Cardiac dysfunction during exercise in young adults with bronchopulmonary dysplasia

Jarno J. Steenhorst[1,2,3], Willem A. Helbing[2,3], Wouter J. van Genuchten[2], Daniel J. Bowen[1], Annemien van den Bosch[1], Nikki van der Velde[1,3], Lieke S. Kamphuis[4], Daphne Merkus[1,5], Irwin K.M. Reiss[6] and Alexander Hirsch[1,3]

[1]Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [2]Department of Pediatrics, Division of Pediatric Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [3]Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [4]Department of Pulmonology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [5]Walter-Brendel Centre of Experimental Medicine, LMU Munich, University Hospital, Munich, Germany. [6]Department of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

Corresponding author: Alexander Hirsch (a.hirsch@erasmusmc.nl)

Shareable abstract (@ERSpublications)
Preterm-born young adults with bronchopulmonary dysplasia have reduced cardiovascular reserve during exercise, caused by impaired left ventricular filling, and might be predisposed to early heart disease https://bit.ly/3usyqnn

Cite this article as: Steenhorst JJ, Helbing WA, van Genuchten WJ, *et al*. Cardiac dysfunction during exercise in young adults with bronchopulmonary dysplasia. *ERJ Open Res* 2024; 10: 00501-2023 [DOI: 10.1183/23120541.00501-2023].

Received: 18 July 2023
Accepted: 2 Feb 2024

Abstract

Background Worldwide, 1–2% of children are born premature and at risk for developing bronchopulmonary dysplasia (BPD). Preterm-born adults are at risk for early cardiovascular disease. The role of BPD is unclear. This study aims to examine cardiorespiratory function during submaximal exercise in young adult survivors of extreme prematurity, with or without BPD.

Methods 40 preterm-born young adults, 20 with BPD (median gestational age 27 weeks, interquartile range (IQR) 26–28 weeks) and 20 without BPD (median gestational age 28 weeks, IQR 27–29 weeks) were prospectively compared to age-matched at term-born adults (median gestational age 39 weeks, IQR 38–40 weeks). Participants underwent exercise testing and cardiovascular magnetic resonance with submaximal exercise.

Results Resting heart rate in BPD subjects was higher than in at term-born subjects (69±10 mL *versus* 61±7 mL, p=0.01). Peak oxygen uptake during maximal cardiopulmonary exercise testing was decreased in BPD subjects (91±18% *versus* 106±17% of predicted, p=0.01). In BPD subjects, cardiac stroke volume change with exercise was impaired compared to at term-born subjects (11±13% *versus* 25±10%; p<0.001). With exercise, left ventricular end-diastolic volume decreased more in preterm-born subjects with *versus* without BPD (−10±8% *versus* −3±8%; p=0.01) and compared to at term-born subjects (0±5%; p<0.001). Exploratory data analysis revealed that exercise stroke volume and end-diastolic volume change were inversely correlated with oxygen dependency in those born prematurely.

Conclusions In preterm-born young adults, particularly those with BPD, resting cardiac function, exercise performance and cardiac response to exercise is impaired compared to controls. Exercise cardiovascular magnetic resonance may reveal an important predisposition for heart disease later in life.

Introduction

Worldwide, 1–2% of children are born very premature, and these numbers are rising [1, 2]. Very premature birth is associated with postnatal oxygen dependency and the development of bronchopulmonary dysplasia (BPD) [3]. Advances in neonatal care, particularly the introduction of exogenous surfactant administration in the early 1990s, resulted in a clear division between “classic” BPD and “new” BPD [3, 4]. In the past decades, survival of very and extreme preterm-born infants, with and without BPD, has increased significantly, leading to a growing population of preterm-born young adults [5].

Preterm-born young adults are predisposed to early cardiovascular disease [6, 7]. Young adult survivors of extreme prematurity have been shown to have cardiac remodelling, including smaller end-diastolic volumes (EDVs) and altered left ventricular (LV) geometry, as measured by cardiovascular magnetic resonance (CMR) at rest [8–10]. Testing "the engine under load" (exercise testing during imaging, using echocardiography) has revealed additional dynamic changes in the cardiac performance of preterm-born young adults [11]. This stress imaging approach has identified reduced cardiac reserve during exercise in adult cardiovascular disease, which has been associated with disease severity and prognosis [12]. Evidence concerning the role of new BPD in cardiovascular disease is limited and the cardiovascular response to exercise in preterm-born young adults is unknown.

The aim of this study is to examine cardiorespiratory structure and function immediately following (sub)maximal exercise in young adult survivors of extreme prematurity with BPD compared to preterm-born young adults without BPD and at term-born (AT) young adults, using CMR as the optimal technique, particularly for the right ventricle, and to reveal dynamic abnormalities that are not apparent on conventional static tests at rest.

Methods

Study design and participants

A total of 60 young adults were included in the study. Preterm-born patients with (n=20) and without (n=20) BPD were recruited out of the Neonatal Intensive Care Unit database of Erasmus MC Sophia children's hospital, the Netherlands. Subjects born <30 weeks of gestational age were eligible for the study. BPD was defined as ⩾28 days of oxygen dependency [3], consisting of invasive ventilation, ventilation by nasopharyngeal tube or oxygen therapy by nasal cannula. Exclusion criteria were 1) known haemodynamically significant heart disease, except as a consequence of pulmonary hypertension; 2) pulmonary disorders other than BPD; 3) kidney disorders; and 4) neurodevelopmental disabilities that would prevent cooperation during cardiopulmonary tests. Subjects born <28 weeks of gestational age were first approached, and, when numbers were insufficient, this was expanded to 28 or 29 weeks of gestational age. To reduce possible genetic and/or socio-economic confounding, AT-born siblings were invited as controls. Because this approach did not recruit a sufficient number of siblings, additional age- and sex-matched controls were recruited from a healthy population through written advertisements (control group n=20).

All participants gave written informed consent. The study protocol was approved by the medical ethics board of Erasmus Medical Center, Rotterdam (MEC2016-427).

