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Association Between Preterm Birth and Arrested Cardiac Growth in Adolescents and Young Adults

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IMPORTANCE Premature birth is associated with substantially higher lifetime risk for cardiovascular disease, including arrhythmia, ischemic disease, and heart failure, although the underlying mechanisms are poorly understood.

OBJECTIVE To characterize cardiac structure and function in adolescents and young adults born preterm using cardiac magnetic resonance imaging (MRI).

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional cohort study at an academic medical center included adolescents and young adults born moderately to extremely premature (20 in the adolescent cohort born from 2003 to 2004 and 38 in the young adult cohort born in the 1980s and 1990s) and 52 age-matched participants who were born at term and underwent cardiac MRI. The dates of analysis were February 2016 to October 2019.

EXPOSURES Premature birth (gestational age ≤32 weeks) or birth weight less than 1500 g.

MAIN OUTCOMES AND MEASURES Main study outcomes included MRI measures of biventricular volume, mass, and strain.

RESULTS Of 40 adolescents (24 [60%] girls), the mean (SD) age of participants in the term and preterm groups was 13.3 (0.7) years and 13.0 (0.7) years, respectively. Of 70 adults (43 [61%] women), the mean (SD) age of participants in the term and preterm groups was 25.4 (2.9) years and 26.5 (3.5) years, respectively. Participants from both age cohorts who were born prematurely had statistically significantly smaller biventricular cardiac chamber size compared with participants in the term group: the mean (SD) left ventricular end-diastolic volume index was 72 (7) vs 80 (9) and 80 (10) vs 92 (15) mL/m^2 for adolescents and adults in the preterm group compared with age-matched participants in the term group, respectively ($P < .001$), and the mean (SD) left ventricular end-systolic volume index was 30 (4) vs 34 (6) and 32 (7) vs 38 (8) mL/m^2, respectively ($P < .001$). Stroke volume index was also reduced in adolescent vs adult participants in the preterm group vs age-matched participants in the term group, with a mean (SD) of 42 (7) vs 46 (7) and 48 (7) vs 54 (9) mL/m^2, respectively ($P < .001$), although biventricular ejection fractions were preserved. Biventricular mass was statistically significantly lower in adolescents and adults born preterm: the mean (SD) left ventricular mass index was 39.6 (5.9) vs 44.4 (7.5) and 40.7 (7.3) vs 49.8 (14.0), respectively ($P < .001$). Cardiac strain analyses demonstrated a hypercontractile heart, primarily in the right ventricle, in adults born prematurely.

CONCLUSIONS AND RELEVANCE In this cross-sectional study, adolescents and young adults born prematurely had statistically significantly smaller biventricular cardiac chamber size and decreased cardiac mass. Although function was preserved in both age groups, these morphologic differences may be associated with elevated lifetime cardiovascular disease risk after premature birth.

Supplemental content

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Premature birth, defined as less than 37 weeks' completed gestation, occurs in 1 in 10 live births worldwide and accounts for almost half a million deliveries in the United States annually.[1,2] Given the dramatic improvements in neonatal care during the 1980s and early 1990s, the edge of viability has rapidly improved from 32 weeks' to approximately 23 weeks' gestation, with an ever-growing number of extremely preterm infants now surviving into adolescence and adulthood. Despite improved medical care, these individuals are at higher risk for pulmonary,[3-5] systemic cardiovascular,[6-11] pulmonary vascular,[12-15] and metabolic[16-18] disease. Because of increased risk for a number of comorbidities, the National Institutes of Health now recommends that preterm birth be considered a chronic medical condition.[4,5]

Despite the previously mentioned multisystem consequences, little is known about the long-term implications of premature birth on cardiac structure and function. A recent Swedish registry study[19] of 2.6 million individuals born from 1987 to 2012 identified a 17-fold increased risk of incident heart failure among children and young adults born extremely preterm, although the mechanisms are largely unknown. In addition, premature birth is associated with higher risk for ischemic disease and arrhythmias.[20,21] A large single-center cardiac magnetic resonance imaging (MRI) study conducted by Lewandowski et al[7,8] at the University of Oxford (Oxford, United Kingdom) of 102 adults aged 25 years who were born at a mean gestational age of 30 weeks between 1982 and 1985 identified a unique left ventricular (LV) geometry with smaller biventricular cardiac chamber size and higher biventricular mass. Furthermore, the degree of prematurity was an independent predictor of biventricular hypertrophy; although LV ejection fraction was preserved, LV strain rates and right ventricular (RV) ejection fraction were lower in preterm-born adults.[7,8] However, echocardiography-based studies[22-24] in younger populations demonstrate preserved biventricular function with smaller biventricular cardiac chamber size and generally lower cardiac mass, raising the question of whether hypertrophy simply develops later in life. In addition, recent studies from both the University of Wisconsin-Madison[12] and the University of Oxford[25] demonstrate substantial functional consequences of these structural abnormalities in adults born preterm, characterized by a blunted stroke volume (SV) response to exercise.

