

Aerobic training intervention in panic disorder: a case-series study

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OBJECTIVES: The anxiolytic effect of regular aerobic exercise in panic disorder patients is well known. However, a protocol for aerobic exercise intervention as an adjunct non-pharmacologic treatment for panic disorder is still lacking. Our aim was to propose and present a pilot study about an aerobic training protocol that could be replicable, safe and viable for other clinical trials with panic disorder patients.

METHODS: A total of 24 exercise sessions (twice/week) of treadmill walking at controlled intensity (75% VO_{2max}) were completed by four panic disorder patients.

RESULTS: No major complications were observed. The benefits of the aerobic training intervention were reflected in favorable changes in the Panic and Agoraphobia Scale, the Cardiac Anxiety Questionnaire, the Anxiety Sensitivity Index and in the Body Sensations Questionnaire scores, in spite of no significant differences in physiological variables.

CONCLUSIONS: The proposed protocol of aerobic training intervention was shown to be a safe and potentially useful tool as adjunct non-pharmacologic treatment of panic disorder. Further studies are needed in order to determine whether higher intensities and/or longer exercise interventions would induce physiological benefits while still being feasible and safe.

KEYWORDS: physical exercise; anxiety; non-pharmacological treatment.

Gomes RM, Sardinha A, Araújo CG, Nardi AE, Camaz Deslandes A. Aerobic training intervention in panic disorder: a case-series study. MEDICALEXPRESS. 2014 Aug;1(4):195-201.

Received for publication on May 06 2014; First review completed on May 17 2014; Accepted for publication on June 04 2014

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INTRODUCTION

Panic disorder (PD) is one of the most prevalent mental illnesses, ranging between 1.7%¹ to 5%². According to the World Health Organization, PD was appointed as the 17th most disabling disease in the world in 2004³.

Although the pharmacological approach is the most commonly used treatment for PD^{4,5}, non-pharmacological treatments, such as Cognitive Behavioral Therapy, have been successfully used as well^{6,7}. In addition to these approaches, a pattern of regular physical exercise has been shown to have anxiolytic effects in both healthy subjects and PD patients⁸⁻¹⁴. Apart from reducing anxiety, the promotion of cardiovascular health may be associated with a better PD prognosis, because these patients tend to present autonomic deregulation, most often reflected by a reduced level of parasympathetic activity¹⁵⁻¹⁷. Evidence has shown that long-term aerobic training can significantly influence cardiac autonomic modulation in healthy individuals, promoting favorable

cardiovascular adaptations, including diminished resting and submaximal exercise heart rate^{18,19}. Despite these beneficial effects, PD patients often avoid and show low tolerance for exercise, probably due to previous experience of somatic symptoms commonly manifested in a panic attack, resulting in a lower cardiorespiratory fitness²⁰⁻²³.

On the other hand, it is well established that physical exercise can contribute to the reduction of PD symptoms through physiological and behavioral changes both acutely^{14,24} and chronically^{12,20,23,25}. These studies corroborate a favorable response to aerobic exercise as an additional treatment for this anxiety disorder, even when the intensity of exercise was not formally controlled. In addition, a recent study compared the effects of Cognitive Behavioral Therapy with 12 weeks of exercise (three times per week, 90 min each) that included aerobic exercise with controlled intensity (60-80% of maximum heart rate), circuit resistance training and game practice. Both interventions demonstrated efficacy in PD treatment, but the resulting effect was greater in a Cognitive Behavioral Therapy group when compared to a group of subjects performing physical exercises²⁶. These results suggest that these patients obtained several benefits

DOI: 10.5935/MedicalExpress.2014.04.07

from both Cognitive Behavioral Therapy and exercise training, such as anxiety attenuation, reduction of panic attacks, antidepressant effect, promotion of interoceptive habituation, etc. However, the authors suggested the need of a aerobic training intervention with specific targets for PD patients' treatment²⁷.

Our objective here is to describe a pilot study and to present preliminary results of anaerobic training intervention protocol as a non-pharmacologic approach to the treatment of PD, with or without combined pharmacotherapy.

