Received: 13 July 2017 | Revised: 20 November 2017 | Accepted: 26 December 2017

DOI: 10.1111/chd.12577

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Intrauterine growth restriction is not associated with decreased exercise capacity in adolescents with congenital heart disease

Andrew D. Spearman MD[1] | Rohit S. Loomba MD[2] | Michael Danduran MS, PhDc[1] | Joshua Kovach MD[1]

[1]Division of Cardiology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[2]Division of Cardiology, Cincinnati Children's Hospital Medical Center, Ohio, USA

Correspondence
Andrew D. Spearman, Children's Hospital of Wisconsin, Medical College of Wisconsin, 9000 Wisconsin Avenue, Milwaukee, WI 53226.
Email: aspearman@chw.org

Abstract

Objective: Multiple studies demonstrate the association of intrauterine growth restriction (IUGR) with impaired aerobic fitness in adolescents and adults. To our knowledge, there are no studies including individuals with the history of both IUGR and congenital heart disease (CHD). Thus, we sought to evaluate the impact of IUGR on exercise capacity in adolescents with CHD.

Study Design: We conducted a retrospective chart review of patients <18 years of age who underwent cardiopulmonary exercise testing (CPET) between August 1, 2003 and July 1, 2016. Individuals with birth weight <10th percentile for gestational age were defined as IUGR. Patients with IUGR were matched with non-IUGR patients by cardiac diagnosis and age at CPET. We excluded patients >18 years of age at time of CPET, those without a documented birth weight, gestational age, or Race.

Results: A total of 282 patients were included with CHD present in 86 IUGR cases and 86 controls. There was no difference in percent predicted exercise duration (IUGR: 65.2% ± 31.2, non-IUGR: 67.4% ± 27.2; $P = .67$). Resting heart rate, chronotropic index, percent-predicted peak oxygen consumption, and pulmonary function were similar between groups. Regression analyses confirmed that IUGR was not independently associated with difference in percent-predicted exercise duration.

Conclusions: Intrauterine growth restriction is not associated with the differences in the measurements of exercise capacity in adolescents with CHD. These findings contrast earlier studies, showing decreased fitness in individuals with low birth weight but without CHD. To our knowledge, this is the first study to examine the impact of IUGR on exercise capacity in patients with CHD.

KEYWORDS

Bruce protocol, cardiopulmonary exercise testing, congenital heart disease, intrauterine growth restriction

1 | INTRODUCTION

Infants exposed to inadequate delivery of nutrients or oxygen are at risk for impaired fetal growth, frequently termed intrauterine growth restriction (IUGR). IUGR is one of the most common pathologies affecting the fetus, occurring in up to 15% of all pregnancies.[1]

Multiple studies demonstrate the association of low birth weight and IUGR with early and late-onset cardiovascular disease, as well as dyslipidemia, diabetes mellitus, and metabolic syndrome.[2–11] Studies also show the association of IUGR with various measures of impaired aerobic and anaerobic fitness in adolescents and adults, although other studies show conflicting findings.[12–24] The association of IUGR with

Abbreviations: BMI, body mass index; CHD, congenital heart disease; CPET, cardiopulmonary exercise testing; IUGR, intrauterine growth restriction.

various late-onset diseases is likely mediated through epigenetic modifications.[25–27]

The previously published studies of IUGR and cardiorespiratory fitness focused on healthy cohorts or used large epidemiologic data sets. To our knowledge, there are no studies of individuals with a history of both IUGR and congenital heart disease (CHD) evaluating aerobic fitness capacity. Additionally, the studies evaluating exercise capacity in patients with low birth weight or IUGR used various measures of fitness, but there are limited studies using the Bruce protocol, which is the most widely used exercise treadmill protocol. Thus, the impact of IUGR on exercise capacity in adolescents with CHD is unknown. We hypothesized that adolescents with a history of IUGR and CHD have decreased exercise capacity compared to their non-IUGR peers.

2 | MATERIALS AND METHODS

2.1 | Patients selection

We conducted a retrospective study of patients <18 years of age who underwent cardiopulmonary exercise testing (CPET) using the Bruce protocol at the Children's Hospital of Wisconsin between August 1, 2003 and July 1, 2016. We cross-referenced documented birth weight and gestational age to obtain a weight-for-gestational age percentile. Individuals with birth weight <10th percentile for gestational age were defined as IUGR. The patients with IUGR were matched with non-IUGR patients by cardiac diagnosis and age at CPET. Matching was performed prior to the collection of CPET data to blind the authors to outcome measurements. We excluded patients 18 years of age or older at time of CPET and those without a documented birth weight, gestational age, or Race. This study was approved by the local institutional review board (IRB).

