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Exercise Capacity and Idebenone Intervention in Children and Adolescents with Friedreich's Ataxia

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Abstract

Objective—To determine the effects of idebenone on exercise capacity in children and adolescents with Friedreich's Ataxia.

Design—Secondary analysis of a randomized double-blind, placebo controlled, phase II clinical trial.

Setting—Clinical research center, exercise physiology laboratory.

Participants—42 subjects (ages 9–17) with genetically confirmed FA.

Intervention—Six-month idebenone regimens of approximately 5, 15, and 45 mg/kg/day or placebo.

Main Outcome Variables—Peak oxygen consumption (peak VO₂) and peak work rate (WR) were measured during incremental exercise tests before and after treatment. Echocardiography and neurological assessments were also completed before and after the idebenone regimen.

Results—Baseline peak VO₂ was 746±246 ml/min (16.2 ± 5.8 ml/kg/min) and WR was 40±23 watts in all subjects combined. Peak VO₂ and WR were correlated with short GAA repeat length and neurological assessments. Relative left ventricular wall thickness (RWT) was increased but left ventricular ejection fraction was normal in the majority of subjects; there was no relationship between any exercise and echocardiographic measure. There were no significant changes in peak VO₂ or WR after idebenone treatment.

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Conclusions—Exercise capacity was severely impaired in these children and adolescents with FA and after 6 months of idebenone treatment did not change by an amount thought to be clinically relevant.

Keywords

Exercise; Genetic Disorder; Idebenone; Friedreich's Ataxia

Introduction

Friedreich's Ataxia (FA) is an autosomal recessive, neurodegenerative disorder characterized by progressive limb and gait ataxia, dysarthria, diminished or absent deep tendon reflexes, and loss of proprioception. Systemic features of FA also include scoliosis, hypertrophic cardiomyopathy, and to a lesser extent diabetes, optic atrophy and hearing loss (1). In the majority of patients (>95%), the causative mutation is a homozygous expansion of a guanine adenine adenine (GAA) repeat in the frataxin gene. This mutation results in reduced expression of the mitochondrial protein frataxin (2). The shorter GAA repeat expansion is known to be a primary determinant of the amount frataxin produced and is related to onset and rate of progression of disease (3).

In cells of patients with FA, there is a concentration deficit in the respiratory chain enzyme complexes I, II and III, and the Krebs cycle enzyme aconitase. ATP repletion may be limited by these enzyme deficiencies (4). As a result of decreased iron binding in the mitochondria, iron overload may lead to the formation of reactive oxygen species and oxidative damage (5). Therefore, both mitochondrial dysfunction and oxidative tissue damage could contribute to overall metabolic insufficiency in FA.

Several studies examining cardiac and skeletal muscle ATP synthesis, using magnetic resonance spectroscopy, have noted impaired bioenergetics (6–8) in patients with FA. A similar deficit in ATP production has been observed in patients with mitochondrial myopathy (9). In these patients, even mild physical exertion led to exercise intolerance. Exercise testing in subjects with mitochondrial myopathy demonstrated that peak work capacity and oxygen uptake were reduced by approximately 50% relative to controls (10). Based upon the similar underlying mitochondrial dysfunction, we hypothesized that patients with FA may also have significantly diminished exercise capacity.

Several therapies are currently being examined for the treatment of FA (11). Based upon the biochemical defects identified, one potential therapy is the use of antioxidants. Idebenone is a lipid-soluble, short chain benzoquinone with a structure similar to coenzyme Q₁₀, and is a potent antioxidant and electron carrier (12). Theoretically, idebenone therapy may improve mitochondrial function in vivo by facilitating electron flow through the electron transport chain thereby reducing oxidative stress. A three-month open-label study with oral coenzyme Q₁₀ and vitamin E demonstrated an increase in the maximum rate of skeletal and cardiac muscle ATP production in patients with FA (13). The improvement was sustained for the duration of the 6-month study. However, another study using 6 weeks of idebenone treatment failed to show any change in ATP repletion after aerobic or ischemic exercise of the calf muscle in patients with FA (14). The lack of an idebenone effect may have been due to insufficient duration, dose, or compound activity.

Previous studies have suggested that idebenone may partially reverse FA-cardiomyopathy (15,16). Five milligrams of Idebenone per kilogram of body weight per day (mg/kg/day) may be effective for reducing cardiac hypertrophy. However, evidence suggests that higher

doses might be more effective for significant neurological improvement in individuals who have FA (17).