■ METHODS

Participants

The study protocol was approved by the institutional Research Ethics Committee and all the participants signed an informed consent form before attending the evaluation and the exercise training sessions. Consecutive PD patients were recruited in the Outpatient Psychiatry unit located in the Psychiatric Institute of our University and were invited to participate in a pilot study of 24 sessions of aerobic training intervention protocol for PD. To be included in the study, patients had to be symptomatic, according to the current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for PD (unexpected panic attacks in the last month). If patients were on medication, no wash-out was performed and care was taken to maintain the same prescription until the end of the training intervention. Exclusion criteria comprised the presence of relevant psychiatric comorbidities or other medical conditions that contraindicate or preclude the participation in an exercise training program and the attendance to psychotherapy sessions. Although depression symptoms were not formally assessed, mildly depressed patients with PD as the primary diagnosis were also included.

Patient 1. A 65-year-old female patient reported changes in mood and behavior, which she described as depression (undiagnosed) after an abrupt marriage separation at the age of 39. She had PD diagnosed at age 53, the same age as when she had her first panic attack. Before the psychiatric diagnosis, the patient sought different medical specialists, due to her symptoms (tremor, sweating, cold waves, tachycardia, suffocation alarm and impending death sensation); nevertheless, none of the doctors found relevant clinical abnormalities and she was reassured that she was "healthy". She described a story of long-term sedentarism and had no previous experience with treadmill walking; she was not using drugs related to PD treatment during the study.

Patient 2. A 48-year-old female patient had her first panic attack at the age of 35, accompanied by tachycardia and shortness of breath. The subsequent panic attacks occurred predominantly at night. According to the patient, these attacks were typically triggered by acute stress (e.g. financial and marital problems). She had previous experience with regular physical activity and was familiar with treadmill walking. She was not in regular use of medications during the period of the study.

Patient 3. A 49-year-old female patient was diagnosed as having PD at the age of 44. She has been in regular use of clonazepam (1.5 mg) and fluoxetine (20 mg) since then. Before consulting a psychiatrist, she sought a cardiologist and pulmonologist, due to symptoms of chest pain and shortness of breath. Her first panic attack was associated with having been stuck in a crowd in a tunnel on New Year's

Eve, which caused some suffocation related to the smoke from the vehicle engines. In this episode, she reported having felt shortness of breath, tachycardia, anxiety, heat and cold waves. In addition, she reported having suffered many traumas during childhood, had marital separation and frequent problems with her family, which she related to her anxious, aggressive and depressive temper. She regularly smoked about one pack/day, was sedentary and had never previously walked on a treadmill.

Patient 4. A 46-year-old female patient had her first panic attack at the age of 37 after being fired from her job. Panic symptoms consisted predominantly of distress, headache, dizziness, sweating and suffocation alarms. She reported avoidance of tunnels, bridges and overcrowded places; moreover, she referred to frequent episodes of sadness, high anxiety and insomnia. At the time of the study, she was taking clonazepam (0.5 mg) and citalopram (20 mg). She has a long-term history of sedentarism and had never walked on a treadmill before this study.

Psychological evaluation

After volunteering to participate, the four patients went through a structured interview designed to explore each of the necessary criteria for the main diagnoses of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I - the Mini International Neuropsychiatric Interview (MINI) version 5.0²⁸, in order to assess current psychiatric disorders and to confirm the presence of the inclusion criteria. Data collection occurred individually and was performed by one of the investigators (A.S.).

Subjects were later requested to fill in the following self-report instruments: Panic and Agoraphobia Scale²⁹, Anxiety Sensitivity Index³⁰, Agoraphobic Cognitions Questionnaire and Body Sensations Questionnaire³¹, Cardiac Anxiety Questionnaire³² and Mobility Inventory for Agoraphobia³³. The Panic and Agoraphobia Scale is a 13-item rating scale developed for measuring severity of agoraphobia with or without panic attacks. The Anxiety Sensitivity Index is a 36-item inventory that evaluates the extent to which a person believes that anxiety-related sensations can be catastrophic. The Agoraphobic Cognitions Questionnaire has 14 items regarding thoughts that occur when the person experiences anxiety. The Body Sensations Questionnaire has 17 items and describes body sensations that can potentially elicit anxiety. The Cardiac Anxiety Questionnaire is an 18-item instrument designed to evaluate how threatening the subject considers the experienced cardiac symptoms. The Mobility Inventory is a 27-item inventory for the measurement of self-reported agoraphobic avoidance behavior and frequency of panic attacks.

