CHEST

Association of Bronchopulmonary Dysplasia and Right Ventricular Systolic Function in Young Adults Born Preterm

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BACKGROUND: Adults born preterm are at a higher risk of cardiopulmonary disease and premature death. Preterm birth is associated with abnormalities in right ventricular (RV) structure and function, but the impact of bronchopulmonary dysplasia (BPD), a common complication of extremely preterm birth, on these parameters remains unknown.

RESEARCH QUESTION: Are preterm birth and BPD associated with alterations in RV structure and function in early adulthood?

STUDY DESIGN AND METHODS: Echocardiographic and spirometry data were obtained from the Health of Adults Born Preterm Investigation (HAPI). RV structure and performance were evaluated by using echocardiography, and respiratory function was assessed by using spirometry.

RESULTS: The study comprised 86 young adults born preterm before 30 weeks of gestation, including 28 with moderate to severe BPD, and 85 adults of the same age born full term. Individuals were assessed at a mean age of 23 years. RV systolic function was altered in the preterm group, with lower tricuspid annular plane systolic excursion and lower RV s' and RV outflow tract velocity time integral values, especially in those born preterm with BPD. Nine (36%) participants born preterm with BPD, six (13%) participants born preterm without BPD, and six (8%) participants born full term had a tricuspid annular plane systolic excursion value < 16 mm, a marker of RV systolic dysfunction (P value for the comparison between preterm no BPD and BPD, .032). No difference was found in RV diastolic function or estimates of pulmonary artery pressure between groups. Although respiratory function was altered in those born preterm, and more so in the case of BPD, no association was observed between spirometry indices of respiratory function and RV systolic function.

INTERPRETATION: Preterm birth is associated in adulthood with alterations in RV systolic function, which are more pronounced in the case of BPD.

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ABBREVIATIONS: A4C = apical four-chamber; BPD = bronchopulmonary dysplasia; BSA = body surface area; ICC = intraclass correlation coefficient; PAAT = pulmonary artery acceleration time; RV = right ventricular; RVET = right ventricular ejection time; RVOT = right ventricular outflow tract; TAPSE = tricuspid annular plane systolic excursion; VO_2max = maximal oxygen consumption; VTI = velocity time integral

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Take-home Points

Study Question: Are RV structure and function altered in young adults born preterm (<30 weeks of gestation) with and without BPD?

Results: We found alterations in markers of RV systolic function in those born very preterm, and these alterations were more pronounced in those with a history of BPD.

Interpretation: Long-term follow-up of RV systolic function may be needed in this at-risk population.

Each year, preterm birth occurs once in every 10 births worldwide.[1] The past few decades have seen major advances in neonatal care, leading to higher survival rates of individuals born preterm and rising numbers of young and middle-aged adults born prematurely,[2,3] in whom studies show higher risk of cardiovascular disease and related death.[4-7]

The last trimester of pregnancy and the early postnatal period are critical for cardiac maturation and development.[8-12] Clinical studies are now revealing the mid- to long-term consequences of the abrupt interruption of in utero cardiovascular development and maturation associated with preterm birth. Infants born very preterm (< 32 weeks of gestation) exhibit alterations in right ventricular (RV) function that persist through infancy and which are aggravated in the presence of bronchopulmonary dysplasia (BPD), a pulmonary complication of very preterm birth.[13] Adults born preterm also exhibit alterations in RV structure and function,[14-16] in addition to higher rates of obstructive lung disease[17,18] and pulmonary vascular disease.[19-21] Whether the deleterious impact of BPD on RV function persists later in life, however, remains to be determined.

We hypothesized that preterm birth would lead to alterations in RV structure and function that would be more severe in the case of BPD. The aim of the current study therefore was to evaluate RV structure and performance using echocardiographic assessments in young adults born preterm, with and without a history of BPD, compared with young adults born full term.