Given the substantial improvements in neonatal care over the past 3 decades, it is unclear to what extent the prior MRI findings[7,8] of smaller biventricular cardiac chamber size with biventricular hypertrophy and depressed LV and RV function in adulthood are broadly generalizable to children and adults born during more recent eras of neonatal care. The objective of this study was to comprehensively evaluate cardiac structure and function in adolescents and young adults born prematurely using cardiac MRI. Our central hypothesis was that adolescents and adults born prematurely would have altered cardiac structure and function compared with term-born controls.

Key Points

Question What are the consequences of premature birth for later cardiac structure and function?

Findings In this cardiac magnetic resonance imaging–based cross-sectional cohort study, adolescents (n = 20) and young adults (n = 38) born moderately to extremely preterm (≤32 weeks) demonstrated statistically significantly smaller biventricular cardiac chamber size and lower biventricular mass compared with 52 age-matched participants who were born at term. Cardiac function was preserved, with a hypercontractile strain pattern in adults.

Meaning Adolescents and young adults born prematurely had statistically significantly smaller biventricular cardiac chamber size with preserved function, notably without a hypertrophic response, which may contribute to their increased lifetime cardiovascular risk.

Methods

Participants

In this cross-sectional cohort study, adolescent (n = 20) and young adult (n = 38) participants who were born moderately to extremely premature were recruited from the Newborn Lung Project, a cohort of infants born with very low birth weight (<1500 g) between 1988 and 1991 (25 adults) or 2003 and 2004 (20 adolescents) in Wisconsin or Iowa and followed up prospectively at the University of Wisconsin-Madison,[26-30] or from the general public with confirmation of birth history from neonatal records (13 individuals with gestational age ≤32 weeks or birth weight <1500 g). The dates of analysis were February 2016 to October 2019. Comprehensive neonatal records were available for all participants in the preterm group. Age-matched control participants who were born at term from the same birth years were recruited from the local population (n = 52), with a subset of adolescents recruited from prior participation in the Newborn Lung Project as normal birth weight control participants at age 2 years.[31,32] Participants were free of cardiovascular or respiratory illness and were nonsmokers. All participants and adolescents' guardians were informed of the objective and risks of the study and provided written informed consent, including assent for adolescents, in accordance with the standards set by the Declaration of Helsinki.[33] The protocols were approved by the Institutional Review Board at the University of Wisconsin-Madison.

Cardiovascular MRI Acquisition and Analysis

Cardiac MRI was performed at rest on a clinical 3-T MRI scanner (Discovery MR750; GE Healthcare) or 3-T positron emission tomography (PET)-MRI scanner (GE Signa PET/MR Discovery 750W; GE Healthcare). To characterize cardiac function, a prospective electrocardiogram-gated, multislice balanced, steady-state free precession sequence was acquired during an end-expiratory breath hold with a field of view of 35 × 35 cm, spatial resolution of 1.4 × 1.4 mm, slice thickness of 7 mm, 17 slices, breath hold length of 13 seconds, and 20 reconstructed cardiac phases.

Analysis of volumetric cardiac images was performed by an analyst from the University of Wisconsin-Madison Medical Imaging Research Support image analysis core laboratory, who was blinded to birth history and used commercially available software (cvi42, version 5.6.6; Circle Cardiovascular Imaging Inc). The LV and RV end-diastolic volume (EDV), end-systolic volume (ESV), SV, cardiac output (CO), and ventricular mass were calculated from short-axis, cine-balanced, steady-state free precession series. Ventricular volumes and mass in end-diastole were indexed to body surface area. Three slices from the LV and RV (base, mid, and apex) short-axis and long-axis cine MRI scans were used to analyze longitudinal, circumferential, and radial dimensions and strain as a function of time, including average peak strain and systolic and diastolic strain rate, using commercially available software (Segment, version 2.2 R6423 strain analysis module; Medviso).[34]

Statistical Analysis

Data were initially stratified by age group (adolescents or adults) and birth status (term or preterm). Baseline anthropometric and MRI data were compared across birth status within each age group using unpaired Wilcoxon rank sum tests. Neonatal characteristics were compared between adolescent and adult preterm birth cohorts using unpaired Wilcoxon rank sum tests. To evaluate the association between preterm birth and cardiovascular characteristics for the entire group, separate linear regression models were developed to predict each cardiovascular variable with age and birth status (term or preterm) as covariates. Finally, to investigate the association of preterm birth characteristics with subsequent cardiac function, we a priori selected chronological age, gestational age, total days on assisted ventilation, and patent ductus arteriosus, and multivariable regression models were used to predict cardiac mass and function. The level of statistical significance was assessed a priori at $P < .05$, and all tests were 2-tailed. Data are presented as means (SDs), unless otherwise noted. Statistical analyses were performed in R (R Foundation for Statistical Computing),[35] and graphs were generated using Prism GraphPad, version 7 (GraphPad Software).

