



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

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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, four 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

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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 [10, 11] 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 analyzed, 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 ± 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 1 and the total work time (specific session) was 20 min per group for 4 weeks, four times a week.

Table 1 General characteristics of the whole group analysis

	WBVT (N = 10)	AER (N = 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 ²)	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

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 four series of 5-min walking on a treadmill (Technogym Med. Excite - Cesena, Italy) with a 1-min 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 ± 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 1-min restore. The WBVT group was tested to at 26 Hz frequency, 4 mm amplitude with an acceleration of 106.64 m/s², 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, VO₂ in ml/min; VO₂/kg in ml/min/kg; carbon dioxide production, VCO₂ in ml/min; excess post-exercise oxygen consumption, EPOC in ml/min/kg; and respiratory exchange ratio, RER in VCO₂/VO₂) were evaluated in the last exercise session of training protocol (T_1).

VO₂ 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 (VO₂ avg) 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.

VO₂, VCO₂, 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_0) and repeated at the end of the protocol (T_1). 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 × 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 AAAs [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 \pm 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 ± 0.11 and 3.25 ± 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 ± 4.96 and 13.22 ± 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 3rd and the 7th min was found in the AER group compared to the WBVT one; oxygen consumption becomes equal between the 8th and the 15th min, and then reverses the trend between the 16th and the 20th 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 ± 1.16 and 18.55 ± 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 min 41 \pm 42 s in the WBVT group vs 28 min 30 \pm 51 s in the AER group; the time necessary for

$\text{VO}_{2\text{ avg}}$ to return to the baseline ($\pm 1\%$) was 92 ± 3 min for the WBVT group and 151 ± 14 min for the AER group ($p < 0.01$).

To simplify the representation of recovery, RER data are reported as difference (Δ) between the end of exercise and baseline values (Fig. 5). Baseline values were the following: 0.86 ± 0.07 and 0.87 ± 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 ± 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 ± 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

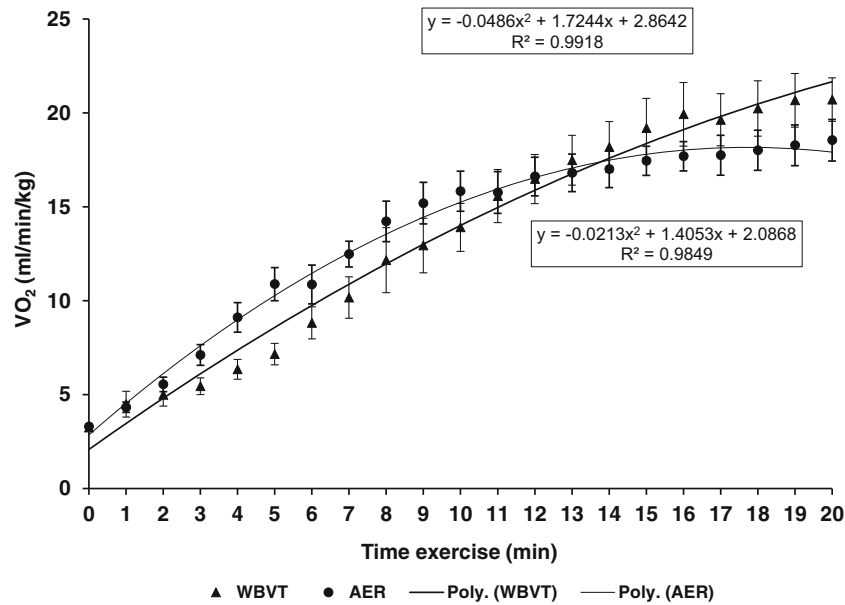


Fig. 1 Oxygen consumption curve during exercise, normalized to body mass (VO_2/kg), in the two different training groups (WBVT and AER). Triangles and circles indicate the values of energy consumption average ($\text{VO}_{2\text{ avg}}$) measured during rehabilitation treatments in WBVT and AER groups, 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 3rd and the 7th, compared to WBVT group. Oxygen consumption becomes equal between the 8th and the 15th min. Then, between the 16th and the 20th min, the WBVT exercise produced a significant increase ($p < 0.05$) in respect to the AER

increases $\text{VO}_{2\text{ avg}}$ 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 $\text{VO}_{2\text{ avg}}$ 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 $\text{VO}_{2\text{ avg}}$. As a result, in general, the $\text{VO}_{2\text{ avg}}$ curves during both training types were similar at the beginning and between the 8th and the 15th min, but diverged significantly between the 3rd and the 7th and after the 16th min. Surprisingly, the vibratory exercise has a significantly $\text{VO}_{2\text{ avg}}$ peak higher than the

