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ORIGINAL ARTICLE

Heart Rate Recovery Following Exercise Testing in Pediatric Patients with Acyanotic Repaired Congenital Heart Disease

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Abstract

Attenuated heart rate recovery (HRR) following peak exercise has been shown to be a predictor of mortality in populations of adults with Fontan palliation, coronary artery disease, heart failure, and heart transplantation. However, few have studied HRR in children and adolescents with congenital heart disease (CHD). This case-control study compared HRR patterns from exercise stress testing in children and adolescents with and without repaired acyanotic CHD (raCHD). Retrospective analysis included patients aged 10–18 years who had exercise testing between 2007 and 2017. The raCHD cohort included patients with Tetralogy of Fallot, transposition of the great arteries, coarctation, truncus arteriosus, atrioventricular septal defect, pulmonary outflow obstruction, aortic stenosis and/or insufficiency, or septal defects. Those in the control cohort were matched for age, sex, BMI, peak METs achieved, and peak heart rate (HR). HR at 1-min intervals throughout the 10-min recovery period and HRR patterns were analyzed. The study included $n = 584$ individuals (raCHD: $n = 146$), median age 14 years old, 67.1% male. The cohorts had similar resting and peak HRs. Linear mixed-effects models (LMM) suggested statistically significant cohort-by-time interaction for HR in exercise recovery, with the largest mean difference at minute-6 (2.9 bpm, $p = 0.008$). When comparing lesion types, LMM found no cohort or cohort-by-time interaction. While minute-6 of exercise recovery was statistically significant, the difference was 2.9 bpm and may not have clinical significance. These results suggest that HRR in pediatric raCHD patients should not vary from their healthy peers, and an attenuated HRR may not be directly attributed to underlying raCHD.

Keywords Congenital heart disease · Exercise · Heart rate · Exercise recovery · Children · Adolescents

Introduction

Cardiopulmonary exercise testing has evolved into a valuable component in routine evaluation of patients receiving cardiac care for assessment of functional capacity, heart rate (HR) variability, exercise induced ischemia and arrhythmias. Numerous studies have demonstrated the utility of exercise stress testing in predicting adverse outcomes, with much of the attention being paid toward measures of oxygen consumption. However, one often overlooked element of exercise testing in clinical practice is the pattern of HR recovery (HRR) following peak exercise. Studies in adults have demonstrated that HRR is a predictor of mortality on 5-year follow-up in those without known cardiac disease [1], as well as a predictor of sudden death in asymptomatic adult males [2]. Studies have also identified HRs at precise time points during the exercise recovery period have predictive utility. In a study of > 40,000 adults without cardiovascular disease, van de Vegte and colleagues found that the HRR at 10 s after peak exercise predicted mortality over 6 years [3]. Cole et al. identified that a decline in HR from peak of ≤ 12 bpm after 1-min of exercise recovery was predictive of mortality after adjusting for heart disease and other standard cardiac risk factors [4]. In a sample of > 2000 adults, Johnson and Goldberger observed that a delay in HRR at minute 5 of exercise recovery was a significant predictor of all-cause mortality over 9 years [5].

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Studies focusing on HRR patterns in patients with congenital heart disease (CHD) are limited. In 2005, Diller et al. [6] found that peak oxygen consumption (VO_{2peak}) was correlated with hospitalization and death in adults with CHD. In a follow-up study, Diller et al. observed that blunted HRR at 1, 2, 3 and 5 min was a predictor of mortality over a median follow-up of 28 months in adults with CHD [7].

In children and adolescents specifically, studies have shown that HRR is typically more rapid compared to adults [8]. Although the research in adults cannot be simply extrapolated to children, the assessment of HRR patterns may still have some prognostic utility. Attenuated HRR 1–2 min after peak exercise has been reported in children with cardiometabolic risk factors such as elevated waist circumference, blood pressure, triglycerides, and C-reactive protein levels, [9] and has been correlated with poor cholesterol profiles and higher BMI [10]. In children and adolescents who have had cardiac transplant, Giardini et al. reported poor outcomes in those who had attenuated HRR > 6 years after transplant, possibly related to poor parasympathetic reinnervation [11].

