Cardiopulmonary exercise testing for patients with anorexia nervosa: a case-control study

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Title

Cardiopulmonary exercise testing for patients with anorexia nervosa: A case control study

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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.

Methods CPX was performed with 14 female patients with AN 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 ΔHR (heart rate at the AT - resting heart rate).

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

Conclusion This study showed that AT and AT-METS were lower in patients with AN than in HC. Patients with AN should be prescribed light-intensity aerobic exercise, and the current findings may help develop future physical management guidelines for patients with AN.

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

Keywords

Anorexia nervosa, Cardiopulmonary exercise testing, Anaerobic threshold, Metabolic equivalents, Physical activity

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]. Hyperactivity is one of the symptoms of AN. Starvation and hyperactivity lead to weight loss, and they are associated with physiological changes that promote compulsive behavior [6]. Many patients 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 hyperactivity [7].

Both appropriate nutrition therapy and physical activity management are necessary. Hyperactivity during refeeding in patients with AN is associated with increased energy demands to achieve weight gain, poorer clinical outcomes, longer hospital stays, and increased psychiatric complications [8]. In this regard, physical activity management refers to the teaching of exercise limitations and appropriate physical activity levels necessary to prevent further weight loss in patients with AN. The importance of nutritional therapy for patients with AN is well established [5]. On the other hand, the treatment guidelines for eating disorders do not include criteria for exercise intensity based on the specific exercise physiology traits of patients with AN with regard to safe levels of physical activity [9-13]. Systematic reviews and proposed recommendations in the guidelines for exercise in the treatment of AN are also not evidence-based with regard to exercise physiology [14].

Cardiopulmonary exercise testing (CPX) can provide information on biological responses based on exercise intensity. We applied CPX to patients with AN 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 values below the AT indicate that exercise can 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, is considered to be safe. Exercise intensity below AT is associated with less increase in sympathetic activity, a smaller degree of blood pressure elevation, and fewer arrhythmias.

The components of AT comprise a complex system. AT is a comprehensive metabolic index of ventilation (external respiration), circulation, and metabolism (internal respiration), and is defined by gas exchange, oxygen transport to skeletal muscle, and oxygen availability in skeletal muscle [16]. Exercise performance requires an appropriate heart rate (HR) response during exercise, based on normal autonomic nervous system function [17].

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 [18]. AT-METS is the MET when AT is reached, and any activity above this value indicates anaerobic metabolism.

The purpose of this study was to evaluate the exercise tolerance of patients with AN compared to HC using CPX.

Methods

The participants were 14 patients with AN and 14 healthy controls (HC). All participants were female. The patients were admitted to a specialized eating disorder unit at Kyushu University Hospital between March 2015 and January 2019. Patients admitted to the eating disorders unit were those with AN who had low body weight and were scheduled to undergo treatment by a specialist (eating disorder therapist) for the purpose of regaining weight and receiving psychotherapy, especially cognitive-behavioral therapy. Patients with bulimia nervosa admitted for eating behavior stabilization were excluded from this study. In the final study cohort, we included patients with AN who provided informed consent for participation in the study. All participants were admitted for medical instability due to eating disorders. 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 Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria [19]. Healthy adult females with no underlying medical conditions were recruited as HC. All participants were confirmed by their physicians to have no contraindications to CPX [20]: 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 before participating in 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. We defined exercise history as habit of exercising via extracurricular activities, athletic clubs, etc., for at least two years in the past.

Cardiopulmonary exercise testing

Nutritional therapy was administered to the patients with AN after hospitalization, and all of them regained weight and experienced improvement in their physical condition. The patients with AN in this study were hospitalized for an average of 103.5 days and gained an average of 5.3 kg. CPX was performed prior to discharge. During 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. Moreover, a physician checked the physical condition of all participants when performing CPX. Emergency equipment was always available and ready for use when CPX was performed. CPX was performed by the first author, who received training from a

CPX specialist.

The laboratory was set up in an environment with good lighting and ventilation, temperature of 20–25 °C, 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). This device comprises a respiratory flow meter, oxygen analyzer, and 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 75XLIII; Konami Sports Life Co., Ltd, Kanagawa, Japan) was used as a load device during CPX implementation. During 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 [21]. The ramp load intensity was set to 5 $Watt/min^{-1}$ for the patients with AN, and 20 $Watt/min^{-1}$ for the HC.

