7 and 11 years was performed with a paired t-test.

The study compared multiple echocardiographic variables and required corrections for multiple testing. The Sidak correction for correlated variables was used.

The corrected alpha level based on a mean correlation factor of 0.251 between different measurements equaled 0.0107. Based on this calculation, if the unadjusted P value was <0.0107, then the risk of type I error was <5%. Finally, statistical significance in the presented paper for M-mode measurements was defined as $P = 0.01$ on a 2-sided test; in all other analyses, statistical significance was defined as $P = 0.05$ on a 2-sided test.

Sample size estimations were based on the assumption that the follow-up rate among ELBW children would be as high as 90% (80 children). The presumed frequency of the primary endpoints was adopted from previously published studies that evaluated healthy Polish children aged 6–7 years whose LVH incidence ranged from 2% to 3.3%. Assuming that the risk of type I error equaled 5% (1-sided test) and the control group would include 40 children, a study with a power of 80% should demonstrate a 15% difference in the incidence of the primary endpoints between the ELBW and control groups.

The birth weight, gestational age, and age at evaluation were presented as a median and 25th–75th percentile, other quantitative variables as mean and standard deviation (SD) values. The qualitative variables were presented as number (n) and percentage (%).

Data were analyzed using SPSS statistical software, version 25 (2020 by IBM, USA).

RESULTS

Characteristics of the studied groups

Sixty-four children born as ELBW infants, who constituted 79% of the cohort evaluated at the age of 7 years during the first follow-up assessment, entered the current study at a mean age of 11 years. Their median birth weight was 875 g (25th–75th percentile, 750 g–960 g), and their median gestational age was 27 weeks (25th–75th percentile, 25–28 weeks). Nineteen of them had been small for their gestational age (30%), a majority of them had received surfactant (49 participants, 77%), and almost all of them had required mechanical ventilation (58 participants, 91%). Nineteen infants had been treated surgically for patent ductus arteriosus (30%), and 26 children had been receiving oxygen at 36 weeks of postmenstrual age (41%). The control group consisted of 36 full-term children, corresponding to 90% of the same group from the previous study 4 years earlier.

There were no significant demographic differences at the age of 7 years between the returning participants in the current study and the children who failed to return after the first follow-up study (data available on request).

The children from the ELBW group had lower birth weights (median, 875 g vs 3570 g; P <0.001) and younger gestational ages (median, 27 weeks vs 40 weeks; P <0.001) than the control group. They were also less likely to have been born via vaginal delivery (20% vs 86%; P <0.001). The incidence of multiple pregnancy in the ELBW group was

Table 1. Comparison of selected demographic and clinical variables in the study groups and their control groups

	Study group (n = 64)	Control group (n = 36)	P value
Demographic variables			
Female	43 (67)	17 (47)	0.06[a]
Birth weight, g, median (25th–75th percentile)	875 (750–960)	3570 (3395–3880)	<0.001[b]
Gestational age, weeks, median (25th–75th percentile)	27 (25–28)	40 (39–40)	<0.001[b]
Vaginal delivery	13 (20)	31 (86)	<0.001[a]
Multiple pregnancy	9 (14)	0 (0)	0.02[a]
Small for gestational age	19 (30)	2 (6)	0.004[a]
First follow-up			
Age at evaluation, years, median (25th–75th percentile)	6.5 (6.4–6.8)	6.9 (6.4–7.4)	0.04[b]
Height, cm, mean (SD)	116 (6.3)	124 (7.4)	<0.001[c]
Height, z-score, mean (SD)	−1.08 (1.3)	0.21 (1.0)	<0.001[c]
Weight, kg, mean (SD)	19.5 (3.8)	25.2 (5.3)	<0.001[c]
Weight, z-score, mean (SD)	−0.92 (1.3)	0.26 (1.2)	<0.001[c]
Second follow-up			
Age at evaluation, years, median (25th–75th percentile)	11 (10.8–11.3)	10.7 (10.2–11.1)	0.01[b]
Height, cm, mean (SD)	141 (8)	146 (8)	0.003[c]
Height, z-score, mean (SD)	−0.88 (1.2)	0.20 (1.1)	<0.001[c]
Weight, kg, mean (SD)	33.7 (8.2)	40.4 (9.9)	<0.001[c]
Weight, z-score, mean (SD)	−0.92 (1.3)	0.24 (1.2)	<0.001[c]

Data are presented as the number (percentage) of patients unless otherwise indicated.

