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Association between Physical Activity and Chronotropic Incompetence in Patients with Complex Congenital Heart Disease

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Purpose: Although chronotropic incompetence (CI) is common in patients with complex congenital heart disease (CHD) and is associated with adverse cardiovascular outcomes, few data are available regarding modifiable predictors of CI in this escalating patient population. We tested the hypothesis that higher levels of physical activity (PA) are associated with a lower prevalence of CI in patients with complex CHD and evaluated the receiver operating characteristic curve to identify the PA level that best predicted CI.
Methods: We evaluated 111 adolescents with complex CHD. CI was defined as the failure to achieve 80% of the chronotropic response index during peak cardiopulmonary exercise test. Self-reported habitual activity was obtained using a global PA questionnaire.
Results: CI was identified in 45 of the 111 cases (40.5%). After adjusting for potential confounding variables, the high PA group demonstrated a lower odds ratio for having CI (odds ratios, 0.25; 95% confidence interval, 0.06–0.99) compared with the low PA group. The most accurate cut-point for PA to predict the prevalence of CI was 15 metabolic equivalents (METs)-hours/week (areas under the curve, 0.71; 95% confidence interval, 0.61–0.81; sensitivity, 71%; specificity, 69%).
Conclusion: Our findings demonstrate that higher levels of PA are associated with a lower prevalence of CI, independent of potential confounders, and that 15 METs-hours/week of PA provides a cut-point for accurately predicting the presence of CI in adolescents with complex CHD.

Keywords: Chronotropic incompetence, Physical activity, Exercise test, Congenital heart disease

Introduction

An abnormal heart rate response to exercise is clinically significant because of its association with autonomic dysfunction and poor clinical outcomes[1]. Heart rate increases linearly during progressive exercise due to increases in sympathetic activity coupled with concomitant decreases in parasympathetic stimulation[2]. However, in some individuals, a blunted or attenuated increase in heart rate during exercise may be observed, signifying "chronotropic incompetence (CI)[3,4]." Importantly, CI has been shown to be an independent predictor of subsequent cardiovascular events and a heightened cardiovascular mortality in patients with heart failure[5,6]. Although CI is also common in patients with complex congenital heart disease (CHD) and is associated with adverse cardiovascular outcomes[7-9], this response remains under-appreciated, as few data are available regarding modifiable predictors of CI in this escalating patient population. While there is a much higher prevalence of CI (34%–62%) in patients with CHD, as compared with their healthy age-matched counterparts, the underlying mechanisms responsible for the diminished heart rate reserve remain unclear[7-9]. Previous studies have suggested that the higher prevalence of CI in patients with CHD may be due to congenital cardiac anomalies, damage to the sinoatrial node during cardiovascular surgical procedures, or both, ultimately resulting in autonomic dysfunction or downregulation/desensitization of the associated beta-adrenergic receptors in the synaptic gap[10-12]. However, it remains unclear whether certain characteristics are linked with CI and whether these are modifiable in patients with CHD.

Although higher levels of physical activity (PA) are associated with an enhanced exercise capacity, improved cardiovascular risk factor profile, altered autonomic nervous function, and quality of life as well as psychosocial outcomes in patients with CHD[13-16], it remains unclear whether it can also attenuate the risk of CI in patients with CHD. Interestingly, maximal heart rate and chronotropic index have been reported to increase following exercise training in patients with heart failure[17-21]. Accordingly, higher levels of PA may favorably impact the chronotropic response to exercise in patients with heart failure and other cardiovascular diseases[22]. We tested the hypothesis that higher levels of PA are associated with a lower prevalence of CI in patients with complex CHD, independent of potential risk factors. Additionally, we evaluated the receiver operating characteristic curve to identify the PA level that most accurately predicted CI in patients with complex CHD.

Methods

This study was conducted from November 2015 to February 2016 using data collected during outpatient visits to the pediatric department of Sejong General Hospital in Bucheon, Korea. Among 240 adolescents who had a confirmed CHD diagnosis in the medical chart, 228 patients were eligible for the study. Initial exclusions (n=12) included patients with arrhythmias that were unrelated to CHD (n=3) and those with incomplete responses to the PA questionnaire (n=9). Additionally, we excluded a subset of adolescents without complex CHD (n=117) who did not undergo cardiopulmonary exercise test. The remaining 111 patients with complex CHD (61 boys and 50 girls, aged 13–18 years) served as our study population. We obtained patient demographic information, diagnosis of CHD, related medical conditions, cyanosis, prescribed medications, and serial surgery data from the medical record. Written informed consent was obtained from the guardians/parents and patients prior to participation. The study protocol adhered to the standards of the Declaration of Helsinki and was approved by the Clinical Trials Board of Sejong General Hospital (No. 2019-0385).