Physiological evaluation

Following the initial interview and again after completing the 24 sessions of aerobic training, subjects were submitted to a maximal cardiorespiratory exercise test in a specialized exercise medicine clinic; this was performed through an individualized ramp protocol in a CG-04 electromagnetically-driven cycloergometer (Inbrasport, Brazil). Expired gas was continuously collected using a Prevent pneumotach (MedGraphics, United States) and sampled and analyzed by VO2000 (MedGraphics, United States). Resting and exercise heart rates were obtained from the continuous electrocardiographic monitoring (Micromed, Brazil) and expressed in bpm. These data provided the proper medical clearance of the patients for participating in the aerobic

training intervention protocol and for the prescription of the exercise training intensity based on the target heart rate zones and percentage of the measured VO_{2max} .

Aerobic training protocol

The aerobic training protocol consisted of 24 sessions, twice a week, with 30 minutes of treadmill (INBRAMED, Brazil) walking. At each session, subjects started with a 5-min warm-up slow walk (approximately 3 km/h) which was followed by 20 minutes of exercise (brisk walking on the inclined treadmill) with the goal of achieving 75% of VO_{2max} and ended with a 5-min cool-down slow-pace walk (the same pace used at warm-up, with a reduction in speed of 0.5 km/h per minute until the end of exercise). All aerobic exercise sessions were held individually and under close supervision of one of the investigators (R.M.G.). Before the exercise sessions, two familiarization sessions were held. These sessions included a visit to the training site, explanation and habituation with the setting, treadmill walking, and instruction on the use of scales for quantification of physical sensation and effort during exercise. During training sessions, heart rate was continuously monitored (Polar, Finland) and blood pressure (BP) measured (Diasyst, Switzerland). The following scales were also applied: Feeling Scale³⁴ and Perceived Exertion Scale (6-20 points)³⁵. Patients also completed a visual analogue scale (VAS) for anxiety, 0-10 points referring to how much fear/anxiety they felt, in which 0 represents absolutely no fear/anxiety and 10 equivalent to an episode with a greater sense of fear/anxiety in life than they had ever experienced.

Figure 1 illustrates the full sequence and the measurement times for each of these physiological and psychological variables.

Statistical analysis

Repeated measures ANOVAs were conducted to compare the results at baseline, 12, and 24 sessions of aerobic training on the dependent variables (Panic and Agoraphobia Scale, Cardiac Anxiety Questionnaire, Agoraphobic Cognitions Questionnaire, Anxiety Sensitivity Index, Body Sensations Questionnaire, Mobility Inventory and VO_{2max} as described in the legend of Figure 1); this was followed by a Tukey *post-hoc* test when appropriate. The Friedman and Tamhane *post-hoc* tests were applied when data distribution was nonparametric. Data analysis was performed using SPSS[®] 17.0 for Windows and Prism 5 (GraphPad, United States).

RESULTS

Four female patients (aged 48-65 years) with a formal PD diagnosis comprised the study's sample and successfully completed the 24 sessions and evaluations of the exercise protocol.

At baseline, all patients reported mild depressive symptoms. Two patients were not taking any medication, and the other two were taking an association of Clonazepam and selective serotonin reuptake inhibitors (Citalopram and Fluoxetine).

