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**Supplementary Methods**

**Patients and Setting**

We conducted a randomized controlled trial (RCT) in patients with post-treatment primary lung cancer at Duke University Medical Center (DUMC) and Memorial Sloan Kettering Cancer Center (MSK). The study was conducted at DUMC between February, 2010 and May, 2013, continuing at MSK from April, 2017 to March, 2018 (for a total accrual period of 4.3 years), with final post-intervention testing conducted in July, 2018. The reason for the disruption in trial conduct was due to the principal investigator (LWJ) leaving DUMC to join MSK in February, 2014. Other major eligibility criteria were: (1) ≥ 1 year to <10 years after completion of all definitive therapy (i.e., surgery and adjuvant radiation or chemotherapy, as applicable), (2) cardiorespiratory fitness (peak oxygen consumption (VO2peak) below age-sex-matched sedentary normative levels, (3) review and clearance of exercise electrocardiogram by a cardiologist (AY), (4) age 21-80, (5) ECOG <1, (6) life expectancy >4 months, (7) performing less than 150 minutes of structured moderate-intensity exercise per week. All study procedures were reviewed and approved by the institutional review boards. Participation in intervention groups continued for a maximum of 16 weeks or until withdrawal of consent, whichever came first.

**Randomization and Blinding**

Following confirmation of eligibility, patients were randomly allocated in a 1:1:1:1 ratio to receive either one of the three exercise regimens [aerobic training (AT), resistance training (RT), or combined training (CT)] or attention-control (AC). The random allocation sequence was generated and implemented using REDCap with a random permuted block design. Two stratification factors were employed: (1) adjuvant treatment with chemotherapy (yes vs. no), and sex (male vs. female). Group allocation was concealed until treatment intervention was assigned. The trial primary statisticians (JH and SMT) generated the random sequence; dedicated study coordinators enrolled patients, and the clinical research team at each center assigned participants to treatment group. Exercise physiologists implementing the study interventions were not randomly allocated to study treatment arms. Neither patients nor exercise physiologists were blinded to group allocation. Participants and study investigators were blinded to results at prerandomization and postintervention. Study investigators and statisticians were blinded to treatment allocation.

**Study Interventions**

All interventions were initiated ≤14 days post-randomization. Treatment interventions were standardized between patients in each arm on the basis of modality, dose intensity, progression, and schedule. Interventions were also matched in terms of setting (clinic-based), monitoring (one-on-one monitoring/session), frequency (three times weekly), duration (20 to 60 mins/session), and length (16 weeks). All exercise treatment regimens were specifically designed to improve CRF. Dedicated study personnel with at least Bachelor’s degrees in Exercise Science implemented the interventions and individually monitored all sessions. No informational material was provided to study participants. All intervention sessions were conducted in a dedicated exercise training facility at both institutions. Exercise physiologists’ adherence to the protocol was reviewed on weekly basis by the study investigators (MM, LJ, JS). All sessions were by appointment only with patients contacted <24 hrs following an unscheduled missed session. Rescheduling of missed sessions was permitted within the 16-week intervention period.

Aerobic Training: AT consisted of 48 supervised cycle ergometer sessions delivered 3 times-weekly for 16 consecutive weeks. Following an initial 2-week ramp period, the intensity of each session was conducted at one of five different dose intensities (i.e., 55%, 65%, 75%, 80%, and >95%) of peak oxygen consumption (VO2peak) for 20 to 60 mins/session. The duration of each session was intensity dependent: low / moderate-intensity sessions (55% to 75%) were longer duration (>30 to 60 mins), and higher-intensity sessions (~ 80%) were shorter duration (~15 to 30 mins). Interval sessions (>95% VO2peak) consisted of 60 secs to 120 secs at peak workload followed by 120 secs to 180 secs of active recovery for 4 to 10 intervals. Intensity was individualized to each patient on the basis of workload (i.e., cycle ergometry wattage) corresponding to a specific percent of ventilatory thresholds measured during the pre-randomization or midpoint (week 8) cardiopulmonary exercise test (CPET). The planned exercise dose (a function of training intensity and duration) was scheduled such that physiological stress was continually altered and progressively increased in conjunction with appropriate rest and recovery sessions to optimize physiological adaptation across the entire intervention period (i.e., nonlinear periodized dose scheduling).[1] Specifically, in week 1, participants performed 3 sessions/week, at an intensity of 55% VO2peak for ~ 30 mins/session. From week 2 to 5, participants performed 3 sessions/week at 55% to 65% VO2peak. In weeks 6 to 11, two sessions were dosed at 55%-70% VO2peak for 30 to 60 mins; the remaining session was dosed at 70%-80% VO2peak (i.e., ventilatory threshold) for 15-30 mins. From week 12 onwards, two sessions were dosed at 55%-75% VO2peak for 30 to 60 mins; the remaining session was dosed at 85%->95% VO2peak (i.e., interval training).[1]