Subjects and Methods

Study Population

We investigated data collected from the Health of Adults Born Preterm Investigation (HAPI), described in detail elsewhere.[7,22] We studied young adults aged 18 to 29 years born preterm in 1987 to 1997 at ˂ 30 weeks of estimated gestational age and compared them vs full-term control subjects (37-41 weeks' gestational age). Term control subjects were identified by each preterm participant, among friends or siblings of the same sex and age (±2 years), to minimize socioeconomic and lifestyle differences between groups. Exclusion criteria included severe neurocognitive impairment and pregnancy. Participants with respiratory illness were not excluded. None of the participants reported a history of VTE. Participants from the pilot HAPI study were not included in the current research, as RV-specific echocardiographic views were not acquired and RV functional parameters were not measured during that earlier phase.

This investigation was approved by the Ethic Review Board from Sainte-Justine University Hospital (number 3901), McGill University Health Centre, and Sir Mortimer B. Davis Jewish General Hospital Research Institute (number 2139). All participants provided written informed consent.

Cardiac Imaging Assessment

The participants remained at rest and in the left lateral decubitus position for echocardiographic views acquisition on a Vivid E9 ultrasound machine with standard transducers (GE Healthcare). Standard echocardiographic measurements were extracted and analyzed according to the American Society of Echocardiography guidelines[23] and with the QLAB analysis package (Philips), EchoPac PC software (GE Healthcare), and Tomtec-Arena platform version 4 (TOMTEC Imaging Systems GmbH, 2017).

Tricuspid annular plane systolic excursion (TAPSE) was performed in the apical four-chamber (A4C) view by measuring the maximal systolic displacement traveled by the tricuspid annulus from a line of interrogation aligned with the RV apex. A TAPSE value < 16 mm was considered abnormal.[23] The tricuspid systolic to diastolic duration ratio was measured from the continuous-wave Doppler sampled at the tricuspid inflow.[24] Pulmonary artery acceleration time (PAAT), RV ejection time (RVET), and the RV outflow tract (RVOT) velocity time integral (VTI) were obtained from the spectral envelope at the RVOT obtained by pulsed wave Doppler sampled in

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the parasternal short-axis window at the tip of the pulmonary valve. Triscuspid inflow velocities (E and A velocities) by pulsed wave Doppler were obtained in the A4C. RV tissue velocities and the RV myocardial performance index (ie, the Tei index) were obtained from the tissue Doppler imaging at the RV lateral wall in the A4C. RV dimensions were estimated by the internal diameter in diastole by M-mode echocardiography in the parasternal long-axis view, as well as by the end-diastolic and end-systolic areas in the A4C view. PAAT and the PAAT/RVET ratio are reportedly indicators of pulmonary artery afterload, and TAPSE/PAAT is a surrogate marker of the RV-pulmonary artery coupling.[25]

Echocardiography determinations are shown as "not determined" for RV measures when the RV focus view was not obtained, resulting in a missing part of the apex or of the lateral wall, and when pulsed wave or tissue Doppler imaging was not obtained. All echocardiographic images were acquired by a trained technician and all measurements obtained by experienced operators (J. S. and G. A.), all blinded to subjects' group or condition. Intra-rater and inter-rater variability were assessed in a subset of 50 participants (25 born full term and 25 born preterm) for various parameters: TAPSE, tricuspid systolic to diastolic duration ratio, RVOT VTI, RV end-diastolic area, PAAT, and RVET. Consistency intraclass correlation coefficients (ICCs) were determined by using a two-way mixed model. Intra-rater and inter-rater agreement were considered poor (ICC $<$ 0.40), fair (ICC between 0.40 and 0.59), good (ICC between 0.60 and 0.74), or excellent (ICC $>$ 0.75), according to Cicchetti.[26]

Covariates

To account for growth differences between groups, RV dimensions were indexed to body surface area (BSA). The BSA was calculated by using the Mosteller formula.[27] Moderate to severe BPD was defined as the chronic use of supplemental oxygen after 36 weeks' postmenstrual age, in the participants born preterm, as retrieved from medical charts.[28] Office BP measurements on the day of the study were taken in accordance with guidelines and have been detailed elsewhere.[7] Spirometry was performed at rest by using a Jaeger CareFusion Oxycon Pro Spirometer to obtain FEV_1 and FVC. Maximal oxygen consumption (VO_2max), a surrogate marker of exercise capacity, was estimated by using the Huet questionnaire.[29]

Statistical Analysis

Descriptive statistics were calculated as means with SDs and counts with proportions. Our study had an 80% power to detect a mean difference of 1.5 mm (0.5 SD) in TAPSE, which was the study's primary outcome measure, between two groups of 64 individuals, using a two-sided Student *t* test. This difference consists of an effect size d of 0.5, which is medium according to Cohen.[30] Comparisons between two groups were performed by using the Student *t* test (continuous variables) or Fisher exact test (categorical variables). The false discovery rate method[31] was used to adjust *P* values for multiple comparisons, and *P* values $<$ .05, following adjustment for multiple comparisons, are indicated in the tables.