Demographic characteristics

Perinatal characteristics were obtained by chart review of the Neonatal Intensive Care Unit admission. Collected characteristics were gestational age, birth weight, days of oxygen dependency and surgical closure of ductus arteriosus. At the first visit, current length, weight, medical history and self-reported physical activity, using the International Physical Activity Questionnaire [13], were collected (figure 1). Body surface area (BSA) was calculated using the Mosteller formula [14]. Mean arterial pressure (MAP) was calculated as (systolic blood pressure+(2×diastolic blood pressure))/3. MAP during exercise was measured at 50% of predicted workload during cardiopulmonary exercise testing (CPET). Systemic vascular resistance was defined as MAP/cardiac index and measured at rest and during exercise.

Echocardiography and CPET

Parameters related to LV diastolic function, valvular disease, three-dimensional (3D) LV strain and two-dimensional (2D) right ventricular (RV) strain were determined using echocardiography (EPIQ7 ultrasound system, Philips Medical Systems, Best, the Netherlands). Forced expiratory volume in 1 s (FEV_1) and forced vital capacity were predicted by the reference values of the Global Lung Function Initiative 2012 [15]. CPET was performed on an upright cycling ergometer (Ergoselect 200P, Ergoline, Bitz, Germany) with breath-by-breath gas analysis (CareFusion, San Diego, CA, USA). Maximal oxygen uptake (V'_{O_2max}) during CPET was predicted by the WASSERMAN *et al.* [16] formula. Exercise protocol consisted of a ramped protocol until exhaustion. Peak V'_{O_2} during CPET was considered as V'_{O_2max}.

Cardiovascular magnetic resonance

To avoid two consecutive physical challenges for participants on one day, (exercise) CMR was performed on the second visit. CMR took place on a clinical 1.5T magnetic resonance imaging (MRI) system (SIGNA artist, GE Healthcare, Milwaukee, WI, USA), using a large flex coil, positioned around the left side of the thorax to cover the entire heart, with electrocardiographic gating. The protocol included breathhold steady-state free precession (SSFP) cine imaging, native T1-mapping and real-time free-breathing SSFP during rest and exercise. SSFP cine images were obtained during breathhold in a

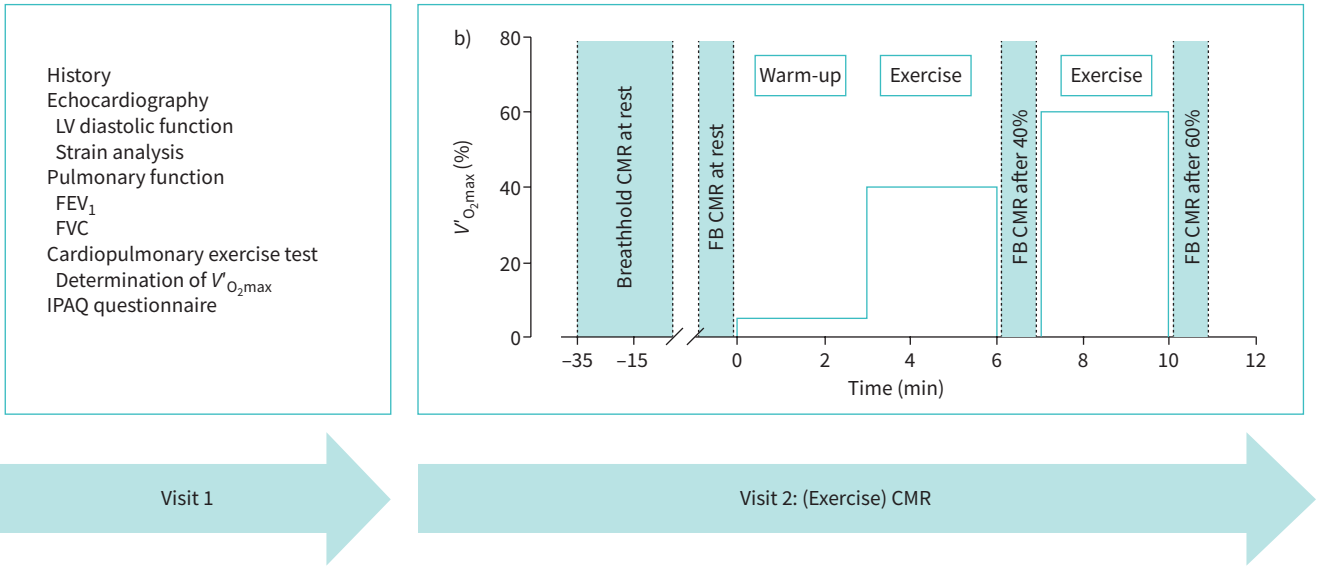

FIGURE 1 Schematic overview of the study protocol. LV: left ventricular; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; V'_{O_2max}: maximal oxygen uptake; IPAQ: International Physical Activity Questionnaire; CMR: cardiovascular magnetic resonance; FB: free-breathing.

contiguous stack of short-axis views, with coverage from base to apex, and in all three long-axis views. Typical scan parameters were one slice per breathhold, slice thickness 6 mm, inter-slice gap 4 mm, repetition time (TR) 3.8 ms, echo time (TE) 1.7 ms, flip angle 65°, number of excitations (NEX) 1, array coil spatial sensitivity encoding (ASSET) 2, field of view 360×288 mm, acquired matrix 200×280 mm with 30 reconstructed phases per cardiac cycle. Native T1-mapping was performed in a mid-ventricular short-axis view using a modified look-locker inverse recovery sequence with a 5(3)3 acquisition scheme with a slice thickness of 8 mm, TE/TR 1.6/3.6 ms, flip angle 35°, ASSET 2, field of view 360×288 mm and acquired matrix 192×140 mm.

Exercise CMR was performed using free-breathing single-shot real-time SSFP images at rest and after two submaximal exercise intensities (figure 1). Typical parameters were slice thickness 8 mm, inter-slice gap 0 mm, TR 3.2 ms, TE 1.4 ms, flip angle 65°, NEX 0.5, ASSET 3.0, field of view 360×288 mm, matrix 128×100 mm with 30 phases per slice starting at the base of the heart. Temporal resolution was 58 ms. Scanning time was equal in each subject.