Very little information has been published regarding exercise capacity in patients with FA. Both increased muscle oxygen recovery time (18) and decreased ATP repletion (6,7) have been reported after exercise in specific muscle groups in individuals with FA. However, whole body exercise capacity has not been examined. Moreover, since antioxidants have been demonstrated to improve muscle ATP formation, it is possible that higher doses and prolonged treatment with idebenone may improve exercise capacity. The purpose of this study was to examine the influences of FA and idebenone therapy on exercise capacity in a group of affected children and adolescents.

Methods

Subjects

The present investigation was a secondary analysis of data acquired in a phase II clinical trial conducted at the National Institutes of Health, Mark O. Hatfield, Clinical Research Center in Bethesda, Maryland (NCT00229632). (19). Forty-eight subjects with genetically confirmed FA were enrolled in the 6 month, randomized, double-blind, placebo-controlled study of the effect of idebenone therapy on a biomarker for antioxidant status. This main trial outcome was previously reported and is therefore not included in this secondary analysis of exercise capacity. Eligible participants were aged 9–17 years, weighed 30–80 kg, neurologically symptomatic, and able to walk 25-feet with or without an assistive device. No subject was exposed to idebenone or other antioxidants or dietary supplements for at least one month prior to enrollment. Exclusion criteria included hypersensitivity to idebenone, serious concomitant illness, and abnormal laboratory values for platelet count, white cell count, hemoglobin, alkaline phosphatase, bilirubin, or serum transaminases. All subjects underwent medical screening and physical exam prior to enrollment. Informed consent was obtained from all subjects or their legal guardians at screening. Assent was obtained from minor subjects. This study was approved and conducted in accordance with policies and procedures set forth by the respective Institutional Review Boards and was in compliance with the Declaration of Helsinki.

Study Drug and Dosing

Idebenone (US FDA investigational drug number 62,926) and matching placebo were supplied by Santhera Pharmaceuticals (Liestal, Switzerland). Subject randomization assignments were generated by a third party (Hesperion Ltd, Allschwil Switzerland). The randomization assignment was stratified by weight (≤ 45 or >45 kg) to maintain the dose range, and the shorter GAA repeat length (≤ 800 or >800) to control for disease progression. The total dose of idebenone was stratified by body weight (≤ 45 or >45 kilograms): low-dose (180 or 360 mg), intermediate-dose (450 or 900 mg), or high-dose (1350 or 2250 mg). Thus, the low-dose was approximately 5 mg/kg/day, intermediate-dose 15 mg/kg/day, and high-dose 45 mg/kg/day. The total dose was divided and patients were instructed to take the drug 3 times daily with food. Adherence was monitored by entries into a daily log, pill counts, and drug serum concentration at the end of the study.

Neurological Assessments

The subjects were assessed using the International Cooperative Ataxia Rating Scale (ICARS) and the Friedreich Ataxia Rating Scale (FARS). The scales were merged into a single, one hour exam to ensure accuracy and minimize confounding by fatigue. The total scores of these scales have been demonstrated to be reliable and valid instruments for assessing disease status (20,21). The ICARS range is 0–100 points and the FARS range is 0–

117 points with the higher scores reflecting a greater degree of disability. A single rater performed all baseline and follow-up assessments. All testing maneuvers were performed at the same time of day at baseline and follow-up in the same order, and in the same setting to minimize subject variability.

Echocardiography

All subjects underwent standard echocardiographic examination (22) using a single instrument (Phillips 5500, Andover, MA). Subjects were placed in the left lateral decubitus position while digital acquisition was performed during continuous breathing using standard adult windows. Offline analysis (DigiView, Digisonics Inc., Houston TX) was blinded to all subject information and was performed by an experienced sonographer. All studies were independently over-read by a cardiologist with discrepant assessments resolved by consensus.