2.2 | Bruce treadmill protocol

The Bruce protocol is a maximal exercise challenge consisting of 3-minute stages of increasing intensities to exhaustion and utilized a T-2100 Treadmill (GE Healthcare, El Paso, Texas, USA) for all patients included in the study.[28] Twelve-lead electrocardiogram monitoring (CASE Cardiosoft V6.61, GE Healthcare) was obtained for all patients. Metabolic monitoring (Encore 29c, VMAX, Palm Springs, California) was obtained for only selected patients based on ordering physician discretion. Maximal effort was determined if two of the following three criteria were met: (1) heart rate ≥85th% of predicted maximum, (2) respiratory exchange ratio >1.10, or (3) patient's subjective report of a maximal effort (rating of perceived exertion of >9 on a 1–10 scale). The comparison of physiologic data to established normative values within the pediatric population was done to establish the percent of predicted.

2.3 | Univariate analyses

Descriptive endpoints are described using absolute frequencies and percentages, whereas continuous endpoints are described using mean and standard deviation. All continuous variables possessed a normal distribution.

Patients' characteristics were compared between the IUGR and the non-IUGR groups using chi-square analyses for descriptive endpoints and *T* tests for continuous variables. CPET variables were compared between the two groups using similar methodology.

2.4 | Regression analyses

Next, linear regression analyses were conducted to model the impact of IUGR and other variables on percent-predicted exercise duration. Independent variables included in the regression analyses included age, gender, IUGR status, CHD status, and body mass index (BMI). Regression analyses were also rerun with birth weight in lieu of IUGR status. A similar regression analysis was repeated including only those patients with CHD. All of the independent variables remained the same, except CHD status was excluded.

All statistical analyses were done utilizing SPSS Version 20.0 (Chicago, Illinois, USA). A *P* value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

A total of 282 patients were included in the final analyses, which included 141 patients in both IUGR and non-IUGR groups. The patients in the IUGR group were less likely to be male (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.4-0.9; $P = .02$). Term gestation was most frequent in both groups with a mean gestational age of 39.1 weeks in the IUGR group and 38.1 weeks in the non-IUGR group ($P < .01$). As expected, birth weight significantly differed between the two groups with a mean of 2.5 kg in the IUGR group and a mean of 3.2 kg in the non-IUGR group ($P < 0.01$) (Table 1).

CHD was present in 86 (61%) patients of both the IUGR and the non-IUGR cohort (OR = 1.0; 95% CI = 0.6-1.6; $P = 1.0$). There was no significant difference in Race, circulation type, history of surgical or catheter-based cardiac intervention, or proportion of patients with pulmonary hypertension between the two groups (Table 1).

When analyzing the CHD subset of both IUGR and non-IUGR groups, the patients' characteristics were similar to the entire cohort (Table 2). The types of CHD present in the cohort are listed in Table 3 with equal numbers of each CHD subtype present in both IUGR and non-IUGR groups. The most common CHD diagnoses represented are hypoplastic left heart syndrome, tetralogy of Fallot, and ventricular septal defect (VSD).

3.2 | Cardiopulmonary exercise testing performance

Age at cardiopulmonary exercise testing was similar between the two groups (IUGR: 12.4 ± 3.1 years, non-IUGR: 12.2 ± 3.2 years; $P = .54$). Body mass index and proportion of patients on a β-blocker at the time of CPET were also similar between the two groups (Table 1).

There was no difference in percent-predicted exercise duration (IUGR: 65.2% ± 31.2, non-IUGR: 67.4% ± 27.2; $P = .67$). Resting heart rate, chronotropic index, percent-predicted peak VO2, PETCO2, RQ, and VE/VCO2 slope were similar between groups (Table 1). There was