Resistance Training: RT consisted of 48 supervised sessions delivered 3 times-weekly for 16 consecutive weeks. Following an initial 2-week ramp period, RT exercises were progressively trained to perform three sets of 6 to 18 repetitions of 14 resistance exercises (i.e., chest press, seated row, lateral pull down, pec deck, bicep curl, triceps extension, push up, leg press, leg curl, leg extension, hip abduction, hip adduction, step up, and sit-to-stand) alternating between lower and upper extremity muscle groups for 30-60 minutes/session. Intensity was individualized to each patient on the basis of maximal strength corresponding to a specific percent of a one one-repetition maximum (1-RM) measured during the pre-randomization or midpoint (week 8). Specifically, in Week 1 to 2, participants performed 3 sessions/week, at an intensity of 50-60% of their 1-RM for 2-3 sets of 10-15 repetitions for both upper and lower body exercises. From Week 3 to 8, participants performed 1 session/week at 70-80% of 1-RM for 3 sets of 8-10 repetitions for upper body exercise; 1 session/week at 60-65% of 1-RM for 3 sets of 15-18 repetitions for lower body exercises; the remaining session was a combination of the two previous days. In Weeks 9 to 16 participants performed 1 session/week at 75-85% of 1-RM 3 sets of 6-10 repetitions for upper body exercises; 1 session/week at 70-75% of 1-RM for 2-3 sets of 10-12 repetitions for lower body exercises; the remaining session was a combination of the two previous days.

Combination Training: CT group consisted of three AT sessions plus two to three RT sessions/week following a similar dosing schedule and intensity as for each single modality prescription (described above) for 30 to 90 mins/session. Of note, sequencing of AT and RT, both within each session and across the entire treatment period, was designed to exploit the complementary properties of AT and RT to augment CRF response. For instance, if planned AT intensity was >80% VO2peak, RT intensity was implemented at a lower intensity and vice versa. We posited that such an approach might augment CRF response without causing excessive fatigue and avoiding potential interference effects.

Attention Control: AC consisted of 3 supervised stretching sessions per week, of 10 to 20 different positions for 20 to 45 secs/stretch following a standardized progressive approach for a total of 20 – 45 min/session.[2]

**Treatment Tolerability and Safety**

Safety: Safety of each exercise session was evaluated using a combination of heart rate (continuous), blood pressure (every 10 minutes), oxygen saturation (every 5 minutes) and rate of perceived exertion (every 15 minutes). Dose modification of any session was permitted and performed by the exercise physiologist monitoring each session using standardized criteria defined in the study protocol (for dose-modification guidelines see **Table S1)**.

Tolerability: Treatment tolerability was evaluated via standardized recording of session attendance as well as adherence to the planned dose of each session. The exercise physiologist reported all modifications to the planned treatment dose using a standardized template.

In AT, “planned” dose of all sessions was quantified as MET.hrs /session. The “planned” intensity of each session was multiplied by the corresponding session duration to calculate MET/session; all sessions were summed to derive total “planned” cumulative MET-hours (MET.hrs)/patient.[3] AT sessions in Weeks 1 to 8 and 9 to 16 were quantified using baseline and midpoint CPET data, respectively. Calculation of “completed” METs was quantified as the actual intensity and duration of each attended session. The average METs was assigned to sessions in which intensity was reduced (during the session), whereas missed sessions were assigned zero METs. All sessions were summed to derive total “completed” cumulative MET-hours (MET.hrs)/patient.” Relative dose intensity (RDI) defined as the ratio of total “completed” to total “planned” cumulative dose.[2] For context, 45 mins at 30 Watts is equivalent to 1.32 MET.hrs /session; 20 mins at 82 Watts is equivalent to 1.08 MET.hrs /session.