We further compared RV parameters in full term, preterm/no BPD, and preterm/BPD, treated as a three-level ordinal-independent variable, using linear regression analysis. Pairwise comparisons were not performed due to a lack of power. Normality of distribution of residuals was assessed visually and by using the Shapiro-Wilk test. Statistical significance was determined as *P* values $<$ .05. Number of missing data, due to technical difficulties in visualizing the right ventricle, is shown in the tables. Missing data were distributed evenly across groups. All analyses were performed by using R version 3.6.0 (International Open Source collaborative).[32]

Results

Study Population

Neonatal and adult characteristics of the study population are provided in Table 1, and baseline characteristics according to BPD status in those born preterm are provided in e-Table 1. Mean gestational age at birth was 27.2 weeks in the preterm group. A history of moderate to severe BPD was found in 28 (33%) of the participants born preterm. Birth weight percentile was lower in those born preterm. Preterm participants with BPD were more exposed to surfactant. As adults, height, weight, and BSA were decreased in the preterm group. BMI, tobacco smoking, and exercise capacity (as shown by estimated VO_2max) were similar across groups. Respiratory function was more severely altered in individuals born preterm with BPD. These differences highlight the increasingly severe birth conditions across the three study groups.

RV Dimensions

All three RV dimensional estimates (ie, internal diameter in diastole, end-diastolic and end-systolic areas) were smaller in the preterm group, but these differences did not remain following indexation to BSA (Table 2).

RV Function

We found evidence of decreased RV systolic function in young adults born preterm, with a significantly lower TAPSE, lower RV s', and an increased tricuspid systolic to diastolic duration ratio in the preterm group. Difference in RVOT VTI did not reach statistical significance, and fractional area change was similar between groups. In contrast, markers of diastolic function (E/A [ratio of the tricuspid peak early (E) and atrial (A) inflow velocities] and E/e' [ratio of the early diastolic tricuspid inflow velocity to the early peak RV free wall diastolic velocity by tissue doppler imaging], deceleration time) were all similar between groups, suggesting no significant impairment of RV diastolic function in our cohort of young adults born preterm. RV myocardial performance index, a marker of global (systolic and diastolic) RV function, was also similar between groups (Table 2).

Pulmonary Valve

Doppler velocity of tricuspid regurgitation was absent or insufficient to estimate pulmonary pressure in the large

majority of the study participants. Systolic pulmonary artery pressure was estimated at 19.0 ± 6.5 mm Hg in six participants from the term group and could not be measured in any participants from the preterm group. PAAT, PAAT/RVET ratio, and TAPSE/PAAT were similar between groups (Table 3).

Association of RV Systolic Function With Moderate to Severe BPD

An abnormal (< 16 mm) TAPSE value was significantly more frequent in participants with a history of BPD (n = 9 [36%]) compared with those born preterm without a history of BPD (n = 6 [13%]) (P = .032) (Fig 1). A significant trend in worsening of parameters of RV systolic function (TAPSE, RVOT VTI, systolic/diastolic duration ratio, and RV s') was observed among groups of increasing severity (full term, preterm/no BPD, and preterm/BPD); this trend was not observed for markers of diastolic function and pulmonary artery measurements (Table 4).

Association of RV Systolic Function With Respiratory Characteristics

Given the observed associations between RV function, preterm birth, and BPD, we sought to evaluate the association between the markers of RV systolic function with the parameters of adult respiratory function (FEV_1 and FVC) and with neonatal characteristics (gestational age and birth weight percentile). None of these parameters was associated with alteration in markers of RV systolic function (Table 5).