TABLE 1 Univariate analysis of all patients

	Non-IUGR (141)	IUGR (n = 141)	OR (95% CI)	*P* value
Gender (male)	80 (56)	61 (43)	0.6 (0.4-0.9)	.02
Gestation age (wk)	38.1 ± 2.9	39.1 ± 1.8	–	<.01
Birth weight (kg)	3.2 ± 0.7	2.5 ± 0.4	–	<.01
Birth weight percentile	48.7 ± 26.9	3.4 ± 2.9	–	<.01
Race			–	.22
African American	27 (19)	30 (21)		
American Indian	1 (1)	0 (0)		
Asian	1 (1)	5 (3)		
Hispanic	14 (19)	20 (14)		
Caucasian	98 (70)	86 (62)		
Congenital heart disease	86 (61)	86 (61)	1.0 (0.6-1.6)	1.00
Circulation type			–	.59
Biventricular	115 (82)	113 (80)		
1.5 Ventricle	0 (0)	1 (1)		
Functionally univentricular	26 (18)	27 (19)		
History of surgical or catheter-based cardiac intervention	76 (53)	72 (51)	0.8 (0.5-1.4)	.63
Pulmonary hypertension	2 (1)	5 (3)	2.5 (0.4–13.5)	.24
Age at CPET (years)	12.2 ± 3.2	12.4 ± 3.1	–	.54
BMI at CPET	20.5 ± 6.2	20.1 ± 5.7	–	.52
BMI percentile at CPET	58.5 ± 33.1	52.7 ± 37.6	–	.17
β-Blocker at time of CPET	2 (1)	4 (2)	2.0 (0.3–11.2)	.40
Exercise duration percent predicted (%)	67.4 ± 27.2	65.2 ± 31.2	–	.67
Peak VO_2, percent predicted (%)	78.2 ± 26.2	76.0 ± 22.1	–	.76
FEV_1, percent predicted (%)	88.1 ± 15.3	83.7 ± 16.2	–	.13
FVC, percent predicted (%)	88.1 ± 16.4	86.0 ± 15.5	–	.48
FEV_1/FVC ratio	89.9 ± 6.1	88.5 ± 7.3	–	.30
FEF 25–75, percent predicted (%)	92.7 ± 22.0	88.2 ± 27.4	–	.32
Resting heart rate (beats per minute)	78.3 ± 15.3	79.6 ± 13.9	–	.47
Chronotropic index	89.9 ± 8.6	88.7 ± 12.2	–	.34
Peak end-tidal CO_2	35.4 ± 5.4	32.3 ± 6.4	–	.08
Respiratory quotient	1.0 ± 0.08	1.0 ± 0.07	–	.20
VE/VCO_2 slope	27.4 ± 3.6	28.7 ± 6.5	–	.53

Abbreviation: CO_2, carbon dioxide; CPET, cardiopulmonary exercise testing; FEF, forced expiratory flow; FEV_1, fractional exhaled volume in 1 second; FVC, forced vital capacity; IUGR, intrauterine growth retardation; VCO_2, volume exhaled carbon dioxide; VE, ventilatory equivalent; VO_2, oxygen consumption.

no statistically significant difference in any of the pulmonary function assessments. FEV_1, FVC, FEV_1/FVC ratio, and FEF 25–75 were all similar between the two groups (Table 1).

Univariate analysis on the CHD subset was similar to the entire cohort with no difference in percent-predicted exercise duration (IUGR: 70.1% ± 31.8, non-IUGR: 62.8% ± 26.2; *P* = .29). No statistically significant differences were observed in the other measurements of CPET performance (Table 2).

Regression analyses demonstrated that IUGR was not independently associated with difference in percent-predicted exercise duration when BMI, gender, CHD, IUGR, and age were also included in the model (Table 4). Regression analyses using the CHD subset were again similar to the entire cohort with no difference in percent-predicted exercise duration. Regression analyses were repeated with birth weight as a continuous variable in lieu of IUGR status. These analyses demonstrated that birth weight was not independently associated with difference in percent-predicted exercise duration.

4 | DISCUSSION

Earlier studies of IUGR and health outcomes focused on healthy patient cohorts or large epidemiologic studies. As IUGR can occur in all patient populations, including patients with CHD, we sought to

TABLE 2 Univariate analysis of patients with history of congenital heart disease

	Non-IUGR (86)	IUGR (n = 86)	OR (95% CI)	*P* value
Gender (male)	52 (61)	39 (45)	0.5 (0.3-0.9)	.04
Gestation age (wk)	38.0 ± 2.5	38.9 ± 2.0	–	.01
Birth weight (kg)	3.2 ± 0.6	2.5 ± 0.5	–	<.01
Birth weight percentile	47.1 ± 26.1	3.1 ± 2.8	–	<.01
Race			–	.39
African American	18 (21)	16 (19)		
American Indian	1 (1)	0 (0)		
Asian	1 (1)	3 (3)		
Hispanic	7(8)	13 (15)		
Caucasian	59 (69)	54 (63)		
Circulation type			–	.59
Biventricular	60 (70)	58 (67)		
1.5 Ventricle	0 (0)	1 (1)		
Functionally univentricular	26 (30)	27 (32)		
History of surgical or catheter-based cardiac intervention	76 (88)	72 (84)	0.7 (0.3-1.6)	.38
Pulmonary hypertension	0 (0)	3 (3)	–	.08
Age at CPET (years)	11.5 ± 3.2	11.9 ± 3.2	–	.46
BMI at CPET	19.1 ± 5.1	20.5 ± 6.4	–	.11
BMI percentile at CPET	52.3 ± 33.6	56.4 ± 37.7	–	.45
β-Blocker at time of CPET	0 (0)	3 (3)	–	.08
Exercise duration percent predicted (%)	62.8 ± 26.2	70.1 ± 31.8	–	.29
Peak VO_2, percent predicted (%)	80.6 ± 22.5	75.7 ± 17.4	–	.49
FEV_1, percent predicted (%)	83.5 ± 13.9	82.8 ± 16.4	–	.86
FVC, percent predicted (%)	82.2 ± 14.4	86.3 ± 15.9	–	.25
FEV_1/FVC ratio	90.7 ± 6.8	87.3 ± 7.1	–	.06
FEF 25–75, percent predicted (%)	90.1 ± 24.7	86.5 ± 29.8	–	.57
Resting heart rate (beats per minute)	80.6 ± 14.9	80.4 ± 13.9	–	.95
Chronotropic index	87.9 ± 8.3	88.3 ± 12.8	–	.82
Peak end-tidal CO_2	34.5 ± 4.4	31.9 ± 6.3	–	.16
Respiratory quotient	1.0 ± 0.08	1.1 ± 0.08	–	.11
VE/VCO_2 slope	28.0 ± 3.6	29.0 ± 7.3	–	.66

