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Original research article

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Cardiac dysfunction during exercise in young adults with bronchopulmonary dysplasia

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Take home message: 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.

Abstract

Background: Worldwide, 1-2 % of children is 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.

Aim: This study aims to examine cardiorespiratory function during submaximal exercise in young adult survivors of extreme prematurity, with or without BPD.

Methods: Forty premature born young adults, 20 with BPD (median[IQR] gestational age (GA), 27 [26-28] weeks) and 20 without BPD (GA age 28 [27-29] weeks) were prospectively compared to age-matched at term born (AT) adults (GA 39 [38-40] weeks). Participants underwent exercise testing and cardiovascular magnetic resonance (CMR) with submaximal exercise.

Results: Resting heart rate in BPD subjects was higher than in AT born subjects (69±10 vs. 61±7 mL, p=0.01). Peak oxygen uptake at maximal CPET was decreased in BPD patients (91±18 vs. 106±17% of predicted, p=0.01). In BPD subjects cardiac stroke volume (SV) change with exercise was impaired compared to AT subjects (11±13% vs. 25±10%; p<0.001). With exercise, left ventricular end-diastolic volume decreased more in preterm borns with versus without BPD (-10±8% vs. -3±8%; p=0.01) and compared to AT subjects (0±5%; p<0.001). Exploratory data analysis revealed that exercise SV 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 CMR 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 nineties, resulted in a clear division between 'classic' BPD and 'new' BPD (3, 4). In the past decades, survival of very and extreme premature born infants -with and without BPD- has increased significantly, leading to a growing population of preterm born young adults (5).

Premature born young adults are predisposed to early cardiovascular disease (6, 7). In young adult survivors of extreme prematurity, cardiac remodeling (smaller end-diastolic volumes (EDV), altered left ventricular (LV) geometry), as measured by cardiovascular magnetic resonance (CMR) at rest, has been shown (8-10). Testing 'the engine under load' (exercise-testing during imaging (using echocardiography)) has revealed additional dynamic changes in cardiac performance of premature 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

Sixty young adults were included in the study. Preterm born subjects 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 hemodynamically significant heart disease, except as a consequence of pulmonary hypertension; 2) pulmonary disorders other than BPD. 3) kidney disorders; 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, expanded to 28 or 29 weeks of gestational age. To reduce possible genetic and/or socio-economic confounding, AT born siblings were asked as controls. Since this approach did not recruit 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 CPET. Systemic vascular resistance was defined as MAP/cardiac index and measured at rest and during exercise.

Echocardiography and cardiopulmonary exercise testing

Parameters related to LV diastolic function, valvular disease, 3D LV strain, and 2D right ventricular (RV) strain were determined using echocardiography (EPIQ7 ultrasound system, Philips Medical Systems, Best, The Netherlands). FEV1 and forced vital capacity was predicted by the reference values of the global lung function initiative 2012 (15). CPET was performed on a upright cycling ergometer (Ergoselect 200P, Ergoline, Bitz, Germany) with breath-by-breath gas analysis (CareFusion, San Diego, CA, USA). Maximum oxygen consumption (VO_{2max}) during CPET was predicted by the Wasserman formula (16). Exercise protocol consisted of a ramped protocofl until exhaustion. Peak VO_2 during CPET was considered as VO_{2max}.

Cardiovascular magnetic resonance

To avoid two consecutive physical challenges for subjects on one day, (exercise) cardiovascular magnetic resonance (CMR) was performed on the second visit. CMR took place on a clinical 1.5T 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 breath-hold 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 breath-hold in a 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 breath-hold, slice thickness 6 mm, inter-slice gap 4 mm, TR 3.8, TE 1.7, flip angle 65°, NEX 1, ASSET 2, field of view 360×288 mm, acquired matrix 200×280 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 8mm, TE/TR 1.6/3.6, flip angle 35°, ASSET 2, field of view 360×288mm, and acquired matrix 192×140.

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, TE 1.4, 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 msec. 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 standardize exercise intensities, a recently validated VO_2-based approach was used (17). Workload was calculated by the formula: $W = 183.3 * {}^{10}\log(VO_2\ kg^{-1}) - 181.6$ (17). Exercise intensities were chosen to remain within the technical limits of the push-pull ergometer (0-100W) (17). Imaging was performed directly after cessation of exercise, as imaging during exercise led to extensive movement artefacts. Heart rates were monitored directly after cessation of exercise and at end of 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 anonymized and analyzed in a random order blinded to subject group by a CMR reader with >3 years of experience (JS), checked by an experienced CMR specialist with >20 years of experience (AH). 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 analysis. Papillary muscles and trabeculations were included in the blood volumes. All CMR derived volume and mass measurements were indexed for BSA.