The procedure for the exercise loading was as follows: first, rest for 4 minutes, then warm up for 4 minutes, following which exercise loading was performed. After discontinuing the exercise loading, a cool-down was performed for 4–6 minutes. Once AT was reached, the exercise load was stopped and CPX was terminated. Before and after CPX, all participants underwent measurements with regard to HR, blood pressure, and arterial oxygen saturation, and a 12-lead electrocardiogram (ECG) was performed. During CPX, the HR, blood pressure, and arterial oxygen saturation were monitored every minute. Further, 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 [20]. 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 ($\dot{V}O_2$) (ml/min), carbon dioxide output ($\dot{V}CO_2$) (ml/min), respiratory rate (RR) (f/min), and minute ventilation ($\dot{V}E$) (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. Since 1 METS corresponds to an oxygen uptake of approximately 3.5 ml/min/kg, AT-METS was calculated by dividing the oxygen uptake at AT by 3.5.

Statistical analysis

A Shapiro–Wilk test was performed to assess normality. Continuous variables are represented by mean ± standard deviation (SD) or median (range: minimum–maximum) according to the distribution of the variables.

First, multiple regression analysis by the stepwise method was performed with the AT of both groups as the dependent variable and age, BMI (kg/m^2), group (AN or HC), and ΔHR as the independent variables. For age, BMI, and ΔHR, the normality of the variables was confirmed in advance by the Shapiro-Wilk test, and the shape of the distribution was confirmed by histogram analysis. 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". Furthermore, we developed a correlation matrix table, but since there were no variables with | r |> 0.9, we targeted all variables.

The mean differences in AT (ml/kg/min), AT-METS, and ΔHR (bpm) between the AN and HC groups were compared by an unpaired t-test. For the unpaired t-test, power was calculated for each variable. We defined ΔHR (bpm) as (HR at the AT - resting HR) (bpm). The resting HR is the HR at the start of CPX.

Multiple regression analysis by the stepwise method was performed with the AT of the AN group (AN-AT) as the dependent variable and age, BMI (kg/m^2), record low BMI (kg/m^2), the period (years) with past BMI <15 (kg/m^2), the presence or absence of exercise history, and ΔHR as the independent variables. The total duration during which BMI was <15 in the past (period with past BMI <15) among the participants was 1.5 ± 1.3 years. Patients with AN with BMI <15 (kg/m^2) were classified as the most severe cases [19].

In all analyses, a difference was considered significant at P<0.05. SPSS (IBM) ver. 28 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/m^2), and body surface area (BSA[m^2]) 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 ± standard deviation.

The parameters obtained in CPX are presented in Table 2. 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 powers in the unpaired t-test were 1.00 (AT), 0.99 (AT-METS), and 0.99 (HR at the AT), respectively.

No significant difference was found between the resting HR of the AN group and that of the HC group (AN: 72.6 ± 11.1 vs. HC: 75.1 ± 8.7 bpm, P=.524). Contrastingly, the HR at the AT of the AN group was significantly lower than that of the HC group (AN: 94.6 ± 12.6 vs. HC: 125.1 ± 17.0 ml/kg/min, P<.001) (**Table 2**), and the ΔHR of the AN group was significantly lower than that of the HC (AN: 20.6 ± 8.0 vs. HC: 50.1 ± 18.8 bpm, P<.001).

The results of the multiple regression analysis of both groups are shown in Table 3. Age and BMI were excluded from the independent variables. The results of the analysis of variance (ANOVA) were significant, and the coefficient of determination (R^2) was 0.650, indicating a highly adequate fit. The standard partial regression coefficient (β) of ΔHR and group were .449 and .420, respectively, indicating that ΔHR and the difference of groups make a moderate contribution to AN-AT. The Durbin–

Watson ratio of 1.814 was acceptable, and there were no outliers where the predicted value exceeded 3 SD of the measured value.

The results of multiple regression analysis of only the AN group are shown as follows. Age, BMI, previous minimum BMI, past duration of BMI <15, and exercise history were excluded from the independent variables. The result of 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 ΔHR was .778, indicating that ΔHR 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.