Figure 2 summarizes our most relevant results. There was a significant reduction in symptoms of Panic and

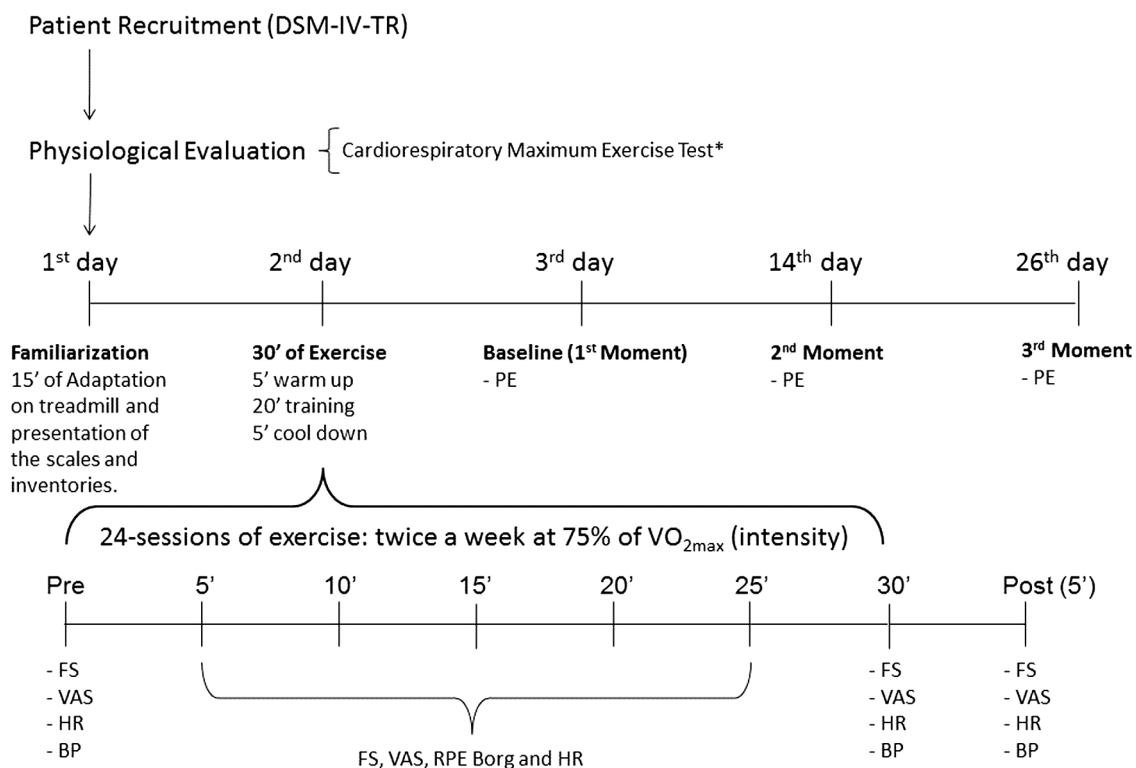


Figure 1 - Exercise training program PE = Psychological Evaluation (Panic and Agoraphobia Scale, Anxiety Sensitivity Index, Agoraphobic Cognitions Questionnaire, Body Sensations Questionnaire, Cardiac Anxiety Questionnaire and Mobility Inventory); VO_{2max} = Maximum Oxygen Uptake; FS = Feeling Scale; VAS = Visual Analogue Scale for Anxiety; RPE Borg = Rate of Perceived Exertion Scale of Borg; HR = Heart Rate; BP = Blood Pressure. *Test performed at 1 week before and after, respectively, of the exercise aerobic training protocol.