Results

Participant Baseline Characteristics

Adolescents born prematurely were of a similar sex distribution and similar age as their term-born counterparts (**Table 1**). Of 40 adolescents (24 [60%] girls), the mean (SD) age of participants in the term and preterm groups was 13.3 (0.7) years and 13.0 (0.7) years, respectively. Of 70 adults (43 [61%] women), the mean (SD) age of participants in the term and preterm groups was 25.4 (2.9) years and 26.5 (3.5) years, respectively. Although the adults in the preterm group were about 1 year older than the adults in the term group, the adult participants were born in the same birth years. Participants who were born preterm were shorter and demonstrated higher systolic, diastolic, and mean systemic blood pressure. Overall, gestational age and birth weight were similar in the adolescent and adult preterm cohorts. Compared with the adolescent cohort, the adult cohort had lower Apgar scores at birth and longer time on invasive ventilation, although total days on assisted ventilation (invasive and noninvasive combined) and days in the neonatal intensive care unit were not statistically significantly different between the 2 cohorts. Overall, 42 of 58 (72%) infants born preterm required invasive ventilation. Adults born prematurely were also statistically significantly less likely to receive antenatal corticosteroids or surfactant, reflecting changing neonatal practice patterns during the late 1980s and early 1990s. Rates of patent ductus arteriosus requiring treatment and bronchopulmonary dysplasia were similar between groups.

Biventricular Structure and Function

Main cardiac structure and function outcomes assessed via MRI are listed in **Table 2**. Notably, participants who were born prematurely from both age cohorts had statistically significantly smaller biventricular cardiac chamber size compared with participants in the term group: the mean (SD) LV EDV index was 72 (7) vs 80 (9) and 80 (10) vs 92 (15) mL/m^2 for adolescents and adults who were born prematurely compared with age-matched participants in the term group, respectively ($P < .001$), and the mean (SD) LV end-systolic volume index was 30 (4) vs 34 (6) and 32 (7) vs 38 (8) mL/m^2, respectively ($P < .001$). Stroke volume index was also reduced, with a mean (SD) of 42 (7) vs 46 (7) and 48 (7) vs 54 (9) mL/m^2 ($P < .001$) for adolescents and adults who were born prematurely compared with age-matched participants in the term group, respectively, although biventricular ejection fractions were preserved. Resting heart rates and cardiac indexes were similar between participants who were born at term or preterm within each birth cohort.

However, contrary to prior single-center studies[7,8] in adults born prematurely, although consistent with prior studies[22,23] in children, the LV and RV mass indexes were also statistically significantly smaller in adolescents and adults born preterm, without a statistically significant difference in the ratio of RV mass to LV mass to suggest a differential ventricular hypertrophy response. The mean (SD) LV mass index was 44.4 (7.5) vs 39.6 (5.9) for adolescent term vs preterm and 49.8 (14.0) vs 40.7 (7.3) for adult term vs preterm; the mean (SD) RV mass index was 6.1 (1.0) vs 5.7 (0.9) for adolescent term vs preterm and 9.6 (2.6) vs 8.5 (1.8) for adult term vs preterm.

To further characterize contractile function, biventricular strain was analyzed. Although there were no statistically significant differences in biventricular strain among adolescents, adults born prematurely demonstrated statistically significantly higher LV longitudinal, RV longitudinal, and RV circumferential strain compared with term-born adults, suggesting a hypercontractile heart (**Figure** and **Table 3**). The mean (SD) LV longitudinal strain was −12.7 (2.8) vs −14.2 (2.4) for term vs preterm, the mean (SD) RV longitudinal strain was −11.7 (3.1) vs −13.5 (3.6) for term vs preterm, and the RV circumferential strain was −8.3 (2.1) vs −10.8 (2.4) for term vs preterm adults.

Table 1. Baseline Characteristics[a]

Characteristic	Adolescents			Adults			All
	Mean (SD)			Mean (SD)			
	Term (n = 20)	Preterm (n = 20)	*P* value[b]	Term (n = 32)	Preterm (n = 38)	*P* value[b]	*P* value[c]
Male, No. (%)	9 (45)	7 (35)	.75	13 (41)	14 (37)	.94	.65
Chronological age, y	13.3 (0.7)	13.0 (0.7)	.09	25.4 (2.9)	26.5 (3.5)	.02	.12
Anthropometric measures for adolescents and adults							
Height, m	1.65 (0.08)	1.58 (0.09)	.01	1.72 (0.09)	1.68 (0.08)	.06	.002
Weight, kg	54.7 (14.0)	47.1 (8.3)	.10	69.5 (9.9)	75.9 (24.0)	.71	.92
Body surface area, m^2	1.57 (0.22)	1.44 (0.16)	.05	1.82 (0.17)	1.86 (0.29)	.96	.39
Body mass index[d]	20.0 (4.1)	18.7 (2.5)	.43	23.3 (1.8)	26.9 (8.4)	.08	.13
Systolic BP, mm Hg	110 (5)	115 (6)	.01	114 (9)	116 (11)	.45	.11
Diastolic BP, mm Hg	60 (5)	66 (5)	.004	70 (6)	73 (8)	.10	.003
Mean systemic BP, mm Hg	77 (4)	82 (4)	.001	84 (6)	87 (8)	.15	.01
Neonatal characteristics for adolescents and adults born prematurely							
Gestational age, wk	NA	28.5 (1.9)	NA	NA	29.0 (2.7)	NA	.35
Birth weight, g	NA	1150 (270)	NA	NA	1187 (397)	NA	.99
Apgar score at 1 min	NA	4.8 (2.1)	NA	NA	4.3 (2.3)	NA	.40
Apgar score at 5 min	NA	7.7 (1.3)	NA	NA	6.7 (1.7)	NA	.03
Antenatal corticosteroids, No. (%)	NA	16 (80)	NA	NA	11 (29)	NA	.001
Surfactant, No. (%)	NA	14 (70)	NA	NA	10 (26)	NA	.01
Postnatal corticosteroids, No. (%)	NA	3 (15)	NA	NA	6 (16)	NA	.99
Invasive ventilation days	NA	6.4 (14.0)	NA	NA	11.8 (13.6)	NA	.05
CPAP days	NA	8.9 (13.0)	NA	NA	2.1 (5.9)	NA	.01
Total days on assisted ventilation[e]	NA	13.7 (19.0)	NA	NA	14.2 (14.6)	NA	.58
Days on oxygen	NA	33 (39)	NA	NA	45 (89)	NA	.99
Days in the NICU	NA	52.8 (17.4)	NA	NA	61.3 (28.3)	NA	.18
Patent ductus arteriosus, No. (%)	NA	6 (30)	NA	NA	18 (47)	NA	.24
Bronchopulmonary dysplasia, No. (%)[f]	NA	9 (45)	NA	NA	15 (39)	NA	.99
Neonatal sepsis, No. (%)	NA	3 (15)	NA	NA	14 (37)	NA	.12