TABLE 1] Neonatal and Adult Clinical Characteristics

Characteristic	Term (n = 85)		Preterm (n = 86)		*P* Value
	ND	Mean ± SD or No. (%)	ND	Mean ± SD or No. (%)	
Neonatal characteristics					
Male sex	0	36 (42)	0	38 (44)	.88
Gestational age, wk	1 (1%)	39.6 ± 1.1	0	27.2 ± 1.4	…
Birth weight, g	0	3,373 ± 363	0	963 ± 225	…
Birth weight percentile, %	1 (1%)	47 ± 24	0	35 ± 17	.0003
Small for gestational age	1 (1%)	7 (8)	0	6 (7)	.78
Maternal preeclampsia	0	6 (7)	0	19 (22)	.0084
Antenatal steroids	…	…	2 (2%)	35 (42)	…
Use of surfactant	…		5 (6%)	36 (44)	…
Moderate to severe BPD	…	…	1 (1%)	28 (33)	…
Adult characteristics					
Age, y	0	23.2 ± 2.4	0	23.3 ± 2.3	.86
Height, cm	0	170 ± 8	0	166 ± 9	.0009
Weight, kg	0	69.4 ± 15.3	0	61.6 ± 11.8	.0003
BMI, kg/m^2	0	23.9 ± 4.6	0	22.4 ± 3.7	.023
Body surface area, m^2	0	1.8 ± 0.22	0	1.68 ± 0.19	.0001
Education high school or higher	1 (1%)	7 (8)	0	6 (7)	.78
Current tobacco smoking	0	6 (7)	0	19 (22)	.0084
Estimated VO_2max, mL/kg/min	4 (5%)	45 ± 8	3 (3%)	43 ± 8	.38
Heart rate on study day, beats/min	0	69 ± 13	0	75 ± 12	.0013
SBP on study day, mm Hg	0	116 ± 13	0	119 ± 14	.097
DBP on study day, mm Hg	0	68 ± 8	0	72 ± 9	.0023
FEV_1, z score	9 (11%)	−0.002 ± 0.907	8 (9%)	−0.876 ± 1.135	< .0001
FVC, z score	9 (11%)	0.369 ± 0.878	8 (9%)	−0.115 ± 0.957	.0013
LVEF, %	12 (14%)	56.8 ± 6.5	10 (12%)	56.8 ± 6.8	.96

P values were calculated by using the Student *t* test (quantitative variables) or Fisher exact test (qualitative variables). BPD = bronchopulmonary dysplasia; DBP = diastolic BP; LVEF = left ventricular ejection fraction; ND = not determined; PIH = pregnancy-induced hypertension; SBP = systolic BP; VO_2max = maximal oxygen consumption.

TABLE 2] RV Measurements According to Term or Preterm Status

Variable	Term		Preterm		*P* Value
	ND	Mean ± SD	ND	Mean ± SD	
M-mode dimensions					
RV internal diameter, mm	1 (1%)	23.3 ± 3.7	1 (1%)	21.5 ± 3.4	.0010[a]
RV internal diameter (indexed), mm/m^2	1 (1%)	13.1 ± 2.1	1 (1%)	12.9 ± 2	.68
Functional 2D assessment					
RV end-diastolic area, mm^2	27 (32%)	21.1 ± 5.4	19 (22%)	18.7 ± 4.3	.0097[a]
RV end-diastolic area (indexed), mm^2/m^2	27 (32%)	11.8 ± 2.5	19 (22%)	11.2 ± 2.2	.20
RV end-systolic area, mm^2	27 (32%)	12.9 ± 3.7	20 (23%)	11.5 ± 3	.019
RV end-systolic area (indexed), mm^2/m^2	27 (32%)	7.2 ± 1.71	20 (23%)	6.83 ± 1.4	.19
RV longitudinal RV length in diastole, mm^2	20 (24%)	79 ± 8.8	15 (17%)	76 ± 10.3	.067
RV longitudinal RV length in diastole (indexed), mm^2/m^2	20 (24%)	44.8 ± 5.1	15 (17%)	45.6 ± 5.8	.39
Systolic function					
RV TAPSE, mm	14 (16%)	20.7 ± 3.9	14 (16%)	19.1 ± 3.5	.012[a]
RV TAPSE < 16 mm	14 (16%)	6 (8%)	14 (16%)	15 (21)	.057
RV systolic/diastolic duration ratio, %	20 (24%)	70.3 ± 18.8	18 (21%)	79.2 ± 23.7	.0091[a]
RVOT VTI, cm	2 (2%)	18.2 ± 2.5	3 (3%)	17.6 ± 3.1	.13
RV fractional area change, %	27 (32%)	38.4 ± 8.3	20 (23%)	38.2 ± 8.3	.89
RV s′, cm/s	5 (6%)	13.5 ± 1.8	2 (2%)	12.5 ± 1.6	.0007[a]
Diastolic function					
RV TV E/A	8 (9%)	1.75 ± 0.44	6 (7%)	1.74 ± 0.36	.89
RV TV deceleration time, ms	8 (9%)	208 ± 50	6 (7%)	193 ± 51	.057
RV TV E/e′	11 (13%)	3.66 ± 0.75	6 (7%)	3.71 ± 0.68	.67
Myocardial performance index by tissue Doppler imaging					
RV myocardial performance index	14 (16%)	0.453 ± 0.123	12 (14%)	0.466 ± 0.122	.53