A MRI-compatible, push-pull ergometer (Lode BV, Groningen, the Netherlands) was used to enable taller subjects to perform the tests. To standardise exercise intensities, a recently validated V'_{O_2}-based approach was used [17]. Workload was calculated using the formula: $W=183.3\times^{10}\log(V'_{O_2}\,kg^{-1})-181.6$ [17]. Exercise intensities were chosen to remain within the technical limits of the push-pull ergometer (5–100 W) [17]. Imaging was performed directly after cessation of exercise because imaging during exercise led to extensive movement artefacts. Heart rates were monitored directly after cessation of exercise and at the end of the scan. Mean heart rate during imaging was used in calculations, to account for heart rate recovery after (temporary) cessation of exercise.

Analyses were done using commercially available post-processing software (Qmass software version 8.1, Medis Medical Imaging, Leiden, the Netherlands). Images were anonymised and analysed in a random order blinded to subject group by a CMR reader with >3 years of experience (J.J. Steenhorst), checked by an experienced CMR specialist with >20 years of experience (A. Hirsch). Epi- and endocardial contours were manually drawn in the end-diastolic and end-systolic phase. In exercise CMR, only endocardial contours were drawn. To reduce breathing artefacts, end-diastolic and end-systolic images during end-inspiration and end-expiration were excluded from the analysis. Papillary muscles and trabeculations were included in the blood volumes. All CMR-derived volume and mass measurements were indexed for BSA.

Statistical analysis

The main outcome was stroke volume change during exercise. Secondary outcomes were cardiac structure and function as assessed by (exercise) CMR and exercise capacity as assessed by CPET.

Continuous, parametric variables are presented as mean±SD and were tested with a one-way ANOVA with Tukey's *post hoc* testing. Continuous nonparametric variables are presented as median (interquartile range (IQR)) and were tested with a Kruskal–Wallace test with Dunn's *post hoc* testing. Categorical data are presented as n (%) and were tested between groups using Fisher's exact test.

In exploratory analyses within the total preterm-born cohort, associations of the primary outcome stroke volume change during exercise and relevant secondary outcomes were assessed with birth weight, oxygen dependency, gestational age and self-reported metabolic equivalent time (MET) used for exercise per week. A multivariate linear analysis was used to assess the primary outcome with variables listed above, corrected for sex and surgically corrected patent ductus arteriosus. p-values <0.05 were considered significant.

Statistical analyses were performed using SPSS (version 25, IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA).

Results

Participant characteristics

All 60 subjects completed both visits and were included in the analyses (33 female (55%), age 23±2 years). No CMR data were missing. Median time between visits was 8 days (IQR 2–18 days). Of the 20 control subjects, eight (40%) were a sibling of one of the preterm-born subjects, of whom five (25% of total controls) had BPD and three (15%) did not.

No significant differences were found between the three groups in age, sex, weight, body mass index, BSA or METs per week (table 1). Between the preterm-born subjects with and without BPD, there was no significant difference in gestational age and birth weight. 12 out of 20 preterm-born subjects with BPD (60%) were on room air or 21% oxygen therapy at 36 weeks postmenstrual age and were therefore considered to have "mild" BPD [3].

Pulmonary function and cardiopulmonary testing

FEV_1 was significantly decreased in the preterm-born subjects with BPD compared to the preterm-born subjects without BPD and AT-born subjects (table 1). Forced vital capacity was similar in all three groups. During CPET, V'_{O_2max} was lower in the preterm-born group with BPD compared to AT-born subjects. No differences were found in preterm-born without BPD and AT-born subjects.

Echocardiography and CMR at rest

None of the subjects had any relevant valvular disease. In terms of LV diastolic function parameters, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e') was slightly increased in preterm-born subjects without BPD compared to AT-born subjects. This effect was not observed in subjects born preterm with BPD.

Preterm-born subjects with and without BPD had lower CMR-derived LV EDVs compared to AT-born subjects. BPD subjects also had lower resting stroke volume compared to AT-born subjects. Resting cardiac index in the BPD group was preserved as a consequence of their higher heart rate. RV EDV was reduced in subjects born preterm with BPD compared to AT-born subjects (table 1).

Exercise CMR

Immediately following exercise intensities of both 40% and 60% of V'_{O_2max}, stroke volume was lower in preterm-born subjects with and without BPD compared to AT-born subjects, resulting in attenuated cardiac index increase (figure 2 and supplementary table S1). Preterm-born subjects had lower LV EDV during exercise compared to AT-born subjects, irrespective of BPD status. The decrease in LV EDV from rest to 40% V'_{O_2max} was larger in BPD subjects compared to preterm-born subjects without BPD and to AT-born subjects (figure 3 and supplementary table S1). LV ejection fraction was not different between groups, and increased during exercise compared to rest. Exercise revealed increased systemic vascular resistance in BPD subjects compared to preterm-born and AT-born subjects. Heart rate recovery during the time of the scan was not different between groups.

In exploratory analyses of the preterm-born cohort, stroke volume and LV EDV change from rest to exercise (40% V'_{O_2max}) were significantly associated with duration of oxygen dependency (figure 4). Lower stroke volume at rest was significantly associated with lower birth weight and prolonged oxygen dependency. Multivariable analysis revealed that the duration of oxygen dependency was the only variable