Statistical analysis

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 ± standard deviation [SD] and tested with an one-way ANOVA with Tukey post-hoc testing. Continuous non-parametric variables are presented as median [interquartile range (IQR)] and tested with a Kruskal-Wallace test with Dunn's post hoc testing. Categorical data is presented as numbers with percentages and tested between groups by a Fischer's exact test.

In exploratory analyses within the total preterm born cohort, associations of primary outcome stroke volume change during exercise and relevant secondary outcomes were assessed with birth weight, oxygen dependency, gestational age, self-reported metabolic equivalent time used for exercise per week (METs). 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 are considered significant.

Statistical analyses were performed using SPSS (version 25, IBM SPSS Statistics, IBM corporation).

Results

Participants characteristics

All 60 subjects completed both visits and were included in the analyses (33 (55%) female, age 23±2 years). No CMR data was missing. Median [IQR] time between visits was 8 [2 -18] days. Of the 20 control subjects, 8 (40%) were a sibling of one of the preterm subjects with (5 (25%)) or without BPD (3 (15%)).

No significant differences were found between three groups in age, sex, weight, body mass index, BSA and 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 (60%) preterm born subjects with BPD were on room air or 21% oxygen therapy at 36 weeks post menstrual age and are therefore considered 'mild' BPD (3).

Pulmonary function and cardiopulmonary testing

FEV1 was significantly decreased in the preterm born subjects with BPD compared to the preterm born subjects without BPD and at term born (AT) subjects (Table 1). Forced vital capacity was similar in all three groups. During CPET, VO_{2max} was lower in the preterm born group with BPD compared to AT subjects. No differences were found in preterm without BPD and AT participants.

Echocardiography and CMR at rest

None of the subjects had any relevant valvular disease. Of LV diastolic function parameters, E/e' was slightly increased in preterm born subjects without BPD compared to AT subjects. This effect was not observed in subjects born preterm with BPD.

Preterm born subjects with and without BPD had lower CMR derived LV EDV compared to AT 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 subjects (Table 1).

Exercise CMR

Immediately following exercise intensities of both 40% and 60% of VO_{2max}, stroke volume was lower in preterm subjects with and without BPD compared to AT subjects, resulting in attenuated cardiac index increase (Figure 2 and Supplemental Table 1). Preterm subjects had lower LV EDV during exercise compared to AT subjects, irrespective of BPD status. Decrease in LV EDV size from rest to 40% VO_{2max} was larger in BPD subjects compared to preterm subjects without BPD and to AT subjects (Figure 3 and Supplemental Table 1). LV EF was not different between groups, and increased during exercise compared to rest. Exercise revealed increased systemic vascular resistance in BPD subjects compared to preterm en AT subjects. Heart rate recovery during time of scan was not different between groups.

In exploratory analyses of the preterm cohort, stroke volume and LVEDV change from rest to exercise (40% VO_{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 duration of oxygen dependency as the only variable independently associated with percentage stroke volume change from rest to 40% of VO_{2max} (β with 95% confidence interval: -0.160 (-0.3204 to -0.0001), adjusted p-value 0.048).

Discussion

This study has several main findings. I) Resting heart rate in BPD subjects was higher than in AT subjects. II) Peak oxygen uptake at maximal CPET was decreased in BPD patients. III) CMR at rest showed reduced LV and RV volumes in BPD subjects compared to AT subjects, with lower resting stroke volume. IV) Exercise related stroke volume was impaired in both preterm groups compared to AT subjects. This was most pronounced in BPD subjects. V) Impaired stroke volume with stress resulted from a larger decrease of LV EDV during exercise in BPD subjects, while LV end-systolic volume decrease for all groups was similar. VI) Systemic vascular resistance during exercise was increased in BPD subjects. VII) 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 LV and RV 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 comparison between groups and studies (20). For most of the information thus far obtained, it is unknown how BPD patients relate 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 summarized 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 an increased heart failure risk, largely independent of etiology (23). Previous observations including decreased exercise capacity, FEV1 and decreased biventricular volumes at rest in preterm born subjects with BPD were confirmed in our study. An impaired exercise related systolic function, as we noted with exercise MRI, has previously been observed for the left ventricle with echocardiography during exercise in preterm born young adults (without BPD) at 60% of VO_{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 decrease 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 of impaired functional response of the pulmonary vasculature to stress (25, 26). This is a situation with similarities to patients with (borderline) pulmonary hypertension or a Fontan circulation, where reduced flow through the pulmonary circulation hampers LV preload, limiting exercise capacity (27-29). Another factor in reduced ventricular volume during exercise could be impaired RV preload and/or LV/RV diastolic function, hampering LV ventricular filling (30, 31). This has not been studied for 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 suffered from prolonged postnatal oxygen dependency, since 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).

