Blunted maximal and submaximal responses to cardiopulmonary exercise test in patients with Parkinson's Disease

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Blunted maximal and submaximal responses to cardiopulmonary exercise test in patients with Parkinson Disease

Running Head: Maximal exercise test in Parkinson Disease

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Abstract

OBJECTIVE: To investigate submaximal and maximal responses during maximal cardiopulmonary exercise tests in patients with Parkinson Disease (PD).

DESIGN: Cross-sectional.

SETTING: The Brazilian Parkinson Association.

PARTICIPANTS: Forty-eight patients with PD (66±8 years old, modified Hoehn & Yahr stages 2-3, "on" state) and 20 age-matched controls without PD (64±9 years old).

INTERVENTIONS: Maximal cardiopulmonary exercise test on a cycle ergometer.

MAIN OUTCOME MEASURES: Oxygen uptake (VO_2), systolic blood pressure (SBP) and heart rate (HR) assessed at rest, submaximal intensities (i.e. anaerobic threshold - AT and respiratory compensation point - RCP) and maximal intensity (peak exercise).

RESULTS: Compared to the control subjects, the patients with PD presented lower VO_2, HR and SBP at RCP and peak exercise (VO_2: 14.6±3.6 vs. 17.9±5.5 and 17.7±4.8 vs. 21.5±6.6 $ml.kg^{-1}.min^{-1}$; HR: 119±17 vs. 139±12 and 132±20 vs. 158±13 bpm; SBP: 151±17 vs. 172±20 and 166±21 vs. 187±24 mmHg, $p \leq 0.05$, respectively). They also present lower HR at AT (102±14 vs. 110±13 bpm, $p \leq 0.05$); while VO_2 and SBP at this intensity were similar to the control subjects.

CONCLUSION: Patients with PD presented blunted metabolic and cardiovascular responses to submaximal and maximal exercise test, especially at intensities above AT, which are in line with autonomic disturbances present in PD. Future study needs to determine how this affects performance, participation and responses of these patients to exercise training at different intensities.

KEYWORDS: Parkinsonism, autonomic dysfunction, exercise test, oxygen consumption, rehabilitation.

Abbreviations

AT: Anaerobic threshold

HR: Heart rate

PD: Parkinson`s Disease

RCP: Respiratory compensation point

SBP: Systolic blood pressure

Introduction

Parkinson`s Disease (PD) is a progressive neurologic disorder characterized by distinct hallmarks of motor dysfunction, including rigidity, bradykinesia, postural instability and resting tremor. In addition, patients with PD also commonly present non-motor abnormalities, such as metabolic, autonomic and cardiovascular dysfunctions [1-4], which may contribute to the mortality in this population [5, 6].

In the last years, the knowledge about rehabilitation and exercise in PD are emerging management options, and the maximal cardiopulmonary exercise test could be a good tool to evaluate cardiovascular parameters and risk, since abnormal responses to such test has been associated with worse prognosis in others populations [7], [8]. Previous studies investigating peak responses during cardiopulmonary exercise tests in patients with PD found contradictory results. Some authors [9, 10] reported blunted peak responses of oxygen uptake (VO_2), heart rate (HR) and systolic blood pressure (SBP) in patients with PD in comparison with control subjects, while others [11-13] reported no difference.

The achievement of peak responses, however, may be difficult in patients with PD because of the inherent motor limitations of the disease [14]. Thus, evaluation of the submaximal responses to exercise may bring additive knowledge. Some previous studies have reported submaximal responses at the same absolute workload comparing patients with PD and control subjects. Werner et al. (2006) reported similar HR and SBP at stage 2 of the modified Bruce protocol, while Protas et al. [15] suggested higher VO_2 at different submaximal absolute workloads in patients with PD. The higher VO_2, however, suggest a higher energy demand for the same absolute workload in PD, which may influence cardiovascular responses. Hence, to improve knowledge in this regard, it is also important to compare responses at the same relative effort, which to the best of our knowledge have not been studied before.