RV dimensions and mass measurements are shown indexed to body surface area and measured in diastole. *P* values were calculated by using the Student *t* test. 2D = two-dimensional; ND = not determined; PA = pulmonary artery; RV = right ventricular; RVOT VTI = right ventricular outflow tract velocity time integral; TAPSE = tricuspid annular plane systolic excursion; TV = tricuspid valve; TV E/A = ratio of the tricuspid peak early (E) and atrial (A) inflow velocities; TV E/e' = ratio of the early diastolic tricuspid inflow velocity to the early peak RV free wall diastolic velocity by tissue doppler imaging.
[a]$P < .05$ after adjustment for multiple comparisons according to the false discovery rate method.

Reproducibility

Echocardiographic measurements were reproducible, with good or excellent intra-rater and inter-rater agreement in all studied parameters. Specifically, intra-rater and inter-rater ICCs were 0.75 and 0.77 for end-diastolic area, 0.73 and 0.76 for TAPSE, 0.85 and 0.75 for the systolic to diastolic duration ratio, 0.89 and 0.86 for RVOT VTI, and 0.80 and 0.74 for the PAAT/RVET ratio, respectively.

Discussion

This study describes the long-term functional aspects of the right ventricle in a cohort of young adults born preterm with and without BPD using echocardiographic assessment. We found that young adults born preterm exhibit RV systolic impairments compared with the group born full term and that these alterations are more severe in cases of history of BPD. We found no significant alteration of RV diastolic function and pulmonary artery pressure among participants from our study.

RV diameter and systolic and diastolic areas were lower in adults born preterm, which is consistent with a previous study[14] showing smaller nonindexed RV dimensions in adults born preterm. However, we found no significant difference in RV size after adjusting for BSA, which was smaller in those born preterm. These results differ from those obtained by Lewandowski et al,[14] Goss et al,[16] and Mohamed et al,[15] who report, using echocardiography and/or MRI measurements, smaller RV volumes and dimensions even after indexing for BSA or adjusting for height. These three studies

TABLE 3] Pulmonary Artery Measurements According to Term or Preterm Status

Pulmonary Artery Measurements	Term		Preterm		*P* Value
	ND	Mean ± SD	ND	Mean ± SD	
PAAT, ms	2 (2%)	129.7 ± 22.6	3 (3%)	127.5 ± 21.0	0.51
PAAT/RV ET	2 (2%)	0.421 ± 0.065	3 (3%)	0.420 ± 0.064	0.91
TAPSE/PAAT	15 (18%)	0.163 ± 0.043	16 (19%)	0.155 ± 0.040	0.24

P values were calculated by using the Student *t* test. ET = ejection time; ND = not determined; PAAT = pulmonary artery acceleration time; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

found conflicting results regarding indexed RV mass in preterm adults, which was larger in Lewandowski et al[14] and Mohamed et al[15] but smaller in Goss et al.[16] MRI assessment of RV dimensions was reported to be more accurate than two-dimensional echocardiography.[33] In addition, echocardiographic visualization of the right ventricle can be challenging, leading, in our study, to a number of missing data points due to inadequate images. These limitations may explain the discrepancies observed between our study and previously published literature.

