Metabolic Equivalents of Safe Physical Activity Levels at Anaerobic Threshold in Anorexia Nervosa Patients

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Abstract

Purpose Patients with anorexia nervosa (AN) require appropriate nutrient therapy and physical activity management. Eating disorder treatment guidelines do not include safe, evidence-based intensity criteria for exercise. This study used cardiopulmonary exercise testing (CPX) to evaluate the exercise tolerance of patients with AN and develop treatment guidelines to optimize their physical activity.

Methods CPX was done with 14 female AN patients admitted to a specialized eating disorder unit between 2015 and 2019. Their anaerobic threshold (AT) was determined by assessing their exercise tolerance using CPX and compared with 14 healthy controls (HC). The metabolic equivalents (AT-METS) were compared when AT was reached. We examined factors related to AT (AN-AT) in the AN group, including age, body mass index (BMI), previous lowest weight, minimum BMI, past duration of BMI < 15, exercise history, and Δ HR (heart rate at the AT - resting heart rate).

Results The AT of the AN group (BMI: 15.7 [Mean] $\pm$ 1.8 [SD]) was significantly lower than the HC group (BMI: 19.7 $\pm$ 1.8) (AN: 10.0 $\pm$ 1.8 vs HC: 15.2 $\pm$ 3.0 ml/kg/min, $P < 0.001$). AT-METS was also significantly lower in the AN than the HC group (AN: 2.9 $\pm$ 0.52 vs HC: 4.4 $\pm$ 0.91, $P < 0.001$). AN-AT was highly influenced by Δ HR.

Conclusion The AT-METS level for these AN patients was 2.5-3.3 METS, and this index can be used by clinicians to teach AN patients a safe exercise intensity. CPX and AT-METS are useful tools for clinicians to manage physical activity in AN patients.

Level of evidence III: Evidence obtained from case-control analytic studies

What Is Already Known On This Subject?

Exercise tolerance is decreased in patients with AN, and CI is known to be a factor in the decreased exercise tolerance of patients with AN.

What This Study Adds?

This study shows the intensity of physical activity that is safe for AN patients with impaired exercise tolerance. Specifically, 2.5-3.3 METS is safe for AN patients. Clinicians can use AT-METS to provide practical guidance on physical activity levels to their patients with AN.

Introduction

Anorexia nervosa (AN) is a severe mental disorder characterized by malnutrition. It has a high prevalence of comorbid psychiatric disorders, marked resistance to treatment, and high risk of death from physical complications [1, 2]. AN affects almost all body systems, including the brain, heart, liver, gastrointestinal tract, bones, and muscles [3, 4]. For these reasons, early nutritional recovery is necessary in the treatment

of patients with AN [5]. Overactivity is one of the symptoms of AN. Many patients with AN are at increased risk for a variety of serious medical complications, such as fractures, electrolyte imbalances or sudden death, that can be caused or exacerbated by overactivity [6].

Both appropriate nutrition therapy and physical activity management are necessary. However, evidence-based reports of treatment for AN, especially for medical interventions such as re-nutrition, are limited [7]. In addition, the treatment guidelines for eating disorders do not include criteria for exercise intensity based on the specific exercise physiology traits of AN patients with regard to safe levels of physical activity [8–12]. Systematic reviews and proposed recommendations in the guidelines for exercise in the treatment of AN are also not evidence-based on exercise physiology [13].

Cardiopulmonary exercise testing (CPX) is often used to assess the exercise tolerance of patients with cardiovascular disease to determine exercise intensity for cardiac rehabilitation and to manage physical activity in daily life [14]. We applied CPX to AN patients to evaluate their exercise tolerance. Among the parameters obtained from CPX, the anaerobic threshold (AT) was used as an index of exercise tolerance. The AT is the upper limit of aerobic exercise intensity, and intensity below that allows exercise to be performed without the accumulation of lactic acid and without acidosis [15]. Thus, AT is a useful indicator of exercise tolerance, and exercise intensity below AT, i.e., the state of aerobic metabolism of the organism, is considered to be safe. CPX can provide data on AT and metabolic equivalents (AT-METS) when AT is reached during an exercise load. MET is a unit that expresses the intensity of physical activity relative to that expended by the body at rest. METS are used clinically to prescribe physical activities that a patient can safely perform [16].