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 (VO_2/kg), has a rapid decrease in both groups. The best linear fit slope (polynomial II) shows a faster reduction in the WBVT group ($p < 0.05$)

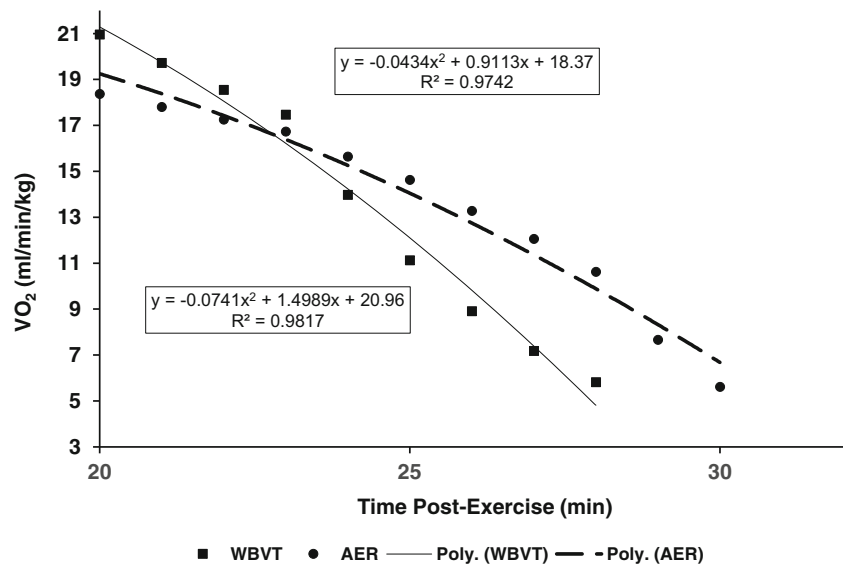
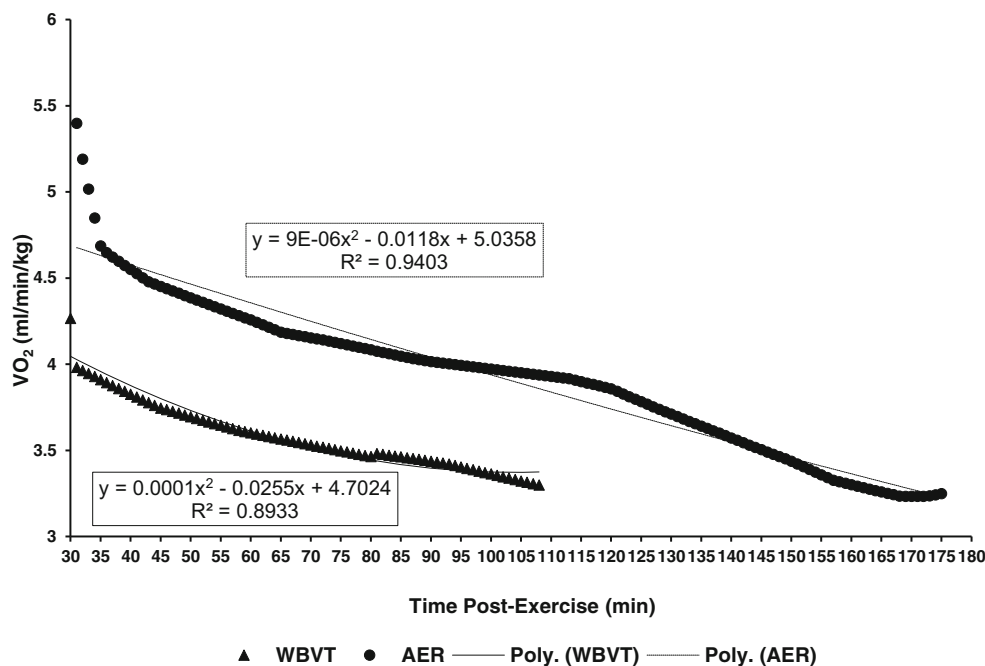