Abbreviations: BP, blood pressure; CPAP, continuous positive airway pressure; NA, not applicable; NICU, neonatal intensive care unit.

[a] Categorical variables are expressed as No. (%), and continuous data are expressed as mean (SD).

[b] *P* values are by unpaired Wilcoxon rank sum tests within each age cohort.

[c] *P* values are for all individuals in the term and preterm groups across age cohorts by least-squares means from an age-adjusted linear model.

[d] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[e] Total days on assisted ventilation include the combination of invasive and noninvasive (CPAP) ventilation.

[f] Bronchopulmonary dysplasia is defined clinically by the use of supplemental oxygen at 36 weeks' postmenstrual age.

Sex Differences in Cardiac Structure

The MRI volumetric data were analyzed by sex using least-squares means from an age-adjusted linear model (eTable in the Supplement). Biventricular volumes (SVi) were smaller in both male and female individuals born preterm compared with the sex-specific individuals born at term ($P < .05$ for all). The mean (SD) LV EDVi was 94.2 (2.5) vs 80.4 (2.6) ($P < .001$) for male term vs preterm and 82.7 (1.9) vs 74.8 (1.7) ($P = .003$) for female term vs preterm. The mean (SD) LV ESVi was 40.3 (1.5) vs 33.7 (1.5) ($P = .003$) for male term vs preterm and 33.7 (1.0) vs 30.0 (0.9) ($P = .007$) for female term vs preterm. The mean (SD) LV SVi was 53.9 (1.9) vs 46.7 (1.9) ($P = .01$) for male term vs preterm and 48.9 (1.3) vs 44.7 (1.2) ($P = .02$) for female term vs preterm. The mean (SD) RV EDVi was 99.4 (3.5) vs 86.7 (3.6) ($P = .02$) for male term vs preterm and 84.0 (2.2) vs 74.7 (2.0) ($P = .003$) for female term vs preterm. The mean (SD) RV ESVi was 46.0 (2.0) vs 40.8 (2.0) ($P = .08$) for male term vs preterm and 36.3 (1.3) vs 30.9 (1.2) ($P = .003$) for female term vs preterm.

However, the magnitude of the difference between term and preterm values for SVi, LV mass index, and RV mass index appeared to be greater in male individuals compared with female individuals (13.4% vs 8.6% smaller for SVi, 21.4% vs 9.1% smaller for LV mass index, and 15.5% vs 6.8% smaller for RV mass index). This finding suggests that boys born prematurely may be more susceptible to cardiac growth arrest than girls born prematurely.