CO_2, carbon dioxide; CPET, cardiopulmonary exercise testing; FEF, forced expiratory flow; FEV_1, fractional exhaled volume in 1 s; FVC, forced vital capacity; IUGR, intrauterine growth retardation; VCO_2, volume exhaled carbon dioxide; VE, ventilatory equivalent; VO_2, oxygen consumption

investigate the effect of IUGR on exercise capacity in patients with CHD. This study provides evidence that IUGR is not associated with differences in measurements of exercise capacity in adolescents. Furthermore, this study gives initial evidence that patients with IUGR and CHD do not have differences in the measurements of exercise capacity compared to the patients with CHD but no history of IUGR.

There are a number of differences in our study compared to the previous studies of IUGR and exercise capacity. First, our study included a large cohort of adolescents with a history of CHD. The majority (172/282, 61%) of participants in our study had a history of CHD who underwent routine follow-up CPET, whereas the remainder of study participants were healthy individuals who had CPET for other indications, including chest pain, syncope, arrhythmia, and shortness of breath. The previously published studies examining the association between birth weight and exercise capacity included large population-based studies, which likely included a minority of patients with CHD, given the reported incidence of CHD (<5%), if any at all.[12,17,19,21–24,29]

Next, our study used the Bruce protocol for the measurements of exercise capacity. To our knowledge, only one previous study used a treadmill test with the Bruce protocol for the assessment of cardiorespiratory fitness in patients with a history of low birth weight or IUGR.[20] Similar to Touwslager et al, we found no significant association with birth weight and exercise capacity. Though they reported a possible association of birth weight with peak oxygen consumption, this

TABLE 3 Types of CHD and percent[a]

Primary CHD diagnosis	Number of patients (%)
Atrial septal defect	1 (1)
Atrioventricular septal defect	5 (6)
Bicuspid aortic valve	4 (5)
Coarctation of the aorta	6 (7)
Coronary anomaly	7 (8)
Double inlet left ventricle	2 (2)
Double outlet left ventricle	4 (5)
Ebstein's anomaly	1 (1)
Hypoplastic left heart syndrome	15 (17)
Mitral valve prolapse	2 (2)
Pulmonary atresia with intact ventricular septum	3 (3)
Pulmonary atresia with VSD	3 (3)
Partial anomalous pulmonary venous return	1 (1)
Pulmonary valve stenosis	1 (1)
Subaortic stenosis	1 (1)
Tetralogy of Fallot	11 (13)
Transposition of the great arteries	2 (2)
Tricuspid atresia	7 (8)
Truncus arteriosus	1 (1)
Ventricular septal defect	9 (10)

[a]Numbers represent the number of patients with each type of CHD (IUGR and non-IUGR).

finding was attenuated with adjustment for parental BMI. Other previous studies of IUGR and cardiorespiratory fitness examined exercise capacity with multiple modalities including a 20-meter shuttle run test, the modified Canadian Aerobic Fitness Test (mCAFT), a standardized step test, the UKK 2-kilometer walk test, and cycle ergometer.[12,14,17,19,21–24] The variable outcomes of these studies may partially reflect the intrinsic differences in the study modalities. We advocate the use of standardized treadmill exercise protocols for optimal assessment of exercise capacity. The Bruce protocol is the most widely used treadmill exercise test and allows reproducible evaluation of patients of all ages and fitness levels; however, other treadmill exercise tests, such as the modified Balke protocol, are also beneficial for assessing exercise capacity in healthy populations.[30,31]

Additionally, we did not observe the differences in resting heart rate or chronotropic index, which has been found previously.[32–37] This discrepancy may be partially owing to the impact of CHD on sinus node function, as well as the finding that effect size of birth weight on heart rate increases with age.[33]

Evidence shows that regular exercise is cardioprotective and can decrease the risk of metabolic disease in the general population and those with history of IUGR.[24,38–40] For example, Laaksonen et al.[24] showed that birth weight was not associated with cardiorespiratory fitness in middle-aged men, but it was associated with metabolic syndrome in middle-aged men. They found that leisure-time physical activity and cardiorespiratory fitness modified the association between birth weight and metabolic syndrome. There are limited human studies, though, evaluating if regular exercise can similarly decrease the risk of cardiovascular disease in patients with a history of IUGR.