Left ventricular (LV) chamber dimensions were determined by point to point measurements from the parasternal long axis window. LV mass calculations were performed using the ASE-modification of the Penn formula as reported by Devereaux (1986)(23) and were then indexed for height in meters^{2.7}. Relative wall thickness (RWT) was determined as previously described and values for RWT greater than 0.39 were considered abnormal in this study(24). Left ventricular ejection fraction (EF) was calculated from point to point measurements using the Teicholz formula(22). Pulsed and tissue Doppler imaging was employed to characterize LV diastolic function with 3 sequential beats acquired at 50 mm/sec sweep speeds and averaged. Peak rapid early LV filling (E wave) and late diastolic (A wave) blood velocities were obtained with pulsed Doppler sample volumes placed between the mitral valve tips in the apical 4 chamber view and the E/A ratio calculated. Tissue Doppler sample volumes were placed at the anterolateral wall annulus and early diastolic tissue displacement velocity sampled (E') as a measure of early relaxation (25). Peak systolic tissue velocity (S') was determined as a measure of LV systolic function.

Exercise Testing Procedures

Subjects underwent an exercise test protocol using a semi-recumbent cycle ergometer (Corival Recumbent, model 929900, Lode BV, Netherlands) at baseline and after six months of Idebenone. The test included a 3-minute stage of unloaded pedaling maintaining a cadence of at least 40 rpm followed by a 10 watt increase in work rate every three minutes. Subjects were encouraged to work to exhaustion. Testing was stopped if the subjects could no longer maintain the required pedaling cadence. Ventilatory expired gas analysis was performed using a metabolic cart (SensorMedics Vmax, Yorba Linda, CA) to determine peak oxygen consumption (VO_2), and respiratory exchange ratio (RER). The metabolic cart was calibrated before each test. Heart rate (HR) was determined by continuous ECG monitoring (SensorMedics Cardiosoft, Yorba Linda, CA)

Cardiac output (Q) was measured continuously using thoracic electrical bioimpedance (Physioflow, Manatec Inc, France). Thoracic electrical bioimpedance is a noninvasive technology that quantifies changes in thoracic impedance with changing blood flow. The use of TEB to measure resting and exercise cardiac output has been reported to be both reliable and valid when compared to direct Fick and dye dilution methods (26–30).

Statistical Analysis

This study was a secondary analysis of data acquired during a phase II clinical trial (19). The trial's main outcome variable, which was a biomarker of antioxidant status, was not included in this secondary analysis of data. For this secondary analysis the primary variables of interest were peak VO_2 and peak work rate. Additional variables of interest included

echocardiographic data, and FARS and ICARS. In this study, it was anticipated that a 30% increase in peak VO_2 would be clinically relevant. An increase in peak VO_2 of this magnitude has been reported in one subject with FA (31) and represents the approximate upper limit of increases that can be expected following aerobic exercise training (32). Based on the variance in peak VO_2 presented in Table 2 for the entire group of subjects receiving idebenone, it was calculated that 19 subjects would be required to observe a post-intervention increase of 30% (215 ml/min) at an $\alpha=0.05$ and $\beta=0.20$. Analysis of Variance (ANOVA) was used to test for baseline drug group differences and differences in pre to post treatment change scores between placebo and drug groups and among drug groups for a dose effect. Pearson product moment correlations were used to assess the relationship among exercise variables, neurological assessments and GAA repeat length. All statistical tests with a p-value ≤ 0.05 were considered significant.

Results

Forty two of 48 subjects completed exercise testing at baseline and follow-up (Fig 1). The subjects were mild to moderately symptomatic based upon a mean ICARS score of 40 ± 14 and a mean FARS score of 59 ± 17 . Thirty-eight of 42 (90%) subjects had an RWT greater than normal (> 0.39), indicating of a degree of hypertrophic cardiomyopathy (24). Eight subjects had a resting ejection fraction of less than 55% and the average ejection fraction was 60%.

At baseline peak VO_2 and WR for all subjects combined were 746 ± 246 ml/min and 40 ± 23 watts, respectively. Peak VO_2 was also expressed in body weight relative terms yielding a mean peak VO_2 for subjects in this study of 16.2 ± 5.8 ml/kg/min (see Discussion for comparison to published data for healthy subjects). Despite a large group variance, the overall relationship between peak VO_2 and WR was linear ($r=0.80$, $p=0.001$, Figure 2). Average peak heart rate (HR) was 146 ± 22 bpm with a peak RER of 1.02 ± 0.09 . For peak VO_2 and WR respectively, there were significant relationships with the short GAA allele and neurological assessments (Figures 3 and 4).

Since there was some degree of hypertrophic cardiomyopathy in the majority of patients, correlations between cardiac parameters and exercise capacity were also explored. There was no correlation between cardiac size (RWT or LVmass), resting diastolic function (E' or E/A) or systolic function (EF or S') with peak VO_2 or WR. During exercise average cardiac output increased by 88% with a 17% increase in stroke volume and 59% increase in heart rate.