However, it is also possible that differences in study population may also contribute to differences in results obtained among cohorts. For example, Lewandowski et al[14] reported a higher BMI in participants from their cohort, and a similar trend is observed in the study by Goss et al,[16] whereas we and others[34] do not. A previous study[35] has shown an association between overweight and RV hypertrophy in healthy female adults. In contrast, although Mohamed et al[15] also report smaller RV end-diastolic areas and volumes in preterm-born individuals, BMI was similar in those born term and preterm in their cohort. Additional studies performed in various preterm populations, and meta-analysis of these studies, will help determine whether preterm birth per se is responsible for smaller RV dimensions and volumes, or whether this association is only seen in selected populations.

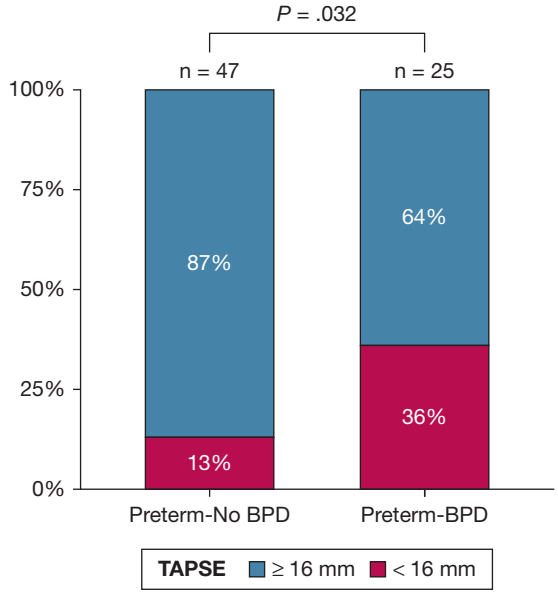

Figure 1 – *Proportion of preterm individuals with abnormal TAPSE values according to history of BPD. BPD = bronchopulmonary dysplasia. TAPSE = tricuspid annular plane systolic excursion. P value calculated by using Fisher exact test.*

The mechanics of the RV contraction are unique, occurring mainly longitudinally, due to the muscle fiber arrangement.[36-38] This characteristic allows a strong correlation between the systolic motion of the tricuspid annulus toward the RV apex (TAPSE) and RV systolic function. Thus, TAPSE is a sensitive method to estimate RV systolic function by echocardiography, with higher values indicating better function.[23,39] TAPSE can also be influenced by pulmonary vascular resistance.[40] Previous studies have shown reduced TAPSE values in preterm infants from birth to 1 year of age compared with full-term control subjects.[13,41] Lower TAPSE and decreased RV function are associated with increased mortality in preterm newborns with BPD and pulmonary hypertension.[42] In our study, and in agreement with a previous study conducted in adults born preterm,[15] TAPSE was significantly lower in the preterm group. TAPSE reportedly has a high reproducibility and correlates strongly with RV ejection fraction measured by radionucleotide angiography ($r = 0.92$).[39] Tissue Doppler-derived tricuspid lateral annular systolic velocity (RV s') was also decreased in the preterm group, suggestive of altered RV systolic function. Along with TAPSE, RV s' is a validated marker of RV systolic function, especially in young populations.[43] Although measurements of RV s' were not previously reported in preterm young adults, to our knowledge, these results are consistent with findings from neonates reported in a recent meta-analysis.[44] We also observed an increase in