In RT, “planned” dose of all resistance exercises in each session was quantified as volume load/exercise. The “planned” intensity of all resistance exercises in a given session was calculated by multiplying sets, repetitions and weight to calculate volume load/session; all sessions were summed to derive total “planned” cumulative volume load (volume load/patient). RT sessions in Weeks 1-2 were used for the purpose of dose finding for resistance exercises in which 1-RM was not evaluated. Intensity of each resistance exercise in Weeks 3 to 8 and 9 to 16 were quantified using baseline and midpoint 1-RM data for exercise in which a 1-RM was conducted, respectively. Calculation of “completed” intensity of each session was calculated by multiplying the actual number of sets, repetitions, and weight performed to calculate volume load/patient. The mean volume load was assigned to sessions in which intensity, defined by sets, repetitions and weight, was reduced (during the session), whereas missed sessions were assigned zero volume load. RDI was defined as the ratio of total “completed” to total “planned” cumulative dose. For context, a leg press performed at 60% of 1RM for 2 sets and 12 reps is equivalent to a volume load of 1680 lbs.

In CT, AT and RT RDI were first quantified separately as outlined above. An overall RDI was calculated as the average RDI of AT and RT.

**Primary and Secondary Endpoints**

The primary endpoint was cardiorespiratory fitness (VO2peak; ml O2.kg-1.min-1) assessed by a symptom-limited CPET on an electronic braked cycle ergometer (Corival, Lode) test with 12-lead ECG monitoring (Mac® 5000, GE Healthcare) according to standard procedures.[4]In brief, following three mins of rest, patients began cycling at an individualized 10-20 watts and were subsequently increased 5-20 watts every minute thereafter until exhaustion or a symptom-limitation was achieved. Breath-by-breath (averaged every 30 secs) expired gases were analyzed continuously by a calibrated metabolic measurement system (Parvo Medics, TrueOne 2400). Acceptable CPET criteria included any of the following: (1) a plateau in VO2, concurrent with an increase in workload, (2) respiratory exchange ratio ≥ 1.0, (3) attainment (± 10 bpm) of age-predicted heart rate, and (4) volitional exhaustion as measured by a rating of perceived exertion (RPE) ≥ 18 on the Borg scale. A second pre-randomization CPET was performed to account for learning effects.[4] VO2peak was defined as the highest recorded 30s average during the last 90 seconds of the CPET. All CPETs were conducted in a dedicated research laboratory by dedicated exercise physiologists at both institutions. Two patients at follow-up completed all assessments except CPET due to hip pain (n=1) and newly diagnosed severe aortic stenosis (n=1).

Secondary endpoints were resting cardiopulmonary end points [i.e., heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP)] as well as other measures acquired at peak CRF (i.e., VO2peak; L O2.min-1, respiratory exchange ratio, ventilation, heart rate, and SBP and DBP, as previously described[2]), upper and lower body maximal strength [1 repetition maximum (RM) leg press; lbs, 1RM chest press; lbs, 1RM seated row, lbs; assessed using standard guidelines][5], body weight and composition [weight; kg, percentage of lean and fat mass assessed via a dual-energy x-ray absorptiometry (Lunar DPX, General Electric) or air displacement plethysmography (Life Measurement Incorporated, Concord, CA)], and patient-reported outcomes (PROs) including quality of life [Functional Assessment of Cancer Therapy – Lung (FACT-L)[6] that contains the subscales for physical well-being, social well-being, emotional well-being, and functional well-being that comprise the FACT-G[7], plus a lung cancer subscale, Functional Assessment of Chronic Illness Therapy - fatigue scale (FACIT-fatigue),[8] pain (Brief Pain Inventory),[9] and sleep quality (Pittsburgh Sleep Quality Index)[10]].

All end points were evaluated at pre-randomization (study treatments were initiated ≤14 days) and were repeated ≤14 days of the final treatment session at postintervention (Week 17). Tolerability was assessed by multiple endpoints including: rate of lost to follow up (LTF; lack of completion of postintervention assessments), attendance (ratio of total attended to planned treatments), permanent discontinuation (treatment discontinuation prior to week 16), treatment interruption (missing ≥3 consecutive planned sessions), dose modification [≥10% of sessions requiring modification (reduction / escalation) of intensity and/or duration], pre-treatment dose modification (reduction of pre-treatment session intensity), early session termination (termination of session prior to planned duration), and relative dose intensity (RDI, defined as the ratio of total “completed” to total “planned” cumulative dose).[2] Early session termination was not assessed in RT. Safety was evaluated by the type and prevalence of serious (i.e., life-threatening, hospitalization, significant incapacity, important medical events) and non-serious (e.g., knee, back pain) adverse events during CPET and training sessions by Exercise Physiologists. Non-protocol exercise was assessed using a validated survey.[11]

Dedicated study personnel with at least a Bachelors degree in exercise science conducted all study assessments. Physiologic assessments were standardized in terms of time of day, order of assessments, pre-assessment fasting and exercise restrictions, and CPET procedures at all time-points.