Various animal models of IUGR reported exercise as an intervention to reduce risk for cardiovascular disease with mixed results. Reyes et al.[41] found that aerobic exercise training for adult IUGR rat offspring had variable effects on vascular bed vasoconstriction and vasodilation. Notably, their baseline assessment of exercise capacity prior to beginning the exercise training regimen showed no difference in exercise capacity in 10-week-old IUGR and control rats. Oliveira et al.[42]

TABLE 4 Regression analysis of exercise duration

Percent-predicted exercise duration for all patients (CHD and non-CHD patients, with and without IUGR)	β-Coefficient	*P* value
BMI	−.6	.16
Male gender	−.2	.81
CHD	−.4	.50
IUGR	−.7	.25
Race	−.8	.06
Circulation type	−.4	.15
Pulmonary hypertension	1.3	.19
History of intervention	.4	.51
β-Blocker	−1.6	.22
Birth weight	−4.6	.61
Percent-predicted exercise duration for CHD patients (CHD patients, with and without IUGR)	**β-Coefficient[a]**	***P* value[b]**
BMI	−.4	.23
Male gender	−.8	.69
IUGR	.3	.80
Race	.3	.15
Circulation type	−.1	.77
Pulmonary hypertension	.9	.64
History of intervention	.2	.71
β-Blocker	−.2	.43
Birth weight	−9.2	.54

Abbreviations: BMI, body mass index; CHD, congenital heart disease; IUGR, intrauterine growth retardation.
[a]β-Coefficient represents change in dependent variable (percent-predicted exercise duration).
[b]*P* value $< .05$ is considered statistically significant.

described that aerobic training normalized pathologic vascular and antioxidant changes provoked by IUGR.

Conversely, though, Reyes et al.[43] also demonstrated that exercise itself can act as a secondary stressor with detrimental effects to susceptible populations. They randomized offspring of their rat model of IUGR to a sedentary group or a 6-week exercise protocol. They found that male IUGR offspring had compromised cardiac function by following the exercise protocol, whereas there was no effect in male control offspring. Furthermore, they found paradoxically increased oxidative stress in male IUGR offspring after the exercise protocol. Similarly, Laher et al.[44] reported that aerobic exercise increased myocardial oxidative stress and negatively altered glutathione homeostasis in adult obesogenic/diabetic *db/db* mice. These findings raise concern about the long-term effects of exercise in vulnerable populations, that is, individuals with history of IUGR and CHD.

Possibly as an adaptive strategy, several studies report that low birth weight and IUGR are associated with decreased physical activity.[14,45–49] Kajantie et al.[47] reported that unimpaired adults who were born <1500 grams exercise significantly less than their term peers during leisure time activity—including threefold more likely to have short exercise sessions (<30 min), 2.75-fold more likely to exercise with low intensity (walking), 1.6-fold more likely to exercise infrequently (once per week or less), and 1.6-fold more likely to "not exercise much."

In summary, just as there are data that prenatal stressors and IUGR are associated with epigenetic modifications, there is evidence that the beneficial effects of physical activity are mediated through epigenetic modifications.[50–55] We speculate that IUGR may mediate epigenetic changes to genes involved in cardiorespiratory fitness, which may obscure response to exercise regimens. IUGR may act as a primary insult initiating epigenetic modifications. These epigenetic changes may predispose to disease, increase susceptibility to secondary stressors, or modify response to treatment.

Our study has several limitations. We are limited by the difficulty inherit in the IUGR diagnosis. Using an IUGR definition of birth weight <10th percentile for gestational age will invariably include patients who are "constitutionally small for gestational age" and also exclude a minority of patients with true IUGR but birth weight percentile >10th percentile for gestational age. Although birth weight percentile is a common criteria for IUGR status, our diagnosis of IUGR is weakened by the lack of prenatal data, including prenatal growth indices and ultrasound Doppler measurements of fetoplacental physiology. Next, inherent with a retrospective study, our results are influenced by selection, reporting, and survival bias. Our patients underwent exercise testing for various indications, which we were not able to match. Matching our cohort by age at CPET and cardiac diagnosis does not match by functional status. Sicker patients with IUGR may not have been recommended for CPET owing to higher degree of illness. Survival bias may also be present as the sicker IUGR patients may have died before reaching an appropriate age to undergo CPET. It is possible that this selection and survival bias may explain the animal model findings in which exercise was found to have deleterious effects. Severity of illness does not factor into what animals are evaluated as long as inclusion criteria are met, which mitigates the effects of selection bias in animal models. Additionally, several animal models evaluate the animals early in life versus human studies where neonates, infants, and young children are not evaluated. Additionally, there are several other possible confounders that we were unable to assess, including infant growth trajectory, pubertal status at time of CPET, amount and intensity of leisure time physical activity, and parental factors such as parental BMI and physical activity during pregnancy.