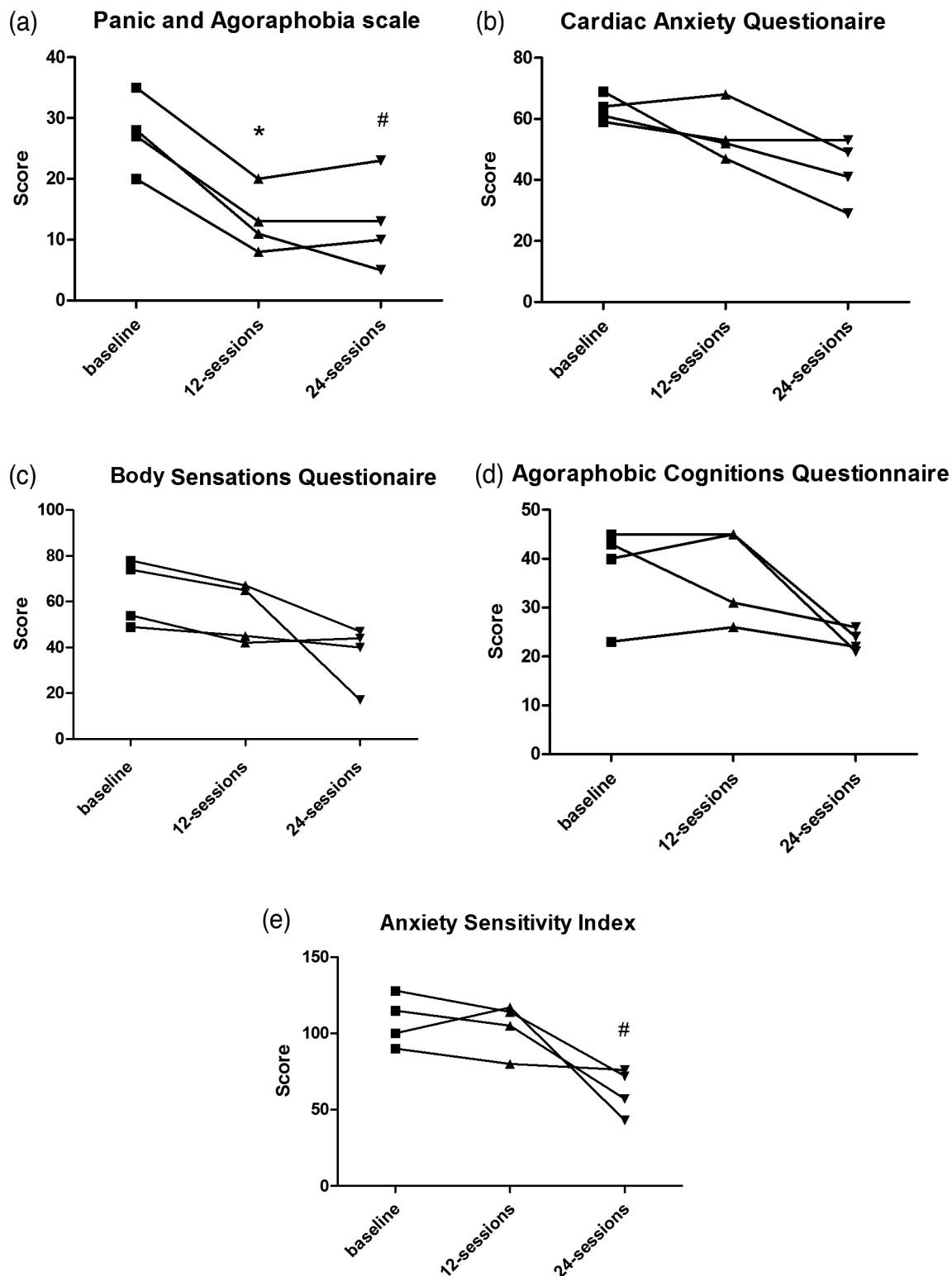


Figure 2 - Effect of 12 sessions and 24 sessions of aerobic exercise in Panic and Agoraphobia Scale, Cardiac Anxiety Questionnaire, Body Sensations Questionnaire, Agoraphobic Cognitions Questionnaire and Anxiety Sensitivity Index *Significant difference between baseline and 12 sessions; # Significant difference between baseline and 24 sessions.

Agoraphobia ($X^2 = 6.53$; $p = 0.03$), Body Sensations ($X^2 = 6.50$; $p = 0.03$), Agoraphobic Cognitions ($X^2 = 6.53$; $p = 0.03$) and Anxiety Sensitivity ($X^2 = 6.50$; $p = 0.039$). Moreover, there was a tendency in reduction in symptoms of Cardiac Anxiety ($X^2 = 5.73$; $p = 0.057$), showing a decrease in Panic and Agoraphobia score from baseline to 12 sessions ($p = 0.03$), but no significant difference from baseline to 24-sessions ($p = 0.07$) and between 12 sessions to 24 sessions ($p = 1.00$). We also observed a decrease in Anxiety Sensitivity Index after 24 sessions ($p = 0.01$), with no significant difference after 12 sessions ($p = 0.98$). There was no significant difference between 12 sessions and 24 sessions compared with baseline ($X^2 = 3.00$; $p = 0.22$).