**Study Oversight**

The trial was designed and conducted by the authors. All the authors confirm that the trial conformed to the protocol and attest to the accuracy and completeness of the data. The senior author wrote the first draft of the manuscript. All authors had full access to the data and were involved in data interpretation, in writing and reviewing subsequent manuscript drafts, and in making the decision to submit the manuscript for publication. Trial conduct was monitored by the data safety and monitoring board at each study location.

**Statistical Considerations**

All analyses were conducted under the intention-to-treat (ITT) principle. Missing values for the primary endpoint (n=11) were imputed with both multiple imputation using a Monte Carlo Markov single-chain method assuming a multivariate normal distribution and initial mean and covariance estimates derived using the expectation–maximization algorithm, and last observation carried forward (LOCF). Multiple imputation models included age, baseline and postintervention VO2peak (O2.kg-1.min-1), resting endpoints (SBP, DBP, and heart rate), and peak endpoints (SBP, DBP, HR, ventilation, and respiratory exchange ratio), and 10 imputation datasets were created after 400 burn-in imputations with 200 imputations between datasets. Results of both approaches were similar thus only data from LOCF analyses are reported. LOCF was also used for missing values in secondary end points. Changes between baseline and week 17 were estimated for each patient individually; the mean change within each treatment group was used to estimate group differences. The primary analysis used an Analysis of Covariance (ANCOVA) to estimate the association of study group with change from baseline to week 17 for the primary and secondary end points. Comparisons between exercise regimens were for exploratory purposes only. Analyses were adjusted for baseline values of the end point, and other variables displaying imbalance across group assignment. Hence, all analyses were adjusted for age, body mass index (BMI), and comorbidities [i.e., coronary artery disease, chronic obstructive pulmonary disease (COPD), and hypertension]. The proportion of patients in each treatment group with a VO2peak improvement greater than the technical error (TE) was evaluated as previously described.[12] Fisher’s Exact tests were used to compare rates of adverse events between study arms. Tolerability measures were compared across arms with the Kruskal-Wallis test for continuous variables and the Fisher’s Exact test for categorical variables. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

**Supplementary Table 1.** Exercise Treatment Dose Modification Guidelines

|  |  |
| --- | --- |
| **Health-Related Event** | **Action** |
| * Any serious eventa | * Early termination |
| * Any patient request for early termination | * Early termination |
| * Any non-serious adverse eventb | * If planned session intensity 55% to 75% workload   + Session modified to reduce workload   + Dose could be adjusted up to 3 times before session termination * If planned session intensity ≥85% workload   + Session duration reduced to maintain intensity   + Patient encouraged to complete longest duration safely possible.   + For interval sessions, if patient not able to complete interval duration. Intervals were terminated after 2 consecutive intervals where unable to achieve at least half the planned duration. |
| * Treatment interruption ≥ 21 consecutive planned sessions | * Repeat cardiopulmonary exercise / one-repetition maximal test or start planned prescription from week 1 dosing |

a Any grade 3 event, exercise accident, or at the discretion of exercise physiologist monitoring the treatment session.

b Any non-serious, health-related event including but not limited to abnormal heart rate or blood pressure response, lower extremity pain, excessive fatigue, or at the discretion of exercise physiologist monitoring the treatment session. If health-related event did not subside after a maximum of three dose modifications, session was terminated.

