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ORIGINAL ARTICLE

Chronotropic incompetence to exercise in anorexia nervosa patients during the body-weight recovery phase as an index of insufficient treatment

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Abstract
Resting bradycardia is an important symptom for early diagnosis of anorexia nervosa (AN) during weight loss, and it improves with body-weight recovery. However, chronotropic incompetence (CI) in exercise is observed in some patients with AN despite amelioration of resting bradycardia in the recovery phase. We examined the relationship between CI in exercise and other parameters in patients with AN during the recovery phase. Ninety-two girls with AN (aged 13–20 years, median 15 years) performed cardiopulmonary exercise tolerance tests with a bicycle ergometer in the post-treatment recovery phase. Subjects with a peak-heart rate (HR) of < 160 beats/min (bpm) on subjective maximum loading were assigned to the CI+ group ($n = 7$), and those with a peak-HR of ≥ 160 bpm were assigned to the CI− group ($n = 85$). The peak-oxygen uptake (VO_2) of both groups was below the normal range. Although there was no difference in peak-VO_2 between these groups, both the resting-HR and ΔHR (peak-HR − resting-HR) were significantly lower in the CI+ group than in the CI− group (82 ± 8 vs. 93 ± 16 bpm, respectively; 72 ± 14 vs. 89 ± 13 bpm, respectively), suggesting lower exercise tolerance in patients with CI during the recovery phase of AN. Interestingly, the $\Delta VO_2/\Delta HR$ value was higher in the CI+ group than in the CI− group (0.31 ± 0.13 vs. 0.26 ± 0.06, respectively), suggesting excessive stroke volume for maintaining the cardiac output in patients with CI during their recovery phase. These data suggest that CI could be an index of insufficient recovery of AN and utilized for ideal exercise treatments of patients with AN during the recovery phase.

Keywords Eating disorder · Autonomic dysfunction · Physical activity · Exercise therapy

Introduction

Anorexia nervosa (AN) is the most frequent type of eating disorder in which dietary abnormalities related with desire for weight loss or obesity phobia cause emaciation. It occurs mainly in young females aged 10–29 years, with the inability to overcome mental stress as an etiological factor. AN is not rare; the incidence in young females is approximately 0.3% [1]. It is the psychiatric disease with the most unfavorable prognosis of which mortality rate within 10 years after diagnosis is 7.7% [2].

In 80% of patients with eating disorders, cardiac complications such as bradycardia, hypotension, arrhythmia and QT prolongation are observed, influencing the prognosis [3]. In particular, bradycardia is frequently detected in patients with AN and considered to be an adaptive response of the autonomic nervous system to malnutrition [4–6]. Recently, resting bradycardia during the weight loss phase of AN was found to be an important index for early diagnosis, and was ameliorated with body-weight recovery [4, 6, 7]. However, we often encounter patients with chronotropic incompetence (CI) during exercise despite amelioration of resting bradycardia in the recovery phase. CI is broadly defined as the inability of the heart to increase its rate to compensate for increased activity or demand [8], and refers to limited response of the heart rate (HR) to an increase in the intensity of exercise. It reduces exercise tolerance, restricts the quality of life (QOL) and increases the mortality rate [8–10].

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Roche et al. evaluated the impact of CI in patients with AN [11]. According to their study, CI is caused by cardiac sympathetic withdrawal in patients with AN, and the patients with CI exhibited higher body mass deficit and more severe limitation to maximal exercise. These results suggest that CI may be useful as an index for severity and/or exercise tolerance of AN. However, their report only described the acute phase of AN, and its influence during the recovery phase is unknown. In this study, we analyzed the presence of CI in relatively large number of patients with AN during the recovery phase, and clarified the relationship between CI and other parameters in patients who underwent cardiopulmonary exercise tolerance tests before the start of exercise therapy.