Discussion

In this study, the exercise tolerance of patients with AN was lower than that of HC, in line with the findings of a previous study by Biadi et al [22]. The exercise tolerance of patients with AN in this study was moderate-to-severe according to the Weber–Janicki classification [23], 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. 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 patients with AN using more readily available clinical data without performing CPX. Further investigation of factors such as body composition and autonomic function test results is warranted.

For patients with AN, a low BMI has been shown to be associated with a higher risk of underweight-related death [24]. A BMI <13 kg/m^2 has also been proposed as a cutoff value for poor prognosis [24]. Low BMI (BMI <13–14 kg/m^2) is associated with a faster rate of decrease in BMI and an increase in the number of patients who require emergency hospitalization due to difficulty in walking or impaired consciousness [25]. A BMI of 13–14 kg/m^2 represents the boundary at which body composition changes significantly [25], and as the BMI falls below this value, the source of energy changes from fat to protein [25, 26]. During starvation, a BMI of 13 kg/m^2 may be the tipping point at which the homeostatic mechanism breaks down [26]. Thus, anaerobic metabolism is presumed to be very dangerous for patients with AN. Therefore, in this study, CPX was terminated when AT was reached. When comparing exercise intensity above and below AT, that below AT has the following characteristics: no sustained increase in lactate concentration, the ability to perform the exercise for a longer period of time without fatigue, less increase in sympathetic nerve activity, a smaller increase in blood pressure, and reduced incidence of arrhythmia. Among other factors, a metabolic state with reduced incidence of arrhythmia is physically safer for patients with AN, who often have coexisting electrolyte abnormalities. Elevated lactate concentration constitutes a risk among patients with AN, since it implies that the glycolytic system is facilitated. In other words, greater utilization of carbohydrates is an additional risk for patients with AN who present with low body weight and low nutrition.

The AT-METS of our patients with AN was 2.9 ± 0.52. Physical activity of 2.8 METS is the equivalent of playing with children or caring for animals. Further, 3.0 METS represents activities like normal walking or indoor cleaning [27,28]. The AT-METS of HC in this study was 4.4 ± 0.91. Physical activity of 4.0 METS is equivalent to activities like jogging or riding a bicycle. Finally, 4.5 METS represents activities like sapling planting and garden weeding [27,28].

Patients with AN often have a blunted sympathetic response to maximal exercise, i.e., a variable response insufficiency [29]. Chronotropic incompetence (CI) is defined as an inability to raise the HR appropriately and to match cardiac output to metabolic demands during activity. In the present study, the increase in HR from the start of exercise to AT was suppressed in our patients with AN. This study suggests that the AN group was exercising below 50% of their age-adjusted maximum HR at the time that their AT was reached. Further, the ΔHR of our patient group was shown to have a significant effect on AT. CI is associated with exercise intolerance [30]. The autonomic abnormalities of patients with AN may persist even after weight regain, and more careful management of physical activity is needed for patients with AN with CI [31].

In this study, the respiratory rate at AT attainment was not significantly different between the two groups, but the minute ventilation rate was significantly lower in the AN group than in the HC group. This may be attributed to the AN group's body size, i.e., emaciation. It is suggested that the oxygen content of the blood may not increase sufficiently in patients with AN, with decreased minute ventilation comprising one factor. Reduced systolic ventricular function is not a major factor contributing to the reduced exercise capacity of patients with AN [32]. It has been reported that older patients have decreased oxygen availability in skeletal muscle [33] and decreased lean mass [34], both of which are determinants of decreased exercise tolerance. However, the association between AT, muscle mass, and skeletal muscle strength of patients with AN remains unclear. Another factor that may define AT is exercise habits [35], but this study did not show an association between exercise and AT in our patients with AN. It is particularly interesting that the decreased AT in 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 [36]. Other studies have shown that physical activity has a positive impact on AN treatment. Exercise and physical therapy can help patients with AN recover from their physical and mental problems [37]. Maintaining safe physical activity during the refeeding period for patients with AN is beneficial for restoring body composition, maintaining bone mineral density, and mental status [8]. Furthermore, previous studies have shown that exercise with nutritional support improves the quality of life and psychological well-being [38]. However, there is no consensus or recommendation regarding how physical activity should be managed in patients with AN, and implementation varies among specialized centers [8]. One systematic review of exercise in patients with eating disorders included 18 studies [14], only one of which was a meta-analysis focusing on AN treatment. The present study focuses on patients with AN who were underweight but not because of eating disorders alone. The findings of our study, which assessed the exercise physiology of patients with AN, provide 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 [32]. A BMI <14 (kg/m^2) was noted as an indicator of high medical risk in patients with AN [39], 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 (kg/m^2) are prohibited from physical activity [40]. A BMI of ≤13–14 (kg/m^2) has been reported to be a marker for consciousness impairment and gait disturbances [26]. However, the BMI 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 HC. AN-AT was highly influenced by ΔHR, but not influenced by age, BMI, previous minimum BMI, past duration of BMI <15, or exercise history. Patients with AN should be prescribed light-intensity aerobic exercise, and the current findings may help develop future physical management guidelines for patients with AN.

