Unveiling the specific role of psychological and cardiorespiratory variables in the therapeutic effect of an aerobic exercise training protocol for panic disorder

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BACKGROUND: There is limited evidence regarding the use of exercise training in the treatment of panic disorder.

OBJECTIVE: To describe the role of psychological and cardiorespiratory variables in the therapeutic effect of a 12-week exercise training in panic disorder patients.

METHODS: Eleven symptomatic panic disorder patients completed 24 sessions, 2 sessions/week, 70%VO₂max) aerobic exercise training in addition to regular pharmacological treatment. Assessment was performed at baseline, six and 12-week periods. Exercise training intensity was individualized according to maximal cardiopulmonary exercise testing data.

RESULTS: Patients who exercised in conjunction with pharmacotherapy obtained significant improvements in several variables. Exercise training produced a selective, rather than a general anxiolytic impact. An early (6-week) effect was observed in fear of physiological arousal, interoceptive conditioning and in the frequency and intensity of panic attacks. Smaller additional 12-week effects were found in health concerns and agoraphobic cognitions, with no significant impact in agoraphobia.

CONCLUSION: A 12-week aerobic exercise training protocol was well-tolerated and able to improve several psychological and cardiovascular indicators in most patients with panic disorders. Further studies are needed to identify the best training protocols and long-term effects of exercise, as well as interactions between cardiorespiratory and psychological variables in this context.

KEYWORDS: Mental health, Anxiety sensitivity, Interoceptive exposure, Exercise, Cardiovascular risk.

INTRODUCTION

Preliminary results indicating a potential positive role of aerobic exercise interventions designed to promote interoceptive habituation in the treatment of panic disorder (PD) have been reported.¹⁻⁷ There is evidence of the positive effects of exercise on anxiety and its clinical use as an adjunct tool to established treatment strategies such as cognitive behavioral therapy (CBT) or pharmacotherapy.⁸⁻¹¹ However promising as these are, there is no positive current evidence supporting the use of aerobic exercise alone as an effective treatment for PD. Specific investigations on the clinical effects of aerobic exercise on the psychopathology of PD, its interaction with standard treatment approaches and details on the optimal type, intensity, frequency and duration that might further support the clinical administration in PD patients are still lacking. Longitudinal studies have also failed to present elucidative data on the cardiorespiratory changes and fitness condition before and after participation in exercise programs and on the interactions between those variables and anxiety symptoms improvement. Besides, exercise protocols reported so far include general and

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unsupervised exercise prescriptions, with poor control of exercise intensity, cardiorespiratory and psychological variables during sessions.\textsuperscript{10-12} Also, at the time of writing, there is scarce information about the specific effect of exercise in the psychological constructs implicated in the psychopathology of panic and whether the observed gains are generalized or mediated by any of these variables.

Given these gaps in knowledge, we designed this study aimed to further understand the behavior and interactions between several psychological and cardiorespiratory variables possibly implicated in adding exercise to the pharmacological treatment of PD. A secondary goal of this paper would be to raise hypotheses about the potential role of those parameters in the positive impact of exercise in the treatment of anxiety and in improving patients’ cardiovascular condition. Our hypothesis is that exercise might play a role in promoting habituation to physiological cues, therefore directly influencing panic symptom occurrence, as well as in enhancing physical health and fitness variables.\textsuperscript{13} To empirically test this idea, we designed an individually supervised exercise protocol, with direct control of training intensity and assessment of psychological and cardiorespiratory variables.