Table 2. Cardiac Structure and Function Assessed via Magnetic Resonance Imaging

Variable	Adolescents Mean (SD) Term (n = 20)	Adolescents Mean (SD) Preterm (n = 20)	P value[a]	Adults Mean (SD) Term (n = 32)	Adults Mean (SD) Preterm (n = 38)	P value[a]	All P value[b]
Global measures							
Heart rate, beats/min	97 (17)	96 (20)	.58	66 (12)	71 (11)	.08	.21
Cardiac output, L/min	7.1 (1.8)	5.7 (1.6)	.01	6.4 (1.3)	6.3 (1.4)	.74	.06
Cardiac index, L/min/m^2	4.5 (1.0)	4.0 (0.8)	.07	3.5 (0.7)	3.4 (0.7)	.47	.13
LV							
EDV, mL	125 (20)	104 (17)	<.001	168 (38)	149 (31)	.03	<.001
EDVi, mL/m^2	80 (9)	72 (7)	.008	92 (15)	80 (10)	<.001	<.001
ESV, mL	53 (11)	43 (6)	.004	70 (19)	60 (16)	.10	<.001
ESVi, mL/m^2	34 (6)	30 (4)	.10	38 (8)	32 (7)	.003	<.001
SV, mL	73 (14)	61 (15)	.004	98 (22)	88 (19)	.09	.002
SVi, mL/m^2	46 (7)	42 (7)	.06	54 (9)	48 (7)	.004	<.001
Ejection fraction, %	57.7 (5.8)	57.9 (6.1)	.99	58.7 (4.5)	59.8 (5.4)	.37	.48
Mass, g	70 (17)	57 (13)	.005	92 (32)	77 (22)	.05	<.001
Mass index, g/m^2	44.4 (7.5)	39.6 (5.9)	.03	49.8 (14.0)	40.7 (7.3)	.004	<.001
Mass ÷ EDV, g/mL	0.55 (0.08)	0.55 (0.08)	.79	0.54 (0.10)	0.51 (0.08)	.33	.30
RV							
EDV, mL	128 (26)	103 (23)	<.001	176 (49)	156 (35)	.14	.002
EDVi, mL/m^2	81 (11)	71 (12)	.03	96 (19)	84 (13)	.01	<.001
ESV, mL	57 (15)	42 (10)	<.001	79 (28)	70 (21)	.21	.005
ESVi, mL/m^2	36 (7)	30 (6)	.02	43 (12)	37 (9.1)	.07	.001
SV, mL	71 (14)	60 (14)	.01	97 (23)	86 (19)	.07	.003
SVi, mL/m^2	46 (7)	42 (7)	.08	53 (10)	46 (7)	<.001	<.001
Ejection fraction, %	56.0 (5.2)	58.7 (4.3)	.07	55.6 (5.2)	55.8 (6.5)	.89	.27
Mass, g	10 (2)	8 (2)	.02	18 (6)	16 (4)	.28	.02
Mass index, g/m^2	6.07 (0.96)	5.74 (0.89)	.26	9.62 (2.60)	8.45 (1.80)	.06	.01
Mass ÷ EDV, g/mL	0.07 (0.01)	0.08 (0.01)	.07	0.10 (0.02)	0.10 (0.02)	.78	.72
RV mass ÷ LV mass	0.14 (0.03)	0.15 (0.02)	.25	0.20 (0.04)	0.21 (0.04)	.13	.28

Abbreviations: EDV, end-diastolic volume; EDVi, end-diastolic volume index; ESV, end-systolic volume; ESVi, end-systolic volume index; LV, left ventricle; RV, right ventricle; SV, stroke volume; SVi, stroke volume index.

[a] *P* values are by unpaired Wilcoxon rank sum tests within each age cohort.

[b] *P* values are for all individuals in the term and preterm groups across age cohorts by least-squares means from an age-adjusted linear model.

Consequences of Neonatal Characteristics

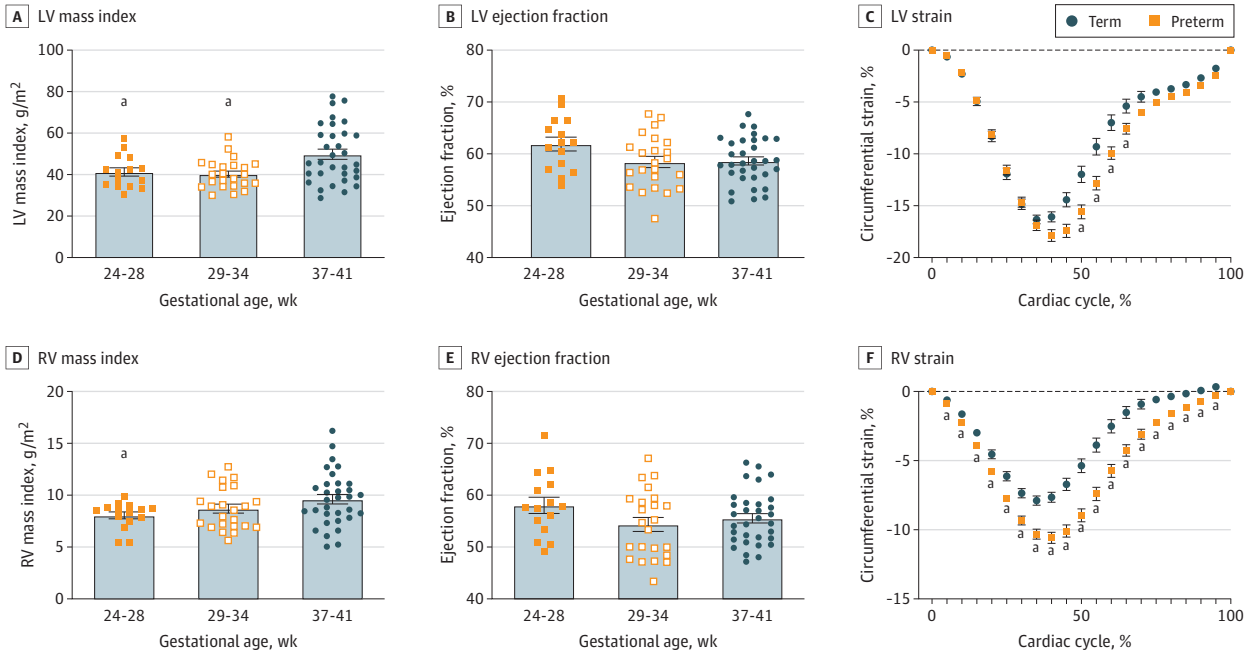
Based on previous studies[8,12] identifying gestational age, total days on assisted ventilation, and patent ductus arteriosus as univariate predictors of adult pulmonary vascular disease and RV size and function, these parameters were selected a priori for multivariable analysis (**Table 4**). Gestational age and total days on assisted ventilation were statistically significantly associated with RV mass index, although these parameters failed to associate with LV mass index. Furthermore, gestational age was inversely associated with biventricular ejection fractions.