Fig. 3 Late component of the excess post-exercise oxygen consumption (EPOC). Triangles and circles indicate the values of WBVT and AER groups, respectively. In the slow component (after 30 min), VO_2 avg, normalized to body mass (VO_2/kg), remains at higher values for AER group compared to WBVT group



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

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 VO_2 avg to return to the baseline (1%) was 92 min for the WBVT group and 151 min for the AER group ($p < 0.01$)

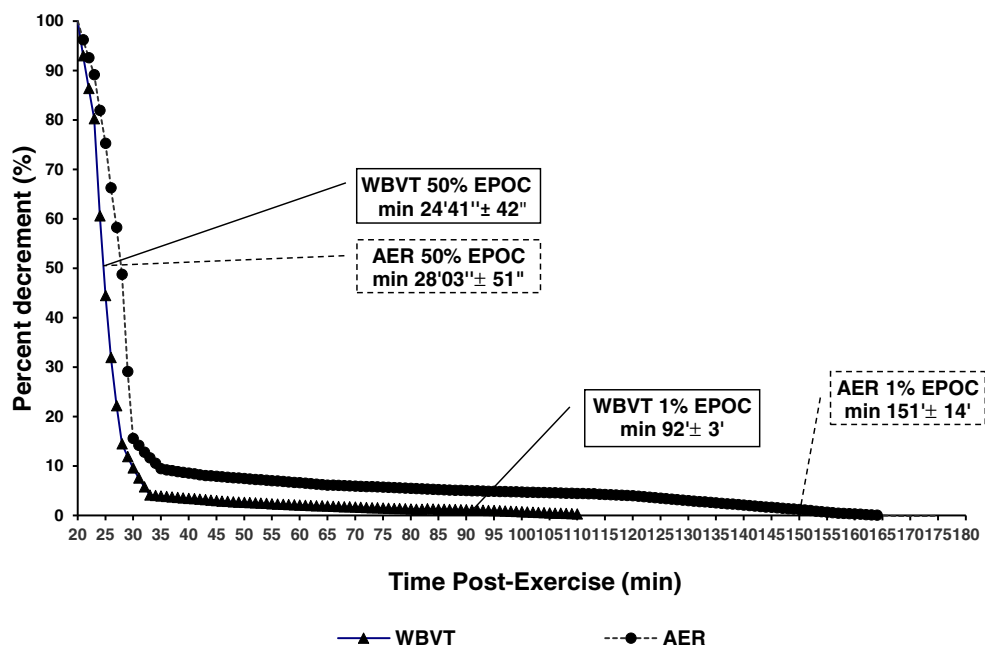
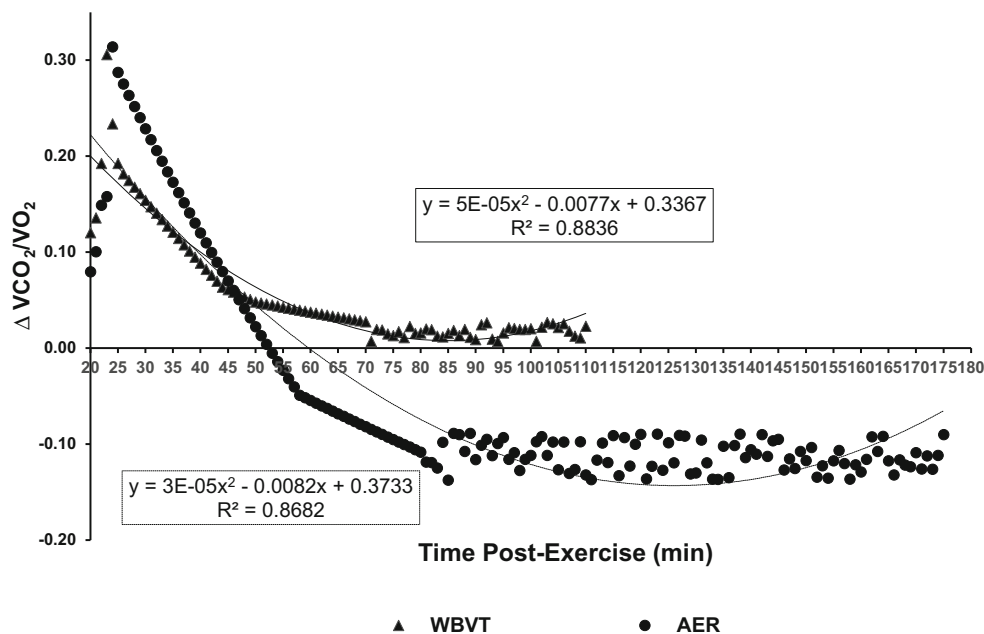