**Supplementary Table 2.** Comparison of Exercise Treatment Modalities on Primary and Secondary End points

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Difference between Arms**  **(AT vs. CT)** | **P§** | **Difference between Arms**  **(RT vs. CT)** | **P§** | **Difference between Arms**  **(AT vs. RT)** | **P§** |
| **Variable** |  |  |  |  |  |  |
| **Primary End point** |  |  |  |  |  |  |
| VO2peak, ml O2.kg-1.min-1 | –0.1 (2.2) | 0.96 | –1.4 (2) | 0.04 | 1.3 (2) | 0.03 |
| **Secondary End points** |  |  |  |  |  |  |
| **Peak Cardiopulmonary Function** |  |  |  |  |  |  |
| VO2peak, L O2.min-1 | 0 (0.2) | 0.80 | –0.1 (0.2) | 0.10 | 0.1 (0.1) | 0.04 |
| RER | 0.1 (0.1) | 0.04 | 0 (0.1) | 0.32 | 0.1 (0.1) | 0.09 |
| Ventilation, L O2.min-1 | 0 (8) | 0.53 | –5 (7) | 0.02 | 5 (8) | 0.006 |
| Heart rate, beats.min-1 | 6 (12) | 0.17 | 0 (12) | 0.71 | 6 (11) | 0.04 |
| Systolic blood pressure, mmHg | –1 (20) | 0.70 | 0 (19) | 0.84 | –1 (21) | 0.74 |
| Diastolic blood pressure, mmHg | –1 (8) | 0.65 | –1 (10) | 0.93 | 0 (9) | 0.55 |
| **Strength** |  |  |  |  |  |  |
| 1 RM leg press, lbs | –17 (28) | 0.08 | 8 (41) | 0.30 | –24 (35) | 0.01 |
| 1 RM chest press, lbs | –8 (13) | 0.01 | 14 (26) | 0.21 | –22 (25) | 0.002 |
| 1 RM seated row, lbs | –11 (11) | <0.001 | 5 (16) | 0.75 | –16 (13) | 0.001 |
| **Body Weight and Composition** |  |  |  |  |  |  |
| Weight, kg | 1 (2) | 0.25 | 0 (2) | 0.23 | 0 (2) | 0.87 |
| Lean body mass, % | –2 (3) | 0.01 | 0 (3) | 0.62 | –2 (3) | 0.04 |
| Fat mass, % | 2 (3) | 0.01 | 0 (3) | 0.62 | 2 (3) | 0.04 |

§Wilcoxon rank sum P value for delta change between groups from baseline to week 17.

**Abbreviations:** AC, attention control, AT, aerobic training; RT, resistance training; CT, combination training. FACT-L, Functional Assessment of Cancer Therapy-lung, FACT-G, Functional Assessment of Cancer Therapy-general; FACIT, Functional Assessment of Chronic Illness Therapy.

**Supplementary Table 3.** Reasons for Exercise Dose Modifications

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dose Modification | AT  (n=24) |  | RT  (n=23) |  | CT  (n=20) |
| Dizziness | 0 (0) |  | 0 (0) |  | 2 (0.1) |
| Exercise-induced tachycardia | 4 (0.3) |  | 0 (0) |  | 2 (0.1) |
| Myalgia | 0 (0) |  | 5 (0.3) |  | 5 (0.3 |
| Low heart rate | 16 (1.1) |  | 0 (0) |  | 2 (0.1) |
| Back pain | 4 (0.3) |  | 1 (0.1) |  | 16 (1.1) |
| Shortness of breath | 3 (0.2) |  | 1 (0.1) |  | 22 (1.5) |
| Fatigue | 6 (0.4) |  | 21 (1.4) |  | 27 (1.8) |
| Equipment | 50 (3.4) |  | 1 (0.1) |  | 25 (1.7) |
| Arthralgia | 4 (0.3) |  | 26 (1.8) |  | 48 (3.3) |
| Other / Non-specific | 166 (11.3) |  | 581 (39.6) |  | 430 (29.3) |

Data presented as number of events (%)

**Abbreviations:** AT, aerobic training; RT, resistance training; CT, combination training.

**Supplementary Table 4.** Adverse Events

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | AT  (n=24) |  | RT  (n=23) |  | CT  (n=20) |  | AC  (n=23) |  | *P†* |
| Abnormal heart rate response | 1 (4) |  | 0 (0) |  | 0 (0) |  | 0 (0) |  | 1.00 |
| Abnormal blood pressure response | 0 (0) |  | 1 (4) |  | 0 (0) |  | 0 (0) |  | 0.73 |
| Arthralgia | 3 (13) |  | 15 (65) |  | 12 (60) |  | 3 (13) |  | <0.001 |
| Back pain | 6 (25) |  | 4 (17) |  | 5 (25) |  | 2 (9) |  | 0.45 |
| Electrocardiogram abnormalities\* | 1 (4) |  | 1 (4) |  | 1 (5) |  | 0 (0) |  | 0.89 |
| Dizziness | 3 (13) |  | 3 (13) |  | 4 (20) |  | 0 (0) |  | 0.16 |
| Dyspnea | 1 (4) |  | 0 (0) |  | 2 (10) |  | 0 (0) |  | 0.17 |
| Headache | 1 (4) |  | 2 (9) |  | 1 (5) |  | 0 (0) |  | 0.63 |
| Low oxygen saturation | 0 (0) |  | 1 (4) |  | 2 (10) |  | 0 (0) |  | 0.13 |
| General fatigue | 2 (8) |  | 5 (22) |  | 5 (25) |  | 1 (4) |  | 0.16 |
| Pain in extremity | 2 (8) |  | 5 (22) |  | 4 (20) |  | 0 (0) |  | 0.06 |
| Lower extremity fatigue | 2 (8) |  | 0 (0) |  | 4 (20) |  | 0 (0) |  | 0.02 |
| Muscle Soreness | 0 (0) |  | 4 (17) |  | 4 (20) |  | 0 (0) |  | 0.008 |
| Peripheral motor neuropathy | 0 (0) |  | 0 (0) |  | 0 (0) |  | 0 (0) |  | - |
| Sick | 1 (4) |  | 5 (22) |  | 5 (25) |  | 0 (0) |  | 0.01 |
| Other | 0 (0) |  | 2 (9) |  | 1 (5) |  | 0 (0) |  | 0.26 |