Strength and limitations

To our knowledge, this study is the first to demonstrate the AT-METS level of patients with AN based on CPX.

The study has several limitations. First, the sample size was small. AT and AT-METS each showed significant differences between the two groups, but both powers were too high. With a larger sample size, the AT and AT-METS of patients with AN might have been better defined. Second, the study was limited to Japanese female patients with AN and did not include older patients or HC. Third, our definition of exercise history is not supported by sufficient scientific evidence. Fourth, during CPX, the exercise load applied was limited to an AT level deemed to be safe for patients with AN. Therefore, peak $\dot{V}O_2$ was not obtained, and the full exercise capacity of these patients was not assessed. Fifth, we did not measure cardiac function, autonomic nervous system activity, respiratory function, or skeletal muscle function during exercise; thus, factors that might contribute to poor exercise tolerance by patients with AN could not be identified. Finally, CPX is not readily available in all clinical settings. In the future, we will attempt to include more cases with more data on body composition and detailed exercise history to help clinicians assess exercise tolerance without the use of CPX.

What is already known on this subject?

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

What this study adds?

The results of this study show that AT-METS in patients with AN is lower than that in HC.

Declarations

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Conflicts of interest

The authors have no conflicts of interest or competing interests to declare. The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The datasets generated and analyzed 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.

References

1. Mitchell JE, Peterson CB (2020) Anorexia nervosa. N Engl J Med 382:1343-1351. https://doi.org/10.1056/NEJMcp1803175

2. Fayssoil A, Melchior JC, Hanachi M (2021) Heart and anorexia nervosa. Heart Fail Rev 26:65-70. https://doi.org/10.1007/s10741-019-09911-0

3. Westmoreland P, Krantz MJ, Mehler PS (2016) Medical complications of anorexia nervosa and bulimia. Am J Med 129:30-37. https://doi.org/10.1016/j.amjmed.2015.06.031

4. Voderholzer U, Haas V, Correll CU, Korner T (2020) Medical management of eating disorders: an update. Curr Opin Psychiatry 33:542-553. https://doi.org/10.1097/YCO.0000000000000653

5. Bargiacchi A, Clarke J, Paulsen A, Leger J (2019) Refeeding in anorexia nervosa. Eur J Pediatr 178:413-422. https://doi.org/10.1007/s00431-018-3295-7

6. Godier LR, Park RJ (2014) Compulsivity in anorexia nervosa: a transdiagnostic concept. Front Psychol. Jul 17;5:778. https://doi.org/10.3389/fpsyg.2014.00778. eCollection 2014

7. Zunker C, Mitchell JE, Wonderlich SA (2011) Exercise interventions for women with anorexia nervosa: a review of the literature. Int J Eat Disord 44:579-584. https://doi.org/10.1002/eat.20862

8. Achamrah N, Coeffier M, Dechelotte P (2016) Physical activity in patients with anorexia nervosa. Nutr Rev 74:301-311. https://doi.org/10.1093/nutrit/nuw001

9. Couturier J, Isserlin L, Norris M, Spettigue W, Brouwers M, Kimber M, McVey G, Webb C, Findlay S, Bhatnagar N, Snelgrove N, Ritsma A, Preskow W, Miller C, Coelho J, Boachie A, Steinegger C, Loewen R, Loewen T, Waite E, Ford C, Bourret K, Gusella J, Geller J, LaFrance A, LeClerc A, Scarborough J, Grewal S, Jericho M, Dimitropoulos G, Pilon D (2020) Canadian practice guidelines for the treatment of children and adolescents with eating disorders. J Eat Disord 8:4. https://doi.org/10.1186/s40337-020-0277-8