\section*{METHODS}

\textbf{Participants.} The present study was approved by the local Research Ethics Committee (Case \# 15LIV3\_09) and all participants signed an informed consent prior to participation. Patients with PD were consecutively recruited in an outpatient psychiatry unit in the Panic and Respiration Laboratory of the Federal University of Rio de Janeiro. Participants were diagnosed using a structured interview designed to explore each of the necessary criteria for the main diagnoses of DSM-IV Axis I - the Mini International Neuropsychiatric Interview (MINI) version 5.0\textsuperscript{14}. Data collection occurred individually and was performed by the same trained researcher. Inclusion criteria accepted patients that met the DSM-IV criteria for PD and remained symptomatic despite current medical treatment. Exclusion criteria comprised the presence of relevant psychiatric comorbidity, current psychotherapy treatment and medical conditions that counter indicate the participation in an exercise program. Participants were examined by a psychiatrist; pharmacotherapy based on antidepressants and/or benzodiazepines was naturalistically prescribed or adjusted. Drug prescriptions and dosages were maintained until the end of the study. Although depression symptoms were not directly evaluated, mildly depressed patients with PD as the primary diagnosis were included.

\textbf{Procedures.} After agreeing to participate, patients were submitted to psychological evaluations and to a psychiatric screening interview using the MINI. In this same visit, pharmacotherapy treatment was adjusted, and physical evaluation was scheduled. If patients were considered healthy by a medical examination that included a cardiopulmonary exercise test (CPET), they were consecutively allocated into the exercise program. Psychological assessments were repeated 6 weeks and 12 weeks after baseline and anthropometric and CPET was repeated by the end of 12 weeks to evaluate possible morphological and cardiorespiratory training-induced changes.

\textbf{Psychological Evaluation.} Subjects were requested to fill in the following self-report instruments: the Panic and Agoraphobia Scale (PAS\textsuperscript{15}), the Anxiety Sensitivity Index (ASI\textsuperscript{16}), the Agoraphobic Cognitions Questionnaire (ACQ\textsuperscript{17}), the Body Sensations Questionnaire (BSQ\textsuperscript{17}), the Cardiac Anxiety Questionnaire (CAQ\textsuperscript{18}) and the Mobility Inventory for Agoraphobia (MI\textsuperscript{19}).

\textbf{Medical-physiological Evaluation.} Following psychiatric examination and psychological assessment, patients were submitted to a medical-physiological evaluation to assess cardiorespiratory responses to exercise and to ensure the safety of participation in the exercise program. Anthropometrical data, resting spirometry and electrocardiogram were obtained prior to the maximum CPET in a leg cycle ergometer (CatEye EC-1600, CatEye, Japan or Inbrasport CG-04, Inbrasport, Brazil). CPET followed an individualized ramp protocol targeting duration between 8 and 12 minutes to achieve exhaustion, that is, the incapacity to continue to pedal at a minimum of 60 rpm. Patients were strongly encouraged by verbal stimuli to reach the maximum effort during the CPET. During the CPET, expired gases were collected by a Prevent pneumotachograph (MedGraphics, USA) coupled to a mouthpiece, with concomitant nasal occlusion, and quantified by a VO\textsubscript{2}000 metabolic analyzer (MedGraphics, USA), periodically calibrated by means of a 2-l syringe with gases of known concentration. The metabolic analyzer enabled the quantification of pulmonary ventilation and partial fractions of oxygen and carbon dioxide, expressed and analyzed every 10 sec. Following a standardization pattern, VO\textsubscript{2}\textsuperscript{max} values were reported every minute during the CPET, through the mean of six readings obtained during each minute. Thus, the value of the largest mean obtained referring to a given minute was considered the VO\textsubscript{2}\textsuperscript{max}\textsuperscript{20} and it was used to guide the exercise intensity for the training sessions. Before and after the CPET, patients were required to fill in the State-Trait Anxiety Inventory - state anxiety (STAI).\textsuperscript{21}