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 showed increased resting systemic vascular resistance in preterm born young adults, but no differences between BPD and non-BPD preterms (33). 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 ESV, EF or strain in preterms with BPD. In contrast, Dartora et al., in a echocardiographic study with different composition and size of the study population, recently showed a decrease in systolic RV parameters at rest in young adult BPD survivors, which was associated with BPD severity (34). The role of the RV 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 etc.) (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 LV (11). Testing RV functional reserve might benefit from the use of MRI (37, 38).

Strengths

To our knowledge, this study was the first to investigate cardiac structure and performance during exercise using CMR in very premature 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 patients. 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 patient specific $VO_{2max,}$ instead of less reproducible criteria as exhaustion or fixed heart rate zones (17).

Weaknesses

Most important limitations were the relatively low number of patients, 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

In conclusion, preterm born young adults with BPD showed increased resting heart rates and impaired exercise performance compared to at term born young adults. Furthermore, preterm born young adults exhibit attenuated stroke volume increase during exercise compared to at term born controls. Exercise-related impairment of stroke volume was more profound in preterm born young adults with BPD, was attributed to a larger decrease in LV EDV during exercise and was associated with increased neonatal oxygen dependency. This could be an important feature in predisposition to heart failure in a potentially large group of patients.

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Tables

Table 1: Characteristics and baseline measurements of the study population

	Preterm born group with BPD (BPD)	Preterm born group without BPD (PRE)	At term born group (AT)	BPD vs. PRE	BPD vs. AT	PRE vs. 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
Body mass index (kg/m²)	23±2	24 ± 5	22 ± 3	0.90	>0.99	0.35
Body surface area (m²)	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 · 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 · 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						
FEV1 (% of pred)	79±9	95 ± 8	94 ± 11	**<0.001**	**<0.001**	0.95
FVC (% of pred)	97±12	100 ± 8	98 ± 14	0.72	0.96	0.87
Values CPET						
Peak oxygen consumption (ml/min/W)	2299±492	2638 ± 580	2910 ± 702	0.22	**0.005**	0.46
(% of 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
(% of 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
Systemic vascular resistanceat rest (mmHg/mL/m²)	30 ± 5	32 ± 4	29 ± 4	072	0.59	0.18
Systemic vascular resistance during exercise (mmHg/mL/m²)*	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
Cardiovascular magnetic resonance						
Left ventricle						

End-diastolic volume (ml/m²)	80±11	81 ± 13	91 ± 14	>0.99	**0.03**	0.057
End-systolic volume (ml/m²)	33±8	33 ± 6	38 ± 7	>0.99	0.15	0.07
Ejection fraction (%)	59±7	60 ± 4	58 ± 3	>0.99	>0.99	0.77
Mass (g/m²)	53±10	55 ± 10	59 ± 12	0.99	0.42	0.92
Mass/end-diastolic volume (g/ml)	0.67±0.1	0.68 ± 0.1	0.64 ± 0.1	0.94	0.65	0.44
Stroke volume (ml/m²)	47±7	49 ± 8	53 ± 9	>0.99	**0.04**	0.28
Cardiac index (L/min/m²)	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
Right ventricle						
End-diastolic volume (ml/m²)	85±12	89 ± 17	91 ± 14	>0.99	**0.02**	0.17
End-systolic volume (ml/m²)	38±9	41 ± 10	46 ± 10	>0.99	0.07	0.29
Ejection fraction (ml/m²)	55±6	55 ± 5	54 ± 4	0.95	0.50	>0.99
Mass (g/m²)	12±2	12 ± 3	13 ± 3	>0.99	0.13	0.26
Mass/end-diastolic volume (g/ml)	0.92±0.13	0.95 ± 0.17	0.92 ± 0.13	0.90	0.90	0.90

Mean ± standard deviation, median (interquartile range) or number (percentages) are given. BPD – bronchopulmonary dysplasia, PDA – patent ductus arteriosus, FEV1 – forced expiratory volume in 1 second, FVC – forced vital capacity, IPAQ – international physical activity questionnaire, RER – respiratory exchange ratio, MAP – mean arterial pressure

[*] available in 12 subjects in BPD group, 18 in 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 BPD group, 4 in PRE group and 8 in AT group.