1. Cardiopulmonary exercise test and hemodynamic measurements

Peak or symptom-limited cardiopulmonary exercise test was conducted via a Q-Stress TM55 treadmill (Quinton Cardiology Systems, Inc. Bothell, WA, USA), and gas analyzer (TrueOne 2400; ParvoMedics, Salt Lake City, UT, USA) using a breath-by-breath method and analyzed in 15-second intervals. A modified Bruce treadmill protocol was used. Criteria for exercise test termination included: (1) a rating of perceived exertion (6–20 category scale) of >17 (very hard), (2) a peak respiratory exchange ratio (RER) of ≥1.10, (3) the subject requested to stop (i.e., volitional fatigue), or (4) combinations thereof. Peak oxygen uptake, oxygen pulse and RER were directly measured during the progressive exercise test. In addition, we measured oxygen

saturation and obtained ratings of perceived exertion every stage and at peak exercise. Systolic and diastolic blood pressures were obtained at rest, during the last 30 seconds of each 3 minutes stage, and at peak or maximal exercise. Prior to the exercise test, participants assumed the supine position, and resting heart rate was recorded for 5 minutes via electrocardiogram monitor electrocardiographic monitoring (Q-Stress). Heart rate was also measured during each submaximal stage and at maximal exercise. The peak or maximal heart rate determined by 12-lead electrocardiograms (Q-4500; Quinton Cardiology Systems) was defined as the highest attained value during the progressive exercise test. The CI index was calculated using the equation: (maximal heart rate−resting heart rate)/(220−age−resting heart rate)×100, and patients who did not attain 80% of the index were classified as having CI[23].

2. Physical activity assessment

Habitual activity (metabolic equivalents [METs]-hours/week) was assessed using the global PA questionnaire[24]. The survey included 16 questions designed to quantitate PA undertaken in three different environments: work (during school time), transport, and discretionary activity (also known as leisure or recreation). METs were used to quantitate the intensity of physical activities that were documented in the global PA questionnaire. For analytical purposes, 4 METs were assigned to the time spent during moderate-intensity activities, and 8 METs to the time spent during vigorous activities. To assess overall PA, MET scores were calculated separately for individual domains and subdomains. For the calculation of a categorical indicator, the total time spent participating in PA during a typical week, the number of days per week, as well as the intensity of PA were considered. To evaluate the reproducibility of the questionnaire, the same questionnaires were administered repeatedly to 14 patients with CHD, yielding correlation coefficients of 0.66 to 0.99. Patients were then divided into groups according to tertiles of PA levels as low (≤10.0 METs-hours/week); moderate (10.1−23.9 METs-hours/week); and high (≥24.0 METs-hours/week).

3. Statistical analysis

All values are reported as mean±standard deviation, or frequency and percentage, and normal distribution was assessed

using the Kolmogorov-Smirnov test. To compare the differences between the groups with and without CI, Student t-test and Mann-Whitney U-test were employed. Multivariable logistic regression analyses were used to calculate odds ratios and 95% confidence interval of having CI. Because of multicollinearity between PA and peak oxygen uptake (r=0.51, p<0.001), we excluded the latter as an independent variable in the model. Finally, the receiver operating characteristic curve analysis was performed to identify the PA level that most accurately predicted CI. The areas under the curve (AUC) and 95% confidence interval were also obtained. Statistical comparisons were made using the IBM SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA), and significance was set at p<0.05.