TABLE 1 Characteristics and baseline measurements of the study population

				p-value		
	BPD group	PRE group	AT group	BPD *versus* PRE	BPD *versus* AT	PRE *versus* AT
Demographics	n=20	n=20	n=20			
Current						
Female	11 (55)	11 (55)	11 (55)	>0.99	>0.99	>0.99
Age (years)	22±2	23±2	22±2	0.40	>0.99	0.38
Length (cm)	171±8	178±8	177±9	0.70	0.052	0.65
Weight (kg)	67±9	72±15	70±11	0.25	0.55	0.84
BMI ($kg \cdot m^{-2}$)	23±2	24±5	22±3	0.90	>0.99	0.35
BSA (m^2)	1.78±0.15	1.86±0.21	1.85±0.18	0.40	0.59	>0.99
Heart rate (bpm)	69±10	64±8	61±7	0.19	**0.01**	0.46
Perinatal						
Gestational age (weeks)	27.0 (26.1–27.9)	28.4 (27.4–28.6)	39.1 (38.2–40.1)	0.29	**<0.001**	**<0.001**
Birth weight (g)	850±100	1005±200	3300±590	0.33	**<0.001**	**<0.001**
Oxygen dependency (days)	58 (47–72)	13 (7–20)	0 (0–0)	**0.001**	**<0.001**	**0.001**
Surgically corrected PDA	4 (20%)	0	0	0.11	>0.99	>0.99
IPAQ						
Activity per week ($METs \cdot 10^{-3}$)	3.6 (1.5–8.6)	7.2 (2.5–11.2)	4.2 (2.9–9.4)	0.64	>0.99	>0.99
Exercise per week ($METs \cdot 10^{-3}$)	0.5 (0–1.6)	0.8 (0.05–1.6)	1.5 (0.6–2.4)	>0.99	0.09	0.25
Pulmonary function						
FEV_1 (% pred)	79±9	95±8	94±11	**<0.001**	**<0.001**	0.95
FVC (% pred)	97±12	100±8	98±14	0.72	0.96	0.87
CPET values						
Peak oxygen consumption ($mL \cdot min^{-1} \cdot W^{-1}$)	2299±492	2638±580	2910±702	0.22	**0.005**	0.46
Peak oxygen consumption (% pred)	91±18	102±14	106±17	0.90	**0.01**	0.18
Peak heart rate (bpm)	183 (175–192)	187 (181–191)	192 (181–193)	>0.99	0.10	0.58
Peak heart rate (% pred)	92±4	95±4	95±4	0.14	0.08	0.96
Peak breathing reserve (%)	31±13	35±10	32±13	0.56	0.99	0.63
Peak RER	1.24±0.09	1.25±0.08	1.24±0.09	0.97	>0.99	0.98
MAP at rest (mmHg)	95±6	96±8	91±9	0.95	0.22	0.12
MAP during exercise (mmHg)[#]	101±9	98±13	94±9	0.71	0.20	0.54
SVR at rest ($mmHg \cdot mL^{-1} \cdot m^{-2}$)	30±5	32±4	29±4	0.72	0.59	0.18
SVR during exercise ($mmHg \cdot mL^{-1} \cdot m^{-2}$)[#]	43±11	34±9	30±7	**0.022**	**<0.001**	0.29
Echocardiography						
Valvular disease[¶]	0	0	0	>0.99	>0.99	>0.99
Pulmonary artery acceleration time	129 (125–143)	143 (131–151)	140 (127–152)	0.59	>0.99	>0.99
Estimated systolic PAP[+] (mmHg)	19±4	21±6	19±4	0.83	0.96	0.68
Left ventricular diastolic function						
Deceleration time (ms)	173 (133–185)	173 (152–183)	172 (158–198)	>0.99	0.59	0.80
E/A ratio	1.8 (1.3–2.2)	1.8 (1.7–2.5)	2.2 (1.4–2.3)	0.78	>0.99	>0.99
Medial e'	11.9±1.5	12.3±2.5	12.3±2.3	0.80	0.83	0.99
E/e'	7.2±1.4	7.8±1.7	6.4±1.5	0.47	0.25	**0.01**
Left atrial volume index[§]	31±8	26±7	26±9	0.27	0.23	>0.99
Left ventricular 3D strain						
Global longitudinal strain (%)	−20±4	−21±3	−21±2	0.58	0.24	0.81
Global circumferential strain (%)	−28±4	−29±2	−31±3	0.38	0.056	0.38
Global radial strain (%)	40±5	42±3	44±3	0.35	**0.02**	0.37
Right ventricular 2D strain						
Free wall longitudinal strain (%)	−27±3	−27±3	−28±3	0.85	0.36	0.63
CMR						
Left ventricle						
EDV ($mL \cdot m^{-2}$)	80±11	81±13	91±14	>0.99	**0.03**	0.057
ESV ($mL \cdot m^{-2}$)	33±8	33±6	38±7	>0.99	0.15	0.07
EF (%)	59±7	60±4	58±3	>0.99	>0.99	0.77
Mass ($g \cdot m^{-2}$)	53±10	55±10	59±12	0.99	0.42	0.92
Mass/EDV ($g \cdot mL^{-1}$)	0.67±0.1	0.68±0.1	0.64±0.1	0.94	0.65	0.44
Stroke volume ($mL \cdot m^{-2}$)	47±7	49±8	53±9	>0.99	**0.04**	0.28
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	5.7±0.9	5.8±1.1	6.0±1.2	>0.99	>0.99	>0.99
Native septal T1	967±23	959±29	962±26	0.61	0.78	0.96

Continued

TABLE 1 Continued

	BPD group	PRE group	AT group	p-value		
				BPD *versus* PRE	BPD *versus* AT	PRE *versus* AT
Right ventricle						
EDV (mL·m^{-2})	85±12	89±17	91±14	>0.99	**0.02**	0.17
ESV (mL·m^{-2})	38±9	41±10	46±10	>0.99	0.07	0.29
EF (%)	55±6	55±5	54±4	0.95	0.50	>0.99
Mass (g·m^{-2})	12±2	12±3	13±3	>0.99	0.13	0.26
Mass/EDV (g·mL^{-1})	0.92±0.13	0.95±0.17	0.92±0.13	0.90	0.90	0.90

Data are presented as mean±SD, median (interquartile range) or n (%). BPD: bronchopulmonary; PRE: preterm-born adults without BPD; AT: at term-born adults; BMI: body mass index; BSA: body surface area; PDA: patent ductus arteriosus; IPAQ: International Physical Activity Questionnaire; MET: metabolic equivalent time; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CPET: cardiopulmonary exercise testing; RER: respiratory exchange ratio; MAP: mean arterial pressure; SVR: systemic vascular resistance; PAP: pulmonary arterial pressure; E: early diastolic mitral inflow velocity (E-wave); A: late diastolic mitral inflow velocity (A-wave); e': ealy diastolic mitral annulus velocity; CMR: cardiovascular magnetic resonance; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction. #: available in 12 subjects in the BPD group, 18 in the PRE group and 19 in AT group; ¶: defined as more than mild valvular stenosis or regurgitation of any of the heart valves; +: available in 7 subjects in the BPD group, 4 in the PRE group and 8 in the AT group; §: available in 18 subjects in the BPD group, 18 in the PRE group and 19 in the AT group.

independently associated with percentage stroke volume change from rest to 40% V'_{O_2max} (β= −0.160, 95% CI −0.3204 to −0.0001; adjusted p-value=0.048).