[§] available in 18 subjects in BPD group, 18 in PRE group and 19 in the AT group.

Figure legends

Figure 1. Schematic overview of the study protocol. FEV1 – forced expiratory volume in 1 second, FVC – forced vital capacity, VO_{2max} – maximal oxygen consumption, IPAQ – international physical activity questionnaire, CMR – cardiovascular magnetic resonance, FB – Free breathing.

Figure 2. Cardiac performance at rest and during exercise at 40% and 60% of maximal oxygen consumption (VO_{2max}) in preterm born young adults with or without bronchopulmonary dysplasia (BPD).

LV – left ventricular, EDV – end-diastolic volume, ESV – end-systolic volume, RV – right ventricular. Mean ± 95% confidence interval of the mean are shown. *$p<0.05$ for preterm born with BPD vs. at term born young adults, †$p<0.05$ for preterm born without BPD vs. at term born young adults.

Figure 3. Stroke volume (A) and left ventricular end-diastolic volume (LV EDV) (B) change from rest to exercise at 40% of VO_{2max} and from 40% to 60% of VO_{2max} exercise in preterm born young adults. BPD – preterm born young adults with bronchopulmonary dysplasia, PRE – preterm born young adults without bronchopulmonary dysplasia, AT – at term born young adults, VO_{2max} – maximal oxygen consumption. P-values <0.10 are shown. Values are mean ± 95% confidence interval of the mean.

Figure 4. Correlation of stroke volume and LV EDV at rest and change from rest to exercise at 40% of VO_{2max} with birthweight and oxygen dependency in preterm born, young adults without BPD (□) and with BPD (Δ).

LV EDV - left ventricular end-diastolic volume, VO_{2max} – maximal oxygen consumption, BPD – bronchopulmonary dysplasia.

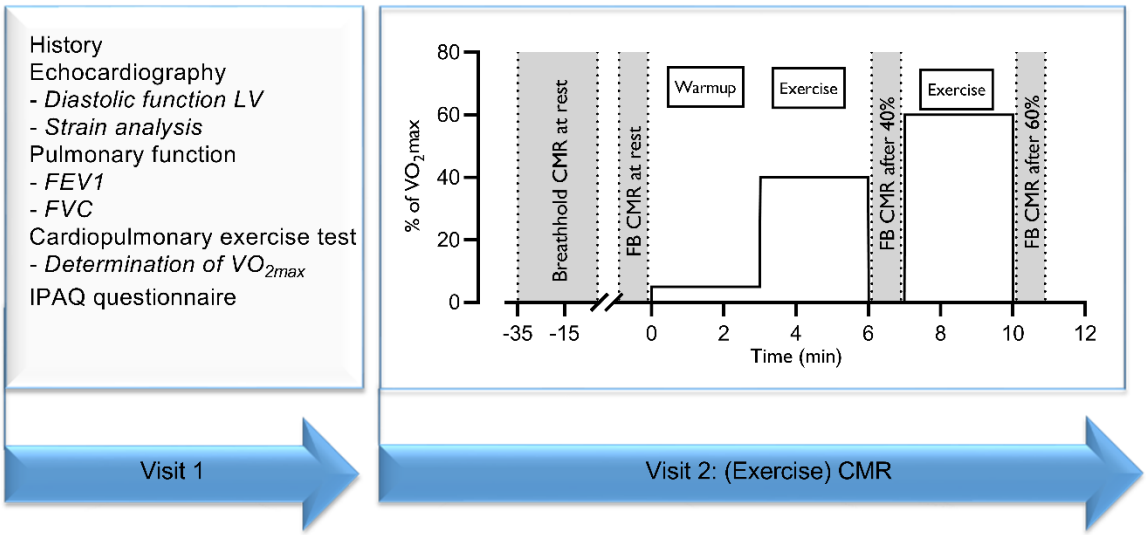
History
Echocardiography
- Diastolic function LV
- Strain analysis
Pulmonary function
- FEV1
- FVC
Cardiopulmonary exercise test
- Determination of VO2max
IPAQ questionnaire
% of VO2max
80
60
40
20
0
Breathhold CMR at rest
FB CMR at rest
Warmup
Exercise
FB CMR after 40%
Exercise
FB CMR after 60%
-35
-15
0
2
4
6
8
10
12
Time (min)
Visit 1
Visit 2: (Exercise) CMR