Chronotropic incompetence (CI) is defined as a decreased heart rate response to exercise. CI is a parameter that can be obtained by CPX, but it is not possible to perform CPX on all AN patients. This study was done to ascertain whether clinical data other than CI could be used to predict factors contributing to the exercise tolerance of patients with AN.

Methods

The participants were 14 patients with AN and 14 healthy controls. All were female. The patients were admitted to a specialized eating disorder unit at Kyushu University Hospital between March 2015 and January 2019. Six had anorexia nervosa restricting type and eight had the binge eating/purging type. AN was diagnosed by a specialized eating disorder therapist according to DSM-5 criteria [17]. Healthy adult women with no underlying medical conditions were recruited as controls. All participants were confirmed by their physicians to have no contraindications to CPX [18]: none had acute myocardial infarction, unstable angina, uncontrolled arrhythmias, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary infarction, acute myocarditis, acute pericarditis, acute aortic dissection, or uncommunicative mental illness. All participants were informed by the examiner about the purpose of CPX and the possibility of complications.

This study was approved by the Ethics Committee of Kyushu University (Ethical Approval Number; 26-191, October 21, 2014.). All participants provided written informed consent prior to entering the study.

Age, duration of illness (years), body mass index: BMI (kg/m^2), previous minimum BMI (kg/m^2), past duration (years) of BMI < 15 (kg/m^2), and exercise history were extracted from medical records.

Cardiopulmonary exercise testing (CPX)

Nutritional therapy was administered to the AN patients after hospitalization, and all had regained weight and experienced improvement in their physical condition. CPX was done prior to discharge. At the time of CPX, none of the participants were suffering from severe hypotension or bradycardia, severe anemia, respiratory disturbances, electrolyte abnormalities, severe liver damage, hypoglycemia, or gait disturbance. In addition, a physician checked the physical condition of all the participants when performing CPX. Emergency equipment was always available and ready for use when CPX was performed.

The laboratory was set up in an environment with good lighting and ventilation, temperature of 20-25 degrees, and humidity of 40-60%. CPX was performed using a continuous expiratory gas analyzer (AE310-S Aero monitor; Minato Medical Science Co., Ltd, Osaka, Japan). The continuous breath gas analyzer consisted of a respiratory flow meter, an oxygen analyzer, and a carbon dioxide analyzer, with breath gas measured by the breath-by-breath method. Before each CPX, the flowmeter and gas analyzer were calibrated. The participant wore a face mask for exhaled gas analysis. A cycle ergometer (AERO BIKE 75XL; Konami Sports Life Co., Ltd, Kanagawa, Japan) was used as a load device during CPX implementation. During the CPX, all participants were instructed to keep the cycle ergometer revolution constant at 60 revolutions per minute. The CPX was performed using a ramp load protocol [19]. The ramp load intensity was set to 5 Watt / min^{-1} for the AN patients, and 20 Watt / min^{-1} for the healthy controls.

The procedure for the exercise loading was as follows: first, rest for 4 minutes, then warm up for 4 minutes, and then exercise loading was done. After discontinuing the exercise loading, a cool-down was performed for 4 to 6 minutes. Before and after CPX, all participants were measured for heart rate, blood pressure, and arterial oxygen saturation, and a 12-lead ECG was performed. During CPX, participants were monitored for heart rate, blood pressure, and arterial oxygen saturation every minute. In addition, the examiner confirmed subjective symptoms such as shortness of breath, chest pain, malaise, and lower limb fatigue. The discontinuation criteria for CPX were based on subjective and objective symptoms [18]. All participants could stop exercising at any time. None of the participants experienced complications during or after CPX.

CPX parameters

In the breath gas analysis of CPX, oxygen uptake ($\dot{V}\text{O}_2$) (ml / min), carbon dioxide output ($\dot{V}\text{CO}_2$) (ml / min), respiratory rate (RR) (f / min), and minute ventilation (VE) (ml / min) were measured. AT was

determined using the trend method and confirmed by the V-Slope method. METS (AT-METS) was calculated at the time AT was achieved.

Statistical Analysis

A Shapiro–Wilk test was performed to assess normality. Continuous variables are represented by mean $\pm$ standard deviation (SD) or median (range: minimum-maximum) according to the distribution of the variables. The mean differences in AT (ml / kg / min), AT-METS, and Δ HR (bpm) between the AN and the healthy control (HC) groups were compared by an unpaired t-test. We defined Δ HR (bpm) as (heart rate at the AT - resting heart rate) (bpm). The resting heart rate is the heart rate at the start of CPX.