Materials and methods

We selected subjects from patients with AN who were admitted to the Department of Pediatrics, Keio University Hospital or who were managed at the outpatient clinic and underwent cardiopulmonary exercise tolerance tests at the Institute for Integrated Sports Medicine, Keio University Hospital between April 1994 and November 2016. AN was diagnosed by pediatricians specializing in psychiatric disease treatment. All subjects were female, and their ages during cardiopulmonary exercise tolerance tests ranged from 13 to 20 years, with a median age of 15. Before cardiopulmonary exercise tests, the attending physicians specializing in pediatric mental health confirmed both nutritional status and autonomic function. The nutritional status involved constant recovery of weight gain and sufficient oral intake (estimated at 40–50 kcal/day or above without intravenous nutrition and tube feeding at the timing of cardiopulmonary exercise test from the interviews on the medical charts). Some of them were subjected to assess reduction of nocturnal bradycardia and normalization of HR variability as indices for recovery of autonomic function. Thereafter, all patients with AN in this study were diagnosed as those in the body-weight recovery phase by pediatricians specializing in psychiatric disease treatment.

The cardiopulmonary exercise tolerance test was performed in an upright position on an electromagnetically braking cycle ergometer (Monark 818E bicycle ergometer, Vansbro, Sweden and Strength Ergo 8, Mitsubishi Electric Engineering, Tokyo, Japan), using a ramp-type protocol, which was preceded by 30 s of unloaded warm-up cranking with a linearly increased work rate (15–20 W/min). The subject continued to exercise until her tolerance limit was reached. A 12-lead electrocardiogram (ECG) was used to continuously monitor HR with a programmable ECG analyzer (PEC-1320 and ECG-1550, Nihon-Koden Co. Ltd., Tokyo, Japan). Oxygen uptake (VO_2), carbon-dioxide output (VCO_2) and minute ventilation (VE) were measured on a breath-by-breath basis using a gas analyzer (MMC-2900C and V-max 29S, Sensormedics Co. Ltd., Anaheim, CA, USA).

In this study, patients with a peak-HR of < 160 beats/min (bpm) during the tests were defined to have CI, according to diagnostic criteria previously reported [12, 13]. The subjects were divided into following two groups: a group with a peak-HR of < 160 bpm (CI+ group) and a group with a peak-HR of ≥ 160 bpm (CI− group). The physical condition, including the body weight and body mass index (BMI) at the exercise test, pre-onset body weight, body weight recovery rate which was calculated by dividing the body weight on testing by the pre-onset body weight, and the presence of amenorrhea, were compared between the two groups. HR and results of cardiopulmonary exercise tolerance tests were also calculated and compared between the two groups.

For statistical analysis, we used the software R ver. 3.2.3 [14]. Student's *t* test was conducted for items with iso-variance, and Welch's *t* test was used for iso-variance-free items. For the presence or absence of menstruation, Pearson's Chi-square test was used. Significance was considered at a p value of < 0.05.

Results

Cardiopulmonary exercise tolerance tests were successfully performed for all subjects, and there were no adverse events during or after exercise. The CI+ group consisted of 7 (7.6%) out of 92 subjects and the CI− group consisted of remainder 85 (92.4%) subjects (Table 1). There were no significant differences in weight, BMI, pre-onset body weight, and the prevalence of amenorrhea between two groups. Although the mean body weight recovery rate was exceeded by 100% in the CI− group whereas by only 92% in the CI+ group, there was no significant difference between two groups ($p = 0.13$, Table 1). All patients in both groups ($n = 7$ with CI+ and $n = 85$ with CI−, respectively) had sufficient oral intake. The parameter values of autonomic function in Holter recording and HR variability analyses of the subjected patients showed also no significant differences between two groups (Table 2).