Table 1. Characteristics of patients (n=111)

Characteristic	Data
Age (yr)	16.2±1.8
Sex	
Male	61 (55.0)
Female	50 (45.0)
Body mass index (kg/m^2)	20.6±3.5
No. of surgical procedures	
0	1 (0.9)
1−2	60 (54.1)
>3	50 (45.0)
Cyanosis	19 (17.1)
Birth weight (kg)	3.00±0.54
No. of medications	
0	41 (36.9)
1−2	49 (44.1)
>3	21 (18.9)
Diseases	
Pulmonary stenosis	3 (2.7)
Aortic stenosis	2 (1.8)
Atrioventricular septal defect	2 (1.8)
Coarctation of the aorta	3 (2.7)
Double outlet right ventricle	6 (5.4)
Fontan circulation	36 (32.4)
Pulmonary atresia with ventricular septal defect	14 (12.6)
Transposition of great arteries	6 (5.4)
Tetralogy of Fallot	34 (30.6)
Others*	5 (4.5)

Values are presented as mean±standard deviation or number (%).
*Anomalous pulmonary venous connection, Ebstein anomaly.

Table 2. Characteristics of patients with and without chronotropic incompetence (CI)

Characteristic	Total	CI group	No CI group	p-value
No. of patients	111	45	66	
Age (yr)	16.2±1.8	15.9±2.1	16.3±1.6	0.186
Male sex	61 (55.0)	26 (57.8)	35 (53.0)	0.625
Body mass index (kg/m^2)	20.6±3.5	20.5±3.3	20.7±3.8	0.829
Birth weight (kg)	3.0±0.5	2.9±0.5	3.1±0.5	0.174
Cyanosis	19 (17.1)	13 (28.9)	6 (9.1)	0.012
No. of surgical procedures	2.6±1.6	3.9±1.9	2.1±1.1	<0.001
No. of medications	1.43±1.8	2.2±2.1	0.9±1.2	<0.001
Rest SaO$_2$ (%)	97.3±3.2	97.1±3.3	97.5±3.1	0.572
Rest HR (beats/min)	75.5±13.9	78.0±16.1	73.8±12.0	0.136
Peak HR (beats/min)	180.0±19.2	161.8±15.4	192.4±8.8	<0.001
HR reserve (beats/min)	104.5±22.1	83.7±16.6	118.7±11.8	<0.001
Rest SBP (mm Hg)	119.8±18.7	113.9±18.2	123.9±18.0	0.005
Rest DBP (mm Hg)	70.6±12.8	65.9±9.7	73.8±13.6	0.001
Peak SBP (mm Hg)	144.6±21.7	141.2±23.9	146.9±19.8	0.194
Peak DBP (mm Hg)	66.1±13.5	65.5±16.0	66.4±11.7	0.738
Peak O$_2$ pulse (mL/beat)	9.7±5.6	9.2±4.6	10.0±6.1	0.773
Peak VO$_2$ (mL/kg/min)	31.5±8.2	27.3±7.3	34.4±7.6	<0.001
RER	1.13±0.11	1.09±0.10	1.15±0.10	0.002
RPE	16.9±1.4	16.8±1.8	17.0±1.2	0.545
Physical activity (METs-hr/wk)	16.0 (10.0−30.0)	10.7 (7.3−16.3)	22.8 (11.5−36.7)	<0.001

Values are presented as number only, mean±standard deviation, number (%), or median (interquartile range).
SaO$_2$: oxygen saturation, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, O$_2$ pulse: oxygen pulse, VO$_2$: oxygen uptake, RER: respiratory exchange ratio, RPE: ratings of perceived exertion, MET: metabolic equivalent.

Results

General characteristics of the 111 subjects are shown in Table 1. The prevalence of CI was identified in 45 of the 111 cases (40.5%). By disease category, CI was most frequent in patients with Fontan disease (58.3%), followed by tetralogy of Fallot (20.6%). Differences in physical and clinical characteristics between the CI and control (No CI) groups are depicted in Table 2. There were no significant differences in age, sex, body mass index, and birth weight between groups. Furthermore, resting heart rate, resting oxygen saturation, peak systolic blood pressure, peak diastolic blood pressure, peak oxygen pulse, and peak rate of perceived exertion did not differ between groups. However, the group with CI demonstrated a higher prevalence of cyanosis (68.4% vs. 31.6%, p=0.012), a lower peak oxygen uptake (27.3±7.3 mL/kg/min vs. 34.4±7.6 mL/kg/min, p<0.001), a higher number of surgical operations (3.9±1.9 vs. 2.1±1.1, p<0.001) and medications (2.2±2.1 vs. 0.9±1.2, p<0.001) than the control group (i.e., No CI). Moreover, the CI group showed a significantly lower peak RER value (1.09±0.10 vs. 1.15±0.10) and PA level than the control group (10.7, 7.3−16. vs. 22.8, 11.5−36.7 METs-hours/week, p<0.001).