Discussion

This study has several main findings. 1) Resting heart rate in BPD subjects was higher than in AT-born subjects; 2) peak oxygen uptake at maximal CPET was decreased in BPD subjects; 3) CMR at rest showed reduced LV and RV volumes in BPD subjects compared to AT-born subjects, with lower resting stroke volume; 4) exercise-related stroke volume was impaired in both preterm-born groups compared to AT-born subjects, which was most pronounced in BPD subjects; 5) impaired stroke volume with stress resulted from a larger decrease of LV EDV during exercise in BPD subjects, while the decrease in LV end-systolic volume was similar for all groups; 6) systemic vascular resistance during exercise was increased in BPD subjects; and 7) impaired RV and LV stroke volume response following exercise was associated with oxygen dependency in the preterm cohort.

For (extremely) preterm-born adults (combining those with and without BPD), a 13-fold increased risk for heart failure was demonstrated in a large Swedish cohort [7]. Underlying mechanisms of this observation are unknown. Potential factors related to increased heart failure risk include abnormal size and shape of the left and right ventricle in premature-born young adults as previously demonstrated by Lewandowski *et al*. [8, 18], and reductions in LV systolic, diastolic and rotational function and lower RV ejection fraction [19].

The preterm population is not homogeneous, hampering comparisons between groups and studies [20]. For most of the information thus far obtained, it is unknown how BPD relates to the findings on increased heart failure risk and mechanisms. The effects of BPD on long-term cardiac outcomes have not been studied extensively [6, 21], and have been hard to assess in large meta-analyses [21, 22].

As summarised in the first paragraph of the discussion section, our study noted several differences between BPD and non-BPD subjects. A remarkable observation was the finding of increased resting heart rates in BPD subjects. Increased resting heart rate in adolescents has been associated with increased heart failure risk, largely independent of aetiology [23]. Previous observations including decreased exercise capacity, FEV_1 and biventricular volumes at rest in preterm-born subjects with BPD were confirmed in our study. Impaired exercise-related LV systolic function, as we noted with exercise MRI, has previously been observed with echocardiography during exercise in preterm-born young adults (without BPD) at 60% of V'_{O_2max} [11]. In our current study, both preterm groups exhibited cardiac systolic dysfunction immediately after exercise as evidenced by decreased stroke volume. This effect was most pronounced in BPD subjects. Strikingly, BPD subjects showed exaggerated decreases in LV EDV compared to preterm-born subjects without BPD. The reduction in LV EDV likely relates to increased pulmonary vascular resistance during exercise [24]. This could result from prematurity-associated decreased angio-/vasculogenesis or from an impaired functional response of the pulmonary vasculature to stress [25, 26]. A similar situation occurs in patients with (borderline) pulmonary hypertension or a Fontan circulation, where reduced flow through the

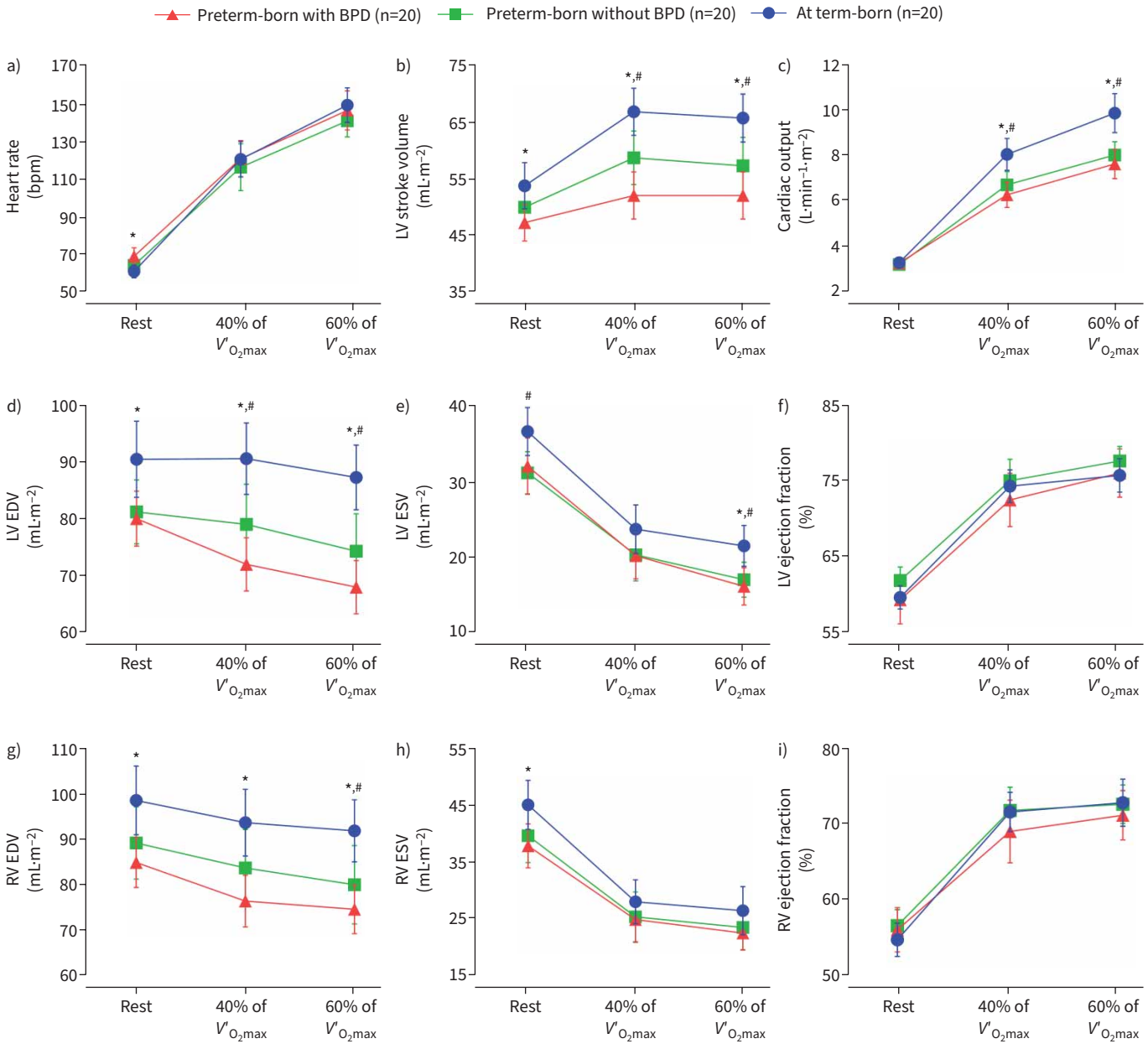

FIGURE 2 Cardiac performance at rest and during exercise at 40% and 60% of maximal oxygen uptake (V'_{O_2max}) in preterm-born young adults with or without bronchopulmonary dysplasia (BPD). Data are presented as mean (95% confidence interval). LV: left ventricular; EDV: end-diastolic volume; ESV: end-systolic volume; RV: right ventricular. *: p<0.05 for preterm-born with BPD *versus* at term-born young adults; #: p<0.05 for preterm-born without BPD *versus* at term-born young adults.