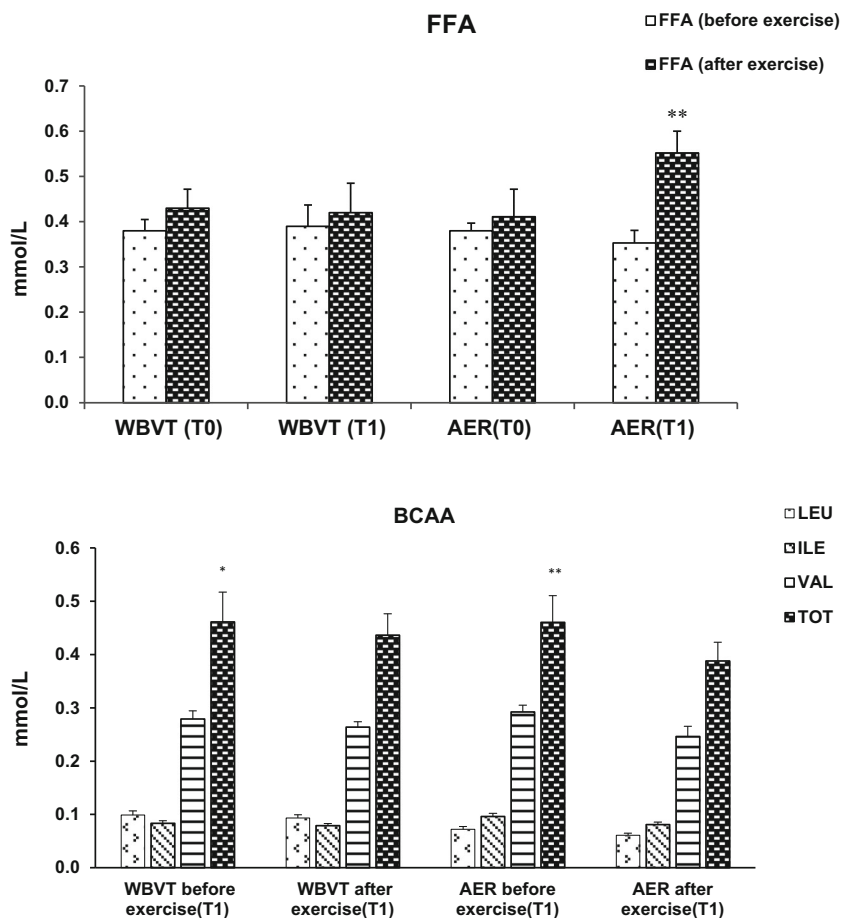
Fig. 5 Respiratory exchange ratio (RER). Triangles and circles indicate the values of WBVT and AER groups, respectively. Data are reported as difference (Δ) between the end of exercise and baseline values. In the WBVT group, the RER value returns close to the baseline values in about 90 min, whereas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



blood and muscles; resynthesis of adenosine triphosphate and creatine phosphate; lactate removal and increase of body

temperature; and circulation and ventilation [29, 30]. The prolonged EPOC component may partly be explained with

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 (* $p < 0.05$; ** $p < 0.01$)



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 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 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 the 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 and 65% of maximal VO_2 (corresponding to 35 to 75% of HR_{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 blood-stream 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_1 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

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.

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

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