\textbf{Exercise Protocol.} Aerobic exercise training protocol consisted of 24 sessions, twice a week, in a 12-week period. Each session encompassed 5 minutes of warm-up walking a typical pace, followed by 20 minutes of exercise (brisk walking in incline treadmill; INBRAMED Export 16 Plus) at an exercise intensity corresponding to 75\% of the VO\textsubscript{2}\textsuperscript{max}, and ended by 5 minutes of cool-
down walk at an easy pace. All exercise sessions were held individually and supervised by the same trained physical educator. In each exercise session, heart rate (HR) monitors were placed in order to obtain the values before the session and at each 5 minute during exercise. Patients were also asked to rate their perception of anxiety (Subjective Units of Distress scale (SUDS)) and of effort (BORG scale). SUDS range from 0 to 10 and BORG, from 6 to 20. Before and after each session, patients were required to fill in the STAI. The detailed exercise protocol used can be consulted elsewhere.

**Statistical Analysis.** Friedman analyses were used to evaluate the results at 6 and 12 weeks for each of the subscales of the psychometric instruments, followed by Dunn’s multiple comparisons post hoc tests conducted to examine any significant changes between moments. Data analysis was conducted using SPSS® 17.0 for Windows and figures were prepared using GraphPad (Prism; p<.05).

## RESULTS

Thirteen patients enrolled in the study, but only eleven completed the exercise program. No differences were observed between patients who completed the study and dropouts concerning demographic, physiological nor psychological variables.

Participants who completed the protocol were 18% (n=2) men and 82% (n=9) women, with median age of 45 years (interquartile limits: 31 & 48). All patients were taking benzodiazepines and 67% (n=10) took benzodiazepines associated with antidepressants (imipramine, fluoxetine, citalopram, sertraline and venlafaxine). Eight patients (53%) also presented mild depressive symptoms.

**Psychological variables.** When compared to baseline, patients who exercised along with pharmacotherapy improved significantly regarding most subscales of the psychometric instruments used. After 12 weeks of treatment, patients in the exercise program presented less panic symptoms, functional impairment, agoraphobic cognitions and health-related anxiety.

Figure 1 shows results for the Panic and Agoraphobia Scale: significant reductions were observed for frequency and intensity of panic attacks (p<0.01), for anxiety (p=0.01), impaired function (p<0.01) and health concerns (p<0.01), but not for the agoraphobia and avoidance behaviors subscale (p=0.11). Dunn’s multiple comparisons test showed that most of the improvement was present by the end of 6 weeks of exercise program, except for health concerns, which improved between 6 and 12 weeks of treatment.

The same tendency was observed in the Cardiac Anxiety Questionnaire, as shown in Figure 2. Scores obtained by the patients in the exercise program dropped after treatment, when compared to baseline (fear and hypervigilance p<0.01 and avoidance p<0.01). Multiple comparisons showed that cardiac anxiety decreased more intensely between 6 and 12 weeks of treatment for all subscales.

In the Mobility Inventory for Agoraphobia (Figure 5), the most relevant difference was observed when patients where unaccompanied in the feared situations. Patients who participated in the exercise program significantly improved their levels of anxiety after 12 weeks, compared to baseline (p=0.01). The more impacting change in anxiety levels was reported between 6 and 12 weeks. Anxiety in feared situations decreased over the 12 weeks of study (p<0.01), also with the more relevant change between 6 and 12 weeks of treatment.

As shown in figure 6, in the Anxiety Sensitivity Index, patients exhibited lower levels of AS after 12
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weeks concerning the total score (p<0.01), fear of cardiorespiratory (p<0.01) and gastric (p<0.01) symptoms. Exercise patients also significantly improved in the fear of losing cognitive control (p<0.01) and of public displays of anxiety manifestations (p<0.01) after the exercise program. Most of the change occurred between six and 12 weeks of participation.

Levels of anxiety were also assessed throughout the 24 sessions of the exercise program, as shown in Figure 7. Subjective perception of anxiety, measured through SUDS before and after each section, demonstrated that anxiety levels before session significantly decreased over time from 3.45 at baseline to 1.81 (p<0.01), with no difference between the baseline and six weeks and six until 12 weeks. The same was observed with subjective anxiety levels after each training session (p<0.01), that varied from 2.00 at baseline to 0.90, by the end of 12 weeks. Anxiety levels after session dropped more intensely in the first six weeks, but this tendency presented no statistical significance in this sample (p=0.06). In the second exercise section, a peak level of pre- and post-anxiety was observed, but means scores started decreasing thereafter.