pulmonary circulation hampers LV preload, limiting exercise capacity [27–29]. Another factor contributing to reduced ventricular volume during exercise could be impaired RV preload and/or LV/RV diastolic function, hampering LV filling [30, 31]. This has not been studied in adults with BPD separately. In our study, no significant diastolic dysfunction was observed in BPD subjects. Differentiation between abnormal RV preload, LV diastolic and pulmonary vascular dysfunction (*i.e.* LV preload) during exercise is important, especially for those who experienced prolonged postnatal oxygen dependency, because these represent different therapeutical targets, relevant for young adults born preterm.

It is important to note that abnormal pulmonary function may also contribute to reduced exercise tolerance, and differentiating the role of the heart *versus* the lungs will contribute to prognostication and therapeutic decision-making [19, 32].

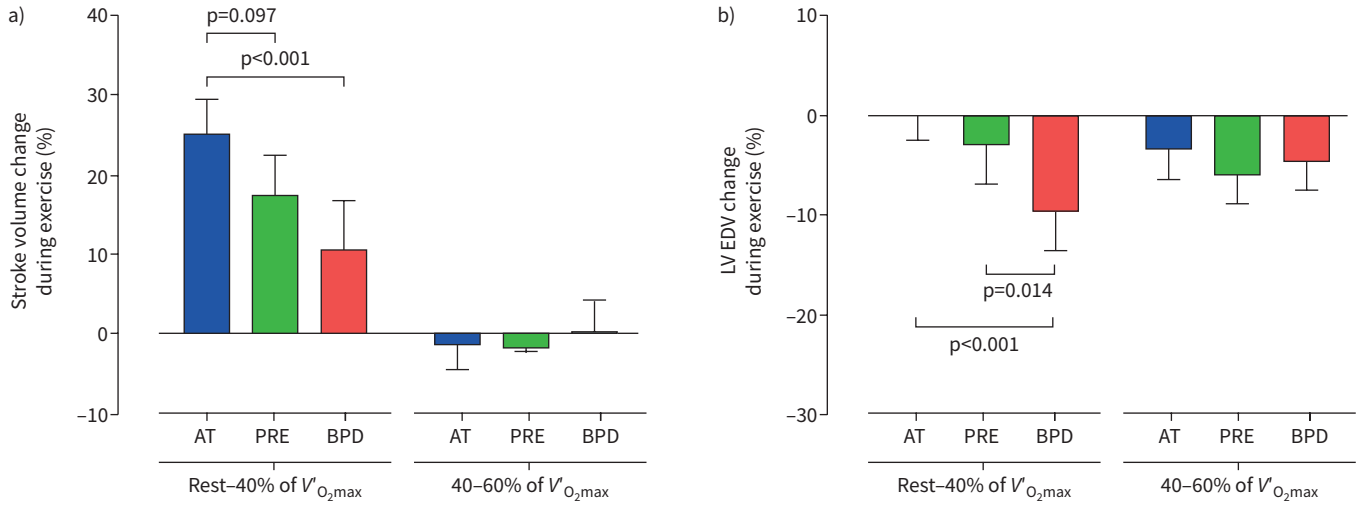

FIGURE 3 Change in stroke volume (a) and left ventricular end-diastolic volume (LV EDV) (b) from rest to exercise at 40% of maximal oxygen uptake (V'_{O_2max}) and from 40% to 60% of V'_{O_2max} exercise in preterm-born young adults with or without bronchopulmonary dysplasia (BPD). Data are presented as mean (95% confidence interval). AT: at term-born young adults; PRE: preterm-born young adults without BPD; BPD: preterm-born young adults with BPD.

Another potential target for therapy is the increased systemic vascular resistance during exercise we noted in the BPD group. A recent population-based study by Hurst *et al.* [33] showed increased resting systemic vascular resistance in preterm-born young adults, but no differences between BPD and non-BPD subjects. In our study, the increased systemic vascular resistance seen solely in BPD subjects was revealed by exercise and could be an important early sign of functional cardiovascular impairments.

Remarkably, we did not find changes in resting RV end-systolic volume, ejection fraction or strain in preterm-born adults with BPD. In contrast, Dartora *et al.* [34], in an echocardiographic study with different composition and size of the study population, recently showed a decrease in RV systolic parameters at rest in young adult BPD survivors, which was associated with BPD severity. The role of the right ventricle in BPD requires additional study.

Prolonged oxygen dependency may result in hyperoxia, which may induce cell cycle arrest. This may be detrimental in the brief myocyte proliferation period of the neonatal/infant heart [20]. Preterm-born infants with BPD are more exposed to hyperoxia, possibly inducing more profound impairments in cardiomyocyte development. Therefore, our observation of impaired RV and LV stroke volume response following exercise (weakly) relating to oxygen dependency in the preterm-born cohort may be important.

Although preterm-born adolescents are at increased risk for heart failure, the age of onset and optimal strategies for treatment have not been elucidated. In this setting, even small changes, as we noted particularly in the BPD group, may be clinically relevant, considering the potential long-term added effects with well-known heart failure risk factors (*e.g.* hypertension, diabetes, smoking) [6, 35, 36]. Timely detection might contribute to improved outcomes. Cardiac evaluation with stress may reveal abnormalities not apparent at rest. This can be done with echocardiography for the left ventricle [11]. Testing RV functional reserve might benefit from the use of MRI [37, 38].