In an unadjusted logistic regression model, the high PA group had a lower odds ratio for having CI (odds ratio, 0.18; 95% confidence interval, 0.06−0.51) compared with the low PA group. After adjusting for age, sex, body mass index, birth weight, cyanosis, RER, number of surgical procedures, and number of medications, the high PA group was approximately 75% less likely to have CI than the low PA group (odds ratio, 0.25; 95% confidence interval, 0.06−0.99) (Table 3).

In the multivariate logistic regression analysis, we found that CI was independently related to the number of operations, the number of medications, and the level of PA (each 4 MET increment) (Table 4). The best cut-point of PA levels for predicting the prevalence of CI was 15 METs-hours/week (AUC, 0.71; 95% confidence interval, 0.61−0.81; sensitivity, 71%; and specificity, 69%; p<0.001) (Fig. 1). Patients with <15 METs-hours/week showed a 3.3-fold higher prevalence of CI than patients with >15 METs-hours/week (odd ratio, 3.33; 95% confidence interval, 1.24−8.97, p<0.001) (data not shown).

Table 3. The ORs and 95% CIs for the prevalence of chronotropic incompetence by physical activity tertiles

Physical activity	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Low (n=38)	1 (Reference)	1 (Reference)
Moderate (n=38)	0.53 (0.21−1.31)	0.86 (0.28−2.65)
High (n=35)	0.18 (0.06−0.51)	0.25 (0.06−0.99)

OR: odd ratio, CI: confidence interval.
Physical activity: low, ≤10.0 metabolic equivalents (METs)−hr/wk moderate, 10.1−23.9 METs−hr/wk high, ≥24.0 METs−hr/wk.
*Adjusted: age, sex, body mass index, birth weight, cyanosis, respiratory exchange ratio, number of surgical procedures, and number of medications.
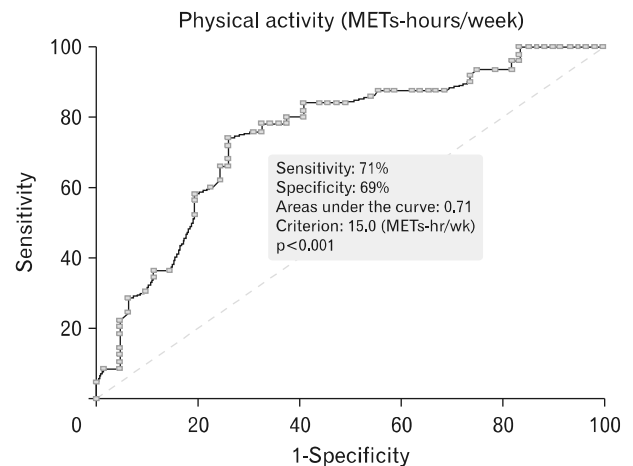
Table 4. Multivariate logistic regression for chronotropic incompetence

Variable	OR (95% CI)
Age	0.92 (0.67−1.25)
Sex	0.42 (0.14−1.29)
Body mass index	1.09 (0.94−1.27)
Birth weight	0.68 (0.25−1.89)
Cyanosis	0.87 (0.21−3.63)
Respiratory exchange ratio	0.49 (0.01−9.60)
No. of surgical procedures	1.90 (1.12−3.20)
No. of medications	1.68 (1.17−2.42)
Physical activity (each 4 METs)	0.96 (0.92−0.99)

OR: odd ratio, CI: confidence interval, MET: metabolic equivalent.

Fig. 1. The receiver operating characteristic curve to identify the optimal physical activity level for the prediction of confidence interval. MET, metabolic equivalent.

Discussion

CI, which is signified by a blunted increase in heart rate during incremental exercise test, is associated with a poor prognosis in patients with CHD[7-9]. Although the attenuated heart rate response is generally attributed to the associated cardiovascular surgery, identifying potential modulators of CI may be helpful in improving patient outcomes. Furthermore, CI closely contributes to impaired exercise capacity[18], which is the single most important variable to predict outcomes in patients with CHD. Although higher levels of PA are associated with enhanced exercise capacity and quality of life and reduced psychological stress in patients with CHD[16,25], it remains unclear whether higher levels of PA are associated with a lower prevalence of CI in this subset. Additionally, no previous reports have delineated the minimal weekly PA dosage, below which there is an increased likelihood of CI in patients with CHD.