TABLE 4] RV Systolic Function According to BPD Status in Preterm Participants

Variable	Term		Preterm: No BPD		Preterm: BPD		*P* Value[a]
	ND	Mean ± SD	ND	Mean ± SD	ND	Mean ± SD	
Systolic function							
RV TAPSE	14 (16%)	20.7 ± 3.9	11 (19%)	19.3 ± 3.3	3 (11%)	18.9 ± 3.9	.016[b]
RV systolic/diastolic duration ratio, %	22 (26%)	68.4 ± 15.6	16 (28%)	75 ± 14.3	5 (18%)	76.9 ± 17.8	.011[b]
RVOT VTI, cm	2 (2%)	18.2 ± 2.5	3 (5%)	18 ± 3.4	0	16.7 ± 2.4	.024[b]
RV fractional area change	27 (32%)	38.4 ± 8.3	16 (28%)	37.1 ± 7.6	4 (14%)	40.1 ± 9.2	.60
RV s′, cm/s	5 (6%)	13.5 ± 1.8	2 (3%)	12.7 ± 1.4	0	12.3 ± 2.0	.0006[b]
Diastolic function							
RV TV E/A	8 (9%)	1.75 ± 0.44	5 (9%)	1.71 ± 0.34	1 (4%)	1.82 ± 0.41	.69
RV TV deceleration time, ms	8 (9%)	208 ± 50	5 (9%)	191 ± 48	1 (4%)	197 ± 57	.14
RV TV E/E′	11 (13%)	3.66 ± 0.75	5 (9%)	3.71 ± 0.66	1 (4%)	3.71 ± 0.74	.69
Pulmonary artery measurements							
PAAT, ms	2 (2%)	130 ± 23	3 (5%)	130 ± 22	0	122 ± 18	.19
PAAT/RV ET	2 (2%)	0.421 ± 0.065	3 (5%)	0.429 ± 0.067	0	0.401 ± 0.054	.36

P values were calculated by using a linear regression model. E/A = mitral inflow peak E-to-A wave velocities ratio; ET = ejection time; ND = not determined; PAAT = pulmonary artery acceleration time; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.
[a]*P* value for the effect of the three-level ordinal independent variable (1 = full term; 2 = preterm/no BPD; 3 = preterm/BPD) on RV systolic function.
[b]$P < .05$ following adjustment for multiple comparisons according to the false discovery rate method.

the systolic/diastolic duration ratio in the adults born preterm and a trend toward a smaller RVOT VTI, which are both indicators of an alteration in RV systolic contractile performance.[23,45]

Moreover, our results suggest a significant association between BPD and alterations in RV systolic function. We found a decreased RV performance in those born preterm with moderate to severe BPD, compared with those with no history of BPD and compared with those born full term, along with an increased prevalence of abnormal TAPSE among the preterm with BPD participants. Although BPD was associated with alterations in spirometry parameters (FEV_1 and FVC), markers of RV systolic function were not affected by respiratory function in adulthood, suggesting that these results cannot be solely explained by the altered adult

TABLE 5] Associations Between Spirometry Values and Markers of RV Structure and Function in Preterm Participants

Variable	FEV_1 (z Score)	FVC (z Score)	Gestational Age	Birth Weight Percentile
RV TAPSE, mm	−0.11 (−0.85, 0.64)	−0.07 (−0.93, 0.8)	−0.11 (−0.71, 0.49)	−0.10 (−0.57, 0.36)
RV systolic/diastolic duration ratio, %	1.11 (−2.54, 4.75)	0.03 (−4.17, 4.22)	−0.14 (−2.91, 2.63)	−0.38 (−2.62, 1.85)
RVOT VTI, cm	0.38 (−0.26, 1.02)	0.62 (−0.12, 1.36)	0.03 (−0.47, 0.53)	0.22 (−0.18, 0.61)
RV fractional area change, %	0.16 (−1.73, 2.05)	−1.14 (−3.25, 0.97)	0.40 (−1.12, 1.91)	−1.31 (−2.4, −0.21)
RV s′, per cm/s	−0.03 (−0.36, 0.29)	−0.03 (−0.36, 0.29)	0.14 (−0.12, 0.4)	0.14 (−0.06, 0.35)

Data are expressed as coefficients β (95% CIs), calculated by using linear models. RV = right ventricular; RVOT VTI = right ventricular outflow tract velocity time integral; TAPSE = tricuspid annular plane systolic excursion.

respiratory status. These results are in line with those from Goss et al,[21] who found evidence of alterations in RV systolic function in adults born preterm free of cardiopulmonary disease. To our knowledge, this study is the first investigating the effect of neonatal chronic lung disease on RV function in adults born preterm. This observation consolidates the hypothesis that BPD (and associated prolonged pulmonary vascular remodeling/afterload) may have long-lasting effects on RV function. In contrast, markers of RV diastolic function (E/A, E/e′, and tricuspid deceleration time) were all similar between groups, suggesting that preterm birth and BPD did not affect RV diastolic function in the current cohort as much as it affected systolic function.