Strengths

To our knowledge, this study is the first to investigate cardiac structure and performance during exercise using CMR in very preterm-born young adults. Additionally, we have studied the oldest population of preterm-born young adults with BPD, born in the post-surfactant era, compared to non-BPD subjects. In BPD, oxygen dependency is important. Our study was able to correlate duration of oxygen dependency after birth with ventricular response to exercise during young adulthood. Furthermore, we used a validated method to ascertain repeatable submaximal exercise intensities related to subject-specific V'_{O_2max}, instead of less reproducible criteria such as exhaustion or fixed heart rate zones [17].

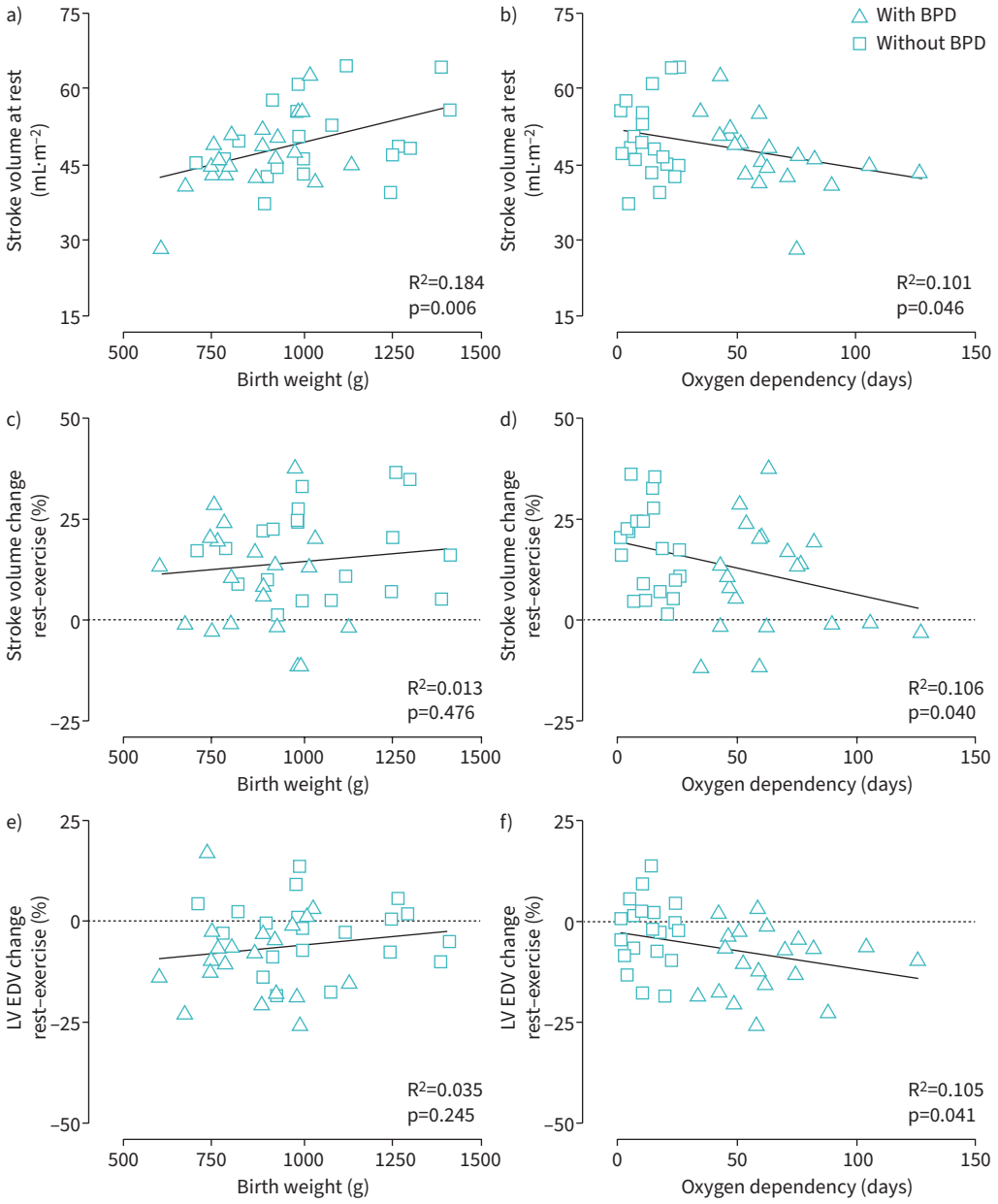

FIGURE 4 Correlation of stroke volume and left ventricular end-diastolic volume (LV EDV) at rest and at change from rest to exercise at 40% of maximal oxygen uptake (V'_{O_2max}) with birthweight and oxygen dependency in preterm-born young adults with and without bronchopulmonary dysplasia (BPD).

Weaknesses

The most important limitations of this study were the relatively low number of subjects, lack of information on pulmonary vascular or ventricular diastolic function during exercise, and inability to scan subjects during exercise. Furthermore, exercise CMR demands a high level of cooperation by subjects, leading to exclusion of subjects with neurocognitive impairments.

Conclusions

Preterm-born young adults with BPD showed increased resting heart rates and impaired exercise performance compared to AT-born young adults. Furthermore, preterm-born young adults exhibited attenuated stroke volume increase during exercise compared to AT-born controls. Exercise-related impairment of stroke volume was more profound in preterm-born young adults with BPD and was

associated with a larger decrease in LV EDV during exercise and increased neonatal oxygen dependency. This could be an important feature in predisposition to heart failure in a potentially large group of patients.

Provenance: Submitted article, peer reviewed.

Ethics statement: Approved by the medical ethics board of Erasmus Medical Center, Rotterdam (MEC2016-427).

Conflict of interest: None declared.