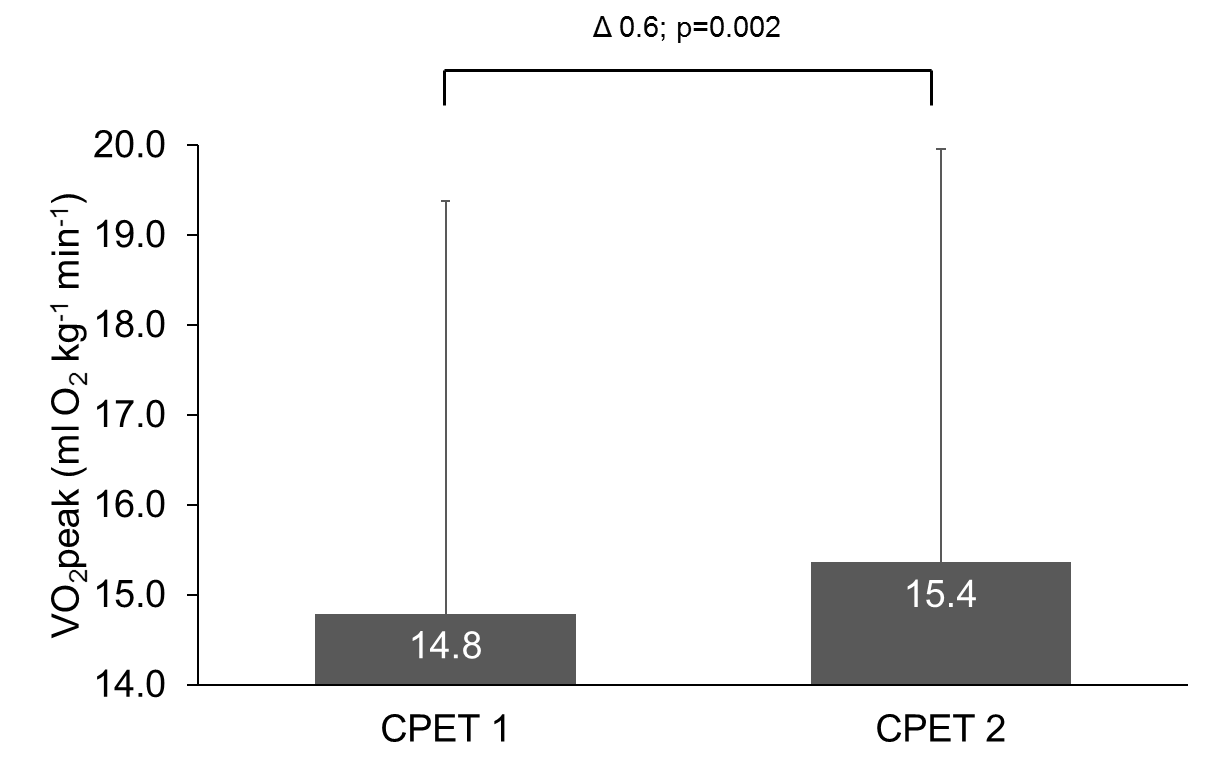
†Fisher’s exact test for differences across four groups.

\*Adverse event during cardiopulmonary exercise test

Data presented as number of patients (%)

**Abbreviations:** AC, attention control, AT, aerobic training; RT, resistance training; CT, combination training.

**Supplementary Figure 1.** Comparison ofCardiorespiratory Fitness Between the Two Cardiopulmonary Exercise Tests (CPET) Conducted at Pre-Randomization.



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