

# Neurological Sciences

## Whole body vibration and treadmill training in Parkinson's disease rehabilitation: effects on energy cost and recovery phases

--Manuscript Draft--

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<b>Abstract:</b>	<p>Background: Although physical treatment is recognized as being beneficial for patients with Parkinson's disease (PD), there is scant literature on the type of rehabilitation program most useful for patients with PD. The aim of the present study was to investigate the effects of two different training protocols (aerobic treadmill training, AER and whole body vibration training, WBVT) on energy cost and adaptations after exercise and recovery phases, by means of the oxygen consumption measurement and the assay of metabolic biochemical substrates.</p> <p>Methods: Twenty male patients with idiopathic Parkinson's disease, aged 51-66 years, were enrolled. Patients were randomly assigned to the training groups. The total work time was 20 min per group for 4 weeks, 4 times a week. In both groups, training intensity was monitored by the ratings of perceived exertion (RPE). Workload was gradually increased until patients worked up to the exertion level of 13 to 15 on the 20-point Borg Scale RPE. The outcome measures were oxygen consumption, free fatty acid (FFA) and amino acid (AA) levels.</p> <p>Results: The oxygen consumption during exercises does not show significant differences between the two training groups. Instead, only in the AER group excess post-exercise oxygen consumption measurements increased significantly (<math>p &lt; 0.01</math>) as well as FFA availability (<math>p &lt; 0.01</math>).</p> <p>Conclusion: The WBVT does not appear to require a long time of recovery and leads to less feeling of fatigue, whereas AER needs an appropriate recovery time after the training session.</p>

**Response to Reviewers:**

The manuscript was revised to meet the suggestion of referee and the number of subjects studied was increased (revisions and corrections in the text are in red bold).

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## **Whole body vibration and treadmill training in Parkinson's disease rehabilitation: effects on energy cost and recovery phases**

### **Abstract**

**Background:** Although physical treatment is recognized as being beneficial for patients with Parkinson's disease (PD), there is scant literature on the type of rehabilitation program most useful for patients with PD. The aim of the present study was to investigate the effects of two different training protocols (aerobic treadmill training, AER and whole body vibration training, WBVT) on energy cost and adaptations after exercise and recovery phases, by means of the oxygen consumption measurement and the assay of metabolic biochemical substrates.

**Methods:** Twenty male patients with idiopathic Parkinson's disease, aged 51-66 years, were enrolled. Patients were randomly assigned to the training groups. The total work time was 20 min per group for 4 weeks, 4 times a week. In both groups, training intensity was monitored by the ratings of perceived exertion (RPE). Workload was gradually increased until patients worked up to the exertion level of 13 to 15 on the 20-point Borg Scale RPE. The outcome measures were oxygen consumption, free fatty acid (FFA) and amino acid (AA) levels.

**Results:** The oxygen consumption during exercises does not show significant differences between the two training groups. Instead, only in the AER group excess post-exercise oxygen consumption measurements increased significantly ( $p < 0.01$ ) as well as FFA availability ( $p < 0.01$ ).

**Conclusion:** The WBVT does not appear to require a long time of recovery and leads to less feeling of fatigue, whereas AER needs an appropriate recovery time after the training session.

**Keywords:** Parkinson's Disease, Rehabilitation, Vibration, Excess Post-Exercise Oxygen Consumption, Amino acids, Free Fatty Acids

## Introduction

Parkinson's Disease (PD) is the second more common neurodegenerative disorder causing motor disability and cognitive dysfunction. A depletion of dopaminergic neurons laying in basal ganglia has been confirmed: several pathogenetic hypotheses have been proposed, but its etiology is still unknown. This disorder is clinically characterized by rest tremor, bradykinesia, rigidity, gait and balance dysfunction with increased risk of fall. L-DOPA, coupled with carbidopa, a peripheral decarboxylase inhibitor, remains the gold standard of symptomatic treatment for PD [1].

In the last decades, the key role of rehabilitation has been recognized: physical exercise has been shown to be fundamental to improve functional outcome of gait, balance and posture; reduce rigidity; preserve quality of life and prevent complications [2]. PD risk in humans has been also found to be significantly reduced by exercise [3]. Rehabilitative interventions include the use of different ergometers, such as treadmill devices providing optical or acoustic cues, and different platform for vibration training.

Treadmill training can be performed with [4] and without [5] body support in order to have immediate and long-term effects on gait parameters. Several studies have showed promising results of this type of training in persons with neurological disorders, in the form of improved balance, walking and obstacle avoidance performance [6].

Whole body vibration training (WBVT) simulates the dynamics of human physiologic gait, run, rising or falling stairs, depending on the vibration intensity and platform position [7]: a frequency higher than 30 Hz could lead to tetanic contraction, while a beneficial stimulation of tendon and joint proprioceptors during muscle stretching can be induced at 20 Hz (duration 30-50 ms, and 4-mm amplitude for whole body such as to trigger the myotatic reflex). Several studies have shown that WBVT is effective in improving muscle strength, gait parameter and postural control in different chronic conditions [8]. PD patients, with proprioceptive deficit, may be potential beneficiaries of WBVT, for enhancement of sensory processing [9]. Ebersbach G et al. showed that WBVT produce effects comparable to those of conventional therapy: both treatments were associated with improved mobility and postural stability [10].

Exercise intervention protocols with treadmill training or WBVT have reported improvements in motor ability, balance and mood in PD patients [11,10] by different mechanisms, as it has been shown in papers based on studies using animal models of PD [12]. However, in the study of these two rehabilitation exercises some important aspects, such as the oxygen consumption ( $VO_2$ ), the excess post-exercise oxygen consumption (EPOC), respiratory exchange ratio (RER), and the adaptations after exercise and recovery phases (free fatty acid and amino acid feedback), were still insufficiently analysed, particularly in PD subjects.

For this reason, the present study was undertaken in order to evaluate  $VO_2$ , EPOC, RER, FFA and AA feedback, in PD patients undergoing exercise training using different technical devices: treadmill and WBVT. The results might have practical implications for PD patients in order to optimize the level and time of training rehabilitation, minimizing the secondary complications such as metabolic aspects of "burnout", fatigue and overtraining syndrome, not yet well evaluated in the literature.

## **Materials and methods**

### **Subjects**

**Twenty** male patients with idiopathic PD, aged **51-66** years, were enrolled, diagnosed according to the clinical diagnostic criteria by Gelb et al [13], not less than  $3 \pm 1$  years before.

Subjects suffering from Parkinsonisms (multiple system atrophy, progressive supranuclear palsy, Lewy body disease, cortico-basal degeneration), as well as subjects scoring lower than 17/30 at the Mini-Mental State Examination, were excluded.

All **20** patients enrolled were at the Hoehn-Yahr's II stage [14]; they were treated with L-DOPA/carbidopa (Table 1) with no side effects or on-off phenomena, and did not change their drug therapy during the entire study period.

Before training, patients were functionally assessed by using the Movement Disorders Society-revised/updated version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-II, III, and IV Sections [15].

Particular care was taken in recruiting subjects with similar body structure (for minimizing a confounding factor, step length in walking or center of mass in WBVT) and levels of disability.

The study was approved by the local Ethical Committee of the Azienda Ospedaliero-Universitaria Pisana in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained prior to participation in the study and after explanation of the protocol.

### **Experimental procedure**

The rehabilitation protocol was performed with the same timing of drug therapy, in order to optimize the pharmacological effects and have a better compliance. As eating a mixed meal causes an increase in the availability of a variety of substrates and hormones, the patients on the test day admitted to the lab consumed standard composition meals.

Subjects were subdivided into two groups as described in Table I and the total work time (specific session) was 20 min per group for 4 weeks, 4 times a week.