Figure 1

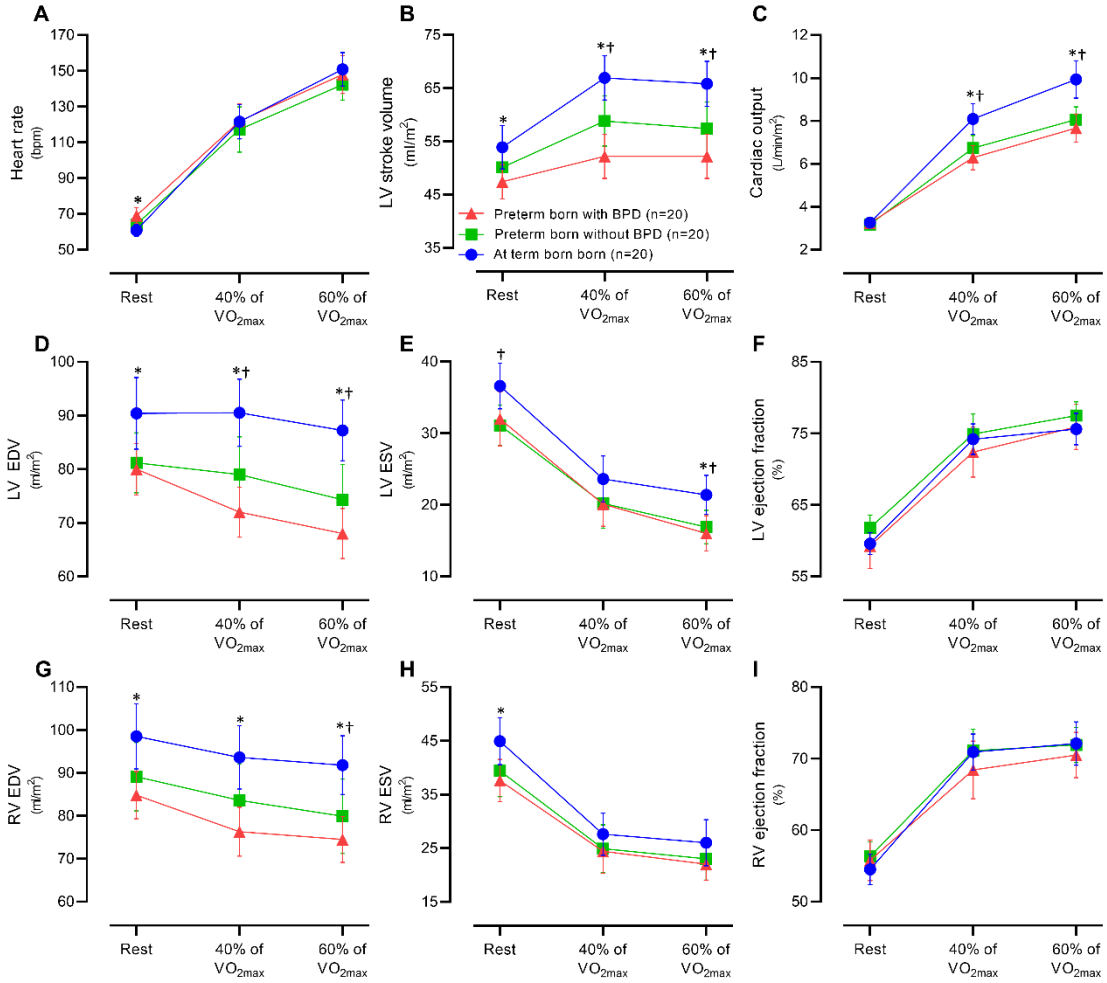
A
Heart rate (bpm)
B
LV stroke volume (ml/m²)
C
Cardiac output (L/min/m²)
Preterm born with BPD (n=20)
Preterm born without BPD (n=20)
At term born born (n=20)
D
LV EDV (ml/m²)
E
LV ESV (ml/m²)
F
LV ejection fraction (%)
G
RV EDV (ml/m²)
H
RV ESV (ml/m²)
I
RV ejection fraction (%)
Rest
40% of VO2max
60% of VO2max