The ventilatory thresholds, i.e. the anaerobic threshold (AT) and the respiratory compensation point (RCP), have been proposed as important relative exercise intensities that express metabolic changes during submaximal exercise [16, 17]. These thresholds resemble the intensity of the efforts of daily activities [18] and provide useful information for physical training prescription [19]. Therefore, the ventilatory thresholds may constitute important submaximal relative intensities to be studied.

Because of the inconsistent results and the lack of data in this area, this study was designed to investigate submaximal and maximal metabolic and cardiovascular responses of patients with PD during a maximal cardiopulmonary exercise test. Since patients with PD are known to have metabolic, autonomic and cardiovascular dysfunctions, the hypotheses were that patients with PD present lower VO_2, HR and SBP at AT, RCP and peak exercise in comparison to control subjects.

Materials and Methods

Subjects

Patients with PD, aged ≤ 50 years, and between 2 and 3 of the modified Hoehn and Yahr stages [20], were studied. Patients were recruited from the Brazilian Parkinson Association. The clinical diagnosis of PD was based on the UK Parkinson`s Disease Society Brain Bank Criteria [21]. Subjects without any known neurological disease matched by gender and age to the patients with PD were studied as controls. They were recruited through verbal invitations and flyers advertisements distributed in the communities close to the university and the Parkinson Association. Subjects were excluded if they presented: i) neurological conditions other than PD, ii) cardiovascular diseases, iii) hypertension (i.e. use of anti-hypertensive medication and/or resting systolic/diastolic blood pressures ≥ 140/90 mmHg – mean of three measures in two

visits), iv) were taking medications that could affect the cardiovascular system, except for the medications used for the treatment of PD; or v) involved in any regular exercise program, except for physiotherapy for the treatment of PD. These criteria were assessed by the patients' medical records, and a physician's interview and clinical examination. All patients with PD were doing physiotherapy that included activities for improving motor control, balance and stretching, but did not involve aerobic stimuli. All subjects signed an informed written consent approved by the local ethical committee. The study was registered in ClinicalTrials.gov (U111-1129-0762).

Experimental Protocol

All subjects underwent a maximal cardiopulmonary exercise test. Before the test, they were instructed not to exercise in the previous 48 h, to eat a light meal 2 h beforehand, and to avoid central stimulant substances, such as caffeine, tea, cola and others for the previous 12 h. Furthermore, all the patients with PD were instructed to take their PD medication 30 min before the start of the test. The test was conducted on a cycle ergometer (Lode, Corival, Netherlands) to minimize any possible influence of motor impairment. Fifteen to twenty minutes before the test, the subjects were familiarized to the cycle ergometer by pedaling at a comfortable intensity for 2-3 minutes. Then, after a rest that assured the return of cardiovascular parameters to baseline, the test was started. An individualized ramp protocol was chosen to promote fatigue between 8 and 12 min of testing. This involved choosing an increment between 3 and 15 watts per minute according to the subjects´ physical conditioning level. All the tests started with an intensity of 0 watts and pedaling frequency was kept between 50 and 60 rpm. The tests were interrupted when the subjects were unable to keep the pedaling frequency.

Inspired and expired gases were collected breath-by-breath during the entire test by a metabolic cart (Medical Graphics Corporation, CPX/D, United States of America). Data were averaged over 30 s intervals for further analyses. Thus, peak oxygen uptake (VO_{2peak}) was directly measured and considered as the highest value obtained during the test. AT was assessed by the nonlinear increase in respiratory exchange ratio and ventilation, as well as by the increase in end-tidal oxygen partial pressure and oxygen ventilatory equivalent. RCP was established by the second nonlinear increase in ventilation, the decrease in the end-tidal carbon dioxide partial pressure and the increase in carbon dioxide ventilatory equivalent [16, 17] (Figure 1).

Auscultatory SBP was measured every 2 min using a mercury sphygmomanometer. Measurements were taken by a physician with extensive experience (more than 10 years) in performing measurements during maximal exercise tests. HR was continuous monitored by a 12-lead echocardiogram (Cardio Perfect, ST 2001, Netherlands) and was registered as 30 s averages. Peak HR was considered as the highest value achieved at the end of the test.