The overall baseline characteristics of the idebenone treatment and placebo groups were balanced with respect to age, GAA repeat number, gender, ICARS and FARS score, and cardiac parameters (Table 1). There were no significant differences in exercise capacity among treatment groups or between all dosage groups combined and placebo (Table 2). Over the six months of treatment, all doses of idebenone were generally well tolerated with similar numbers and types of adverse events across treatment groups (19). None of the idebenone dosage groups achieved a 30% increase in peak VO_2 , which was threshold for clinical relevance in this study. A 30% increase was not observed when the data from the dosage groups was collapsed.

Discussion

Exercise capacity in subjects with FA was lower than that expected for healthy individuals in this age range. Peak VO_2 was decreased by approximately 56% compared to previously published data for 43 healthy subjects, with similar age (14.8 ± 1.7 years), tested in our

laboratory (16.2 vs 36.7 ml/kg/min) (33). Peak work rate was also lower in subjects with FA (40 ± 23 watts) compared to these same healthy subjects (187 ± 48 watts). Cooper and colleagues published regression equations for predicted peak VO_2 based on data from healthy children and adolescents (34). When those regressions were applied to our subjects with FA, average peak VO_2 was decreased by 60% compared to predicted peak VO_2 . A clinically relevant change in exercise capacity was not observed after a 6-month regimen of idebenone therapy in these children and adolescents with FA.

The energy requirement for any given physical activity is finite. Metabolic requirements for instrumental activities of daily living (IADL) therefore fall within a given range that can be equated to body weight normalized VO_2 . This range is encompassed by lower and upper VO_2 limits of 10.5 ml O_2 /kg/min and 17.5 ml O_2 /kg/min (35). Even extremely sedentary but otherwise healthy individuals typically achieve a peak VO_2 that exceeds the upper limit of this range. In the current study, subjects with FA did not achieve a peak VO_2 that exceeded the upper IADL limit. These findings suggest that decreased metabolic capacity may contribute to physical activity intolerance in children and adolescents who have FA.

Factors influencing exercise capacity in subjects with FA could include those associated with the pathophysiology of FA, as well as those associated with adaptation to a sedentary lifestyle. Indeed neurological impairment as assessed by the ICARS and FARS scores was related to a decreased exercise capacity. An estimated 13% decline in peak VO_2 , after nine weeks of bed rest, has been reported in children who had severe skeletal fractures (36). A decrease in peak VO_2 of up to 30% may occur in adults following bed rest (37). The decreased peak VO_2 in the youths with FA was far greater than the reductions found in these previous reports suggesting that other factors related to the pathophysiology of FA may contribute to the impairment in exercise capacity observed in the present study. A single case study demonstrated a 27% increase in peak VO_2 in a subject with FA following exercise training (31). This increase was comparable to that expected for a sedentary individual following training. However, a similar increase in peak VO_2 in the subjects with FA in the current study would not have been large enough to elevate exercise capacity to levels similar to the healthy comparison group or predicted values. It is therefore likely that other factors such as reduced cellular metabolism and or impaired cardiac function may have also contributed to the decreased capacity of the FA subjects.

The majority of subjects with FA had at least some degree of myocardial thickening based upon a $\text{RWT} > 0.39$. However there was no association between any echocardiographic variable and peak VO_2 or peak work rate. An examination of cardiac functional measures by echocardiography revealed that while systolic function was preserved based upon a normal resting EF, there was a degree of diastolic dysfunction as evidenced by a decrease in tissue and filling velocities during diastole (E' and E/A) (38). Impaired cardiac relaxation would reduce filling time and thereby could possibly result in a decreased ability to increase stroke volume during exercise. Indeed, impedance cardiography revealed that cardiac output increased mainly by an increase in heart rate (59%) with minimal change in stroke volume (17%). Previous studies have shown that during maximal exercise in children, SV increases approximately 30% over resting values (39,40). The decreased change in SV observed in this study may represent a limitation affecting exercise cardiac performance.