10. National Guideline Alliance (UK) (2017) Eating disorders: recognition and treatment. National Institute for Health and Care Excellence (UK), London

11. Danish Health Authority (2016) National clinical guideline for the treatment of anorexia nervosa. Quick guide.

12. Harrington BC, Jimerson M, Haxton C, Jimerson DC (2015) Initial evaluation, diagnosis, and treatment of anorexia nervosa and bulimia nervosa. Am Fam Physician 91:46-52.

13. Hay P, Chinn D, Forbes D, Madden S, Newton R, Sugenor L, Touyz S, Ward W; Royal Australian and New Zealand College of Psychiatrists (2014) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. Aust N Z J Psychiatry 48:977-1008. https://doi.org/10.1177/0004867414555814

14. Cook BJ, Wonderlich SA, Mitchell JE, Thompson R, Sherman R, McCallum K (2016) Exercise in eating disorders treatment: systematic review and proposal of guidelines. Med Sci Sports Exerc 48:1408-1414. https://doi.org/10.1249/MSS.0000000000000912

15. Wasserman K, Whipp BJ, Koyl SN, Beaver WL (1973) Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 35:236-243. https://doi.org/10.1152/jappl.1973.35.2.236

16. Wasserman K, Whipp BJ (1975) Exercise physiology in health and disease. Am Rev Respir Dis 112:219-249. https://doi.org/10.1164/arrd.1975.112.2.219

17. Fisher JP, Young CN, Fadel PJ (2015) Autonomic adjustments to exercise in humans. Compr Physiol 5:475-512. https://doi.org/10.1002/cphy.c140022

18. Franklin BA, Brinks J, Berra K, Lavie CJ, Gordon NF, Sperling LS (2018) Using metabolic equivalents in clinical practice. Am J Cardiol 121:382-387. https://doi.org/10.1016/j.amjcard.2017.10.033

19. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. APA Publishing, Washington DC

20. Albouaini K, Egred M, Alahmar A, Wright DJ (2007) Cardiopulmonary exercise testing and its application. Postgrad Med J 83:675-682. https://doi.org/10.1136/hrt.2007.121558

21. Whipp BJ, Davis JA, Torres F, Wasserman K (1981) A test to determine parameters of aerobic function during exercise. J Appl Physiol Respir Environ Exerc Physiol 50:217-221. https://doi.org/10.1152/jappl.1981.50.1.217

22. Biadi O, Rossini R, Musumeci G, Frediani L, Masullo M, Ramacciotti CE, Dell'Osso L, Paoli R, Mariotti R, Cassano GB, Mariani M (2001) Cardiopulmonary exercise test in young women affected by anorexia nervosa. Ital Heart J 2:462-467.

23. Weber KT, Janicki JS (1985) Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol 55:22A-31A. https://doi.org/

24. Hebebrand J, Himmelmann G W, Herzog W, Herpertz-Dahlmann B M, Steinhausen H C, Amstein M, Seidel R, Deter H C, Remschmidt H, Schäfer H (1997) Prediction of low body weight at long-term follow-up in acute anorexia nervosa by low body weight at referral. Am J Psychiatry 154:566-569. https://doi.org/10.1176/ajp.154.4.566

25. Yamashita S, Kawai K, Yamanaka T, Inoo Takehiro, Yokoyama H, Morita C, Takii M, Kubo C (2010) BMI, body composition, and the energy requirement for body weight gain in patients with anorexia nervosa. Int J Eat Disord 43:365-371. https://doi.org/10.1002/eat.20700

26. Kawai K, Yamashita S, Yamanaka T, Gondo M, Morita C, Nozaki T, Takakura S, Hata T, Yamada Y, Matsubayashi S, Takii M, Kubo C, Sudo N (2011) The longitudinal BMI pattern and body composition of patients with anorexia nervosa who require urgent hospitalization: a case control study. Biopsychosoc Med 5:14. https://doi.org/10.1186/1751-0759-5-14

27. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS (2011) 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 43:1575-1581. https://doi.org/10.1016/0002-9149(85)90792-1

28. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS (2000) Compendium of physical

activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 32:S498-504. https://doi.org/10.1097/00005768-200009001-00009

29. Roche F, Barthelemy JC, Garet M, Costes F, Pichot V, Duverney D, Kadem M, Millot L, Estour B (2004) Chronotropic incompetence to exercise separates low body weight from established anorexia nervosa. Clin Physiol Funct Imaging 24:270-275. https://doi.org/10.1111/j.1475-97X.2004.00561.x

30. Brubaker PH, Kitzman DW (2011) Chronotropic incompetence: causes, consequences, and management. Circulation 123:1010-1020. https://doi.org/ 10.1161/CIRCULATIONAHA.110.940577

31. Yoshida Y, Maeda J, Fukushima H, Tokita N, Yamagishi H, Tokumura M (2019) Chronotropic incompetence to exercise in anorexia nervosa patients during the body-weight recovery phase as an index of insufficient treatment. Heart Vessels 34:711-715. https://doi.org/10.1007/s00380-018-1282-6

32. Escudero CA, Potts JE, Lam PY, De Souza AM, Duff K, Mugford GJ, Sandor GGS (2019) Echocardiographic assessment of ventricular function during exercise in adolescent female patients with anorexia nervosa. J Am Soc Echocardiogr 32:394-403.e3. https://doi.org/10.1016/j.echo.2018.10.014

33. Fuller A, Okwose N, Scragg J, Eggett C, Luke P, Bandali A, Velicki R, Greaves L, MacGowan GA, Jakovljevic DG (2021) The effect of age on mechanisms of exercise tolerance: reduced arteriovenous oxygen difference causes lower oxygen consumption in older people. Exp Gerontol 149:111340. https://doi.org/10.1016/j.exger.2021.111340

34. Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG (2005) Accelerated longitudinal decline of aerobic capacity in healthy older adults. Circulation 112:674-682. https://doi.org/10.1161/CIRCULATIONAHA.105.545459

35. Tamai M, Kubota M, Ikeda M, Nagao K, Irikura N, Sugiyama M, Yoshikawa H, Kawamori R, Kamada T (1993) Usefulness of anaerobic threshold for evaluating daily life activity and prescribing exercise to the healthy participants and patients. J Med Syst 17:219-225. https://doi.org/10.1007/BF00996949

36. Ibrahim A, Cutinha D, Ayton A (2019) What is the evidence for using bed rest as part of hospital treatment of severe anorexia nervosa? Evid Based Ment Health 22:77-82. https://doi.org/10.1136/ebmental-2018-300064

37. Kolnes LJ (2017) Exercise and physical therapy help restore body and self in clients with severe anorexia nervosa. J Bodyw Mov Ther 21:481-494. https://doi.org/10.1016/j.jbmt.2016.09.005

38. Moola FJ, Gairdner SE, Amara CE (2013) Exercise in the care of patients with anorexia nervosa: a systematic review of the literature. Mental Health and Physical Activity 6:59-68.

39. Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U (2015) Anorexia nervosa: aetiology, assessment, and treatment. Lancet Psychiatry 2:1099-1111. https://doi.org/10.1016/S2215-0366(15)00356-9

40. Davies S, Parekh K, Etelapaa K, Wood D, Jaffa T (2008) The inpatient management of physical activity in young people with anorexia nervosa. Eur Eat Disord Rev 16:334-340.

https://doi.org/10.1002/erv.847

Tables

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.

Table 2. Parameters at the time AT was achieved in CPX

	Patients with AN (n = 14)	**Healthy controls (n = 14)**	**P value**
Oxygen uptake (ml/min)	398.9 ± 90.7	788.8 ± 178.3	<.001[a]
Carbon dioxide output (ml/min)	414.5 ± 98.2	750.2 ± 162.3	<.001[a]
Gas exchange ratio	1.04 ± 0.06	0.95 ± 0.04	<.001[a]
Respiratory rate (f/min)	23.1 (14.3–35.4)	24.9 ± 4.8	.23[b]
Minute ventilation (l/min)	14.9 ± 3.0	23.4 ± 4.6	<.001[a]
Heart rate (bpm)	94.6 ± 12.6	125.1 ± 17.0	<.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: AT, anaerobic threshold; CPX, cardiopulmonary exercise testing.