Few studies have explored HRR patterns in pediatric patients with CHD. A 2019 study by von Scheidt et al. evaluated post-exercise HRR in a cohort of 103 youth with cyanotic heart disease (i.e., Fontan circulation and pulmonary arterial hypertension), repaired acyanotic CHD (raCHD) and matched controls without cardiac defects [12]. The authors observed chronotropic incompetence and impaired HRR at 1 and 2 min of exercise recovery in the CHD group, and delayed HRR was associated with lower VO_{2peak}. By combining both cyanotic and acyanotic patients into a single group, delay in HRR observed in the von Scheidt study may have been exaggerated as a result of hypoxemia in the cyanotic patients [13].

The purpose of this study was to compare HRR patterns in children and adolescents with and without raCHD and to explore HRR pattern between different raCHD lesions. With survival after congenital heart surgery improving and more patients living through adolescence and beyond, study of the effects of raCHD on long-term cardiac health is necessary. By excluding cyanotic patients from this study, we aim to eliminate a possible confounder, allowing for independent evaluation of children and adolescents with raCHD.

Methods

Data for this retrospective case–control study was extracted from the Children's Mercy Kansas City, Ward Family Heart Center and Pediatric Physical Activity and Cardiac Exercise Science (Ped-PACES) program database, which contains clinical data from all patients who have undergone exercise testing at Children's Mercy Hospital (CMH). Participants were identified if they underwent treadmill exercise stress testing at CMH from January 1, 2007, through December 31, 2016, and were between the ages of 10 to 18 years old at the time of testing. The treadmill exercise protocols included both ramping and incremental protocols, followed by a 10-min monitored post-exercise recovery period including 3-min active recovery (walking: 1.5 mph) and 7 min of passive (seated) recovery. Patient diagnoses were extracted from internal billing data using International Classification of Disease (ICD)-9 and/or ICD-10 codes. Data fidelity was assessed by the PI on a random selection of participants (10% of the sample) where electronic medical records were manually reviewed and matched with the research database.

Patients with the following diagnoses who had previously undergone surgical and/or transcatheter repair were included in the raCHD cohort: Tetralogy of Fallot, transposition of the great arteries, coarctation of the aorta, truncus arteriosus, atrioventricular septal defects, pulmonary valve stenosis, pulmonary artery stenosis, aortic valve stenosis, aortic insufficiency, isolated atrial septal defect, and isolated ventricular septal defect. Exclusion criteria included cyanosis as defined as oxygen saturation < 90%, pulmonary hypertension, high grade heart block, coronary disease, cardiomyopathy, heart transplant, unrepaired CHD, and other CHD not listed above, such as Ebstein anomaly and single ventricle physiology. The control cohort consisted of patients without structural cardiac disease who underwent treadmill exercise testing for exertional complaints such as chest pain, shortness of breath, dizziness, or palpitations, as well as patients with a history of tachyarrhythmia in the absence of structural or functional disease.

Participants were encouraged to exercise until they reported inability to continue, self-terminating the exercise when reaching volitional fatigue. HR was acquired continuously throughout the exercise test and recorded every 1-min throughout the 10-min exercise recovery period via 12-lead ECG (GE CASE, Milwaukee, WI, USA). Patients in both the experimental and control cohorts were excluded from analysis if their exercise testing was deemed inadequate, defined as peak HR < 85% of age-predicted maximum and/or < 190 bpm [14–17]. For patients with multiple tests, data from the earliest test was used. Patients were also excluded from the analysis if > 4 data points for HR were missing, either due to early termination of the study or lack of entry into the database. Finally, patients were excluded if they had a diagnosis of asthma, as this was deemed a confounding comorbidity [18].