Pulmonary function tests and breathing reserve during exercise were not measured in this study therefore a ventilatory limitation to exercise could not be definitively ruled out. However the small increase in SV (described above) along with the low peak heart rate in the presence of a significant exercise effort ($\text{RER} > 1.0$) suggests that cardiac and skeletal muscle dysfunction may play a significant role in exercise limitation. This is consistent with reports that the length of the short GAA repeat is associated with deficits in mitochondrial

ATP synthesis (6,7) and prolonged muscle oxygenation recovery during treadmill walking in subjects with FA (18). In the present study the short GAA repeat length had a modest but significant relationship with peak VO_2 and peak work rate (figures 3 and 4). While these relationships were not as strong as those observed in previous studies using ^{31}P -MRS (6,7), the current data were indirect measures of cellular metabolism and may have been limited by the failure of subjects to achieve maximal levels of aerobic exercise as discussed below.

In patients with mitochondrial respiratory chain defects due to mutations of mitochondrial or nuclear DNA, exercise capacity was 40–50% lower than controls and directly related to the degree of the mutation (10). In persons with FA the degree of GAA mutation may be associated with the degree to which the capacity for oxidative phosphorylation is diminished (6). It appears from studies thus far that a major limitation to aerobic capacity in subjects with FA may be related to ATP production deficiencies occurring in the mitochondria of the myocardium, skeletal muscle, neurons, or perhaps all of these highly metabolic tissues. Further work is needed to determine if exercise limitation is biased toward some of these tissues and not others.

Idebenone has been demonstrated to promote ATP formation in vitro, but a previous study failed to demonstrate such activity in FA subjects in vivo (13). It is possible that this lack of effect was due to insufficient dose or duration. A longer term study with coenzyme Q_{10} and vitamin E treatment demonstrated an increase in the maximum rate of muscle ATP production in patients with FA (12). In this study, we failed to observe any changes in exercise performance following 6 months of idebenone treatment up to approximately 45 mg/kg/day relative to placebo. However, measurements on the whole body level may not accurately reflect changes on the cellular level. Moreover, due to the inter subject variability and potential physical limitations, it is not clear if exercise testing is a reasonable assessment of a drug treatment for this disorder. Given that idebenone treatment in this study showed indications of dose-dependent response in neurological function (19), changes in exercise capacity may require a greater degree of neurological and/or cardiac improvement (i.e. longer duration of study) or a compound more specific to enhancing mitochondrial function.

Study Limitations

Motivational factors and bias introduced by the testing regimen itself may adversely influence exercise tolerance and result in termination of the test before peak VO_2 has been attained. These intervening factors frequently cloud the determination of what might otherwise be interpreted as the physiological maximum (“maximal” VO_2). Several exercise test variables have typically been used as criteria for identification of the attainment of the peak VO_2 . In adults, a minimum peak RER of 1.15 or a peak heart rate of at least 93% of the age predicted maximum heart rate (220 beats per minute minus age in years) are thought to suggest that subjects may have approached their physiologically maximum metabolic capacity at volitional exhaustion on the cycle ergometer (41,42). These criteria are not as well defined in children. Rowland (1996) suggested that a peak RER of 1.02 or higher be used to estimate achievement of maximal oxygen uptake in children (32). An attained heart rate of at least 195 $\pm$ 10 bpm was also suggested as another indicator of maximum aerobic capacity in children when using the cycle ergometer. While in the subjects with FA peak RER met the criterion suggested by Rowland, peak heart rate was lower than expected; only 21 subjects attained an RER $\geq$ 1.0. However, in the subset of subjects who had an RER $\geq$ 1.0, there was still a significant decrease in peak VO_2 (19.5 $\pm$ 5.1 $\text{mlO}_2/\text{kg}/\text{min}$) relative to predicted values. The fact that RER met the criterion for maximum capacity while peak heart rate was lower than expected may suggest that aerobic capacity was limited by localized fatigue in the exercising muscles. It could not be determined whether the subjects with FA in the current study, were able to actually approach their physiological maximum metabolic capacity at volitional exhaustion. Mechanical limitations due to neurological

impairment may have interfered with the ability to assess maximal exercise capacity. It is also possible that the stepwise nature of the exercise testing protocol used in this study contributed to early fatigue. However others have shown that peak VO_2 attained is unaffected by ramp versus step protocols (43). The peak VO_2 attained in the present study may well represent the maximum tolerance for physical activity.