Statistical Analysis

The normality of the data distribution was confirmed by Shapiro-Wilk test. Consequently, the chi-square and T tests were used for comparing differences between the groups (control and PD) regarding categorical and continuous variables, respectively. Significance was defined as $P \leq 0.05$. The data are presented as means ± SD.

Results

Fifty-eight patients with PD and 23 control subjects signed the informed consents. During the preliminary examination, 9 patients with PD were excluded because they had other health problems (e.g. hypertension, cardiovascular disease, etc.); 1 patient with PD was excluded because she was unable to achieve the pedaling frequency of the test and 3 control subjects dropped out because of personal reasons. Thus, 48 patients with PD (35 males and 13 females) and 20 control subjects (12 males and 8 females) completed the experimental protocol. Their characteristics are summarized in Table 1.

There were no between-group differences for gender distribution, age, body mass index, resting SBP, HR and VO_2. The patients with PD were at the moderate stage of the disease, and received the classical anti-parkinsonian medications shown in Table 1.

AT and RCP occurred at similar relative intensities in the patients with PD and the control subjects (AT: 59.9±12.1 vs. 55.7±9.2 % of VO_2peak, p=0.17 and RCP: 81.6±8.6 vs. 83.4±7.8 % of VO_2peak, p=0.41). These intensities corresponded to a similar absolute workloads at AT (41±23 vs. 51±23 watts, p=0.12) but to a lower absolute workload in patients with PD in comparison to control subjects at RCP (73±33 vs. 93±39 watts, p=0.03).

Almost all of the subjects, except for 4 patients with PD and 1 control subject, achieved a respiratory exchanged ratio greater than 1.10 at peak effort. In addition, respiratory exchange ratio obtained at AT, RCP and peak exercise were similar between the patients with PD and the control subjects (AT: 0.94±0.08 vs. 0.92±0.05, p=0.46; RCP: 1.11±0.10 vs. 1.15±0.08, p=0.21; and Peak: 1.25±0.12 vs. 1.26±0.10, p=0.61).

VO_2 responses to the exercise test are presented in Figure 2. VO_2 at RCP and peak exercise were significantly lower in the patients with PD than in the control

subjects (14.6±3.6 vs. 17.9±5.5 ml.kg^{-1}.min^{-1}, p=0.00; 17.7±4.8 vs. 21.5±6.6 ml.kg^{-1}.min^{-1}, p=0.01, respectively) while no differences were observed at AT.

Cardiovascular responses to the exercise tests are presented in Figure 3. SBP at RCP and peak exercise were also lower in patients with PD than the control subjects (151±17 vs. 172±20 mmHg, p=0.00; 166±21 vs. 187±24 mmHg, p=0.00, respectively) and no differences were observed at AT. HR at AT, RCP and peak exercise were lower in the patients with PD than the control subjects (102±14 vs. 110±13 bpm, p=0.04; 119±17 vs. 139±12 bpm, p=0.00; 132±20 vs. 158±13 bpm, p=0.00, respectively). In addition, the percentage of subjects who achieved 90% and 100% of predicted maximal HR were significantly lower in the patients with PD than the control subjects (35.4 vs. 95.0% and 8.3 vs. 50.0%, respectively, all P<0.05).

Discussion

The main findings of the present study were that, in comparison with control subjects, patients with PD presented lower VO_2, HR and SBP at peak exercise and RCP. They also present a lower HR at AT, while VO_2 and SBP at this exercise intensity were similar to the control subjects.