The control cohort was selected by propensity score matching to the raCHD cohort to ensure balance in age, sex, BMI, metabolic equivalents (METs) achieved, and peak HR between the cohorts. Peak HR and percentage of peak HR at 1-min intervals throughout the 10-min exercise recovery period were analyzed. Continuous matching variables and resting HR were summarized by medians and interquartile

range (IQR) for each cohort due to their skewed distributions, and effect sizes for between-cohort differences were evaluated by standardized mean difference (SMD). The distributions of HR and percentage of the peak HR appeared approximately Gaussian, and their data collected over the 10-min period were analyzed using linear mixed-effects models (LMM) with fixed-effects of Cohort (raCHD vs. Control), time, Cohort-by-time interaction, and matching variables. Within the raCHD cohort, HRR patterns were explored by LMM with lesion type, time, lesion type by time interaction, and matching variables as fixed-effects. For both analyses, within-patient dependency was captured with random patient intercepts, random time slopes, and/or different (first-order autoregressive and exponential) correlation structures; the optimal random effects/correlation structure and the best subset of fixed-effects were selected by the Akaike information criterion (AIC). The fixed-effect parameters were obtained by the Restricted Maximum Likelihood method. All analyses were performed in the R programming language [19] using the MatchIt package for propensity score matching [20], the nlme package for LMM analyses [21], and Emmeans package for estimated marginal means from LMM [22].

Results

In total, $n=2068$ patients aged 10–18 years old were identified for having a treadmill exercise test performed in the targeted timeframe. After exclusion for inadequate testing defined as peak HR < 85% of age-predicted max and/or < 190 bpm ($n=765$), failed tests without any HR data ($n=104$), lack of achieved MET data ($n=2$), and fewer than 5 data points ($n=77$), $n=1120$ patients remained, with $n=146$ of those in the raCHD cohort. A 3:1 ratio of control to raCHD patients provided the best balance of variables for matching on age, sex, BMI, METs achieved, and peak HR during exercise, identifying $n=438$ control patients used for comparative analysis. The control and the raCHD cohorts, respectively had a median age at the time of testing of 14 and 13 years old, 67.1% and 67.1% male, and the median BMI was 20.2 and 19.8. The two cohorts had similar medians of matching variables and resting HR. A summary of patient demographics is displayed in Table 1.

Between-cohort SMD ranged from − 0.03 to 0.24 for percentage of peak HR values at each minute interval of exercise recovery. The AIC suggested statistically significant cohort-by-time interaction for HR and percentage of peak HR ($F\_9,5208=2.83$ and 2.80, both $p=0.003$) in exercise recovery in LMM, with statistically significant differences at minute-6 of exercise recovery (2.9 bpm, $p=0.008$; 1.5%, $p=0.009$). No other between-cohort differences for time points in exercise recovery were identified. AIC also suggested age ($F_{1,577}=42.5$, $p<0.001$), sex ($F_{1,577}=11.8$, $p<0.001$), BMI ($F_{1,577}=3.85$, $p=0.05$), METs achieved ($F_{1,577}=12.3$, $p<0.001$), and peak HR ($F_{1,577}=128.1$, $p<0.001$) as covariates. The HR and the percentage of peak HR demonstrated similar patterns (Fig. 1).The raCHD cohort was subdivided by lesion type. The distribution of lesions within the experimental cohort is reported in Table 2.

When comparing HRR pattern by lesion type, AIC suggested HRR associated with time, age, sex, BMI and peak HR, but not with METs achieved, lesion or lesion-by-time interaction (Fig. 2).

Discussion

Abnormal HRR patterns following peak exercise has been identified in adults with and without CHD, where a delay in HRR (generally defined as decrease in HR by < 12 bpm for any minute interval after exercise cessation [4]) has been correlated with mortality and other poor outcomes [1–7]. Considering the differences in rate of HRR following peak exercise in children and adolescents compared to adults [8], it is inappropriate to extrapolate conclusions from adult research to youth. So far, little is known about the HRR patterns in children and adolescents with cardiovascular risk factors including CHD. The purpose of this study was to compare HRR patterns in children and adolescents with and