Trait anxiety significantly decreased over time, with no specific relevant period of change (p<0.01). A slight raise was also observed in the first sessions, decreasing thereafter. No difference was found, however, in state anxiety before session from baseline to 12 weeks (p=0.06). On the other hand, state anxiety after exercise section significantly improved with treatment (p<0.01), with the most expressive, although not significant, decrease observed from 6 to 12 weeks (p=0.17). State anxiety was
also measured before and after each CPET (baseline and final). In both baseline and final assessments state anxiety significantly decreased after test (p<0.01 and p=0.03, respectively). Also, a significant improvement in state anxiety levels before the test was observed comparing baseline and final evaluations (p=0.01), but not after test.

**Physiological variables.** As previously noted, each patient performed 30 min of individualized treadmill exercise distributed over 24 sessions, comprising a total of 12 hours of aerobic activity. HR monitoring during exercise sessions indicated that for the clear majority of sessions, patients’ exercising HR was kept in the proposed target zone, corresponding to about 75% of \( \text{VO}_2 \) max and therefore represented an effective aerobic training load. No relevant clinical complications occurred during the exercise sessions.

A total of 24 successful maximal cardiopulmonary exercise tests were performed in 13 patients, with 11 of them being assessed twice: at baseline and after completing the 12-week exercise intervention program. Table 1 summarizes the most relevant results obtained at CPET at baseline and after 12 weeks of exercise program. Dropout patients (tested at baseline) showed no differences in the tested variables compared participants who completed the program. No clinical or electrocardiographic abnormalities were found that required earlier CPET termination. The obtained maximum HR corresponding was, in median, 92% of age-predicted value.

<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>p-value**</th>
</tr>
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<tbody>
<tr>
<td><strong>Supine resting values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68</td>
<td>68</td>
<td>0.60</td>
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<tr>
<td></td>
<td>[61 - 74]</td>
<td>[59 - 79]</td>
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<td>Systolic blood pressure (mm Hg)</td>
<td>131</td>
<td>129</td>
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<tr>
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<td>[124 - 145]</td>
<td>[120 - 136]</td>
<td></td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77</td>
<td>74</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>[71 - 87]</td>
<td>[70 - 86]</td>
<td></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>140</td>
<td>140</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>[126 - 145]</td>
<td>[134 - 149]</td>
<td></td>
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<tr>
<td>Workload (watts)</td>
<td>62</td>
<td>67</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>[46 - 88]</td>
<td>[60 - 80]</td>
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<tr>
<td>( \text{VO}_2 ) (mL.kg(^{-1}).min(^{-1}))</td>
<td>15.0</td>
<td>16.4</td>
<td>0.46</td>
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<td></td>
<td>[13.4 - 18.9]</td>
<td>[13.2 - 19.6]</td>
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<td><strong>Maximum exercise</strong></td>
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<tr>
<td>Heart rate (bpm)</td>
<td>176</td>
<td>178</td>
<td>0.62</td>
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<tr>
<td></td>
<td>[156 - 181]</td>
<td>[162 - 181]</td>
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<tr>
<td>Workload (watts)</td>
<td>94</td>
<td>102</td>
<td>0.02**</td>
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<tr>
<td></td>
<td>[78 - 132]</td>
<td>[85 - 138]</td>
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<tr>
<td>( \text{VO}_2 ) (mL.kg(^{-1}).min(^{-1}))</td>
<td>18.1</td>
<td>21.9</td>
<td>0.04**</td>
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<tr>
<td></td>
<td>[17.0 - 26.2]</td>
<td>[17.8 - 28.2]</td>
<td></td>
</tr>
<tr>
<td>Age-predicted ( \text{VO}_2 ) (%)</td>
<td>63</td>
<td>74</td>
<td>0.03**</td>
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<tr>
<td></td>
<td>[58 - 75]</td>
<td>[58 a 83]</td>
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<tr>
<td>VE (L.min(^{-1}))</td>
<td>42.0</td>
<td>47.4</td>
<td>&lt;0.01**</td>
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<td>[30.6 - 57.8]</td>
<td>[38.3 - 70.0]</td>
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<td>Systolic blood pressure (mm Hg)</td>
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<td>[194 - 220]</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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<td>100</td>
<td>0.31</td>
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<tr>
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<td>[90 - 102]</td>
<td>[95 - 107]</td>
<td></td>
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<tr>
<td>Duration (min)</td>
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<td>10</td>
<td>0.01**</td>
</tr>
<tr>
<td></td>
<td>[7.5 - 10]</td>
<td>[9 - 11]</td>
<td></td>
</tr>
</tbody>
</table>
Along the 12-week period of the study, patients have not significantly changed their major morphological characteristics, as evaluated by body weight (p=0.13), sum of six skinfolds (p=0.36) and abdominal girth (p=0.50). No significant change has found in resting HR or blood pressure after 12 weeks. While modest changes were seen due to exercise intervention at some of submaximal CPET variables, e.g., median 10% increase in VO\textsubscript{2} and workload at anaerobic threshold exercise intensity, these gains were not significant.