Figure 2

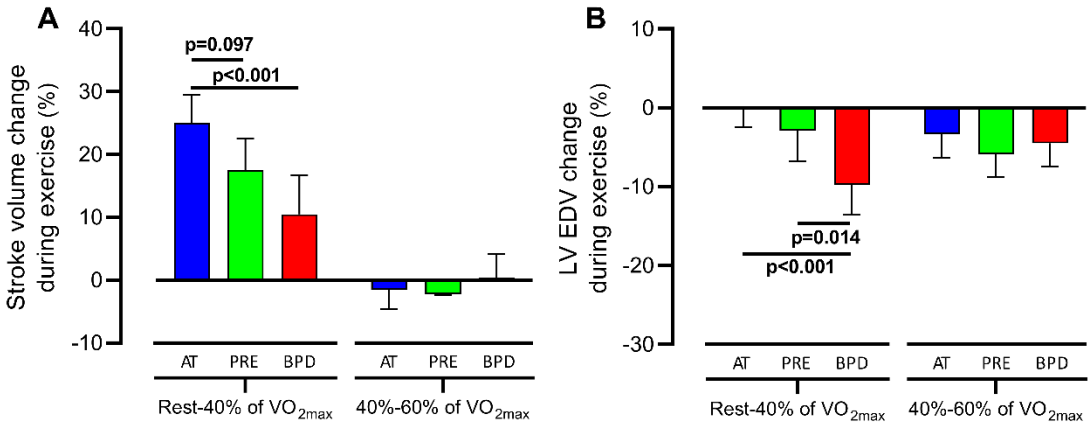
A
Stroke volume change during exercise (%)
40
30
20
10
0
-10
p=0.097
p<0.001
AT
PRE
BPD
AT
PRE
BPD
Rest-40% of VO2max
40%-60% of VO2max
B
LV EDV change during exercise (%)
10
0
-10
-20
-30
p=0.014
p<0.001
AT
PRE
BPD
AT
PRE
BPD
Rest-40% of VO2max
40%-60% of VO2max