The novel finding of the present study was that higher levels of PA are associated with a lower prevalence of CI, independent of potential risk factors. Furthermore, the receiver operating characteristic curve to identify the PA level that best predicted CI was 15 METs-hours/week. Thus, PA levels <15 METs-hours/week were associated with a higher prevalence of CI in patients with CHD. The present results are consistent with previous reports that exercise training reduced the likelihood of CI in patients with heart failure[18-21], and extends these findings to patients with CHD. Therefore, beyond congenital cardiac anomalies, PA may be considered as a modifiable risk factor for CI in patients with CHD. To our knowledge, this is the first study to report that a higher level of PA was associated with a lower prevalence of CI in patients with CHD.

The prevalence of CI is reported at 16% to 22% in the general population[4,26], whereas it is significantly higher in patients with CHD. Norozi et al.[9] found a 34% prevalence of CI in adolescents and adults with CHD after cardiac surgery, whereas Diller et al.[7] who investigated a diverse CHD population of varied ages, reported a 62% prevalence of CI. In the present study, we found an intermediate prevalence of CI, that is, 40%, which is higher than that of the general population. The varied prevalence rates of CI reported in previous studies may be due to differing assessment methodologies and/or different types of CHD and age ranges of the subjects.

The underlying mechanisms of CI in patients CHD remain unclear. According to some reports[27,28], the density of beta-adrenergic receptors was reduced by 50% in the left ventricular myocardium due to myocardial damage following cardiac surgery. This attenuates the beta-adrenergic pathway and myocardial contractility, resulting in CI[27,28]. Other studies in patients with CHD have reported that CI was a result of alterations in autonomic nervous system stimulation or desensitization of synaptic beta-adrenergic receptors[29] due to sinoatrial node damage during heart surgery[10-12]. These results are in accord with our findings relative to the relationship between CI and the number of previous surgeries. Clearly, additional studies are needed to further clarify the underlying mechanisms for CI in patients with CHD. In addition, it is a possible that CI in patients with CHD may results in low PA. Therefore, it is not clear whether higher PA levels produce reductions in CI over time, or whether decreased CI results in low PA. Further studies are needed to exam these associations.

Regular exercise increases heart rate variability due to enhanced resting baroreflex sensitivity and parasympathetic activity with corresponding decreases in catecholamines, angiotensin II, vasopressin, plasma B-type natriuretic peptide and sympathetic activity[30]. Collectively, these adaptations may serve to reduce heart rate at rest and during exercise while modestly increasing the maximal heart rate. This is supported by a meta-analysis in heart failure patients demonstrating that maximal heart rate increased by 4 beats/min following exercise training[17]. The present study confirmed that PA is independently associated with the prevalence of CI and that 15 METs-hours/week may be used to predict this anomaly. This level of PA corresponds to exercising for 40–60 minutes, at 3–4 METs, 5 days per week. Interestingly, a PA volume of 15 METs-hours/week is compatible with the recommended amount of PA for children and adolescents with CHD[31].

The present study has several limitations. First, the results from our cross-sectional study design do not necessarily infer a causal relationship. Accordingly, additional studies are needed to confirm whether structured PA reduces the risk of CI, ideally via a randomized-controlled trial. Secondly, although the PA assessment methodology used in this study has been previously validated, the obtained self-reported data depended on the subjects' subjective perceptions and recall. Therefore, there is a need to confirm the relationship between CI and PA via more objective measurement tools (e.g., accelerometer, personalized activity intelligence scores). Thirdly, although we classified PA into three categories (low, moderate, and high) based on tertiles of PA, these categories may be viewed as somewhat arbitrary. Finally, some prescribed medications may serve as an independent predictor for CI. However, we did not account for potential confounding medications such as beta-blockers and/or calcium channel blockers, which may have negatively impacted chronotropic reserve. It is an interesting to report that CI significantly improves with exercise training in patients with acute coronary syndrome, irrespective of beta-blockers dose changes[32].

Our findings demonstrated that a higher level of PA was independently associated with a lower prevalence of CI, and that 15 METs-hours/week provided the most accurate cut-point for predicting the presence of this prognostic indicator in patients with complex CHD. These results suggest that increasing lifestyle PA, structured exercise, or both, should be considered as modifiable risk factors to reduce the risk of CI in adolescents with CHD, and potentially improve prognosis.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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