Based on observed variance in these subjects with FA, and at an alpha of five percent and 80% power, the necessary and sufficient sample size for observing a clinically relevant interventional change in peak VO_2 of 30% was 19 subjects per group. Therefore, dosage group comparisons in this study may have been underpowered. However, this magnitude of change (30%), thought to represent a clinically relevant improvement in aerobic metabolism, was not observed in the subjects receiving idebenone at any dosage studied. The choice of a 30% increase in peak VO_2 was based on predicted improvements similar to those seen at the upper limit of the adaptation possible with aerobic exercise training. This magnitude of increase would have equaled approximately 215 ml/min in these subjects. Even if aerobic capacity had improved to this magnitude, it remains questionable as to how much the increase would have been improved physical performance and functional capacity.

Summary

Exercise capacity, was severely diminished in children and adolescents with FA. Both peak VO_2 and peak work rate were related to GAA short repeat length and disease severity but not to any echocardiographic parameter. Six months of treatment with varying doses of idebenone did not change exercise capacity relative to placebo treatment. Further investigations related to potential mechanisms that might limit exercise capacity and the intervention effects of specific exercise training or other drug treatments aimed at increasing mitochondrial function may improve the understanding of aerobic impairment and reduced work capacity in individuals with FA.

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Fig 1.
CONSORT Diagram

Fig 2. Relationship between Peak Oxygen Consumption (peak VO₂) and Peak Work Rate. A generally linear relationship was observed indicating that higher Peak work rates were associated with greater peak VO₂.

Figure 3.

Relationships between PeakVO₂ and the short guanine adenine adenine repeat length (GAA1, panel A), Friedreich's Ataxia Rating Scale (FARS, panel B) and International Cooperative Ataxia Rating Scale (ICARS, panel C). Higher PeakVO₂ was generally associated with lower GAA1 repeat length, FARS and ICARS scores. Lower FARS and ICARS scores indicate less disability.

Figure 4. Relationships between PeakVO₂ and the short guanine adenine adenine repeat length (GAA1, panel A), Friedreich's Ataxia Rating Scale (FARS, panel B) and International Cooperative Ataxia Rating Scale (ICARS, panel C). Higher peak work rate was generally associated with lower GAA1 repeat length, FARS and ICARS scores. Lower FARS and ICARS scores indicate less disability.

Table 1

Descriptive data for Idebenone dose and placebo groups.

	Placebo (n=11)	Low dose (n=9)	Intermediate dose (n=13)	High dose (n=9)	All (n=42)
Age (years)	13±2.4	13.8±2.3	13.3±3.1	12.7±1.9	13.2±2.5
ICARS score	36.3±16.0	46.3±13.9	39.7±14.0	38.8±10.0	40±14
FARS score	58.8±17.0	66.3±16.1	60.0±16.8	55.7±13.8	59±17
Gender (male)	7	3	6	5	21
GAA1	732±254	751±240	715±277	772±128	739±230
GAA2	961±170	1090±193	986±194	915±170	987±186
EF (%)	62±8	59±6	59±7	60±6	60±7
RWT*	0.53±0.16	0.59±0.18	0.58±0.19	0.66±0.17	0.59±0.17
LVmass (gm/M ^{2.7})	27±9	29±6	29±10	31±10	29±9

Data presented are means ± one standard deviation unit. GAA is the guanine-adenine-adenine repeat. There were no significant differences in the baseline placebo or dose group characteristics (all p>0.16).

* Relative wall thickness (RWT) is the ratio of two times the posterior wall thickness divided by the left ventricular end diastolic dimension.

Table 2

Peak Oxygen Uptake and Maximum Work Rate for Subjects with FA Before and After Treatment with Idebenone or Placebo.

Dose Group	Peak VO₂ (ml/min)		Peak Work Rate (Watts)	
	Before	After	Before	After
Placebo (n=11)	819 (669, 969)	975 (725, 1225)	44 (29, 59)	46 (28, 64)
Low (n=9)	664 (507, 821)	643 (482, 804)	30 (14, 46)	31 (12, 50)
Intermediate (n=13)	734 (581, 887)	804 (691, 917)	42 (29, 55)	46 (30, 62)
High (n=9)	721 (582, 860)	783 (629, 937)	43 (32, 54)	46 (26, 66)
Total Idebenone (n=31)	719 (634, 804)	753 (670, 836)	39 (31, 47)	43 (34, 52)

Data are means (95 percent confidence intervals). Total Idebenone refers to the collapsed data across the low, intermediate, and high dosage groups. There were no significant differences in peak VO₂ or peak work rate between the dosage groups (all $p>0.43$) or before and after Idebenone (all $p>.15$).