Additionally, there is evidence that CHD increases the risk for IUGR.[56–59] Specifically, a previous retrospective study found that patients with a prenatal diagnosis of CHD had a threefold increased risk of developing IUGR, as defined as birth weight <10th percentile for gestational age.[60] Fetal growth is a complex, multifactorial process influenced by genetic, environmental, and epigenetic factors. The extent to which circulatory changes associated with CHD contribute to growth restriction remains unknown. Given that the etiology of CHD is poorly understood, an underlying etiological factor could contribute to both IUGR and CHD. Our study does not include prenatal or parental data. Thus, our study is not intended to assess the association of CHD and development of IUGR. Rather, the objective of our study is to assess the longer-term outcome of exercise capacity in patients with both CHD and IUGR.

Further research is needed to study the effects of intrauterine growth restriction on cardiovascular and exercise physiology in patients with CHD. Collaboration of multiple institutions with CPET databases may provide greater insight into at-risk IUGR populations, including patients with both IUGR and CHD. Further research is also needed to better understand the effects of exercise on long-term cardiovascular health in individuals with the history of IUGR.

5 | CONCLUSIONS

Intrauterine growth restriction is not associated with the differences in the measurements of exercise capacity in adolescents with CHD. These findings contrast earlier studies, showing decreased fitness in individuals with low birth weight but without CHD. To our knowledge, this is the first study to examine the impact of IUGR on exercise capacity in patients with CHD.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

DISCLOSURES

There are no prior publications or submissions with any overlapping information, including studies and patients.

AUTHOR CONTRIBUTIONS

Conceptualization and study design: Spearman
Assistance in study design: Spearman, Loomba
Data collection: Spearman, Loomba
Analyzed data: Spearman, Loomba

Drafted initial manuscript: Spearman

Performed statistical analysis: Loomba

Manuscript revision: Spearman, Loomba, Danduran, Kovach

Approved final manuscript: Spearman, Loomba, Danduran, Kovach

ORCID

Andrew D. Spearman MD http://orcid.org/0000-0003-2035-5258

Rohit S. Loomba MD http://orcid.org/0000-0002-9116-2835

REFERENCES

[1] Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. *Early Hum Dev*. 2009;85(10):653–658.

[2] Barker DJ, Winter PD, Osmond C. Weight in infancy and death from ischaemic heart disease. *Lancet*. 1989;2(8663):577–580.

[3] Tintu A, Rouwet E, Verlohren S, et al. Hypoxia induces dilated cardiomyopathy in the chick embryo: mechanism, intervention, and long-term consequences. *PLoS One*. 2009;4(4):e5155.

[4] Crispi F, Bijnens B, Figueras F, et al. Fetal growth restriction results in remodeled and less efficient hearts in children. *Circulation*. 2010;121(22):2427–2436.

[5] Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, et al. Fetal cardiovascular remodeling persists at 6 months in infants with intrauterine growth restriction. *Ultrasound Obstet Gynecol*. 2016;48(3):349–356.

[6] Akazawa Y, Hachiya A, Yamazaki S, et al. Cardiovascular remodeling and dysfunction across a range of growth restriction severity in small for gestational age infants. *Circ J*. 2016;80(10):2212–2220.

[7] Ojeda NB, Grigore D, Alexander BT. Intrauterine growth restriction: fetal programming of hypertension and kidney disease. *Adv Chronic Kidney Dis*. 2008;15(2):101–106.

[8] Choi GY, Tosh DN, Garg A, et al. Gender-specific programmed hepatic lipid dysregulation in intrauterine growth-restricted offspring. *Am J Obstet Gynecol*. 2007;196(5):477.e1–7.

[9] Stocker CJ, Arch JR, Cawthorne MA. Fetal origins of insulin resistance and obesity. *Proc Nutr Soc*. 2005;64(2):143–151.

[10] Valdez R, Athens MA, Thompson GH, et al. Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia*. 1994;37(6):624–631.

[11] Barker DJ, Hales CN, Fall CH, et al. Type 2 (non-insulin dependent) diabetes mellitus, hypertension, and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia*. 1993;36(1):62–67.

[12] Boreham CA, Murray L, Dedman D, et al. Birthweight and aerobic fitness in adolescents: the Northern Ireland Young Hearts Project. *Public Health*. 2001;115(6):373–379.

[13] Keller H, Bar-Or O, Kriemler S, et al. Anaerobic performance in 5- to 7-year-old children of low birthweight. *Med Sci Sports Exerc*. 2000;32(2):278–283.