All patients performed a warm-up consisted by exercising on a bicycle ergometer at a load of 50 W for 15 min (comfortable workload) followed by stretching exercises for 5 min.

A 1-week period of supervised adaptation to the exercise was carried out by the two groups. Exercise training intensity was monitored by the RPE scale. Workload was gradually increased until the patient worked up to the

exertion level of approximately 13 to 15 on the 20-point Borg Scale RPE [16]. By using this approach, workload values were monitored, and constantly paralleled the training progression.

#### *Treadmill training*

Aerobic treadmill training (AER) consisted in 4 series of 5-min walking on a treadmill (Technogym Med. Excite - Cesena, Italy) with a 1min restore, at a speed able to maintain 75 % of the heart rate (HR) reserve, calculated by deducting basal HR from the theoretical maximal HR ( $HR_{max}$ ), following the Tanaka's criteria [17]. All patients were able to walk unassisted.

The treadmill was programmed on the setup HR software, monitored via a telemetric system (Heart Rate Telemetry System, Hosand Technology s.r.l, Italy), and the device automatically adjusted speed and/or slope according to the subject's performance in order to keep the patient's HR within the setup range. At the end of the protocol, the final speed was  $4.2 \pm 0.3$  km/h, and the RPE values were similar to those in the WBVT group.

#### *WBVT training*

In WBVT an alternating vibrating platform was employed (Galileo Med L2000, Novotec Medical GmbH, Germany). Through a harness system, in order to normalize workload, patients' body weight was relieved of 20% at the beginning of training ( $T_0$ ), then a progressive increase of 5% body weight was added every week, so that at the end of treatment ( $T_1$ ) the body weight on the vibrating platform was at 100 %. Such an isometric protocol consisted in 1-min 20 series in semisquat position with a 1min restore. The WBVT group was tested to at 26 Hz frequency, 4 mm amplitude with an acceleration of  $106.64 \text{ m/s}^2$ , on the basis of own experience and literature data for the activation frequency of the quadriceps muscle group [18], and at the RPE values expressed in preliminary tests, similar to those in the AER group.

### **Data analysis**

#### *Metabolic data*

Metabolic parameters (oxygen consumption,  $VO_2$  in ml/min;  $VO_2/kg$  in ml/min/kg; carbon dioxide production,  $VCO_2$  in ml/min; excess post-exercise oxygen consumption, EPOC in ml/min/kg; and respiratory exchange ratio, RER in  $VCO_2/VO_2$ ) were evaluated in the last exercise session of training protocol ( $T_1$ ).



VO<sub>2</sub> at rest and during training sessions was assessed by using a telemetrically monitored indirect calorimetry (VO2000, MedGraph, USA). Data collected with "Breath by Breath" method were reported as average oxygen consumption every 1 min (VO<sub>2\_ave</sub>) and assessed as Metabolic Equivalent of Task (MET).

Subjects were monitored for EPOC, in a sitting position in a comfortable environment maintained at constant temperature and ventilation.

VO<sub>2</sub>, VCO<sub>2</sub> and RER were used to assess the prevailing metabolism [19].

#### *Biochemical data*

To measure FFA and AA, in particular branched chain-AA (BCAA) and aromatic AA (AAAr), venous blood was collected into EDTA tube 30 min before exercise and 2 h after exercise. FFA and AA levels were measured at the first exercise session (T<sub>0</sub>) and repeated at the end of the protocol (T<sub>1</sub>). The blood was stored at -80° C until analyzed. The FFA determinations were based on the acyl CoA synthetase/oxidase analysis technique, using a commercially available assay analysis kit (Free Fatty Acids, Half-micro test, Roche, Mannheim, D). Results are given as mmol/L. Amino acid concentrations were assayed using a high-performance liquid chromatography (HPLC) procedure as described by Donati et al. (2009) [20]. Amino acid separation was carried out on a 4.6 x 250 mm Bio-Sil ODS-5S column (particle size, 5 mm) in a Beckman HPLC system (equipped with 32 Karat software). Amino acids were determined by measuring the fluorescence of dansylated derivative with a Jasco spectrofluorometer (340 nm excitation, 525 emission). Norvaline was added as an internal standard to all samples. Levels of AAAr [phenylalanine (Phe), tryptophan (Trp), methionine (Met) and tyrosine (Tyr)] and BCAA [leucine (Leu), isoleucine (Ile) and valine (Val)] are given as mmol/L.

#### **Statistical analysis**

Data are reported as mean ± standard deviation (SD). The analysis of variance (ANOVA) test was used to evaluate differences among multiple conditions. If positive, the Tukey test was used to test for their statistical significance. Student's t test was used to evaluate differences between two conditions. Values of p < 0.05 were considered to be statistically significant.

## Results

All patients tolerated the procedure well and without reporting immediate or delayed adverse effects such as dizziness, discomfort, pain or dyskinesias.

Basal metabolism (measured as  $\text{VO}_{2 \text{ avg}}$ ) resulted in  $3.33 \pm 0.11$  and  $3.25 \pm 0.09$  ml/min/kg for the AER group and the WBVT group, respectively, in line with the values for normal subjects (3.5 ml/min/kg) reported in the literature. We found that  $\text{VO}_{2 \text{ avg}}$  for both groups progressively increased from the beginning of exercise to reach a steady state (Fig. 1). No statistically significant ( $p = 0.61$ ) differences between AER and WBVT groups were observed:  $13.46 \pm 4.96$  and  $13.22 \pm 6.16$  ml/min/kg, respectively (which corresponds to about 4,0 MET).

Considering the trend of  $\text{VO}_{2 \text{ avg}}$  per min of work, a significant ( $p < 0.05$ ) increase between the 3<sup>rd</sup> and the 7<sup>th</sup> min was found in the AER group compared to the WBVT one; oxygen consumption becomes equal between 8<sup>th</sup> and 15<sup>th</sup> min; then reverses the trend between the 16<sup>th</sup> and the 20<sup>th</sup> min, where the WBVT exercise produced a significant increase ( $p < 0.05$ ) in respect to the AER. The  $\text{VO}_{2 \text{ avg}}$  peak was significantly ( $p < 0.05$ ) higher in WBVT than in AER:  $20.70 \pm 1.16$  and  $18.55 \pm 1.11$  ml/min/kg, respectively (which corresponds to about 6,0 MET).

In EPOC evaluation during the fast component (first 10 min)  $\text{VO}_{2 \text{ avg}}$  had a rapid decrease in both groups (Fig. 2). However, the best linear fit slope (polynomial II) shows a faster reduction in the WBVT group:  $0.072$  vs  $0.049$  ml/min/kg for WBVT and AER groups, respectively ( $p < 0.05$ ).

In the slow component (after 30 min),  $\text{VO}_{2 \text{ avg}}$  remained on higher values for AER subjects compared to WBVT patients (Fig. 3), but with a similar decrease ( $0.004$  ml/min/kg).

Considering 100 % the peak value of oxygen consumption (Fig. 4), to assess the decrement rate, the average half time in the EPOC course was  $24 \text{ min } 41 \text{ s } \pm 42 \text{ s}$  in the WBVT group vs  $28 \text{ min } 30 \text{ s } \pm 51 \text{ s}$  in the AER group; the time necessary for  $\text{VO}_{2 \text{ avg}}$  to return to the baseline ( $\pm 1\%$ ) was  $92 \text{ min } \pm 3 \text{ min}$  for the WBVT group and  $151 \text{ min } \pm 14 \text{ min}$  for the AER group ( $p < 0.01$ ).