Table 1 Descriptive statistics

Variables	Control cohort	raCHD cohort	*p* value	SMD
n	438	146		
Age (median [IQR])	14.0 [12.0, 15.0]	13.0 [12.0, 15.0]	0.639	0.02
Male (%)	294 (67.1)	98 (67.1)	> 0.99	< 0.001
BMI (median [IQR])	20.2 [18.2, 22.8]	19.8 [17.5, 22.6]	0.214	0.02
METS achieved (median [IQR])	14.1 [12.8, 15.3]	14.1 [12.8, 14.8]	0.750	0.02
Peak HR (median [IQR])	195.0 [191.2, 200.0]	196.0 [192.0, 199.0]	0.717	− 0.01
Resting HR (median [IQR])	75.0 [67.0, 84.0]	75.0 [66.0, 83.8]	0.841	0.05

raCHD repaired acyanotic congenital heart disease, *HR* heart rate, *SMD* standardized mean difference, *IQR* interquartile range, *METs* metabolic equivalents

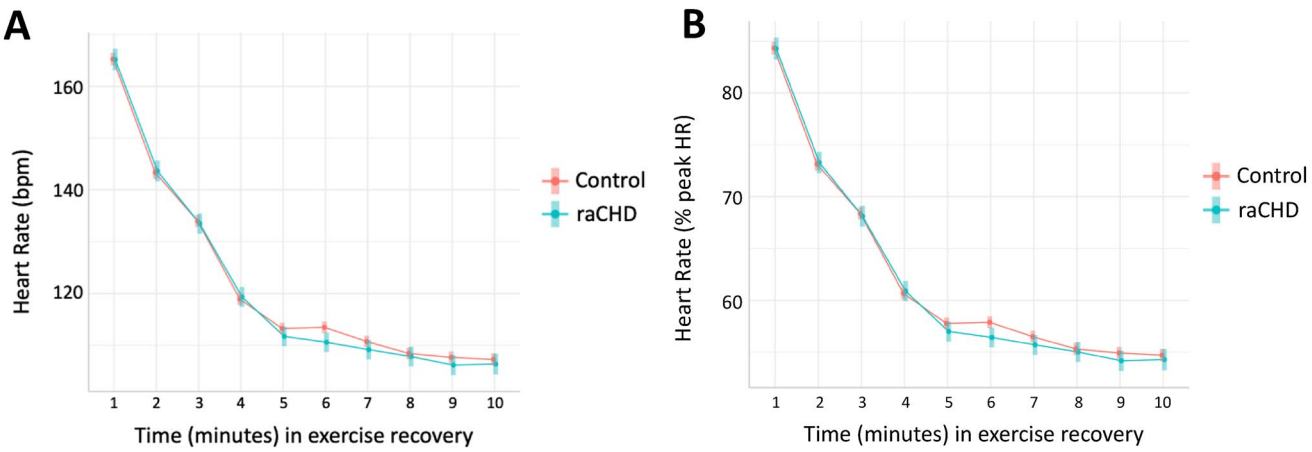

Fig. 1 Estimated marginal means from LMM for HRR pattern for absolute HR (**A**) and HR represented as percentage of peak HR (**B**) comparing control and raCHD cohorts

Table 2 Distribution of raCHD lesion types

raCHD lesion	*n* (% of raCHD cohort)
AS/AI	17 (11.6)
ASD	2 (1.4)
AVSD	2 (1.4)
Coarctation	58 (39.7)
Pulmonary outflow disease	10 (6.8)
Tetralogy of Fallot	25 (17.1)
Transposition	25 (17.1)
Truncus arteriosus	1 (0.7)
VSD	6 (4.1)

raCHD repaired acyanotic congenital heart disease, *AS/AI* aortic stenosis or aortic insufficiency, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *VSD* ventricular septal defect

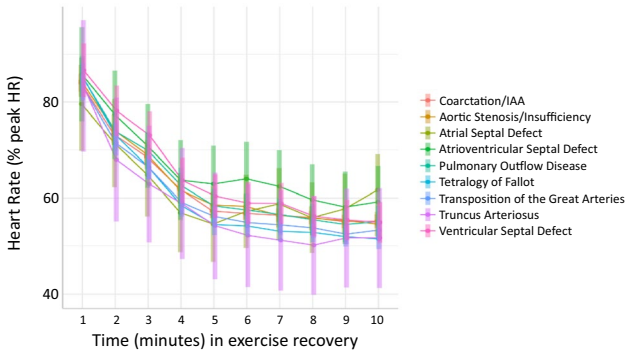

Fig. 2 The estimated marginal means form a LMM with lesion-by-time interaction for HRR pattern across individual raCHD lesions

without raCHD and to explore HRR pattern between different raCHD lesions.