Discussion

We hypothesized that adolescents and adults born prematurely would have altered cardiac structure and function compared with control participants in the term group, and we sought to assess to what extent previous findings[7,8] of cardiac dysfunction and hypertrophy in adults born preterm would be present in 2 cohorts born during more recent eras of neonatal care. Participants were primarily from 2 birth cohorts of premature infants with very low birth weight (<1500 g) born from 1988 to 1991 or from 2003 to 2004 with characterized cardiac structure and function by MRI. Herein, we found that adolescents and young adults in the preterm group had statistically significantly smaller biventricular cardiac chamber size, notably without a hypertrophic response, compared with age-matched peers in the term group.

The results herein suggest that preterm birth has considerable long-term consequences on cardiac structure and function. Blunted cardiac growth and decreased biventricular cardiac chamber size after premature birth have been demonstrated across a range of birth years and postnatal ages. A small echocardiography-based study[36] of 7-year-olds born extremely preterm from 1998 to 2004 demonstrated a nonsignificant suggestion of smaller biventricular cardiac chamber size and reduced LV mass index. Similarly, a larger echo-

Figure. Adult Cardiac Morphometry and Function



Mass index (A and D) and ejection fraction (B and E), stratified by severity of prematurity, demonstrate a statistically significant association of prematurity with biventricular mass. The left ventricle (LV) and right ventricle (RV) are hypercontractile by cardiac strain analysis, most notable in the RV, reaching peak systole and end diastole much later in the cardiac cycle (C and F). Error bars represent the SEM.

[a] $P < .05$ compared with term.

cardiography-based study[22] of 6-year-old children born extremely preterm in 2004 to 2007 demonstrated statistically significantly smaller biventricular cardiac chamber size and lower mass index compared with children born at term. Among adolescents, 18-year-olds born extremely preterm in 1991 to 1992 had lower LV mass and smaller biventricular cardiac chamber size with preserved function by echocardiography compared with control participants born at term.[23] These studies are consistent with our findings of lower biventricular mass and smaller biventricular cardiac chamber size by MRI in adolescent and adult cohorts born prematurely compared with participants born at term. Finally, compared with term-born controls, MRI assessment of 25-year-olds born extremely preterm in 1982 to 1985 also had reduced biventricular cardiac chamber size, but notably with biventricular hypertrophy and reduced RV ejection fraction.[7,8] Given that the findings of reduced biventricular cardiac chamber size are consistent across birth years and chronological ages, a smaller biventricular cardiac chamber size should be considered a key characteristic of the premature heart, which has yet to be substantially mitigated by changes in neonatal care practice.

The reduced LV mass, hypercontractile strain pattern, and preserved ejection fractions in the present study's population are in contrast to the higher biventricular mass, hypocontractile strain pattern, and depressed RV ejection fraction previously identified by Lewandowski et al[7,8] in a similarly aged adult population born in the early 1980s. However, as noted previously, our findings are consistent with echocardiography-based studies[7,8,22,23] in younger cohorts born in a more modern era of neonatal care. Lewandowski et al[7,8] identified gestational age as the key determinant of biventricular mass, with 10% higher RV mass with each category of advancing severity of prematurity. Given that the adult preterm cohort in the present study was of a similar chronological age vs the cohort described by Lewandowski et al[7,8] (27 vs 25 years), with an even greater degree of prematurity (29 vs 30 weeks) and a higher rate of invasive ventilation (42 of 58 [72%] vs 55 of 102 [54%]), we would have predicted a higher biventricular mass in this cohort rather than the observed lower biventricular mass. These differences are not readily explained by differences in baseline adult anthropometrics or demographics, such as obesity or hypertension. However, a notable difference between cohorts is the birth years. Lewandowski et al[7,8] included individuals with birth years from 1982 to 1985, whereas the present study's adult cohort included primarily birth years from 1988 to 1991. Although this distinction may seem subtle, the 1980s were a time of rapid change in neonatal care standards. Substantial advances include the introduction of more lung-protective ventilation, initial use of continuous pulse oximetry allowing for more rapid bedside titration of oxygen supplementation to avoid hypoxia and hyperoxia, and, by the early 1990s, the first widespread use of surfactant and antenatal corticosteroids to speed lung maturation.[37] Notably, the changes in clinical practice during the 1980s were so profound that they led to a change in the presentation, pathology, and ultimately clinical classification of chronic lung disease of prematurity and bronchopulmonary dysplasia. The old bronchopulmonary dysplasia was characterized by lung injury from oxygen toxicity