Multiple regression analysis by the stepwise method was done with the AT of the AN group (AN-AT) as the dependent variable and age, body mass index: BMI (kg / m²), record low BMI (kg / m²), the period (years) when the past BMI <15 (kg / m²), the presence or absence of exercise history, and Δ HR as the independent variables. AN patients with a BMI <15 (kg / m²) were classified as the most severe [17]. For age, BMI, previous minimum BMI, past BMI <15 period, and Δ HR, the normality of the variables was confirmed in advance by the Shapiro-Wilk test, and the shape of the distribution was confirmed by a histogram. Since none of these variables deviated significantly from the normal distribution or had a biased frequency they were not converted into dummy variables or changed. The presence or absence of exercise history was converted into a dummy variable, with exercise history = “1” and the absence of exercise history = “0”. In addition, we developed a correlation matrix table, but because there were no variables with $|r| > 0.9$, we targeted all variables.

In all analyses, a difference was considered significant at $P < 0.05$. SPSS ver. 23 software was used for all statistical analyses.

Results

The clinical background of the participants is shown in Table 1. No difference in age was found between the two groups. The weight (kg), BMI (kg/m²), and body surface area (BSA[m²]) were significantly lower in the AN group than in the HC group ($P < 0.001$). Three participants in the AN group had a history of exercise. All participants were able to perform CPX with no adverse events. The data are expressed as means $\pm$ standard deviation.

Table 1
Clinical characteristics of the study population

	Patients with AN (n=14)	Healthy Controls (n=14)	P value
Age(years)	25.7 ± 8.5	26.5 (24-47)	.077 ^b
Height(cm)	156.8 (152.5 – 172.5)	160.4 ± 4.8	.227 ^b
Body Weight(kg)	39.4 ± 5.2	50.6 ± 4.1	<.001 ^a
BMI(kg/m ²)	15.7 ± 1.8	19.7 ± 1.8	<.001 ^a
Body surface area(m ²)	1.3 ± 0.10	1.5 ± 0.07	<.001 ^a
Data are expressed as mean ± SD or median (range: min. – max.) depending on data distribution.			
P values were calculated with an unpaired T test (a) and Mann–Whitney U test (b).			
Abbreviations: AN, anorexia nervosa; BMI, body mass index.			

Results of CPX: The AT of the AN group was significantly lower than that of the HC group (AN: 10.0 ± 1.8 vs HC: 15.2 ± 3.0 ml/kg/min, P<.001) (Fig. 1). The AT-METS of the AN group was also significantly lower than that of the HC group (AN: 2.9 ± 0.52 vs HC: 4.4 ± 0.91, P<.001) (Fig. 2). The results of the AT-METS calculation are shown in Table 2.

Table 2
Recommended METS (AT-METS) at the AT in the AN and HC groups

METS	Physical Activity	Frequency (N)	
		AN	HC
1.5	Conversation in sitting position, telephone, reading, eating, light office work, knitting / handicraft, type, caring for animals (sitting, mild).	1	0
1.8	Standing conversation, telephone, reading, handicraft.	0	0
2.0	Preparation of food and ingredients (standing, sitting), washing laundry, packing (standing), changing clothes, eating while talking.	0	0
2.3	Dishwashing (standing), ironing, cleaning clothes/laundry, copying (standing), standing work (clerk, factory, etc.).	2	0
2.5	Cleaning: light (collecting garbage, tidying up, changing linen, throwing away garbage), preparing and cleaning up food and ingredients (walking).	1	1
2.8	Playing with children (standing, mild), caring for animals (mild)	3	1
3.0	Normal walking (flat ground, 67m/min, shopping with young children/dogs, etc.), indoor cleaning, cleaning up household items.	5	0
3.3	Walking (flat ground, 81 m/min, commuting, etc.), sweeping carpets, weeping floors.	1	0
3.5	Mop, vacuum cleaner, boxing work, light luggage carrying.	1	0
3.8	Slow jogging (flat ground, slightly faster = 94 m/min), floor polishing, bath cleaning.	0	0
4.0	Jogging (flat ground, about 95-100 m/min), riding a bicycle: less than 16km/hour, leisure, commuting, entertainment, playing with children.	0	4
4.5	Sapling planting, garden weeding, cultivation.	0	6
5.0	Playing with children / caring for animals (walking / running, actively), walking fairly fast (flat ground, fast = 107m / min)	0	0
5.5	Lawn mowing (while walking using an electric lawn mower)	0	1
6.0	Moving / transporting furniture and household items.	0	1
Abbreviations: METS, metabolic equivalents; N, number; AN, anorexia nervosa; HC, healthy control.			