P value: [a]Fisher's exact test, [b]Mann–Whitney U test, [c]Student's t-test

significantly higher (14% vs 0%; $P = 0.02$), and there were significantly more infants who were small for gestational age (30% vs 6%; $P = 0.004$). In the current study, the 11-year-old children in the ELBW group were significantly smaller (mean, 141 cm vs 146 cm; $P = 0.003$) and weighed less than those in the control group (mean, 33.7 vs 40.4 kg; $P < 0.001$). The same significance was found when those values were converted into z-scores. A detailed comparison of the selected demographic and clinical variables in the ELBW and control groups is presented in Table 1.

Echocardiography
In the current study of 11-year-old children, we identified only one ELBW child with LVH. None of the other children who were studied, whether premature or fullterm, fulfilled the criteria for the diagnosis of LV and RV enlargement. We also diagnosed only one ELBW child with LA enlargement.

Absolute and relative M-mode measurements are presented in Table 2. All the results expressed as z-scores for BSA for all the analyzed parameters, except for RVDD, were 0.5 to 1 SD lower in the group of ELBW children than in the controls at both time points, 7 and 11 years of age. There was no difference in RVDD between ELBW and full-term children at 11 years of age. Statistically significant differences between the studied and control groups were observed for RVDD, LVEDD, aortic diameter (AoD), and LAD in 7-year-old children and for LVEDD, LVESD, AoD, and LAD in 11-year-old children.

The comparisons of LVM, LVMI, diastolic parameters, and LV function variables between the two follow-up groups (at the ages of 7 and 11 years) are summarized in Table 3. LVM was consistently smaller in the ELBW children than in the control children at 7 and at 11 years of age. However, the rate of LVM increase in the ELBW group

was comparable to that in the control group, equaling approximately 20% for both of those groups during the 4-year observation period. The LVMI differences were not statistically significant for either 7-year-old or 11-year-old children. The mean difference between the LVMI of the ELBW children and full-term controls was 4.1 g/m$^{2.7}$ at the age of 7 years and 6.2 g/m$^{2.7}$ 4 years later. Stroke volume remained lower in the prematurely born children at ages of 7 and 11 years. No significant differences were found in cardiac indexes in the analyses of 7-year-old and 11-year-old children.

The FS and EF did not differ significantly between the ELBW participants and their controls at the age of 7 years. However, we found higher values of FS and EF in the ELBW children than in the control children four years later.

There were only two 11-year-old ELBW children with fractional shortening <25% (absolute values 23.6% and 23.8%). Left ventricular ejection fraction <55% was diagnosed in two prematurely born children and two fullterm participants (absolute values from 50% to 55%) at the age of 11 years.

A comparison of the results for mean differences between selected echocardiographic measurements, presented as paired t-tests for two time points (7 and 11 years of age) in both analyzed groups of children, is shown in Table 4. Data were presented as z-scores. The mean differences in z-score values in the presented echocardiographic measurements were approximately 0.5 SD for the majority of presented variables in the two analyzed groups, and the confidence intervals were entirely above 1.

Heart rate assessment
The mean value of HR, whether presented as an absolute value or a z-score, was significantly higher in the ELBW chil-

Table 2. Comparison of M-mode echocardiographic measurements in 7- and 11-year-old extremely low birth weight newborns and their controls