At maximal exercise intensity, however, substantial improvements could be found. While no changes could be seen in major hemodynamic variables, such as maximum values of HR (p=0.62) and systolic (p=0.41) and diastolic (p=0.31) blood pressure, maximum expired ventilation and all aerobic performance indicators were significantly improved (p<0.05). Consistent with the low baseline values, % of age-predicted VO\textsubscript{2} max increased 18% (63 to 74%) corresponding to an improvement of 3.8 mL.kg\textsuperscript{-1}.min\textsuperscript{-1} or 1.1 METs (p=0.04). By using the same initial and incremental workload rate, patients were able to tolerate two more minutes of effort at the end of the CPET exercise series (8 to 10 min; p=0.01).

### DISCUSSION

The positive role of exercise training in symptom reduction in addition to traditional pharmacotherapy treatment for PD found in this study is consistent with previous reports in the literature, that point to a superior effect of the combination of regular therapy with exercise training.\cite{6,10} Comparisons over the 12-week period, however, present a clearer interpretation of the data, showing a significant effect in symptom reduction over time. The present outcomes also point to an incremental role of exercise and suggest its usefulness as an adjunct therapy to be added to already established interventions such as pharmacotherapy and/or CBT in the treatment of PD.\cite{10,25}

Our research design provides interesting information on the behavior of several variables implicated in the psychopathology of PD and sheds light on the specific effects of exercise upon each of these variables. In this sense, results clearly point to an early (by 6 weeks) and more expressive effect of exercise in the psychological aspects related to anxiety concerning physiological arousal (somatic-anxiety), body symptoms and interoceptive conditioning. This can be seen in the Panic and Agoraphobia Scale, where differences from baseline were observed in frequency and intensity of PA, anxiety, and functioning and in the general fear of body sensations questionnaire. These results confirm the original prediction of a potential role of exercise in promoting habituation to physiological cues, similarly to the effect of interoceptive exposure techniques.\cite{1,2,25}

The impact of exercise in the frequency and intensity of PA and anxiety is also in agreement with the reported anti panic effect of exercise in laboratory settings.\cite{3,5,6} The main hypothesis is that neurophysiologic changes due to exercise,\cite{16,26} promote an immediate anti panic modulation, as patients can experience autonomic arousal induced by exercise in the absence of panic or in the presence of more attenuated anxiety reactions.\cite{3,5,6} In this sense, exercise could have an additional advantage over regular interoceptive exposure in terms of the intensity of symptoms that can be elicited without panic reactions, which possibly potentiates habituation. Immediate anxiolytic effect of exercise could also be seen within exercise session, with SUDS decreasing after session termination. The same behavior was observed in state anxiety after maximum exercise test (CPET). In-session and over time decrease in SUDS reported by patients, with maintenance of intensity of effort controlled by the assessment of HR, also speak for the habituation effect of exercise.