No significant difference was found between the resting heart rate of the AN group and that of the HC group (AN: 72.6 ± 11.1 vs HC: 75.1 ± 8.7 bpm. $P=.524$). In contrast, the Δ HR of the AN group was significantly lower than that of the healthy controls (AN: 20.6 ± 8.0 vs HC: 50.1 ± 18.8 bpm. $P<.001$).

The results of multiple regression analysis are shown in Table 3. Age, BMI, previous minimum BMI, past duration of BMI<15, and exercise history were excluded from the independent variables. The result of analysis of variance (ANOVA) was significant, and the coefficient of determination (R^2) was 0.605, indicating a highly adequate fit. The standard partial regression coefficient (β) of Δ HR was .778, indicating that Δ HR makes a significant contribution to AN-AT. The Durbin–Watson ratio of 2.503 was acceptable, and there were no outliers where the predicted value exceeded 3 SD of the measured value.

Table 3
Variables predictive of AT in patients with AN

	B	β	P	95% CI	
				Lower limit	Upper limit
Const.	6.032		.000	3.918	8.146
Δ HR	.179	.778	.001	0.088	.270
$R^2=.605$, ANOVA: $P=.001$.					
B: partial regression coefficient, β : standardized partial regression coefficient,					
P: significance probability, CI: confidence interval, Const.: constant, HR: heart rate					

Discussion

In this study, the exercise tolerance of patients with AN was lower than that of healthy controls, in line with the findings of a previous study by Biadi et al [20]. The exercise tolerance of our patients with AN was moderate-severe according to the Weber–Janicki classification [21], which cannot be explained by clinical factors such as BMI, duration of disease, or previous lowest weight. Age, previous minimum BMI, past duration of BMI < 15, and history of exercise were not explanatory factors contributing to the lower AT of our patients with AN.

The AT-METS of our patients with AN was 2.9 ± 0.52 , suggesting that METS of approximately 2.5-3.3 is a safe intensity of physical activity for such patients. The physical activity recommendations are shown in Table 2 [22, 23]. In clinical practice, clinicians must prohibit exercise intensities that may cause further weight loss or physical complications in patients with AN. However, no index exists for teaching safe exercise intensity to AN patients at their actual physical activity level. By using AT-METS, clinicians can indicate to AN patients the exercise intensity that does not exceed the anaerobic metabolic threshold, ensuring safety. In addition, families and school educators of AN patients often ask clinicians what level of exercise intensity is acceptable for their patients.

It is particularly interesting that the decreased AT of our patients was not explained by the various clinical measures we estimated. It would be useful for clinicians to be able to estimate the exercise tolerance of

their AN patients from more readily available clinical data without performing CPX. Further investigation of factors such as body composition and autonomic function test results is warranted.

The components of AT are a complex system. AT is a comprehensive metabolic index of ventilation (external respiration), circulation, and metabolism (internal respiration), defined by gas exchange, oxygen transport to skeletal muscle, and oxygen availability in skeletal muscle [24]. Exercise performance requires an appropriate heart rate response during exercise, based on normal autonomic nervous system function [25]. However, AN patients often have a blunted sympathetic response to maximal exercise, i.e., a variable response insufficiency (CI) [26]. In the present study, the increase in heart rate from the start of exercise to AT was suppressed in our AN patients. In addition, the Δ HR of our patient group was shown to have a significant effect on AT. CI is associated with exercise intolerance [27]. The autonomic abnormalities of AN patients may persist even after weight regain, and more careful management of physical activity is needed for AN patients with CI [28].

Reduced systolic ventricular function is not a major factor in the reduced exercise capacity of patients with AN [29]. It has been reported that older patients have decreased oxygen availability in skeletal muscle [30] and decreased lean mass [31], both determinants of decreased exercise tolerance. However, the association between AT and muscle mass and the skeletal muscle strength of patients with AN is unclear. Another factor that may define AT is exercise habits [32], but this study did not show an association between exercise and AT in our AN patients. It is particularly interesting that the decreased AT of AN was not explained by the various clinical measures we estimated.