Table 3. Variables predictive of AT in all of the participants

	B	**β**	**P**	**95% CI**	
				Lower limit	Upper limit
Const.	7.962		<.001	6.076	9.848
ΔHR	.078	.449	.015	.017	.140
group	2.968	.420	.022	.464	5.473

$R^2 = .650$, ANOVA: P <.001

Abbreviations: AT, anaerobic threshold; B, partial regression coefficient; β, standardized partial regression coefficient; P, significance probability; CI, confidence interval; Const., constant; HR, heart rate.

Figures

Fig. 1

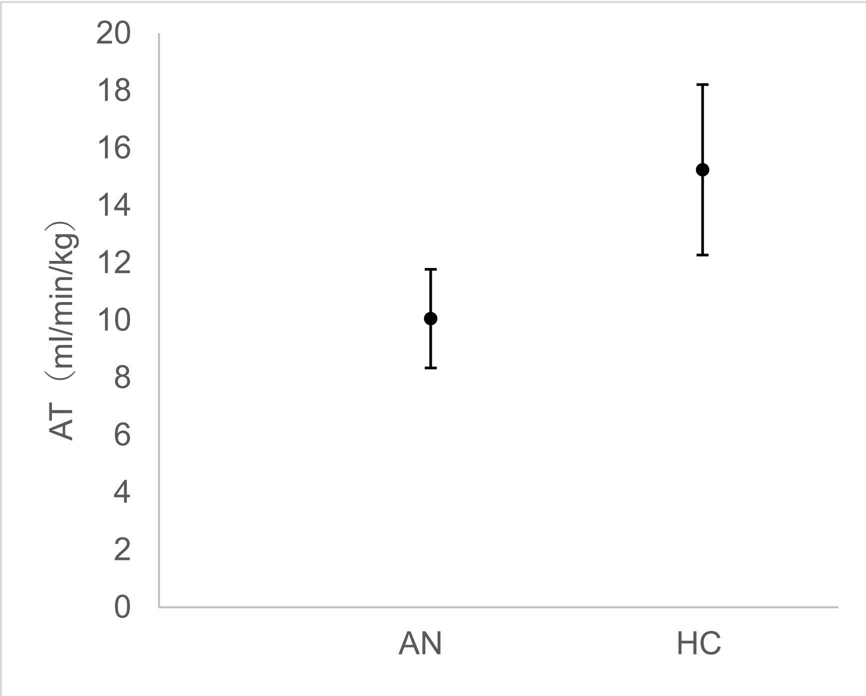

Fig. 2

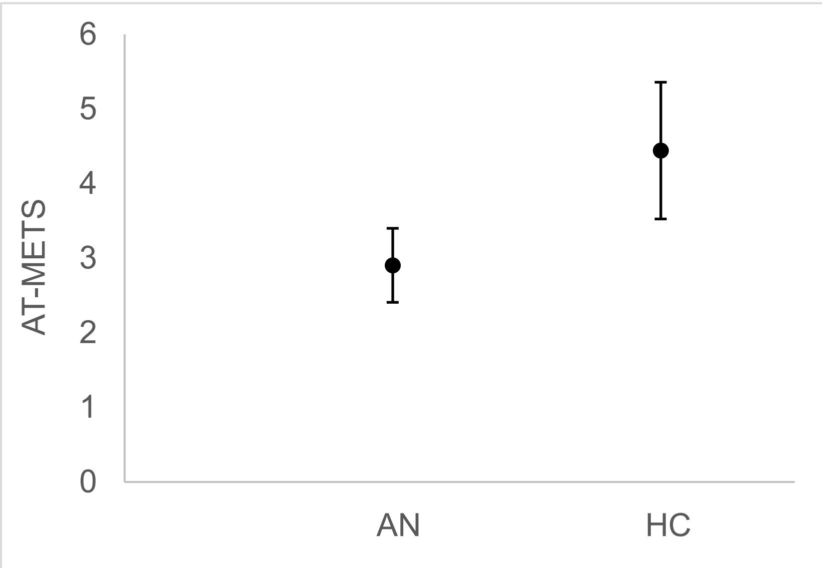

Figure captions

Fig. 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.

Fig. 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.