Figure 3

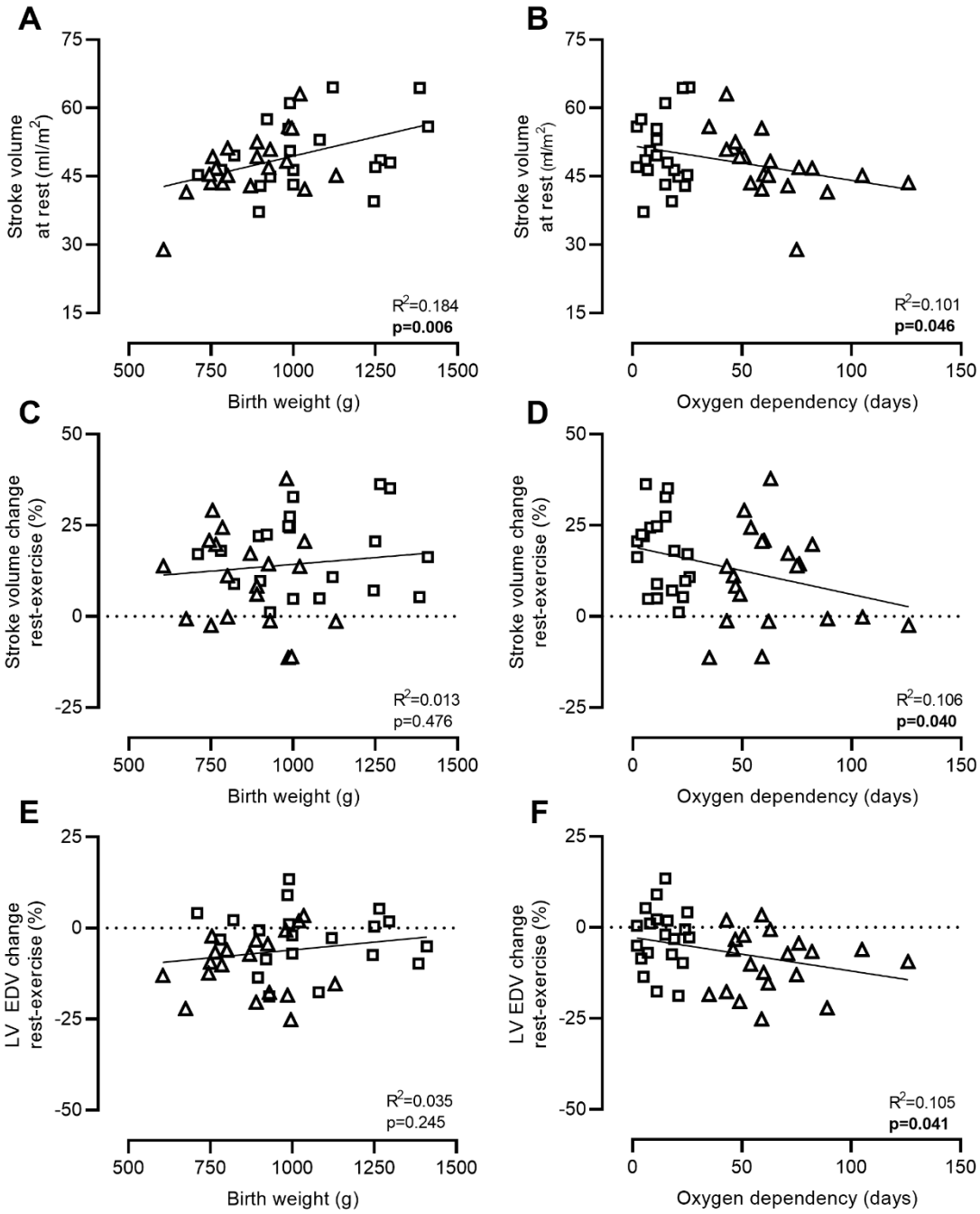
A
Stroke volume at rest (ml/m2)
75
60
45
30
15
R2=0.184
p=0.006
500
750
1000
1250
1500
Birth weight (g)
B
Stroke volume at rest (ml/m2)
75
60
45
30
15
R2=0.101
p=0.046
0
50
100
150
Oxygen dependency (days)
C
Stroke volume change rest-exercise (%)
50
25
0
-25
R2=0.013
p=0.476
500
750
1000
1250
1500
Birth weight (g)
D
Stroke volume change rest-exercise (%)
50
25
0
-25
R2=0.106
p=0.040
0
50
100
150
Oxygen dependency (days)
E
LV EDV change rest-exercise (%)
25
0
-25
-50
R2=0.035
p=0.245
500
750
1000
1250
1500
Birth weight (g)
F
LV EDV change rest-exercise (%)
25
0
-25
-50
R2=0.105
p=0.041
0
50
100
150
Oxygen dependency (days)

Figure 4

Supplemental material:

Article: Cardiac dysfunction during exercise in young adults with bronchopulmonary dysplasia

Authors: J.J. Steenhorst, W.A. Helbing, W.J. van Genuchten *et al.*

Table 1: Left and right ventricular volumes and function at baseline, during exercise and the percentage change as assessed by free-breathing real time CMR.