Table 3. Cardiac Strain

Variable	Adolescents Mean (SD) Term (n = 20)	Adolescents Mean (SD) Preterm (n = 20)	P value[a]	Adults Mean (SD) Term (n = 32)	Adults Mean (SD) Preterm (n = 38)	P value[a]	All P value[b]
LV							
Longitudinal							
Strain, %	-14.3 (2.2)	-14.9 (2.1)	.44	-12.7 (2.8)	-14.2 (2.4)	.04	.02
Systolic SR, % per s	-78.8 (17.0)	-83.7 (8.6)	.50	-52.1 (13.0)	-57.5 (16.0)	.16	.07
Diastolic SR, % per s	63.8 (15.0)	72.9 (14.0)	.08	32.2 (9.2)	37.2 (10.0)	.06	.01
Circumferential							
Global strain, %	-19.7 (2.5)	-21.1 (2.6)	.17	-17.8 (2.3)	-18.3 (3.4)	.30	.08
Base strain, %	-17.2 (3.1)	-17.9 (2.2)	.68	-17.0 (2.2)	-17.2 (2.8)	.45	.43
Mid strain, %	-19.3 (2.2)	-20.5 (2.2)	.13	-17.9 (2.1)	-18.0 (3.1)	.57	.25
Apex strain, %	-22.5 (4.0)	-25.0 (4.3)	.06	-18.4 (4.0)	-19.9 (5.5)	.30	.03
Systolic SR, % per s	-117.0 (20.0)	-129.0 (26.0)	.29	-82.3 (15.0)	-85.1 (19.0)	.32	.07
Diastolic SR, % per s	122.0 (28.0)	134.0 (38.0)	.57	77.7 (18.0)	77.5 (23.0)	.95	.27
Radial							
Global strain, %	29.5 (6.4)	30.8 (8.8)	.76	25.8 (6.8)	27.4 (9.5)	.71	.33
Base strain, %	30.4 (8.9)	33.1 (10.0)	.24	26.4 (9.5)	29.0 (13.0)	.50	.18
Mid strain, %	34.4 (8.4)	34.1 (9.7)	.68	29.7 (8.1)	31.5 (10.0)	.45	.52
Apex strain, %	23.6 (8.1)	25.4 (11.0)	.88	21.4 (9.5)	21.6 (12.0)	.78	.74
Long-axis strain, %	24.8 (5.0)	25.6 (5.5)	.50	18.4 (8.9)	19.8 (7.5)	.52	.35
Systolic SR, % per s	147.0 (32.0)	157.0 (46.0)	.94	107.0 (32.0)	112.0 (42.0)	.89	.34
Diastolic SR, % per s	-203.0 (55.0)	-225.0 (80.0)	.71	-121.0 (47.0)	-131.0 (58.0)	.69	.16
RV							
Longitudinal							
Strain, %	-12.6 (2.6)	-12.3 (3.1)	.91	-11.7 (3.1)	-13.5 (3.6)	.02	.13
Systolic SR, % per s	-69.5 (16.0)	-63.7 (15.0)	.29	-51.3 (15.0)	-60.4 (15.0)	.01	.22
Diastolic SR, % per s	53.2 (20.0)	47.7 (19.0)	.47	36.0 (15.0)	44.0 (15.0)	.04	.31
Circumferential							
Strain, %	-9.7 (2.2)	-10.1 (2.5)	.68	-8.3 (2.1)	-10.8 (2.4)	.001	.001
Systolic SR, % per s	-52.4 (14.0)	-59.2 (16.0)	.22	-38.0 (11.0)	-48.9 (14.0)	.002	.001
Diastolic SR, % per s	45.1 (13.0)	45.7 (15.0)	.64	39.6 (14.0)	42.4 (14.0)	.36	.45

Abbreviations: LV, left ventricle; RV, right ventricle; SR, strain rate.

[a] *P* values are by unpaired Wilcoxon rank sum tests within each age cohort.

[b] *P* values are for individuals in the term and preterm groups across age cohorts by least-squares means from an age-adjusted linear model.

and less protective modes of invasive ventilation, whereas the new bronchopulmonary dysplasia occurs at earlier gestational ages and is considered more of an interruption of normal lung development, including arrested lung alveolar and vascular development.[38-40] Given these parallels and changes in clinical practice, we hypothesize that old and new clinical classifications of cardiomyopathy of prematurity may exist, differentiated primarily based on the cardiac hypertrophic response, similar to and potentially corresponding to the existence of old and new clinical classifications of bronchopulmonary dysplasia. Additional studies will be needed to further assess the inciting neonatal features that promote or limit the cardiac hypertrophic response over time.