■ DISCUSSION

The aerobic training intervention protocol used in this study highlighted the potential beneficial effect of this type of non-pharmacological approach to panic disorder treatment. The patients' clinical improvement was primarily observed in the behavioral variables measured through the scales and questionnaires.

Regarding the severity of PD symptoms, a significant reduction was observed after 12 sessions ($p = 0.03$), but just marginally after 24 sessions of training ($p = 0.07$), as compared to baseline. Several studies have investigated the chronic effects of exercise on clinical response of PD patients and found favorable results after 10 weeks of aerobic training intervention on the severity of symptoms of this anxiety disorder^{12,23,36-38}.

Cardiac anxiety is a PD characteristic and some somatic symptoms of panic attack are similar to cardiologic interurrences. Against our expectations, the Cardiac Anxiety Questionnaire's score in our study did not show a significant result, only a tendency ($p = 0.068$) between baseline and post 24 sessions of training. Results that were more favorable than ours have been previously reported for this variable³⁹, including one study in which the patients had coronary artery disease and were sedentary or physically active with or without psychiatry comorbidity. Their exercise protocol consisted in 30 minutes of aerobic training, followed for 20-30 minutes of strength and stretching exercises. The average scores on the Cardiac Anxiety Questionnaire after intervention period were significant lower for the exercise group; in addition, the severity of cardiovascular disease did not influence cardiac anxiety scores. However, patients having at least one psychiatric comorbidity showed higher scores on the Cardiac Anxiety Questionnaire³⁹.

The anxiety sensitivity is a known precursor of panic attacks for PD patients, in addition to being related, but often misinterpreted, anxiety symptoms. In our study, significant improvement in anxiety sensitivity after 24 sessions of aerobic training was observed. This suggests that aerobic training can reduce anxiety sensitivity by exposing PD patients to the same somatic sensations experienced during a panic attack, which patients begin to associate less with a potential threat or risk to their lives. However, others authors⁹ have found no improvement in anxiety sensitivity when 20 minutes exercises were performed (treadmill walking) both at low (60% of maximum heart rate) and high intensity (90% of maximum heart rate). Furthermore, evaluated individuals had no PD diagnosis; they were only recruited through high anxiety sensitivity (score >25 on Anxiety Sensitivity Index). Broman-Fulks and Storey¹⁰

reported improvement in anxiety sensitivity when the same type of exercise (treadmill walking) was used at an intermediate intensity (70% of maximum heart rate), compared to the control group (no exercise). In contrast, another study⁴⁰ evaluated in what way an active lifestyle can influence the anxiety sensitivity in PD patients and reported that the more physically active they were, the lower were their scores on the Anxiety Sensitivity Index, which also expressed lower anxiety sensitivity. Also supporting our results, other authors¹¹ showed significant reductions in anxiety sensitivity in patients who were submitted to aerobic training as compared to a control group.

Our results showed no significant differences related to cardiac anxiety and mobility for agoraphobia, respectively measured by the Cardiac Anxiety Questionnaire and the Mobility Inventory. Recently, a study²⁶ compared the effect of 12 weeks of aerobic exercise at 60-80% of maximum heart rate with Cognitive Behavioral Therapy. They found that both approaches were effective for PD treatment. The aerobic training was performed only once a week and during two other days patients performed circuit strength training (on the second day) and played sports and games with competitive elements (on the third day), without specific description of these sportive modalities by the authors. They found a significant improvement in both groups, in cognition and mobility for agoraphobia as well as a significant improvement in bodily sensations. Broman-Fulks, et al.⁹ also found significant improvement in bodily sensations after two weeks (six sessions) of training and after a week of follow-up in both low and high intensity groups. Nonetheless, the results were more pronounced in the group that trained at higher intensity; the sample size and different exercise protocols might had been intervening factors that could account for these differences in the findings.