Similarly to some previous studies [9, 10], the present results also revealed a lower peak metabolic and cardiovascular responses to the cardiopulmonary exercise test in the patients with PD in comparison with the control subjects. The mechanisms responsible for the lower peak responses were not studied in the present study. However, they might be due, in part, to the autonomic impairment present in some patients with PD [2, 3]. In fact, in our PD sample, 70.8% of the patients presented a HR decay in the first minute of recovery that was lower than 12 beats/min (data not showed), which is indicative of autonomic dysfunction [22]. It is also known that PD is associated with a blunted

sympathetic response to a stress stimulus [9, 12]. Thus, it is possible to suppose that due to autonomic dysfunction, maximal sympathetic activation during exercise is blunted in patients with PD, which leads to the lower peak HR (as observed by the lower peak absolute values and less patients achieving the predicted maximal HR values for their age), and consequently, lower SBP and VO_2peak. Future studies, should assess sympathetic responses during exercise in this population. Another possibility is that patients presented lower peak responses due to their motor limitations [14]. We controlled this factor by conducting the study on a cycle ergometer, known to enable movement in PD [23], and by evaluating submaximal intensities that imply lower physical effort.

The novelty of the present study was to investigate metabolic and cardiovascular responses at submaximal exercise intensities determined by ventilatory thresholds. Our data demonstrated that these thresholds represented the same relative intensity in both groups, corresponding to, approximately, 59 and 82% of VO_2peak. Regarding the metabolic and cardiovascular responses at these submaximal exercise intensities, VO_2, HR and SBP were lower in patients with PD in comparison with the control subjects at RCP, while HR was also lower at AT. It is important to note that no differences were observed in the resting values. Taking together, these results suggest that blunted metabolic and cardiovascular responses during exercise test in patients with PD are already present at submaximal levels and intensify with increasing exercise intensity. In addition, compromised HR response occurred at lower submaximal exercise intensities and was stronger than the reduced SBP and VO_2 responses.

Concerning the VO_2 responses, studies suggested that patients with PD have mitochondrial dysfunction [1, 4] that might lead to deleterious alterations in aerobic energy supply during exercise. As a consequence, patients with PD have been shown to present elevated lactate levels at submaximal intensities [24] which might explain why RCP,

representing the exercise intensity at which acidosis begins [16], occurred at a lower VO_2 and also led to a lower VO_2peak.

As discussed earlier, the blunted cardiovascular responses to exercise might be, at least in part, related to impaired autonomic function. The HR increase from rest to AT during a progressive exercise is mainly due to parasympathetic withdrawal, while the HR increase above this intensity is mainly due to sympathetic activation [25-27]. As patients with PD present parasympathetic and sympathetic dysfunctions [28, 29] characterized by lower parasympathetic activity at rest [28] and lower increase in sympathetic activity during stimulation [9, 12], these patients could have presented lower reduction in parasympathetic activity and lower increase in cardiac sympathetic activity during the exercise test, which might explain both lower HR at AT and RCP. On the other hand, SBP response during progressive exercise, despite being influenced by HR response, is also affected by peripheral sympathetic activity, which increases especially when metabolic accumulation occurs, i.e. as exercise intensity increases and approaches RCP [30]. So, the blunted response of sympathetic activity to stimuli may also explain the lower SBP response at RCP in the patients with PD. It is important to highlight, however, that autonomic responses were not assessed in the present study and, thus, these are only hypotheses that should be tested in the future.

The results of the present study have some practical relevance, since it was possible to detect cardiovascular response impairment to exercise in patients with PD using HR measured at low submaximal exercise intensities, avoiding the necessity of a maximal effort. Nevertheless, future studies should establish cutoff points for detecting such impairments for clinical use, which may inform rehabilitation professionals about optimal exercise intensity in PD and about the risks associated with different exercise intensities.

Study Limitations

This study had some limitations. As the study aimed to evaluate the effect of PD on cardiovascular responses to exercise, patients with cardiovascular diseases, such as hypertension, and those receiving medications, other than the PD drugs, that affect the cardiovascular responses to exercise were excluded. Although this procedure has been taken to assure that different responses are due to PD per se, it limits the extrapolation of the results for all patients with PD. Thus, future studies should compared patients with and without cardiovascular disease and/or receiving or not cardiovascular medications. Concerning the medication for PD, the patients were on different drugs and doses, which may have affected the results. However, the fact that we did not exclude patients with PD on different medication schemes, enhances the applicability of the results for this specific population. On the other hand, it is not possible to make any inference about PD medications and the responses to exercise, future studies should evaluate this issue, including the calculation of levodopa equivalent dose. Furthermore, only patients at modified Hoehn and Yahr stages 2 – 3 without cardiac disease and hypertension were studied, and the results might be different in the presence of other characteristics, which should be tested in the future. Finally, results are limited to maximal tests performed on cycle ergometer and may be different with treadmill, which should be tested.