		Preterm born group with BPD (BPD)	Preterm born group without BPD (PRE)	At term born group (AT)	BPD vs. PRE	BPD vs. AT	PRE vs. AT
		n=20	n=20	n=20			
Heart rate (bpm)	Rest	69±10	64±8	61±7	0.19	**0.01**	0.46
	40% at start	129±23	130±27	137±21	0.98	0.55	0.66
	40% at end	109±26	107±27	110±21	0.97	>0.99	0.94
	40% mean	121±22	117±27	122±22	0.87	>0.99	0.84
	60% at start	159±22	160±21	161±19	>0.99	0.97	0.99
	60% at end	137±22	133±25	133±18	0.91	0.91	0.92
	60% mean	143±22	142±18	148±20	0.93	0.93	0.73
Left ventricle							
End-diastolic volume (ml/m²)	Rest	80±10	81±12	90±14	0.96	**0.03**	0.058
	40%	72±10	79±15	91±13	0.24	**<0.001**	**0.02**
	60%	68±10	74±14	87±12	0.35	**0.001**	**0.005**
End-systolic volume (ml/m²)	Rest	32±8	31±6	37±7	0.76	0.21	**0.047**
	40%	20±7	20±7	24±7	>0.99	0.25	0.28
	60%	16±5	17±5	21±6	0.98	**0.02**	**0.03**
Ejection fraction (%)	Rest	59±7	62±4	60±3	0.25	0.98	0.33
	40%	72±8	75±6	74±5	0.39	0.62	0.96
	60%	76±7	78±4	76±5	0.60	0.98	0.48
Stroke volume (ml/m²)	Rest	47±7	50±8	54±9	0.53	**0.03**	0.28
	40%	52±9	59±10	67±9	0.07	**<0.001**	**0.02**
	60%	52±9	57±11	66±9	0.21	**<0.001**	**0.02**
Cardiac index (L/min/m²)	Rest	3.2±0.5	3.2±0,5	3.3±0.5	0.93	>0.99	0.89
	40%	6.3±1.3	6.7±1.3	8.0±1.6	0.64	**0.002**	**0.01**
	60%	7.6±1.4	8.1±1.3	9.8±1.8	0.61	**<0.001**	**0.003**
Right ventricle							
End-diastolic volume (ml/m²)	Rest	84±12	90±17	99±16	0.65	**0.016**	0.13
	40%	76±12	84±18	94±17	0.31	**0.003**	0.11
	60%	75±12	80±19	92±14	0.51	**0.002**	**0.04**
End-systolic volume (ml/m²)	Rest	38±8	39±10	45±9	0.83	**0.046**	0.16
	40%	24±9	25±10	28±8	0.99	0.50	0.60
	60%	22±7	23±9	26±9	0.92	0.27	0.48
Ejection fraction (ml/m²)	Rest	57±6	56±4	55±5	0.95	0.71	0.51
	40%	68±9	71±6	71±5	0.43	0.50	0.99
	60%	71±7	72±5	72±7	0.77	0.70	0.99
Change compared to baseline							
Heart rate (%)	Δ rest - 40%	79±34	83±35	102±31	0.91	0.11	0.21
	Δ rest - 60%	113±38	125±32	144±36	0.60	**0.03**	0.21
Left ventricle							
End-diastolic volume (%)	Δ rest - 40%	-10±8	-3±8	0±5	**0.01**	**<0.001**	0.34
	Δ rest - 60%	-14±8	-9±9	-3±8	0.14	**<0.001**	0.10
End-systolic volume (%)	Δ rest - 40%	-39±13	-36±17	-35±13	0.77	0.73	>0.99
	Δ rest - 60%	-49±14	-46±14	-41±14	0.76	0.19	0.54
Ejection fraction (%)	Δ rest - 40%	23±11	21±10	25±9	0.93	0.75	0.53
	Δ rest - 60%	29±14	26±10	27±10	0.67	0.88	0.93
Stroke volume (%)	Δ rest - 40%	11±13	18±11	25±10	0.13	**<0.001**	0.10

	Δ rest - 60%	11 ± 13	15 ± 12	23 ± 12	0.56	**0.006**	0.08
Cardiac index (%)	Δ rest - 40%	97 ± 35	114 ± 35	152 ± 45	0.38	**<0.001**	**0.01**
	Δ rest - 60%	138 ± 49	157 ± 45	201 ± 55	0.49	**0.001**	**0.02**
Right ventricle							
End-diastolic volume (%)	Δ rest - 40%	-10 ± 7	-6 ± 9	-5 ± 6	0.29	0.08	0.78
	Δ rest - 60%	-12 ± 9	-11 ± 8	-6 ± 10	0.92	0.12	0.25
End-systolic volume (%)	Δ rest - 40%	-36 ± 15	-38 ± 14	-38 ± 15	0.88	0.86	>0.99
	Δ rest - 60%	-40 ± 16	-42 ± 14	-41 ± 19	0.96	>0.99	>0.99
Ejection fraction (%)	Δ rest - 40%	23 ± 11	26 ± 8	31 ± 12	0.52	0.061	0.44
	Δ rest - 60%	27 ± 14	28 ± 11	33 ± 14	0.50	0.39	0.50

Mean ± standard deviation. BPD – bronchopulmonary dysplasia, LV – left ventricle, RV - right ventricle, 40% - 40% of maximal oxygen consumption, 60% - 60% of maximal oxygen consumption.