To simplify the representation of recovery, RER data are reported as difference ( $\Delta$ ) between the end-of-exercise and baseline values (Fig. 5). Baseline values were the following:  $0.86 \pm 0.07$  and  $0.87 \pm 0.05$ , in the WBVT and AER groups, respectively. At the start of recovery (first 5 min), there was a similar transient upward deflection in RER values, followed by a gradual and persistent decline until baseline was reached (WBVT group) or surpassed (AER group). In the WBVT group the RER value returns to  $0.87 \pm 0.05$  (close to the baseline values) in about 90 min, whereas the AER group values exceed the baseline by further decreasing to  $0.75 \pm 0.04$  - which differs significantly ( $p < 0.01$ ) from that reached in the WBVT group.

As seen in Fig. 6, FFA availability was significantly ( $p < 0.01$ ) increased only in the AER group at  $T_1$  after exercise, whereas no significant differences were found at  $T_0$  for both groups regardless exercise.

BCAA analysis at  $T_0$  did not show statistically differences between before and after exercise in both WBVT and AER groups, whereas at  $T_1$  a significant decrease in BCAA levels was observed after exercise in the AER ( $p < 0.01$ ) and in the WBVT ( $p < 0.05$ ) groups (Fig. 6), although no significant differences were found among the individual AA.

As far as AAAs are concerned, there were no significant differences in the Phe, Met and Tyr blood levels before and after exercise in the two groups at  $T_0$  and  $T_1$ . The same happened for the total Trp values: instead, increasing of free Trp was observed. Although at  $T_0$  there were no differences before and after exercise in the two groups, at  $T_1$  free Trp values increased after exercise significantly ( $p < 0.05$ ) in the WBVT group and very significantly ( $p < 0.01$ ) for the AER one. Moreover, in the latter free Trp values enhanced significantly ( $p < 0.05$ ) by 60% between  $T_0$  and  $T_1$ .

## Discussion

Among the various types of training for PD patients, treadmill [21] or WBVT [22], the common factor that can be linked to the improvement in symptoms is the high intensity of the exercise, in accordance with studies on PD animal models [23].

In this study, we examined the metabolic impact of two different high intensity training protocols, by means of the measurement of oxygen consumption and the assay of metabolic biochemical substrates, before and after training.

### *Oxygen consumption*

During exercise there is an increase in oxygen uptake to support the increased energy need. Our results show that WBVT increases  $VO_{2\text{ avg}}$  as much as AER with similar RPE and time of work. This consumption attained the average level of 13 ml/min/kg, which corresponds to 4,0 MET.

Our data support strongly that WBVT elicits muscular activity, not only passive vibration. It is likely that eccentric muscle work at 26-Hz vibration induces stretch activation of the muscle [24], and that the  $VO_2$  response is due to the increased number of muscle fibers activated by the vibrations [25].

In our study, monitoring the  $VO_{2\text{ avg}}$  trend since the beginning of exercises provided the opportunity to compare the slope of the curves for the two different training. We have in both WBVT and AER an incremental response of  $VO_{2\text{ avg}}$ . As a result, in general, the  $VO_{2\text{ avg}}$  curves during both training types were similar at the beginning and between the 8<sup>th</sup> and the 15<sup>th</sup> min, but diverged significantly between the 3<sup>rd</sup> and the 7<sup>th</sup> and after the 16<sup>th</sup> min. Surprisingly, the vibratory exercise has a significantly  $VO_{2\text{ avg}}$  peak higher than the non-aerobic exercise: probably, this effect might be related to the static and dynamic nature of exercise.

During the WBVT, the subjects held the same knee angle and the muscles were continuously twitched. On the other hand, during the dynamic walking in the AER, the contraction is reduced in the stance phase of the walk. Literature data suggest that the blood pressure response to static contraction is greater than that caused by dynamic exercise [26] and, when static and dynamic contraction were compared, these responses are higher during static contraction [27].

### *EPOC*

In both WBVT and AER after exercise oxygen uptake does not immediately return to the resting levels, but may be elevated for some period of time [28].

There are two components in EPOC: the rapid (fast) component after the end of exercise, and the prolonged (slow) component which may persist for several hours after exercise. Some of the mechanisms underlying the fast EPOC are well documented as such as replenishment of oxygen stores in blood and muscles; resynthesis of adenosine triphosphate and creatine phosphate; lactate removal and increase of body temperature; circulation and ventilation [29,30]. The prolonged EPOC component may partly be explained with the metabolic shift from carbohydrates to fatty acids as source of energy: the metabolism of fatty acids requires more oxygen than that of carbohydrates [31]. In our study, in the first 30 min after the end of exercise (EPOC early component), a significant decrease in  $VO_{2\text{ avg}}$  was reported in all the patients, significantly faster in the WBVT group, more slowly in the AER one. During the late phase (over 30 min), although a plateau is reached,  $VO_{2\text{ avg}}$  goes to the pre-exercise levels in the WBVT subjects in **92 min** (as mean value), whereas it significantly increases, over **151 min** in average, in the AER group. EPOC duration depends on many factors, such as exercise intensity [32], number and time of exercise sessions [29].

### *RER*

It indirectly shows the muscle's oxidative capacity to get energy and can be used as an index of aerobic metabolism, as it depends on the macro-nutrient used during exercise to recover homeostasis.

Our data showed in the early phase a RER increase, which reflects the onset of hyperventilation in all subject in a greater (but not significant) manner in the WBVT group than in the AER one, when the reduced oxygen request overcomes ventilation rate, and thus a higher  $VCO_2$  is released by lungs.

In the late phase, the significant RER reduction in the AER group suggests a larger use of lipid substrates during such a training type. Increase in fat oxidation is often caused by enhanced FFA blood levels. Many studies have reported the maximal fat oxidation between 33 to 65 % of maximal  $VO_2$  (corresponding to 35 to 75 % of  $HR_{\text{max}}$ ) [33]. The rate of appearance for FFA is increased by enhanced lipolysis and decreased FFA re-esterification. Wolfe et al. [34] reported that the percentage of re-esterification is reduced from 70 % in rest to 25 % during 30-min low/moderate-intensity exercises.

Treadmill exercise is a kind of dynamic movement, as compared to WBVT which is an isometric one. Presumably, treadmill training improves blood flow that facilitate the delivery of FFA from adipose tissue to the working muscles. On the contrary, sustained isometric contractions produce intramuscular and compartmental pressures that can limit blood flow.

### *BCAA and AAAR*

Substantially, our data confirm, in both exercise groups, that the BCAA are significantly consumed, whereas free

Trp, the serotonin precursor, increases. The plasmatic free Trp/BCAA enhanced in all the patients, in particular in the AER group. Serotonin synthesis and dopamine production depend upon the availability of Trp and Tyr which compete for the same transporter. An increase in serotonin availability through exercise, may be helpful in PD.

Interestingly, some studies have indicated that excessive serotonin induced fatigue [35]. As Trp circulates in the bloodstream bound to albumin, when BCAA levels decrease, a larger amount of Trp can reach the nervous system, thus producing a fatigue symptom. Moreover, as also FFA circulate bound to albumin, the excess of blood FFA during exercise displaces Trp from the same protein, with consequently enhanced free Trp levels. It has been hypothesized that the higher Trp levels lead to a serotonin increase, which could be at the origin of central fatigue [36]. The latter is the inability to maintain the normal performance level due to an increased effort perception, and the hypothesized pathogenesis is a neurotransmission dysfunction, such as a decreased serotonergic tone [37]. Furthermore, being the Trp a precursor of serotonin, it might decrease the effects of therapy with L-DOPA in patients of AER group. Some studies on animal models have shown that the administration of a serotonin precursor decreases the effect of L-DOPA in PD mice and monkeys. Such a negative effect of serotonin precursor may be due to either a competition between L-DOPA and serotonin precursor for membrane transport, or the binding of serotonin to its 5HT<sub>1</sub> receptor [38].