In the results of cardiopulmonary exercise tolerance tests (Table 3), the mean peak respiratory quotient (peak-RQ) in the two groups exceeded 1.15, suggesting the completion of peak loading. Resting-HR was significantly lower in the CI+ group ($p = 0.006$), while each group included no patient with resting-bradycardia < 60 bpm. Peak-HR, peak-HR/age-predicted maximal HR (APMHR), rate of change in the HR (ΔHR, or peak-HR − resting-HR) and %HR reserve (ΔHR/[APMHR − resting-HR]) were also significantly lower in the CI+ group ($p < 0.001$, $p < 0.001$, $p = 0.02$ and $p < 0.001$, respectively).

Table 1 Patient Profiles

	CI+ ($n=7$)	CI− ($n=85$)	p
Age (years)	14–20 (median 16)	13–20 (median 15)	0.11
Weight (kg)	44.9 ± 5.8	46.4 ± 5.8	0.55
BMI	18.4 ± 1.9	19.0 ± 1.7	0.50
Pre-onset body weight (kg)	49.8 ± 6.2	44.7 ± 8.2	0.077
Body weight recovery rate (%)	92.1 ± 20.4	105.7 ± 15.9	0.13
Amenorrhea (case)	4 (57.1%)	48 (56.6%)	1.0

Values are mean ± SE. p values were calculated with the unpaired t test

CI chronotropic incompetence, *BMI* body mass index, *weight recovery rate* weight at exam/pre-onset weight, *amenorrhea* patients with primary or secondary amenorrhea

Table 2 Parameters in Holter recording and HRV analyses

	CI+ ($n=3$)	CI− ($n=41$)	p
Minimum heart rate (bpm)	53 ± 6	61 ± 10	0.094
Normal circadian rhythm in HRV (case)	2 (66.7%)	28 (66.7%)	1.0
Mean HF	6.13 ± 1.38	5.61 ± 0.90	0.56

Values are mean ± SE. p values were calculated with the unpaired t test

HRV heart rate variability, *CI* chronotropic incompetence, *HF* high frequency power of spectral analysis of heart rate

Table 3 Parameter values in the exercise test

	CI+ ($n=7$)	CI− ($n=85$)	p
Peak-load (W)	106 ± 26	120 ± 23	0.22
Resting-HR (bpm)	82 ± 8*	93 ± 16*	0.0060*
Peak-HR (bpm)	154 ± 8*	182 ± 11*	<0.001*
Peak-HR/APMHR (%)	80 ± 4*	94 ± 6*	<0.001*
ΔHR (bpm)	72 ± 14*	89 ± 13*	0.020*
% HR reserve	64 ± 10*	90 ± 11*	<0.001*
Peak-RQ	1.32 ± 0.27	1.35 ± 0.15	0.61
Peak-VO_2 (ml/kg/min)	26.1 ± 5.4	26.8 ± 5.7	0.75
Peak-VO_2 (% normal)	75 ± 16	77 ± 16	0.73
$\Delta VO_2/\Delta HR$	0.31 ± 0.13*	0.26 ± 0.06*	0.0043*
$\Delta VO_2/\Delta HR$ (% normal)	108.1 ± 43.3*	82.9 ± 18.0*	0.0073*

Values are mean ± SE. p values were calculated with the unpaired t test

CI chronotropic incompetence, *HR* heart rate, *APMHR* age predicted maximal heart rate (206 − 0.88 × age) [17], *ΔHR* peak-HR − resting-HR, % HR reserve, 100 × (peak-HR − rest-HR)/(APMHR − rest-HR), *RQ* respiratory quotient, VO_2 oxygen uptake, ΔVO_2 peak-VO_2 − resting-VO_2

*$p < 0.05$

Based on the results of expired gas analyses, all subjects exhibited low peak-VO_2 around 75% of normal on average, reflecting the impaired exercise tolerance. There was no difference in peak-VO_2 between the two groups. The $\Delta VO_2/\Delta HR$ value, which was calculated by dividing the change in VO_2 during exercise (ΔVO_2, peak-VO_2 − resting-VO_2) by ΔHR, and indicates the change of stroke volume, was significantly higher in the CI+ group than in the CI− group; it was within the normal range in the CI+ group and below in the CI− group.