It is not advisable to manage the range of activity of patients with AN only with bed rest. In a study by Ibrahim et al, bed rest was not supported for the inpatient treatment of patients with AN [33]. Other studies have shown that physical activity has a positive impact in the treatment of AN. Exercise and physical therapy can help AN patients recover from their physical and mental problems [34]. Maintaining safe physical activity during the refeeding period for AN patients is beneficial for restoring body composition, maintaining bone mineral density, and mental status [35]. Furthermore, previous studies have shown that exercise under nutritional support improves quality of life and psychological well-being [36]. However, there is no consensus or recommendation on how physical activity should be managed in patients with AN, and implementation varies among specialized centers [35]. The findings of the present study, which assessed the exercise physiology of patients with AN, provides an important basis for guiding the physical activity of patients with AN.

A previous study showed that the BMI percentile was independently associated with the exercise endurance of adolescents with AN [29]. A BMI < 14 (kg / m^2) was noted as an indicator of high medical risk in patients with AN [37], and in some institutions patients with a BMI < 15 (kg / m^2) are restricted from physical activity. In other centers, patients with a BMI of $18.5 < (\text{kg} / \text{m}^2)$ are prohibited from physical activity [38]. A BMI of 12 (kg / m^2) or less has been reported to be a marker for the development of consciousness and gait disturbances [39]. However, the BMI level of our patients with AN was not related

to their AT level, indicating that the physical activity of patients with AN should not be defined and managed by BMI alone.

In conclusion, the exercise tolerance of patients with AN was lower than that of healthy controls. AN-AT was highly influenced by ΔHR , but not influenced by age, BMI, previous minimum BMI, past duration of BMI < 15, or exercise history. The AT-METS values of our AN patients with a BMI of 15.7 ± 1.8 ranged from 2.5-3.3 METS, and this index can be used by clinicians to teach AN patients a safe exercise intensity. CPX and AT-METS are useful tools for clinicians to manage physical activity in AN patients. Future research is needed to identify determinants of exercise tolerance other than CI in patients with AN.

Strength And Limits

To our knowledge, this study is the first to demonstrate the safe physical activity intensity level of patients with AN based on CPX assessment of exercise tolerance. With these results as a guide, therapists will be able to instruct their AN patients on safe physical activity in daily life using AT-METS as an index.

The study has several limitations. First, the sample size was small. With a larger sample size, the AT and AT-METS of AN patients might have been better defined. Second, the study was limited to Japanese female patients with AN and did not include older patients or controls. Third, during CPX, the exercise load applied was limited to an AT level safe for AN patients. Therefore, peak $\dot{V}\text{O}_2$ was not obtained, and the full exercise capacity of these AN patients was not assessed. Fourth, we did not measure cardiac function, autonomic nervous system activity, respiratory function, or skeletal muscle function during exercise, so all the factors that might contribute to poor exercise tolerance by AN patients cannot be identified.

Declarations

Funding

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Conflicts of interest

The authors have no conflicts of interest nor competing interests to declare. The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request

Code availability

Not applicable.

Author contributions

KAWAI Keisuke and SUDO Nobuyuki contributed to the study conception and design. Material preparation and data collection were performed by YAMASHITA Makoto, TODA Kenta, ASO Suzuyama Chie, SUEMATSU Takafumi, YOKOYAMA Hiroaki, HATA Tomokazu, and TAKAKURA Shu. Analysis was performed by YAMASHITA Makoto and KAWAI Keisuke. The first draft of the manuscript was written by YAMASHITA Makoto. All authors have read and approved the final manuscript.

Ethics approval

This study was approved by the Ethics Committee of Kyushu University (Ethical Approval Number; 26-191) and the National Center for Global Health and Medicine (Ethical Approval Number NGM-G-003071-00).

Consent to participate

All participants provided written informed consent prior to participation in the study.

Consent for publication

All authors have given their consent for submission of the manuscript.

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Figures

Figure 1

AT of the AN and HC groups Dots and error bars express means and 95% confidence intervals.
Abbreviations: AT, anaerobic threshold; AN, anorexia nervosa; HC, healthy control.

Figure 2

AT-METS of the AN and HC groups Dots and error bars express means and 95% confidence intervals. Abbreviations: AT, anaerobic threshold; METS, metabolic equivalents; AN, anorexia nervosa; HC, healthy control.