## **Conclusions**

The oxygen consumption does not show particular differences between the two kinds of training when they are carried out in order to develop the same workload. Significant differences, instead, exist in EPOC measurements. In fact, in patients undergone to an aerobic exercise it increased more than in the WBVT group. This indicates that in such patients the required time for the recovery of energetic substrates is longer. In patients performing a type of rehabilitation with aerobic exercises it is therefore advisable to program an appropriate recovery time between a training session and the following one. The WBVT does not appear to require a long time of recovery and leads to less feeling of fatigue. However, we should mention that this is a preliminary open study with the limitation of small sample size study population and further studies with a larger sample size and an evaluation of the existence of a remote carry-over effect (follow-up) are needed. In addition, other parameters could be evaluated providing wearable devices to PD patients, as suggested in a recent paper [39].

In conclusion, a correct alternation between training and rest is important to produce the adequate compensation strategies, in particular in PD subjects, who frequently complain of fatigue symptom or the little

known overtraining syndrome which might increase reduced performance, oxidative stress [40] and perception of fatigue [41].

### **Compliance with ethical standards**

### **Conflicts of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

## References

1. *Neurol Sci* (2003) 24(Suppl 3): s165. <https://doi.org/10.1007/s100720300068>
2. Shen X, Wong-Yu IS, Mak MK (2016) Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis. *Neurorehabil Neural Repair* 30:512-27
3. Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, Schatzkin A, Chen H (2010) Physical activities and future risk of Parkinson disease. *Neurology* 75:341-348
4. Gama GL, Celestino ML, Barela JA, Forrester L, Whittall J, Barela AM (2017) Effects of gait training with body weight support on a treadmill vs overground for individuals with stroke. *Arch Phys Med Rehabil* 98:738-745
5. Druzicki M, Guzik A, Przysada G, Kwolek A, Brzozowska-Magoń A, Sobolewski M (2016) Changes in gait symmetry after training on a treadmill with biofeedback in chronic stroke patients: a 6-month follow-up from a randomized controlled trial. *Med Sci Monit* 22:4859-4868
6. Khan F, Amatya B, Galea MP, Gonzenbach R, Kesselring J (2017) Neurorehabilitation: applied neuroplasticity. *J Neurol* 264:603-615
7. Rittweger J (2010) Vibration as an exercise modality: how it may work, and what its potential might be. *Eur J Appl Physiol* 108:877-904
8. Chanou K, Gerodimos V, Karatrantou K, Jamurtas A (2012) Whole-body vibration and rehabilitation of chronic diseases: a review of the literature. *J Sports Sci Med* 11:187-200
9. Hiroshige K, Mahbub MH, Harada N (2014) Effects of whole-body vibration on postural balance and proprioception in healthy young and elderly subjects: a randomized cross-over study. *J Sports Med Phys Fitness* 54:216-224
10. Ebersbach G, Edler D, Kaufhold O, Wissel J (2008) Whole body vibration versus conventional physiotherapy to improve balance and gait in Parkinson's disease. *Arch Phys Med Rehabil* 89:399-403
11. Lauhoff P, Murphy N, Doherty C, Horgan NF (2013) A controlled clinical trial investigating the effects of cycle ergometry training on exercise tolerance, balance and quality of life in patients with Parkinson's disease. *Disabil Rehabil* 35(5):382-387
12. da Silva PG, Domingues DD, de Carvalho LA, Allodi S, Correa CL (2016) Neurotrophic factors in Parkinson's disease are regulated by exercise: Evidence-based practice. *J Neurol Sci* 363:5-15
13. Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. *Arch Neurol* 56:33-39
14. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. *Neurology* 17:427-442



15. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P et al (2008) Movement disorder society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDSUPDRS): scale presentation and clinimetric testing results. *Mov Disord* 23:2129–2170
16. Borg G (1970) Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 2:92-98
17. Tanaka H, Monahan KD, Seals DR (2001) Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 37:153-156
18. Cardinale M, Lim J (2003) Electromyography activity of vastus lateralis muscle during whole body vibrations of different frequencies. *J Strength Cond Res* 17:621-624
19. Leff ML, Hill JO, Yates AA, Cotsonis GA, Heymsfield SB (1987) Resting metabolic rate: measurement reliability. *JPEN J Parenter Enteral Nutr* 11:354-359
20. Donati A, Cavallini G, Bergamini E (2009) Methods for inducing and monitoring liver autophagy relative to aging and antiaging caloric restriction in rats. *Methods Enzymol* 452:441-455
21. Fisher BE, Wu AD, Salem GJ, Song J, Lin CH, Yip J, Cen S, Gordon J, Jakowec M, Petzinger G (2008) The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Arch Phys Med Rehabil* 89:1221-1229
22. Turbanski S, Haas CT, Friedrich A, Duisberg P, Schmidtbleicher D (2005) Effects of random whole-body vibration on postural control in Parkinson's disease. *Res Sports Med* 13:243-256
23. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW (2013) Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol* 12:716-726
24. Bosco C, Komi PV, Ito A (1981) Prestretch potentiation of human skeletal muscle during ballistic movement. *Acta Physiol Scand* 111:135-140
25. Romaiuguère P, Vedel JP, Azulay JP, Pagni S (1991) Differential activation of motor units in the wrist extensor muscles during the tonic vibration reflex in man. *J Physiol* 444:645-667
26. Kaufman MP, Rybicki KJ, Waldrop TG, Mitchell JH (1984) Effect on arterial pressure of rhythmically contracting the hind-limb muscles of cats. *J Appl Physiol* 56:1265-1271
27. Blomqvist CG, Lewis SF, Taylor WF, Graham RM (1981) Similarity of the hemodynamic responses to static and dynamic exercise of small muscle groups. *Circ Res* 48:187-192
28. Bahr R (1992) Excess postexercise oxygen consumption-magnitude, mechanisms and practical implications. *Acta Physiol Scand Suppl* 605:1-70
29. Børsheim E, Bahr R (2003) Effect of exercise intensity, duration and mode on post-exercise oxygen consumption. *Sports Med* 33:1037-1060

30. Scott CB (2011) Quantifying the immediate recovery energy expenditure of resistance training. *J Strength Cond Res* 25:1159-1163
31. Van Loon LJ, Greenhaff PL, Constantin-Teodosiu D, Saris WH, Wagenmakers AJ (2001) The effects of increasing exercise intensity on muscle fuel utilisation in humans. *J Physiol* 536:295-304
32. Smith J, Mc Naughton L (1993) The effects of intensity of exercise on excess postexercise oxygen consumption and energy expenditure in moderately trained men and women. *Eur J Appl Physiol Occup Physiol* 67:420-425
33. Purdom T, Kravitz L, Dokladny K, Mermier C (2018) Understanding the factors that effect maximal fat oxidation. *J Int Soc Sports Nutr* 15:3
34. Wolfe RR, Klein S, Carraro F, Weber JM (1990) Role of triglyceride-fatty acid cycle in controlling fat metabolism in humans during and after exercise. *Am J Physiol* 258:E382-E389
35. Cordeiro LMS, Rabelo PCR, Moraes MM, Teixeira-Coelho F, Coimbra CC, Wanner SP, Soares DD (2017) Physical exercise-induced fatigue: the role of serotonergic and dopaminergic systems. *Braz J Med Biol Res* 50:e6432
36. Bédard C, Wallman MJ, Pourcher E, Gould PV, Parent A, Parent M (2011) Serotonin and dopamine striatal innervation in Parkinson's disease and Huntington's chorea. *Parkinsonism Relat Disord* 17:593-598
37. Newsholme EA, Blomstrand E (1995) Tryptophan, 5-hydroxytryptamine and a possible explanation for central fatigue. *Adv Exp Med Biol* 384:315-320
38. Paul J, Kuruvilla KP, Mathew J, Kumar P, Paulose CS (2011) Dopamine D1 and D2, receptor subtypes functional regulation in cerebral cortex of unilateral rotenone lesioned Parkinson's rat model: Effect of serotonin, dopamine and norepinephrine. *Parkinsonism Relat Disord* 17:255-259
39. Cai G, Huang Y, Luo S, Lin Z, Dai H, Ye Q (2017) Continuous quantitative monitoring of physical activity in Parkinson's disease patients by using wearable devices: a case-control study. *Neurol Sci* 38:1657-1663
40. Gökçe Çokal B, Yurtdaş M, Keskin Güler S, Güneş HN, Ataç Uçar C, Aytaç B, Durak ZE, Yoldaş TK, Durak İ, Çubukçu HC (2017) Serum glutathione peroxidase, xanthine oxidase, and superoxide dismutase activities and malondialdehyde levels in patients with Parkinson's disease. *Neurol Sci* 38:425-431
41. Dogan VB, Koksall A, Dirican A, Baybas S, Dirican A, Dogan GB (2015) Independent effect of fatigue on health-related quality of life in patients with idiopathic Parkinson's disease. *Neurol Sci* 36:2221-2226