Conclusion

Patients with PD presented blunted VO_2, HR and SBP responses to exercise test, especially at intensities above the anaerobic threshold.

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(blinded to reviewer propose).

Conflict of interest

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

References

1. Blin O, Desnuelle C, Rascol O, Borg M, Peyro Saint Paul H, Azulay JP et al. Mitochondrial respiratory failure in skeletal muscle from patients with Parkinson's disease and multiple system atrophy. J Neurol Sci 1994;125(1):95-101.

2. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79(4):368-76.

3. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord 2011;26(3):399-406.

4. Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 1990;54(3):823-7.

5. Diem-Zangerl A, Seppi K, Wenning GK, Trinka E, Ransmayr G, Oberaigner W et al. Mortality in Parkinson's disease: a 20-year follow-up study. Mov Disord 2009;24(6):819-25.

6. Willis AW, Schootman M, Kung N, Evanoff BA, Perlmutter JS, Racette BA. Predictors of survival in patients with Parkinson disease. Arch Neurol 2012;69(5):601-7.

7. Oliveira RB, Myers J, Araujo CG, Abella J, Mandic S, Froelicher V. Maximal exercise oxygen pulse as a predictor of mortality among male veterans referred for exercise testing. Eur J Cardiovasc Prev Rehabil 2009;16(3):358-64.

8. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA 1999;281(6):524-9.

9. DiFrancisco-Donoghue J, Elokda A, Lamberg EM, Bono N, Werner WG. Norepinephrine and cardiovascular responses to maximal exercise in Parkinson's disease on and off medication. Mov Disord 2009;24(12):1773-8.

10. Werner WG, DiFrancisco-Donoghue J, Lamberg EM. Cardiovascular response to treadmill testing in Parkinson disease. J Neurol Phys Ther 2006;30(2):68-73.

11. Canning CG, Alison JA, Allen NE, Groeller H. Parkinson's disease: an investigation of exercise capacity, respiratory function, and gait. Arch Phys Med Rehabil 1997;78(2):199-207.

12. Nakamura T, Hirayama M, Yamashita F, Uchida K, Hama T, Watanabe H et al. Lowered cardiac sympathetic nerve performance in response to exercise in Parkinson's disease. Mov Disord 2010;25(9):1183-9.

13. Stanley RK, Protas EJ, Jankovic J. Exercise performance in those having Parkinson's disease and healthy normals. Med Sci Sports Exerc 1999;31(6):761-6.

14. Katzel LI, Sorkin JD, Macko RF, Smith B, Ivey FM, Shulman LM. Repeatability of aerobic capacity measurements in Parkinson disease. Med Sci Sports Exerc 2011;43(12):2381-7.

15. Protas EJ, Stanley RK, Jankovic J, MacNeill B. Cardiovascular and metabolic responses to upper- and lower-extremity exercise in men with idiopathic Parkinson's disease. Phys Ther 1996;76(1):34-40.

16. Skinner JS, McLellan TM. The transition from aerobic to anaerobic metabolism. Res Q Exerc Sport 1980;51(1):234-48.

17. Wasserman K, Sue DY, Whipp BJ. Principles of exercise testing and interpretation. 2nd Ed. Philadelphia: Lea & Febiger 1994:112-31.

18. Spruit MA, Wouters EF, Eterman RM, Meijer K, Wagers SS, Stakenborg KH et al. Task-related oxygen uptake and symptoms during activities of daily life in CHF patients and healthy subjects. Eur J Appl Physiol 2011;111(8):1679-86.

19. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation. J Cardiopulm Rehabil Prev 2012;32(6):327-50.

20. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 2004;19(9):1020-8.

21. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181-4.

22. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341(18):1351-7.

23. Snijders AH, van Kesteren M, Bloem BR. Cycling is less affected than walking in freezers of gait. J Neurol Neurosurg Psychiatry 2012;83(5):575-6.

24. Landin S, Hagenfeldt L, Saltin B, Wahren J. Muscle metabolism during exercise in patients with Parkinson's disease. Clin Sci Mol Med 1974;47(5):493-506.

25. Alonso DO, Forjaz CL, Rezende LO, Braga AM, Barretto AC, Negrao CE et al. Heart rate response and its variability during different phases of maximal graded exercise. Arq Bras Cardiol 1998;71(6):787-92.

26. Tulppo MP, Makikallio TH, Takala TE, Seppanen T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol 1996;271(1 Pt 2):H244-52.

27. Yamamoto Y, Hughson RL, Peterson JC. Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. J Appl Physiol (1985) 1991;71(3):1136-42.

28. Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllyla VV. Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2001;70(3):305-10.

29. Pursiainen V, Haapaniemi TH, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllyla VV. Circadian heart rate variability in Parkinson's disease. J Neurol 2002;249(11):1535-40.

30. Fisher JP, Adlan AM, Shantsila A, Secher JF, Sorensen H, Secher NH. Muscle metaboreflex and autonomic regulation of heart rate in humans. J Physiol 2013;591(Pt 15):3777-88.

Figure Legends

Figure 1. Example in one patient of the variables considered for assessing the anaerobic threshold (AT) and the respiratory compensation point (RCP) during the maximal exercise test: pulmonary ventilation (VE), oxygen ventilatory equivalent (VE/VO_2), carbon dioxide ventilatory equivalent (VE/VCO_2), end-tidal oxygen partial pressure ($PETO_2$) and end-tidal carbon dioxide partial pressure ($PETO_2$) measured at rest, warm-up, exercise and recovery (Rec)".

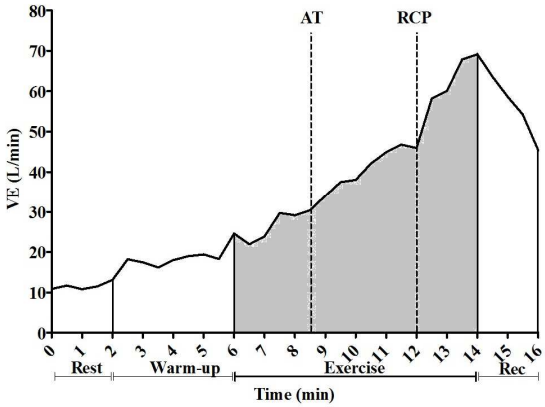
Figure 2. Oxygen uptake (VO_2) measured at anaerobic threshold (AT), respiratory compensation point (RCP) and peak exercise in patients with Parkinson disease (black bars) and the control subjects (white bars). * Significantly different from the control subjects ($P \leq 0.05$).

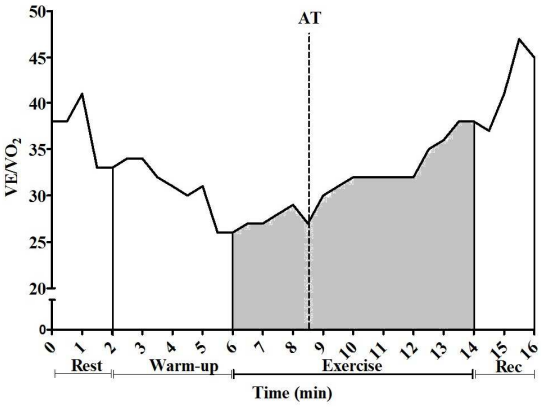
Figure 3. Heart rate (HR, panel A) and systolic blood pressure (SBP, panel B) measured at anaerobic thresholds (AT), respiratory compensation point (RCP) and peak exercise in patients with Parkinson disease (black bars) and the control subjects (white bars). * Significantly different from the control subjects ($P \leq 0.05$).