After 12 weeks, more specific health-related fears are impacted by exercise training, such as the Cardiac Anxiety and the Anxiety Sensitivity subscales, concerning fears of cardio respiratory, gastric and cognitive symptoms. We could hypothesize that the variables that include cognitive information processing, such as restructuring of health-related worries and fears and agoraphobic cognitions could suffer an indirect impact of exercise, possibly through naturalistic evidence of safety provided by the previous reduction in panic symptoms and fear of body symptoms. This is consistent with the smaller and later effects of the exercise program in health and physical concerns and agoraphobic cognitions.

Exercise in this study seems to have a more relevant effect on anxiety reduction through habituation to physiological arousal, and only an indirect impact in cognitive agoraphobic processing. This effect is similar to the observed immediate effect of psychotropic drugs, which only indirectly affect agoraphobia after reduction in panic symptoms.\cite{27} Despite the significant differences observed effect in AS, our study enhances the discussion whether it is the single underlying mechanism through which exercise positively impacts the treatment of PD.\cite{28} Our data suggest that, despite the clear impact of exercise in AS, it does not seem to present any distinct effect on AS when compared to the other measurements of fear of body symptoms. Thus, it is likely that habituation to physiological arousal, potentiated by the anti-panic effect of exercise reduces the occurrence and the fear of involuntary somatic manifestations with a further impact on health. Also, our results show that symptom-related anxiety plays a mediating role in the observed positive effects of exercise in PD patients.

In the long run, exercise avoidance and low levels of everyday physical activity turn out to promote a sedentary...
lifestyle as an indirect effect of PD.\textsuperscript{29} As indicated by Meyer et al.,\textsuperscript{30} low fitness observed in PD patients seem to be a byproduct of physical activity avoidance, and can be directly impacted by exercise interventions aiming to achieve non-clinical control levels. As reduced fitness capacity is directly associated with a higher all-cause mortality\textsuperscript{21} and increased cardiovascular risk\textsuperscript{32} in healthy subjects, the inclusion of an exercise protocol in the treatment of PD can, per se, be useful as a cardio protective strategy for those patients. Moreover, recent cohort studies found that PD is a significant independent risk for the onset coronary heart disease, acute myocardial infarction, and cardiac related mortality.\textsuperscript{25,33,34} One hypothesis is that a sedentary lifestyle and its metabolic consequences might mediate this association (see Sardinha et al.\textsuperscript{25} for details). In this sense, it is possible that exercise plays a double role in the treatment of PD: psychological symptoms and cardiovascular risk reduction.\textsuperscript{25}

**CONCLUSION**

Aerobic exercise does not seem to generally affect symptoms, but rather present a selective specific effect of some aspects of PD psychopathology. It is probably due to this selective effect that exercise does not present satisfactory outcomes when provided alone, tested versus established therapy, but seems to play and important role as an adjunct tool in the treatment.

In physiological terms, the major finding of the study was that a relatively simple and short aerobic exercise training intervention (12-hour of exercise in total or one hour/week) was well tolerated and able to induce significant improvements in several indicators of maximal performance in this sample of 11 patients. Gains ranging from 10 to 20% were observed in test duration, maximum workload and VO\textsubscript{2}\text{max}, bringing their results closer to age and gender-predicted values for healthy peers, which may positively reflect in their physical health and cardiovascular prognosis.

**REFERENCES**