As opposed to earlier reports,[10,15] parameters estimating pulmonary pressures were similar between groups in the current study. We further found no association between markers of RV function and spirometry results. However, Goss et al,[21] using RV catheterization (the gold standard method to obtain measures of pulmonary arterial pressures), found a high rate of pulmonary vascular alterations in a group of healthy adults born preterm without evidence of adult respiratory disease. Furthermore, in children aged 11 to 14 years, pulmonary artery pressures were reportedly higher in cases of extremely preterm birth, and even more so in those who developed BPD.[46] In our study, the low number of individuals in whom tricuspid regurgitation jet could be measured limits our interpretation of the results obtained on pulmonary pressures. Because the differences in pulmonary artery pressures obtained in the study by Goss et al[21] were relatively mild, we did not have sufficient power in our study to make conclusions regarding the presence or absence of clinically relevant pulmonary hypertension in the current cohort.

In addition, we found no difference in the PAAT/RVET and TAPSE/PAAT ratios, showing no evidence of RV-pulmonary artery coupling. These results are similar to those previously reported by Mohammed et al[15] but differ from those by Mulchrone et al.[19] Of note, in the study by Mulchrone et al,[19] full-term participants were very fit, nonsmokers with a mean measured VO_2max of 50 mL/kg per minute vs 38 mL/kg per minute in the preterm group. In contrast, full-term participants in our study were recruited among friends and family of preterm participants, thus ensuring similar socioeconomic background. VO_2max (estimated by using a validated questionnaire) in the current study was similar between term and preterm participants, and the mean value obtained from the term group was lower than that in the study by Mulchrone et al.[19] Differences among the control groups between the two studies may therefore explain some of the observed variations. In addition, the study by Mulchrone et al[19] included a limited number of participants (nine full term, 10 preterm), which limits its generalizability. Hence, the current study adds to the evidence supporting the importance of closely monitoring estimators of RV function in adults born preterm, even in the absence of respiratory disease, to identify early the presence of RV dysfunction and/or pulmonary hypertension.

The current results have clinical implications for individuals born preterm. Indeed, TAPSE values $<$ 16 mm are associated with higher mortality and worst prognosis in patients with pulmonary hypertension.[47,48] This finding is of specific relevance to individuals born preterm given that Goss et al[21] reported that of 11 healthy adults born preterm at 28 weeks of gestational age, three (27%) met criteria for borderline pulmonary hypertension and two (18%) had overt pulmonary hypertension following invasive measurements of pulmonary pressures. Lower TAPSE value is also prognostic of conditions affecting the right ventricle, such as heart failure,[49] and a predictive factor of cardiovascular death in the general population,[50] which might be amplified in individuals born preterm due to the co-occurrence of other cardiometabolic risk factors.[7] A higher systolic/diastolic duration ratio, as in the current study, has been reported as a predictor of adverse clinical outcomes in adults and in children diagnosed with pulmonary hypertension.[51,52]

Study limitations must be recognized. This was a single-center study with a one-time assessment in early adulthood of individuals born preterm $>$ 20 years ago on average. As such, the temporal changes in RV function as this population ages could not be assessed, and we could not evaluate the severity of cardiac and pulmonary disease in early childhood, following neonatal care. Whether our results will apply to the currently younger and/or more premature born subjects who benefited from recent improvements in neonatal care, including increasing use of CPAP and generalization of treatment with surfactant, but in whom the proportion with BPD remains similar, will have to be determined. However, our results are of specific interest in the current cohorts of adults born preterm, often not

identified as having an increased burden of cardiovascular disease. We did not measure diffusing capacity of the lung for carbon monoxide, which could have provided further assessment of pulmonary vasculature. The current study cohort was homogeneous and representative of the general population in the province of Québec, Canada. Our results should therefore be interpreted in light of inherent limitations and validated when generalizing to other populations.

Conclusions

This study is the first, to our knowledge, to show a relationship between alterations in RV systolic function and history of BPD in adults born preterm, thus reinforcing the importance of long-term follow-up of RV function in this population. Future longitudinal studies are necessary to capture the full spectrum of RV alterations following preterm birth and to determine whether these contribute to the increased risk of adverse cardiovascular outcomes in individuals born preterm.

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