[14] Rogers M, Fay TB, Whitfield MF, et al. Aerobic capacity, strength, flexibility, and activity level in unimpaired extremely low birth weight (<or=800 g) survivors at 17 years of age compared with term-born control subjects. *Pediatrics*. 2005;116(1):e58–e65.

[15] Small E, Bar-Or O, Van Mil E, Saigal S. Muscle function of 11- to 17-year old children of extremely low birthweight. *Pediatr Exerc Sci*. 1998;10(4):327–336.

[16] Dodds R, Denison HJ, Ntani G, et al. Birth weight and muscle strength: a systematic review and meta-analysis. *J Nutr Health Aging*. 2012;16(7):609–615.

[17] Ridgway CL, Ong KK, Tammelin T, et al. Birth size, infant weight gain, and motor development influence adult physical performance. *Med Sci Sports Exerc*. 2009;41(6):1212–1221.

[18] Ridgway CL, Brage S, Sharp SJ, et al. Does birth weight influence physical activity in youth? A combined analysis of four studies using objectively measured physical activity. *PLoS One*. 2011;6(1):e16125.

[19] Lawlor DA, Cooper AR, Bain C, et al. Associations of birth size and duration of breast feeding with cardiorespiratory fitness in childhood: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Eur J Epidemiol*. 2008;23(6):411–422.

[20] Touwslager RN, Gielen M, Tan FE, et al. Genetic, maternal and placental factors in the association between birth weight and physical fitness: a longitudinal twin study. *PLoS One*. 2013;8(10):e76423.

[21] van Deutekom AW, Chinapaw MJM, Vrijkotte TGM, Gemke RJBJ. The association of birth weight and infant growth with physical fitness at 8–9 years of age—the ABCD study. *Int J Obes*. 2015;39(4):593–600.

[22] Ortega FB, Labayen I, Ruiz JR, et al. Are muscular and cardiovascular fitness partially programmed at birth? Role of body composition. *J Pediatr*. 2009;154(1):61–66. e1.

[23] Salonen MK, Kajantie E, Osmond C, et al. Developmental origins in physical fitness: the Helsinki birth cohort study. *PLoS One*. 2011;6(7):e22302.

[24] Laaksonen DE, Lakka HM, Lynch J, et al. Cardiorespiratory fitness and vigorous leisure-time physical activity modify the association of small size at birth with the metabolic syndrome. *Diabetes Care*. 2003;26(7):2156–2164.

[25] Waterland RA, Jirtle RL. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic disease. *Nutrition*. 2004;20(1):63–68.

[26] Vickers MH. Early life nutrition, epigenetics and programming of later life disease. *Nutrients*. 2014;6(6):2165–2178.

[27] Majnik AV, Lane RH. The relationship between early-life environment, the epigenome and the microbiota. *Epigenomics*. 2015;7(7):1173–1184.

[28] Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res*. 1971;3(6):323–332.

[29] Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890–1900.

[30] Ahmad F, Kavey RE, Kveselis DA, et al. Responses of non-obese white children to treadmill exercise. *J Pediatr*. 2001;139(2):284–290.

[31] Alpert BS, Flood NL, Strong WB, et al. Responses to ergometer exercise in a healthy biracial population of children. *J Pediatr*. 1982;101(4):538–545.

[32] Phillips DIW, Barker DJP. Association between low birth weight and high resting pulse in adult life: is the sympathetic nervous system involved in programming the insulin resistance syndrome? *Diabet Med*. 1997;14(8):673–677.

[33] Hua Y, Wang F, Zhang T, et al. Relation of birth weight to heart rate in childhood, adolescence, and adulthood (from the Bogalusa Heart Study). *Am J Cardiol*. 2016;118(6):828–832.

[34] Abe C, Minami J, Ohrui M, et al. Lower birth weight is associated with higher resting heart rate during boyhood. *Hypertens Res*. 2007;30(10):945–950.

[35] Longo-Mbenza B, Ngiyulu R, Bayekula M, et al. Low birth weight and risk of hypertension in African school children. *J Cardiovasc Risk*. 1999;6(5):311–314.

[36] Johansson S, Norman M, Legnevall L, et al. Increased catecholamines and heart rate in children with low birth weight: perinatal

contributions to sympathoadrenal overactivity. *J Intern Med*. 2007; 261(5):480–487.

[37] Kerkhof GF, Breukhoven PE, Leunissen RW, et al. Does preterm birth influence cardiovascular risk in early adulthood. *J Pediatr*. 2012;161(3):390–396.

[38] Frasier CR, Moore RL, Brown DA. Exercise-induced cardiac preconditioning: how exercise protects your achy-breaky heart. *J Appl Physiol*. 2011;111(3):905–915.