## Figure captions

**Fig. 1** Oxygen consumption curve during exercise, normalized to body mass ( $\text{VO}_2/\text{kg}$ ), in the two different training groups (WBVT and AER). Triangles and circles indicate the values of energy consumption average ( $\text{VO}_{2\text{ avg}}$ ) measured during rehabilitation treatments in WBVT and AER groups, respectively. Solid lines represent the best linear fit slope (polynomial II).  $\text{VO}_{2\text{ avg}}$  for both groups progressively increased from the beginning of exercise to reach a steady state. In the AER group  $\text{VO}_{2\text{ avg}}$  increase significantly ( $p < 0.05$ ), between the 3<sup>rd</sup> and the 7<sup>th</sup>, compared to WBVT group. Oxygen consumption becomes equal between 8<sup>th</sup> and 15<sup>th</sup> min. Then, between the 16<sup>th</sup> and the 20<sup>th</sup> min, the WBVT exercise produced a significant increase ( $p < 0.05$ ) in respect to the AER

**Fig. 2** Early component of the excess post-exercise oxygen consumption (EPOC). Squares and circles indicate the values of WBVT and AER groups, respectively. During the fast component (first 10 min)  $\text{VO}_{2\text{ avg}}$ , normalized to body mass ( $\text{VO}_2/\text{kg}$ ), has a rapid decrease in both groups. The best linear fit slope (polynomial II) shows a faster reduction in the WBVT group ( $p < 0.05$ )

**Fig. 3** Late component of the excess post-exercise oxygen consumption (EPOC). Triangles and circles indicate the values of WBVT and AER groups, respectively. In the slow component (after 30 min),  $\text{VO}_{2\text{ avg}}$ , normalized to body mass ( $\text{VO}_2/\text{kg}$ ), remains at higher values for AER group compared to WBVT group

**Fig. 4** Percent decrement of the excess post-exercise oxygen consumption (EPOC). Triangles and circles indicate the values of WBVT and AER groups, respectively. Considering 100 % the peak value of oxygen consumption to assess the decrement rate, the average half time in the EPOC course was **24 min** in the WBVT group vs **28 min** in the AER group; the time necessary for  $\text{VO}_{2\text{ avg}}$  to return to the baseline (1%) was **92 min** for the WBVT group and **151 min** for the AER group ( $p < 0.01$ )

**Fig. 5** Respiratory Exchange Ratio (RER). Triangles and circles indicate the values of WBVT and AER groups, respectively. Data are reported as difference ( $\Delta$ ) between the end of exercise and baseline values. In the WBVT group the RER value returns close to the baseline values in about 90 min, whereas the AER group values exceed the baseline ( $p < 0.01$ )

**Fig. 6** Free Fatty Acid (FFA) and branched chain amino-acids (BCAA, Leu = Leucine; Ile = Isoleucine; Val = Valine; Tot = Total) plasma concentrations at  $T_0$  and  $T_1$  in the two different training groups (WBVT and AER) before and after exercise (\*  $p < 0.05$ ; \*\*  $p < 0.01$ )