Support statement: This study was funded by Thoraxfoundation project number 22109, Erasmus MC Sophia Foundation S12-13, and participating departments of Erasmus Medical Center. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Blencowe H, Cousens S, Oestergaard MZ, *et al.* National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; 379: 2162–2172.
2 Zeitlin J, Draper ES, Kollee L, *et al.* Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. *Pediatrics* 2008; 121: e936–e944.
3 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 163: 1723–1729.
4 Northway WH, Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967; 276: 357–368.
5 Zysman-Colman Z, Tremblay GM, Bandeali S, *et al.* Bronchopulmonary dysplasia - trends over three decades. *Paediatr Child Health* 2013; 18: 86–90.
6 Crump C, Howell EA, Stroustrup A, *et al.* Association of preterm birth with risk of ischemic heart disease in adulthood. *JAMA Pediatr* 2019; 173: 736–743.
7 Carr H, Cnattingius S, Granath F, *et al.* Preterm birth and risk of heart failure up to early adulthood. *J Am Coll Cardiol* 2017; 69: 2634–2642.
8 Lewandowski AJ, Bradlow WM, Augustine D, *et al.* Right ventricular systolic dysfunction in young adults born preterm. *Circulation* 2013; 128: 713–720.
9 McKay L, Goss KN, Haraldsdottir K, *et al.* Decreased ventricular size and mass mediate the reduced exercise capacity in adolescents and adults born premature. *Early Hum Dev* 2021; 160: 105426.
10 Goss KN, Haraldsdottir K, Beshish AG, *et al.* Association between preterm birth and arrested cardiac growth in adolescents and young adults. *JAMA Cardiol* 2020; 5: 910–919.
11 Huckstep OJ, Williamson W, Telles F, *et al.* Physiological stress elicits impaired left ventricular function in preterm-born adults. *J Am Coll Cardiol* 2018; 71: 1347–1356.
12 Thein PM, Mirzaee S, Cameron JD, *et al.* Left ventricular contractile reserve as a determinant of adverse clinical outcomes: a systematic review. *Intern Med J* 2022; 52: 186–197.
13 Craig CL, Marshall AL, Sjostrom M, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35: 1381–1395.
14 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; 317: 1098.
15 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
16 Wasserman K, Hansen JE, Sue DY, *et al.* (eds). Principles of Exercise Testing and Interpretation. 4th edn. Philadelphia, Lippincott Williams and Wilkins, 2004.
17 Steenhorst JJ, Hirsch A, van den Berg LEM, *et al.* Standardizing submaximal exercise intensities for use of supine push-pull exercise during cardiovascular magnetic resonance. *Clin Physiol Funct Imaging* 2022; 43: 10–19.
18 Lewandowski AJ, Augustine D, Lamata P, *et al.* Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. *Circulation* 2013; 127: 197–206.
19 Schuermans A, Lewandowski AJ. Understanding the preterm human heart: what do we know so far? *Anat Rec (Hoboken)* 2022; 305: 2099–2112.
20 Greer C, Troughton RW, Adamson PD, *et al.* Preterm birth and cardiac function in adulthood. *Heart* 2021; 108: 172–177.
21 Belfort MB, Sacks SB. Preterm birth and heart failure in infancy and beyond: born with a broken heart? *JAMA Pediatr* 2021; 175: 673–675.
22 Telles F, McNamara N, Nanayakkara S, *et al.* Changes in the preterm heart from birth to young adulthood: a meta-analysis. *Pediatrics* 2020; 146: e20200146.
23 Lindgren M, Robertson J, Adiels M, *et al.* Elevated resting heart rate in adolescent men and risk of heart failure and cardiomyopathy. *ESC Heart Fail* 2020; 7: 1178–1185.

24 Goss KN, Beshish AG, Barton GP, *et al.* Early pulmonary vascular disease in young adults born preterm. *Am J Respir Crit Care Med* 2018; 198: 1549–1558.
25 Chao CM, van den Bruck R, Lork S, *et al.* Neonatal exposure to hyperoxia leads to persistent disturbances in pulmonary histone signatures associated with NOS3 and STAT3 in a mouse model. *Clin Epigenetics* 2018; 10: 37.
26 Steenhorst JJ, Hirsch A, Verzijl A, *et al.* Exercise and hypoxia unmask pulmonary vascular disease and right ventricular dysfunction in a 10- to 12-week-old swine model of neonatal oxidative injury. *J Physiol* 2022; 600: 3931–3950.
27 Gorter TM, Willems TP, van Melle JP. Ventricular interdependence in pulmonary arterial hypertension: providing small pieces of a complex puzzle. *Eur J Heart Fail* 2015; 17: 1–2.
28 Pushparajah K, Wong JK, Bellsham-Revell HR, *et al.* Magnetic resonance imaging catheter stress haemodynamics post-Fontan in hypoplastic left heart syndrome. *Eur Heart J Cardiovasc Imaging* 2016; 17: 644–651.
29 Oliveira RKF, Faria-Urbina M, Maron BA, *et al.* Functional impact of exercise pulmonary hypertension in patients with borderline resting pulmonary arterial pressure. *Pulm Circ* 2017; 7: 654–665.
30 Lewandowski AJ, Raman B, Bertagnolli M, *et al.* Association of preterm birth with myocardial fibrosis and diastolic dysfunction in young adulthood. *J Am Coll Cardiol* 2021; 78: 683–692.
31 Corrado PA, Barton GP, Macdonald JA, *et al.* Altered right ventricular filling at four-dimensional flow MRI in young adults born prematurely. *Radiol Cardiothorac Imaging* 2021; 3: e200618.
32 Duke JW, Lewandowski AJ, Abman SH, *et al.* Physiological aspects of cardiopulmonary dysanapsis on exercise in adults born preterm. *J Physiol* 2021; 600: 463–482.
33 Hurst JR, Beckmann J, Ni Y, *et al.* Respiratory and cardiovascular outcomes in survivors of extremely preterm birth at 19 years. *Am J Respir Crit Care Med* 2020; 202: 422–432.
34 Dartora DR, Flahault A, Luu TM, *et al.* Association of bronchopulmonary dysplasia and right ventricular systolic function in young adults born preterm. *Chest* 2021; 160: 287–296.
35 Goss KN, Everett AD, Mourani PM, *et al.* Addressing the challenges of phenotyping pediatric pulmonary vascular disease. *Pulm Circ* 2017; 7: 7–19.
36 Lewandowski AJ. The preterm heart: a unique cardiomyopathy? *Pediatr Res* 2019; 85: 738–739.
37 La Gerche A, Claessen G, Van de Bruaene A, *et al.* Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging* 2013; 6: 329–338.
38 Cheng S, Li VW, Cheung YF. Systolic and diastolic functional reserve of the subpulmonary and systemic right ventricles as assessed by pharmacologic and exercise stress: a systematic review. *Echocardiography* 2022; 39: 310–329.