Although the mechanisms by which the events surrounding preterm birth alter cardiac development later in life remain elusive, preclinical models support the paradigm of differential cardiac response and programming to neonatal stimuli. For example, changes in postnatal oxygen tension during the first postnatal week influence when cardiomyocytes exit the cell cycle, where hyperoxia may accelerate terminal cell cycle arrest, whereas hypoxia prolongs the postnatal proliferative window.[41] Furthermore, reactive oxygen species are known to activate a number of hypertrophy-signaling kinases and transcription factors. These responses may be further potentiated by mechanical stress, including ventilation,[42-44] and could account for the greater hypertrophic response reported by Lewandowski et al.[7,8] Preterm birth without the secondary insult of oxygen supplementation also is associated with an altered cardiac phenotype. In an animal model of premature birth using sheep born at 0.9 of term in which respiratory support was not required, lambs demonstrated biventricular hypertrophy at 9 weeks after term-equivalent age (infancy), with a greater proportion of immature mononucleated polyploidy (4N) cardiomyocytes.[45] However, this same author group reported in a subsequent study[46] that by age 14.5 months (early adulthood), heart weight and RV wall thickness in sheep were less with fewer cardiomyocytes than in animals born at term.

Strengths and Limitations

A strength of this study is the use of 2 neonatal cohorts to understand the consequences of age on cardiac structure and function after preterm birth. Although both age groups born preterm had a smaller biventricular cardiac chamber size compared with participants born at term, the hypercontractile state was most notable in adults born prematurely, with the RV more altered than the LV. At least 2 potential explanations for this finding exist. First, this result could be attributable to differences in neonatal care, such as lack of treatment with antenatal corticosteroids and longer use of invasive ventilation in the adult cohort, although our adolescent and adult cohorts were otherwise well matched with respect to gestational age, birth weight, total days on assisted ventilation, and days in the neonatal intensive care unit. Second, it is plausible that we have identified the natural progression of prematurity-associated cardiomyopathy with age. Support for this explanation also comes from our group's previous experience in animal models.[47-50] Specifically, treatment of neonatal rat pups with hyperoxia for the first 10 to 14 days after birth, a well-established model of moderate to severe bronchopulmonary dysplasia, resulted in bimodal RV dysfunction.[47] By early adolescence, the RV was well adapted to mild to moderate pulmonary hypertension and equally or even more tolerant to secondary stressors, such as pulmonary artery banding and hypoxia.[47-49] However, when rats exposed to neonatal hyperoxia were aged to 1 year, they developed RV failure secondary to impaired mitochondrial biogenesis and function, despite no further progression of the underlying pulmonary vascular disease.[47,50] Therefore, the hypercontractile RV may represent an early compensatory response to maintain RV-pulmonary vascular coupling, which our group has recently identified as impaired relative to term-born controls in a small cohort of adults born moderately to extremely preterm.[15]

Although this study is strengthened by the inclusion of the 2 well-characterized neonatal cohorts, which allows for a better understanding of the consequences of premature birth for cardiac function over the first 3 decades of life, this study has some limitations. First, a primary limitation is the cross-sectional cohort study design, which suggests but cannot confirm differences in cardiac growth potential across 2 age groups born prematurely, and there may be additional unaccounted-for confounders. Second, a small number of individuals who were born prematurely was studied, although the numbers were higher than those enrolled in the extreme preterm category by Lewandowski et al[7,8] because their study included all degrees of prematurity. Future work in identifying mechanistic insight into increased heart failure and ischemic risk in survivors of preterm birth is warranted and may benefit from focus on myocardial perfusion, fibrosis, metabolism, and function during stress.

Table 4. Multivariable Analysis of Neonatal Predictors of Subsequent Cardiac Size and Function

Neonatal variable	Estimate (SE)	*P* value
LV mass index		
Chronological age	0.064 (0.139)	.65
Gestational age	0.046 (0.585)	.94
Total days on assisted ventilation[a]	0.061 (0.088)	.49
Patent ductus arteriosus	−0.036 (2.100)	.99
RV mass index		
Chronological age	0.157 (0.030)	<.001
Gestational age	0.324 (0.128)	.02
Total days on assisted ventilation[a]	0.038 (0.019)	.05
Patent ductus arteriosus	0.502 (0.460)	.28
LV ejection fraction		
Chronological age	0.166 (0.103)	.11
Gestational age	−0.874 (0.434)	.05
Total days on assisted ventilation[a]	0.023 (0.065)	.73
Patent ductus arteriosus	−3.360 (1.560)	.04
RV ejection fraction		
Chronological age	−0.173 (0.106)	.11
Gestational age	−1.270 (0.447)	.007
Total days on assisted ventilation[a]	−0.056 (0.067)	.41
Patent ductus arteriosus	−0.423 (1.610)	.79

Abbreviations: LV, left ventricle; RV, right ventricle.

[a] Total days on assisted ventilation include the combination of invasive and noninvasive ventilation.

Conclusions

Compared with individuals who were born at term, adolescents and young adults born moderately to extremely preterm during an era consistent with modern neonatal practice had statistically significantly smaller biventricular cardiac chamber size with preserved function, notably without a hypertrophic response. Cardiac strain analyses identified a hypercontractile heart, particularly in the RV, in adults born prematurely. Whether these parameters ultimately predict long-term risk of cardiac dysfunction remains to be determined.

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