[39] Bacon SL, Sherwood A, Hinderliter A, Blumenthal JA. Effects of exercise, diet and weight loss on high blood pressure. *Sports Medicine*. 2004;34(5):307–316.

[40] Tuomilehto J. Nonpharmacologic therapy and exercise in the prevention of type 2 diabetes. *Diabetes Care*. 2009;32(suppl 2):S189–S193.

[41] Reyes LM, Morton JS, Kirschenman R, et al. Vascular effects of aerobic exercise training in rat adult offspring exposed to hypoxia-induced intrauterine growth restriction. *J Physiol*. 2015;593(8): 1913–1929.

[42] Oliveira V, Akamine EH, Carvalho MHC, et al. Influence of aerobic training on the reduced vasoconstriction to angiotensin II in rats exposed to intrauterine growth restriction: possible role of oxidative stress and AT2 receptor of angiotensin II. *PLoS One*. 2014;9(11):e113035.

[43] Reyes LM, Kirschenman R, Quon A, et al. Aerobic exercise training reduces cardiac function in adult male offspring exposed to prenatal hypoxia. *Am J Physiol Regul Integr Comp Physiol*. 2015;309(5): R489–R498.

[44] Laher I, Beam J, Botta A, et al. Short-term exercise worsens cardiac oxidative stress and fibrosis in 8-month-old *db/db* mice by depleting cardiac glutathione. *Free Radic Res*. 2013;47(1):44–54.

[45] Rueda-Clausen CF, Dolinsky VW, Morton JS, et al. Hypoxia-induced intrauterine growth restriction increases the susceptibility of rats to high-fat diet-induced metabolic syndrome. *Diabetes*. 2011;60(2): 507–516.

[46] Whitfield MF, Grunau RE. Teenagers born at extremely low birth weight. *Paediatr Child Health*. 2006;11(5):275–277.

[47] Kajantie E, Strang-Karlsson S, Hovi P, et al. Adults born at very low birth weight exercise less than their peers born at term. *J Pediatr*. 2010;157(4):610–616.

[48] Elhakeem A, Cooper R, Bann D, et al. Birth weight, school sports ability, and adulthood leisure-time physical activity. *Med Sci Sports Exerc*. 2017;49(1):64–70.

[49] Gopinath B, Hardy LL, Baur LA, et al. Birth weight and time spent in outdoor physical activity during adolescence. *Med Sci Sports Exerc*. 2013;45(3):475–480.

[50] Tobi EW, Lumey LH, Talens RP, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet*. 2009;18(21):4046–4053.

[51] Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA*. 2008;105(44):17046–17049.

[52] Zinkhan EK, Fu Q, Wang Y, et al. Maternal hyperglycemia disrupts histone 3 lysine 36 trimethylation of the IGF-1 gene. *J Nutr Metab*. 2012;2012:930364.

[53] Ke X, McKnight RA, Gracey Maniar LE, et al. IUGR increases chromatin-remodeling factor Brg1 expression and binding to GR exon 1.7 promoter in newborn male rat hippocampus. *Am J Physiol Regul Integr Comp Physiol*. 2015;309(2):R119–R127.

[54] Ntanasis-Stathopoulo J, Tzannini JG, Philippou A, Koutsilieris M. Epigenetic regulation on gene expression induced by physical exercise. *J Musculoskelet Neuronal Interact*. 2013;13(2):133–146.

[55] Voisin S, Eynon N, Yan X, Bishop DJ. Exercise training and DNA methylation in humans. *Acta Physiol*. 2015;213(1):39–59.

[56] Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ. Congenital malformations and intrauterine growth retardation: a population study. *Pediatrics*. 1988;82(1):83–90.

[57] Kramer HH, Trampisch HJ, Rammos S, Giese A. Birth weight of children with congenital heart disease. *Pediatrics*. 1990;149(11):752–757.

[58] Rosenthal GL, Wilson PD, Permutt T, Boughman JA, Ferencz C. Birth weight and cardiovascular malformations: a population-based study. The Baltimore-Washington Infant Study. *Am J Epidemiol*. 1991;133(12):1273–1281.

[59] Malik S, Cleves MA, Zhao W, Correa A, Hobbs CA. Association between congenital heart defects and small for gestational age. *Pediatrics*. 2007;119(4):e976–e982.

[60] Wallenstein MB, Harper LM, Odibo AO, et al. Fetal congenital heart disease and intrauterine growth restriction: a retrospective cohort study. *J Maternal Fetal Neonatal Med*. 2012;25(6):662–665.

How to cite this article: Spearman AD, Loomba RS, Danduran M, Kovach J. Intrauterine growth restriction is not associated with decreased exercise capacity in adolescents with congenital heart disease. *Congenital Heart Disease*. 2018;13:369–376. https://doi.org/10.1111/chd.12577