Discussion

In this study, we evaluated the exercise capacity of 92 patients with AN in the body-weight recovery phase by cardiopulmonary exercise tolerance tests focusing on CI. To our knowledge, this is the first report that assessed about CI in patients with AN in the recovery phase although this is an institution-based study. CI was observed in 7.6% (7/92) of our subjects, lower than the rate in the acute phase (59%) that was reported previously [11], suggesting that the frequency of CI in patients with AN is reduced along with the body-weight recovery. In AN patients with CI, resting-HR was significantly lower than in those without CI. Lower resting-HR in the recovery phase is considered remnants of the parasympathetic-nerve-predominant state that is abnormality of autonomic function characteristic for acute-phase AN and thought to be a defense mechanism that suppresses energy consumption [11]. If the autonomic dysfunction is still observed after treatment, amelioration of AN may be insufficient. Because any patients with CI did not have resting bradycardia < 60 bpm in this study, CI might detect residual autonomic dysfunction in patients with AN in the recovery phase more sensitively.

CI may be a useful index of insufficient recovery of AN, especially reflecting both of body weight recovery and autonomic function. Patients with CI tended to demonstrate a lower body-weight recovery rate than those without CI in this study. As the autonomic abnormality in patients with AN may protract after body-weight recovery, it is necessary to assess their autonomic function independently [5]. For evaluation, nocturnal HR measurement and HR variability analysis are generally adopted [5]. In comparison with these methods, CI assessment with exercise tolerance testing can

be conducted in a short period and facilitates the detection of latent changes, which are not detected at rest. In addition, this method is applicable for establishment of the physical activity level. In particular, it is useful to evaluate whether participation in physical education or sports activities is possible for patients in the recovery phase.

Low exercise capacity in the recovery phase usually reflects the decrease in muscle volume, but heart failure may also affect exercise tolerance. Patients in the acute phase of AN often have reduction in left-ventricular mass, considered to be myocardial atrophy caused by malnutrition, deficiency of trace elements and vitamins or decrease in preload, resulting in congestive heart failure [4, 15, 16]. Thus, we should pay attention to the risk of latent heart failure. In this study, the $\Delta VO_2/\Delta HR$ value indicating the change of stroke volume was below the normal range in the CI− group, suggesting the insufficient cardiac function in the recovery phase of AN. On the other hand, the $\Delta VO_2/\Delta HR$ value in the CI+ group was higher than that in the CI− group and was in normal range. It may reflect the excessive ventricular contraction for maintaining the cardiac output during the recovery phase of AN patients with CI that might affect their cardiac reverse.

We generally focus on resting bradycardia (usually < 60 bpm) in patients with AN and used the amelioration of nocturnal bradycardia on Holter recording as an index for evaluating the treatment response. In the acute phase, treatment involving bed-rest is performed. When improvement in weight gain and resting bradycardia is confirmed, patients are regarded as being in the recovery phase. It is important for patients with AN in the recovery phase to gradually return to pre-onset physical activity. In this phase, exercise tolerance is evaluated using cardiopulmonary exercise tolerance tests, and then exercise therapy is started. We believe that daily management must be carefully conducted when CI in exercise test is observed during the recovery phase in patients with AN.

There are some limitations in this study that this was a retrospective design, only the recovery phase during treatment was evaluated, and the long-term course of CI was not assessed. CI has been reported to be an independent prognostic factor for cardiovascular events and/or unfavorable prognosis in healthy adults without symptoms [8, 9, 16, 17]. Likewise, CI may be associated with the prognosis of patients with AN.

In conclusion, patients with AN in the body-weight recovery phase do not have sufficient tolerance for maximal exercise. CI in the recovery phase suggests insufficient amelioration of AN, and more careful management of physical activity may be required for AN patients with CI.

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Compliance with ethical standards

Conflict of interest We have no potential conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The clinical evaluations of the patients were approved by the Internal Ethics Committee of Keio University School of Medicine. For this type of study, formal informed consent is not required.

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