Somewhat surprisingly, despite the strict control of training intensity based on the physiological data obtained in the maximal cardiopulmonary exercise testing at baseline, there was no significant overall improvement in the aerobic fitness of all PD patients, although a 10-15% increase was noted in two (50%) of them. This result differs from the findings of other studies that investigated the aerobic training in PD patients^{12,20,23,25,38}: they found positive benefits for both physiological and behavioral variables. Using a protocol of aerobic training (outdoor running) for 10 weeks, three times a week, 45-60 minutes duration, or a distance of 6.4 km per session, the authors reported a significant increase in aerobic fitness of PD patients compared to baseline. Other studies that used similar protocols for aerobic training, but unfortunately did not control the training intensity, reported very similar findings to the aforementioned studies: they report clinical improvement with increased aerobic fitness of patients^{25,38}.

The anxiolytic effects of acute aerobic exercise are well documented in the literature^{14,24}. One of our goals, therefore, was to fill in an informational gap about the use of a specific aerobic training intervention protocol controlling intensity and volume. Furthermore, this prescription is based on physiological data available from maximal cardiopulmonary exercise testing; their effects might be employed in both qualitative and quantitative evaluations for panic disorder treatment.

Some methodological limitations of this study should be considered. Mean values for the physiological variables

investigated were not statistically significant; this result may have been influenced by the small sample size and by the short period of intervention. Maybe with a longer period of training these data could be changed favorably. In addition, only half of the sample was medicated. On the other hand, it must be considered that no panic attacks occurred in any of the four patients during the maximal tests performed; this may represent a good level of tolerance of the patients to the performance of these tests in a cycle ergometer where she may feel more confident to end the procedure at her own wish. There was only one panic attack during the entire training sessions (Patient 4). Even with a small sample, just one complication occurred over the total of 96 sessions of training with the described duration and intensity; this may reflect the relative safety of aerobic training under carefully controlled intensity-volume for these patients.

The proper cardiorespiratory health status of our patients before the exercise intervention was supported by clinical examination and by the maximal exercise testing. Our results suggest a safe, well-tolerated and viable clinical intervention with aerobic training, as a non-pharmacological treatment for PD patients. The expected improvement of cardiorespiratory fitness seems not to be necessarily related to improvements in psychometric parameters. In other words, exercise prescriptions at lower levels of intensity are also effective for these patients, compatible with their expected lower exercise tolerance²⁰⁻²³, in order to obtain good results on the symptoms of panic. These findings may indicate a direction to be followed in future randomized controlled clinical trials, such as the use of sensitive instruments for measuring behavioral variables of PD severity, or prescribing aerobic training at an appropriate and effective intensity for clinical improvement of PD patients.

RESUMO

OBJETIVO: O efeito ansiolítico do exercício aeróbio regular em pacientes com Transtorno de Pânico é bem conhecido. No entanto, permanece a lacuna de um protocolo de intervenção com exercícios aeróbios como um tratamento adjunto não farmacológico para o transtorno de pânico. Nosso objetivo foi apresentar estudo piloto de um protocolo de treinamento aeróbio que pudesse ser replicável, seguro e viável para outras triagens clínicas com pacientes com transtorno de pânico.

MÉTODO: Pacientes com transtorno de pânico completaram 24 sessões (duas vezes por semana) de caminhada na esteira, com intensidade controlada (75% VO₂max).

RESULTADOS: Não foram observadas complicações importantes. Os benefícios da intervenção com treinamento aeróbio refletiram-se favoravelmente através de mudanças nos escores da Escala de Pânico e Agorafobia, do Questionário de Ansiedade Cardíaca, do Índice de Sensibilidade à Ansiedade e do Questionário de Sensações Corporais, apesar de nenhuma diferença ter se mostrado significativa nas variáveis fisiológicas.

CONCLUSÕES: O protocolo de treinamento aeróbio proposto mostrou ser seguro e uma ferramenta potencialmente útil para o tratamento adjunto não farmacológico do transtorno de pânico. Mais estudos são necessários a fim de avaliar se intensidades mais elevadas e/ou intervenções mais longas com exercícios poderiam induzir benefícios fisiológicos adicionais, ao mesmo tempo permanecendo viáveis e seguros.

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