	First follow-up (at the age of 7 years)			Second follow-up (at the age of 11 years)		
	Study group (n = 64)	Control group (n = 36)	P value[a]	Study group (n = 64)	Control group (n = 36)	P value[a]
Absolute values, cm, mean (SD)						
RVDD	1.20 (0.34)	1.66 (0.38)	0.001	1.66 (0.36)	1.74 (0.47)	0.35
IVSd	0.56 (0.16)	0.58 (0.13)	0.78	0.59 (0.28)	0.66 (0.18)	0.21
LVEDD	3.17 (0.42)	3.65 (0.39)	<0.001	3.79 (0.38)	4.14 (0.39)	<0.001
LVPWd	0.52 (0.10)	0.59 (0.12)	0.02	0.56 (0.12)	0.62 (0.13)	0.03
IVSs	0.83 (0.21)	0.92 (0.14)	0.02	0.93 (0.17)	1.02 (0.19)	0.01
LVESD	2.36 (0.29)	2.67 (0.37)	<0.001	2.51 (0.33)	2.86 (0.30)	<0.001
LVPWs	0.73 (0.13)	0.90 (0.31)	0.003	0.95 (0.19)	0.97 (0.16)	0.64
AoD	1.44 (0.18)	1.65 (0.20)	<0.001	1.75 (0.22)	1.99 (0.26)	<0.001
LAD	1.79 (0.29)	2.13 (0.29)	<0.001	2.1 (0.33)	2.33 (0.33)	0.002
Relative values, cm Expressed as z-score for body surface area (SD)						
RVDD	−1.51 (1.23)	−0.35 (0.94)	0.001	−0.62 (0.85)	−0.60 (1.25)	0.95
IVSd	0.04 (1.19)	−0.10 (1.06)	0.54	−0.47 (1.36)	−0.08 (1.16)	0.16
LVEDD	0.27 (0.98)	0.47 (1.02)	0.001	−1.01 (0.91)	−0.35 (0.79)	<0.001
LVPWd	−0.63 (1.29)	0.24 (0.86)	0.35	−0.23 (1.06)	0.08 (0.99)	0.16
IVSs	0.16 (1.09)	0.52 (0.87)	0.11	−0.23 (1.06)	0.07 (0.99)	0.19
LVESD	0.19 (0.95)	0.66 (1.05)	0.035	−0.29 (0.92)	0.57 (0.65)	<0.001
LVPWs	−1.78 (1.14)	−1.1 (1.26)	0.15	−0.99 (1.27)	−1.11 (1.02)	0.67
AoD	0.25 (1.27)	0.89 (0.99)	0.01	0.63 (1.14)	1.63 (1.30)	<0.001
LAD	−1.01 (1.10)	−0.07 (0.92)	<0.001	−1.75 (0.97)	−0.01 (0.86)	<0.001

Data are presented as the mean (SD).
[a]In order to correct for multiple testing, the Sidak adjustment for correlated variables was used. Significance was defined as a 2-sided $P \leq 0.01$.
Abbreviations: AoD, aortic diameter; IVSd, thickness of the intraventricular septum at end diastole; IVSs, thickness of the intraventricular septum at end systole; LAD, left-atrial dimension; LVEDD, left ventricular dimension at end diastole; LVESD, left ventricular dimension at end systole; LVPWd, left ventricular posterior wall thickness at end diastole; LVPWs, left ventricular posterior wall thickness at end systole; RVDD, right ventricular end-diastolic dimension

Table 3. Analysis of the selected left ventricle parameters in the study and control groups at 7 and 11 years of age

	First follow-up (at the age of 7 years)			Second follow-up (at the age of 11 years)		
	Study group (n = 64)	Control group (n = 36)	P value[a]	Study group (n = 64)	Control group (n = 36)	P value[a]
LVM, g	47.7 (15.3)	65.6 (15.6)	0.001	56.8 (42.7)	78.8 (31.4)	0.008
LVMI, g/m²·⁷	31.9 (9.5)	36 (8.5)	0.04	21.9 (16)	28.1 (17.4)	0.04
Fraction of shortening	32.1 (7.0)	33.0 (6.9)	0.23	33.6 (5.5)	30.8 (4.34)	0.009
Ejection fraction	0.61 (0.10)	0.62 (0.09)	0.33	0.63 (0.07)	0.58 (0.06)	0.005
EDV, mL	52 (17)	72 (19)	<0.001	68 (29)	77 (30)	0.02
ESV, mL	20 (6.5)	27 (9.3)	<0.001	34 (15.6)	40.1 (15.9)	0.004
SV, mL	32 (13.6)	45 (14)	<0.001	39 (10.1)	45.2 (11.4)	0.01
Cardiac index, L/m²	3.34 (1.96)	3.18 (1.74)	0.37	2.81 (0.89)	2.95 (0.69)	0.46
Mean HR, per min	93 (8.1)	86 (7.4)	0.001	86 (7.2)	82 (8.2)	0.05
Mean HR z-score	1.25 (1.34)	0.58 (1.45)	0.01	1.19 (1.2)	0.62 (1.6)	0.03