Fig.1

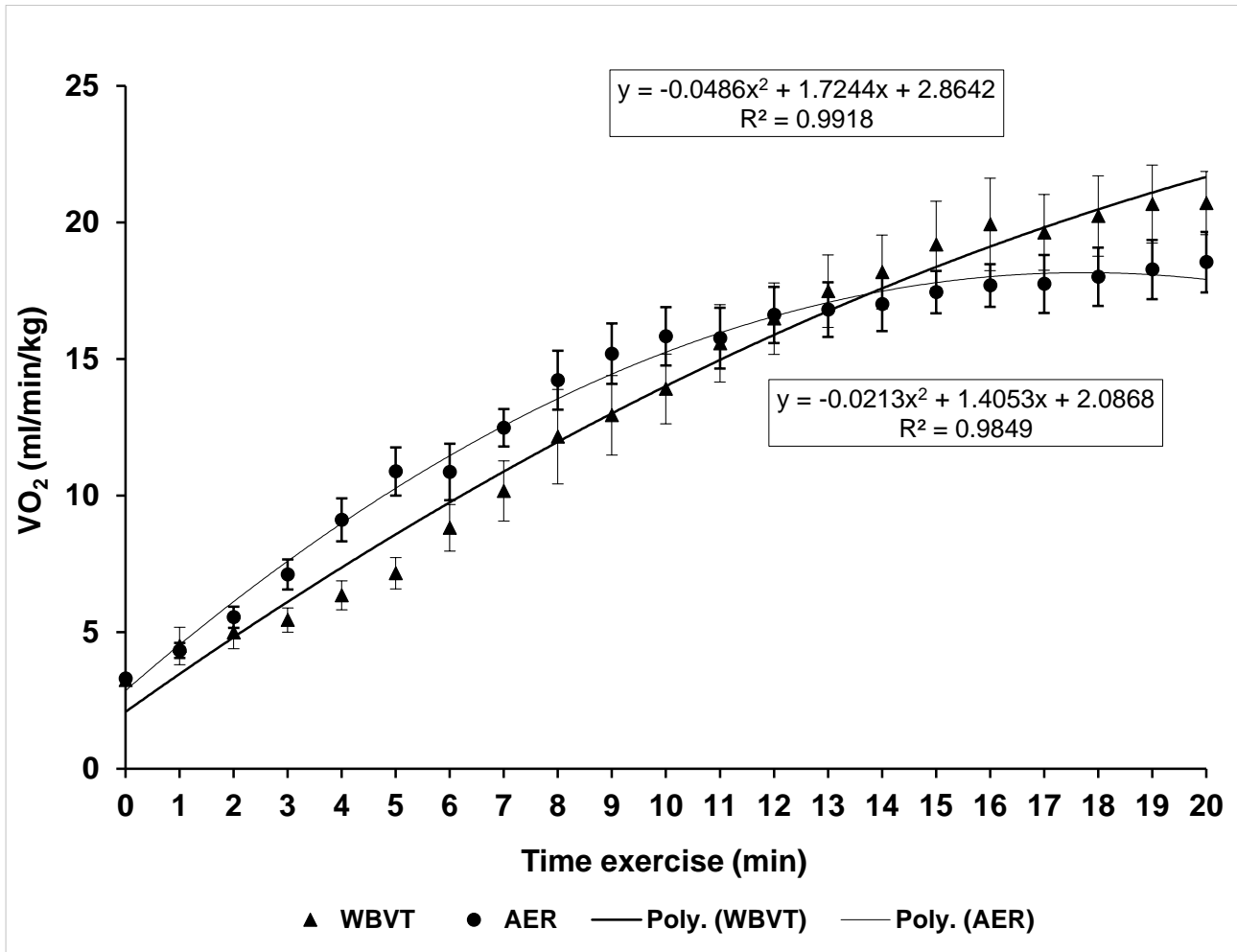


Fig. 2

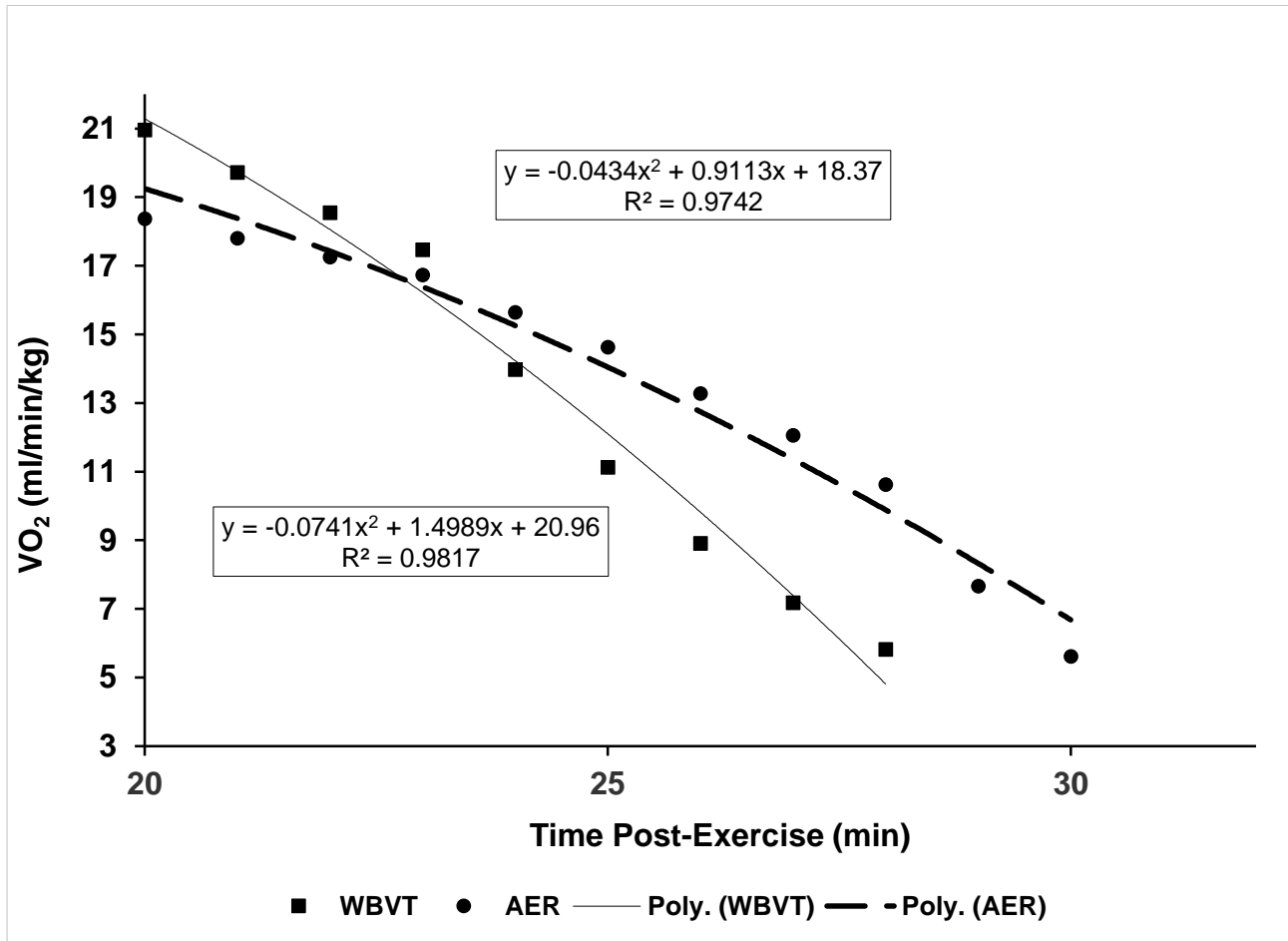


Fig. 3

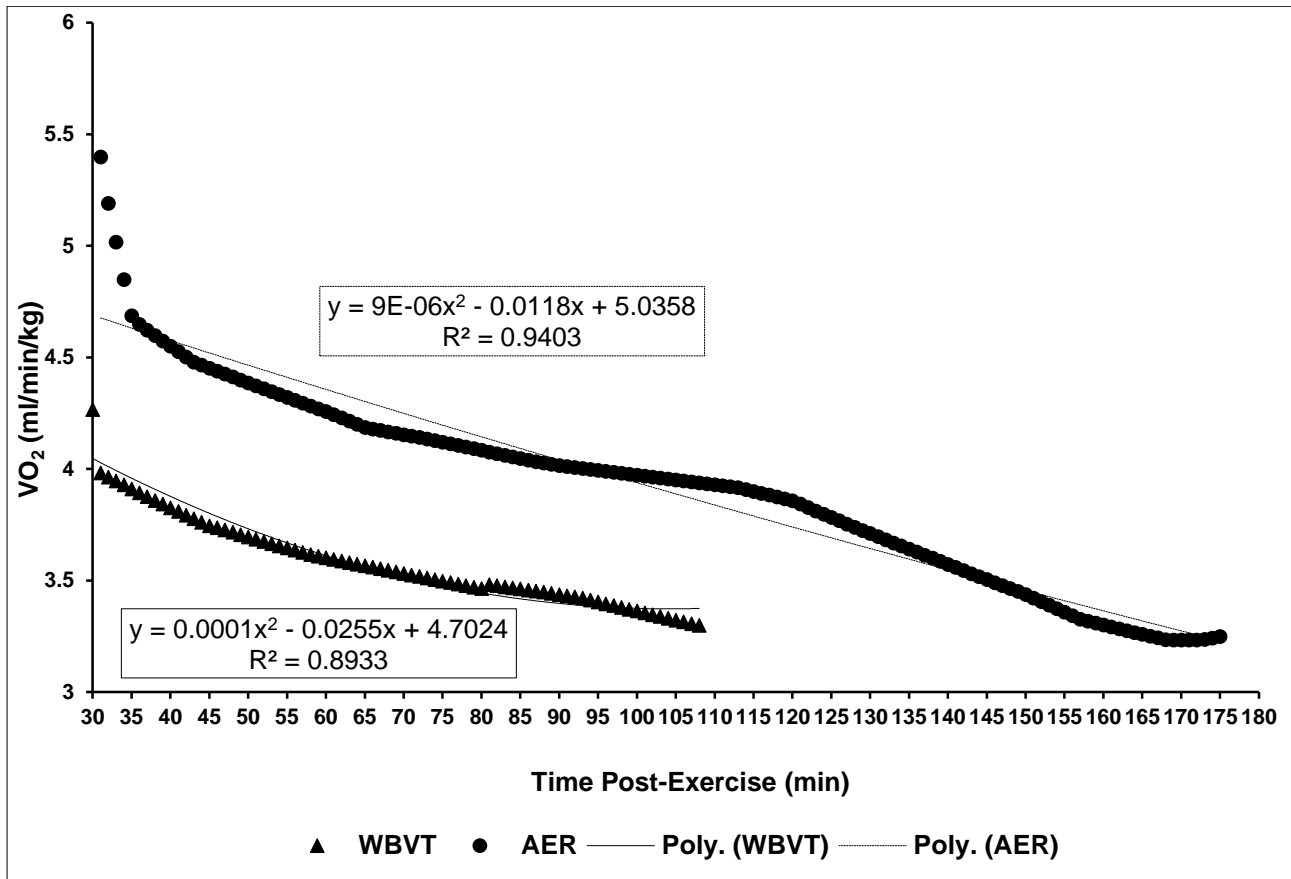


Fig. 4

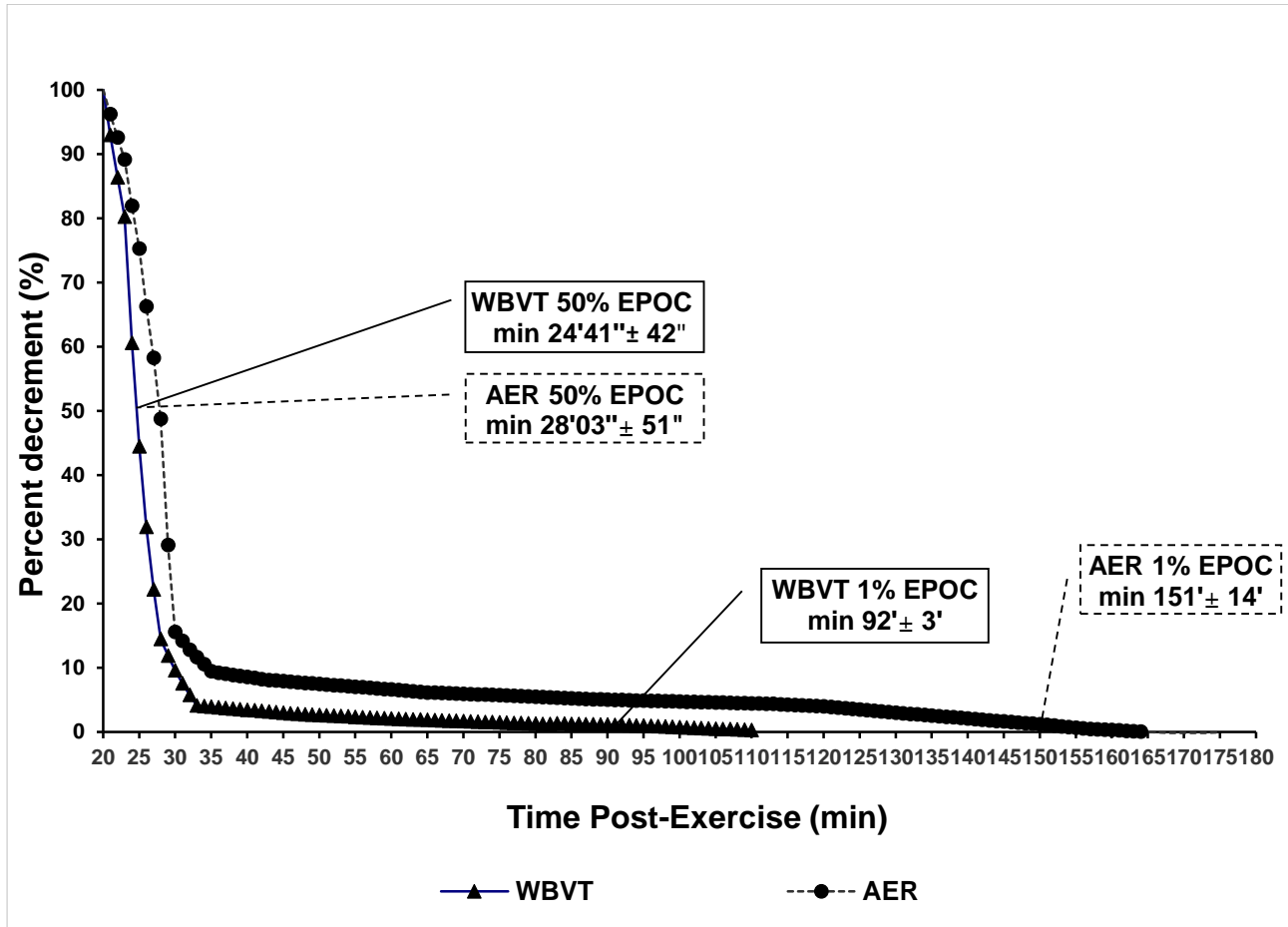


Fig. 5

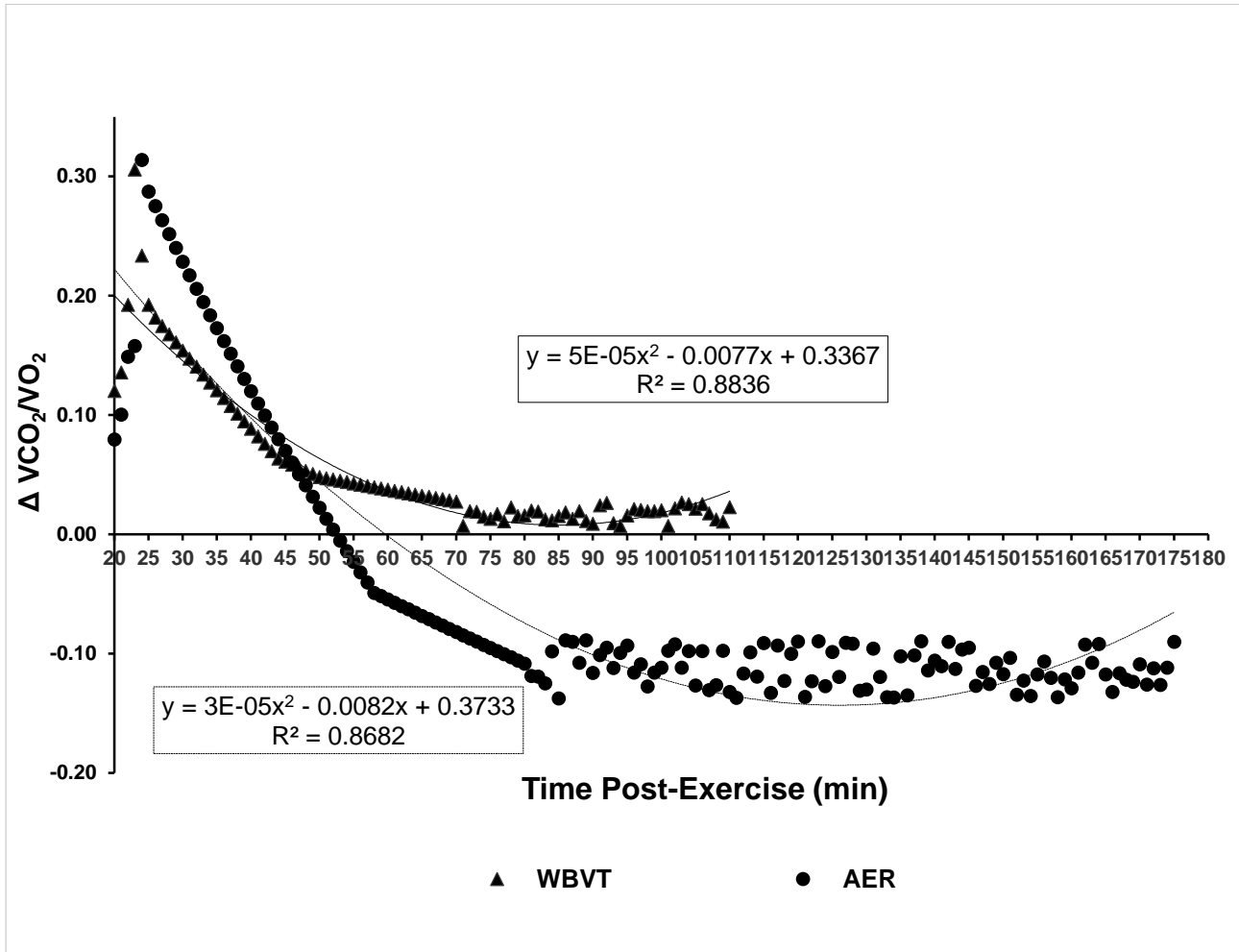
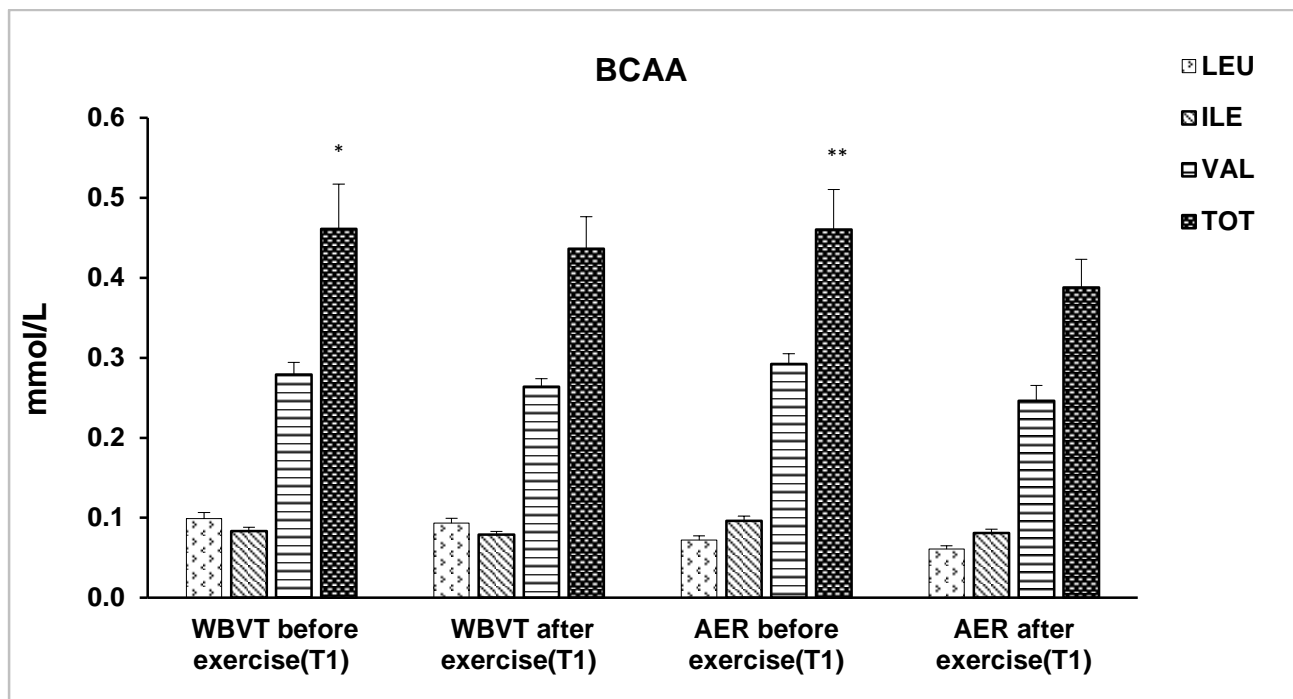
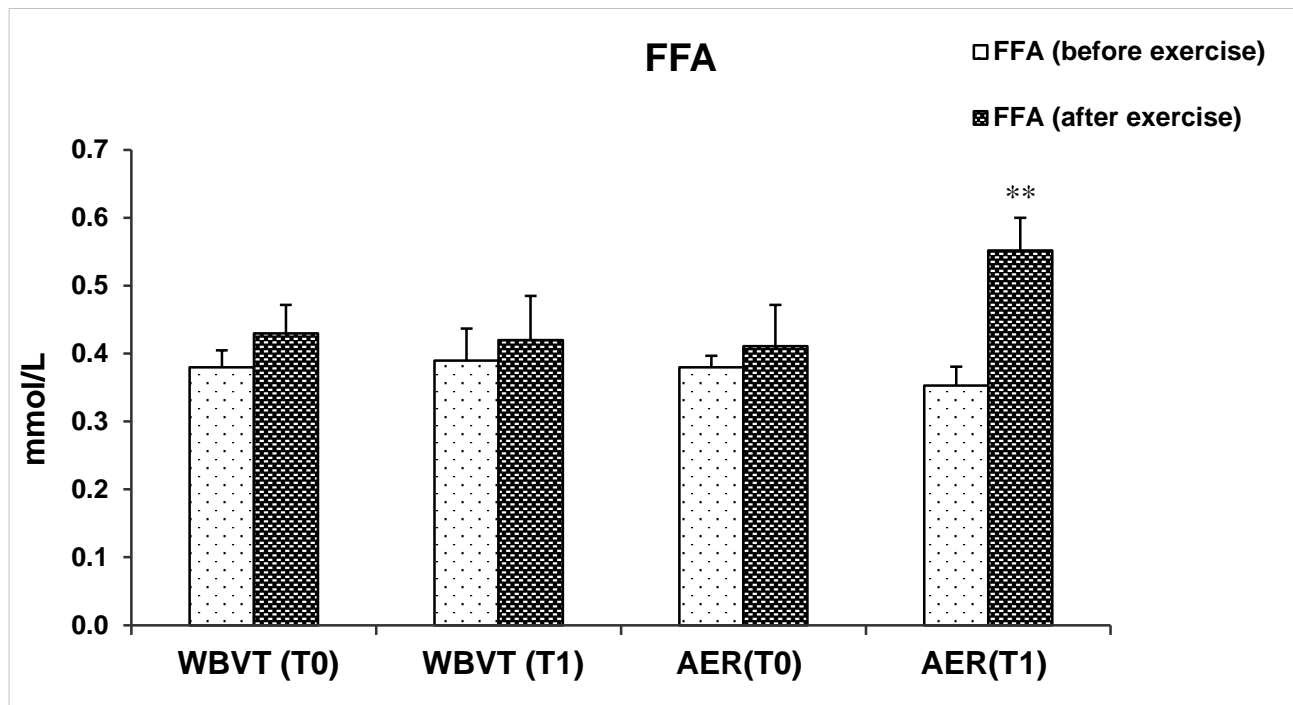




Fig. 6



**Table 1** General characteristics of the whole group analysis

	WBVT ( <i>N</i> = 10)	AER ( <i>N</i> = 10)
Age (years)	58.8 ± 3.9	56.9 ± 4.7
Weight (kg)	80.8 ± 3.3	81.8 ± 2.5
Height (cm)	180 ± 4	178 ± 4
BMI (kg/m <sup>2</sup> )	25.1 ± 1.2	25.8 ± 1.6
Disease duration (years)	3 ± 1	3 ± 1
H&Y	II	II
MDS-UPDRS (motor score)	M-EDL 18.7 ± 2.3 ME 34.9 ± 3.2	M-EDL 18.5 ± 2.9 ME 37.7 ± 4.8
L-DOPA dosage (mg/day)	373.50 ± 51.81	400.60 ± 29.24

*WBVT* whole body vibration training, *AER* aerobic treadmill training, *BMI* body mass index, *H&Y* Hoehn & Yahr stage,

*MDS-UPDRS* MDS unified Parkinson's disease rating scale