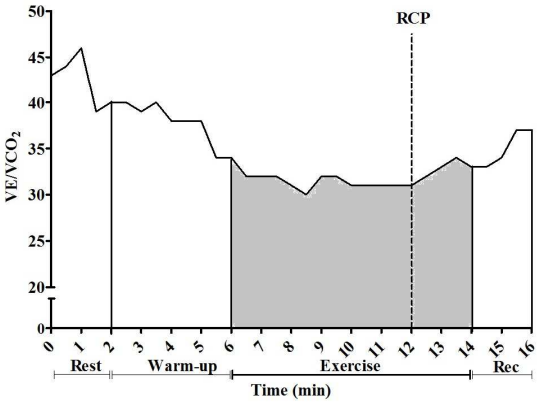
Table 1. Subject characteristics

	Patients with Parkinson Disease (n= 48)	Control Subjects (n= 20)	P value
Gender, male/female	35/13	12/8	0.27
Age, years	66 ± 8	64 ± 9	0.47
Body mass index, kg/m²	25.8 ± 3.8	24.6 ± 3.4	0.24
Resting Systolic Blood Pressure, mmHg	119 ± 10	118 ± 9	0.76
Resting Diastolic Blood Pressure, mmHg	78 ± 6	78 ± 8	0.62
Resting Heart Rate, beats/min	70 ± 7	70 ± 10	0.85
Resting Oxygen Uptake, $ml.kg.^{-1}min^{-1}$	3.0 ± 0.5	3.2 ± 0.7	0.10
Disease Duration, years	9.8 ± 4.4	-----	-----
Hoehn & Yahr modified, n (%)			
Stage 2	17 (35.4)	-----	-----
Stage 2.5	12 (25.0)	-----	-----
Stage 3	19 (39.6)	-----	-----
Medications, n (%)			
Levodopa/Carbidopa	43 (89.6)	-----	-----
Dopamine Agonist	20 (41.7)	-----	-----
Amantidane	19 (39.6)	-----	-----
Seligeline	7 (14.6)	-----	-----

Data are means ± SD.


AT
RCP
VE (L/min)
Rest
Warm-up
Exercise
Rec
Time (min)


AT
VE/VO2
Rest
Warm-up
Exercise
Rec
Time (min)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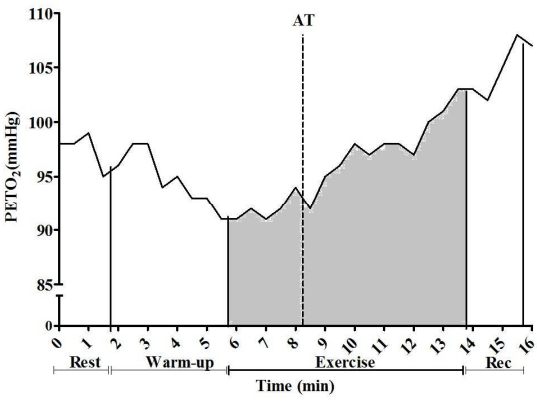
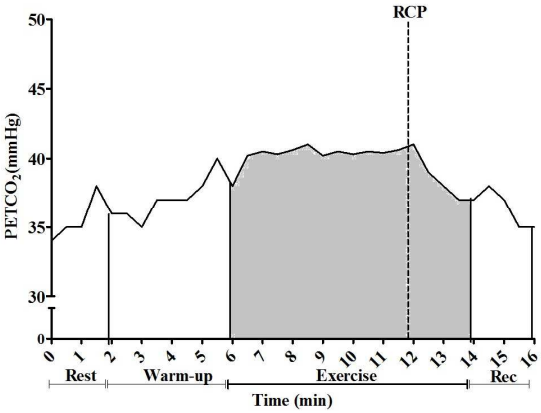
VE/VCO2
Rest
Warm-up
Exercise
Rec
Time (min)


AT
PETO2(mmHg)
Rest
Warm-up
Exercise
Rec
Time (min)


RCP
PETCO2(mmHg)
Rest
Warm-up
Exercise
Rec
Time (min)