Data are presented as the mean (standard deviation).
[a]In order to correct for multiple testing, the Sidak adjustment for correlated variables was used. Significance was defined as a 2-sided $P \leq 0.01$.
Abbreviations: EDV, left ventricular volume at end diastole; ESV, left ventricular volume at end systole; HR, heart rate; LVM, left ventricular mass; LVMI, left ventricular mass index; SV, stroke volume

Table 4. Results of paired t-tests for selected echocardiographic measurements

	Study group (n = 64)	P for paired t-test[a]	Control group (n = 36)	P for paired t-test[a]
RVDD	0.96 (0.55 to 1.37)	0.001	−0.23 (−0.68 to 0.21)	0.29
IVSd	−0.44 (−0.94 to 0.05)	0.08	−0.07 (−0.52 to 0.38)	0.75
LVEDD	−0.42 (−0.80 to 0.04)	0.03	−0.65 (−1.07 to −0.13)	0.03
LVPWd	−0.49 (−0.88 to 0.09)	0.08	−0.34 (−0.85 to 0.18)	0.20
IVSs	−0.06 (−0.39 to 0.27)	0.72	−0.24 (−0.66 to 0.17)	0.23
LVESD	−0.52 (−0.79 to −0.24)	0.001	−0.08 (−0.58 to 0.42)	0.74
LVPWs	0.58 (−0.02 to 1.19)	0.07	0.03 (−0.53 to 0.59)	0.91
AoD	0.54 (0.11 to 0.97)	0.02	0.63 (0.12 to 1.09)	0.01
LAD	0.52 (0.03 to 1.01)	0.04	−0.09 (−0.41 to 0.23)	0.56

Data are presented as the mean difference (95% confidence interval for difference).
[a]In order to correct for multiple testing, the Sidak adjustment for correlated variables was used. Significance was defined as a 2-sided $P \leq 0.01$.
Abbreviations: see Table 2

dren than in the controls at age 7. The HR values remained higher in 11-year-old ELBW children, but the differences between the study group and fullterm controls were smaller at this point than at 7 years of age.

DISCUSSION

The study presented here is a follow-up to the one performed 4 years earlier that evaluated heart structure and function in 7-year-old children born prematurely as ELBW infants [3].

As in the previous study [3], we did not find any significant differences in the development of cardiac complications between the ELBW children and full-term participants. Previous studies reported similar observations [10, 11].

The cardiac dimensions, such as LV, LA, and AoD, were smaller in the 11-year-old ELBW children, as shown in the M-mode analysis. The results were comparable to those of our previous study, in which the same group of 7-year-old ELBW patients was diagnosed in a similar fashion. Other echocardiographic studies reported similar observations in such groups of patients [12, 13]. From 7 to 11 years of age, there was no decrease in the ratio of average RV dimensions between ELBW children and their full-term counterparts that was observed 4 years earlier in the same population. We believe that one possible explanation is the specificity of the M-mode and its use in the evaluation of RV dimensions, which were assumed to be the least precise and objective.

The LV of the ELBW children remained smaller than that of the controls over the 4 years between the two studies. However, there was no significant difference in the cardiac index, calculated as cardiac output adjusted for BSA, between the studied groups and the control groups of children at 7 or 11 years of age. One possible explanation for the unchanged value of the cardiac index could be faster HR compensating for the smaller SV in the ELBW participants, as previously reported in a number of studies [10, 13]. The differences in the evaluated parameters regarding LVM were the same at ages 7 and 11 in the two groups. However, the absolute value of the LVM and the LVMI adjusted for the child's height were significantly smaller in the ELBW children than in control children at 11 years of age.