Our results revealed a statistically significant between-cohort difference at minute-6 of exercise recovery. However, we believe the mean difference of ~ 3.0 bpm between the experimental and control cohort is unlikely of any clinical significance. Our findings are contrary to the results of von Scheidt et al. who studied HR responses during treadmill exercise in children and adolescents with and without CHD. von Scheidt and colleagues demonstrated that HRR within the first 2-min of exercise recovery was delayed in the CHD cohort compared to the non-CHD control cohort [12]. The discrepancy in conclusions from von Scheidt et al. and our study may be due to their inclusion of participants with cyanotic heart disease (i.e., pulmonary hypertension, Fontan palliation). Increasing levels of cyanosis observed with exercise in those with cyanotic heart disease may amplify the degree of oxygen deficit acquired with progressive increases in exercise intensity. Oxygen deficit is defined as the oxygen equivalent of the energy required during exercise, which is not derived from oxygen consumption. The delay in oxygen transport to the muscle during exercise of progressively increasing intensity results in utilization of oxygen stores in the blood and muscle. In exercise recovery, these oxygen stores need to be replenished, resulting in excess post-exercise oxygen consumption and transport [23–27]. The sample used in this study consisted of acyanotic repaired CHD, where exercise-related changes in oxygen saturation and the degree of oxygen deficit should be similar to cardiotypical peers.

The mechanism of delayed HRR has been studied by several groups. Researchers hypothesize that an increase in sympathetic tone, withdrawal of vagal tone and an increase in catecholamines drive the increase in HR during exercise. When exercise is discontinued, the parasympathetic system reinstates, and vagal stimulus is responsible for the HRR [28]. As such, abnormal or delayed HRR can be due

to both impaired sympathetic and parasympathetic cardiac autonomic nervous activity (CANA) [29]. This mechanism helps to explain the changes in HRR pattern after pediatric heart transplant, when the heart is denervated. However, in patients with raCHD a disruption to their CANA would be rare, suggesting HRR pattern should not be altered. This aligns with our results that showed no significant difference between the raCHD patients and controls.

Knowing that raCHD alone should not affect the HRR pattern in our pediatric patients can be helpful in clinical practice. Specifically, should a patient with raCHD have marked delayed HRR following peak exercise, it may be a result of other factors of health and, should prompt further investigation. It is important to recognize that those with raCHD often have other comorbidities associated with poor cardiorespiratory fitness like their cardio-typical peers. Singh, Curran and Rhodes evaluated patients with repaired CHD and reported that HRR at 1-min following peak exercise was improved in patients who participated in the cardiac rehabilitation program when compared to those who did not participate in the program [30]. This suggests that improved cardiorespiratory fitness can positively impact HRR in patients with CHD as well and exercise prescription should continue to be utilized to improve the overall health of our patients.

We recognize there were limitations to this study. The data were collected from a single center which may result in greater homogeneity within the sample. Given the retrospective nature of the study, there was lack of randomization and likely referral bias for those who were being evaluated by exercise stress test. By excluding patients who did not meet peak exercise criteria as defined above, we may have eliminated those with a more fragile cardiac status, and thus those who may present with an attenuated HRR and worse cardiac outcomes. This data was meant to serve as an overview of all-comers with raCHD. Future studies with more granular data including residual cardiac lesions, disease severity and outcomes are needed.

Conclusion

Patterns of HRR can be a useful element of exercise testing and has been shown to have prognostic significance for many different populations. However, in children and adolescents with raCHD, we identified no clinically significant differences in HRR pattern compared to cardio-typical peers. Our results suggest the finding of delayed HRR in a pediatric patient with raCHD should prompt further investigation into other physiologic abnormalities.

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Data Availability Data available upon request.

Code Availability Not applicable.Consent for Publication Not applicable.

Consent for Publication Not applicable.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was waived by this retrospective study from the Hospital Institutional Review Board.

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