A number of studies have reported a significant association between extreme prematurity and cardiovascular complications. Mohlkert et al. [13] demonstrated structural cardiac changes in this particular group of patients that resulted in evident systolic and diastolic dysfunction of the LV. Altered myocardial function was also described in infancy [14, 15]. Hoki et al. [16] studied a group of almost 500 children hospitalized in infancy due to apparent life-threatening events to identify potential predictors of cardiac disease. During 7 years of observation, the only clinical parameter indicating future heart problems was prematurity. In another study, Bolton et al. [17] demonstrated impaired hemodynamics of the large vessels in children

born extremely prematurely. Echocardiography of those patients when they were 11 years old clearly showed an increased augmentation index, reflecting higher systemic arterial stiffness as calculated from the ascending aortic pressure waveform. However, some studies speculated that fetal growth restriction played a larger role than prematurity in cardiac morphology and/or postnatal cardiac adaptation [18, 19]. A cardiac evaluation of prematurely born adults showed some serious structural and functional changes in their hearts, including LVH and systolic and diastolic dysfunction of the LV [12].

One of the most important findings of our present study was the verification that the ELBW and control groups have the same rate of heart growth. We recorded a 20% increase in the LVM in both populations, with the difference in heart mass remaining unaltered at 7 and 11 years of age. Therefore, we hypothesized that the decreased heart size of the ELBW children resulted mostly from damage in the early perinatal period of life, whereas their further development was similar to that of healthy full-term children. The transition process from fetal to neonatal circulation in preterm infants is complex, and it can be more challenging in extremely low birth weight infants with hemodynamic instability [20]. This hypothesis could be also supported by the results of the study by Bokiniec et al. [21]. Compared with term neonates on the 28th day of life, preterm neonates evaluated at week 40 of postconceptional age had reduced myocardial thickness already at that age.

We further supported the above conclusions of comparable development of the hearts in ELBW and full-term children with a unique paired t-test for selected echocardiographic measurements expressed as z-scores for the two time points (7 and 11 years of age). Our results showed similar intensities of heart growth in both the studied and control groups over the 4 years between follow-up studies. The z-score differences in the majority of the echocardiographic parameters evaluated with the paired t-test were less than 0.5 SD in the ELBW children. Hence, we could assume that the hearts of these children were developing harmoniously, without overgrowth or involution.

The results of two studies of 7-year-old children in 2013 [3] and a recent study of 11-year-old children indicated that the most serious impact on ELBW children's heart lesion development occurred in the fetal and early postnatal age, when cardiomyocyte hyperplasia plays a pervasive role [22]. Our results indicated that the later development of extremely premature children's hearts remained stable and balanced, similar to the heart development of their full-term peers.

However, although our studies showed that the structural and functional cardiac changes in extremely prematurely born children did not constitute a clinical problem during infancy or school age, we recommend further echocardiographic follow-up investigations to monitor for potential cardiovascular complications in adulthood.

The strengths of our study included its multicenter, population-based design and the objectivity of the ob-

servations, which were based on standardized echocardiographic assessments. In the follow-up evaluation at 11 years, we enrolled satisfactory numbers of representatives for both the study and control groups, which justified and substantiated our conclusions.

Limitations

The main limitation of our study was the lack of a parallel clinical evaluation to determine whether the observed structural cardiac findings and faster HR in ELBW children affected their daily lives/routines. Moreover, there was no formal test of interrater reliability; however, post hoc analysis did not reveal any statistically significant differences in the measurements between the two echocardiographers.

CONCLUSIONS

The analyzed ELBW children had smaller heart sizes than the full-term controls at both the ages of 7 and 11 years. Almost all of their echocardiographic parameters, expressed as z-scores normalized for BSA, were 0.5–1 SD lower in the two follow-up assessments over 4 years of observation. We observed that the heart growth of the ELBW group was comparable to that of the full-term controls, and it increased by approximately 20% in both groups during the 4-year observation period. We believe that the most critical cardiac lesions occur in the fetal and early postnatal life of extremely premature children; therefore, despite their normal cardiac development up to this point during school age, they would require repeated monitoring to diagnose possible cardiac complications later in life.

Article information

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