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ORIGINAL ARTICLE

Panic disorder and exercise avoidance

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Objectives: 1) To identify whether patients with panic disorder in general and those with the respiratory subtype in particular actively avoid exercise; 2) to investigate physiological differences in cardiopulmonary function parameters in patients with panic disorder in general, patients with the respiratory subtype of panic disorder, and healthy controls upon exercise challenge.
Methods: Patients with panic disorder were classified as having either the respiratory or the non-respiratory subtype. Both groups were compared to controls in terms of exercise avoidance patterns and performance on cardiopulmonary exercise testing.
Results: Patients with panic disorder exhibited higher exercise avoidance scores and worse performance on cardiopulmonary exercise testing as compared with controls. No differences were found between patients with the respiratory and non-respiratory subtypes.
Conclusions: Exercise avoidance is present in panic disorder and is associated with poorer performance on cardiopulmonary exercise testing. These findings are not limited to patients with the respiratory subtype of the disorder.

Keywords: Anxiety disorders; exercise test; cardiopulmonary exercise testing; panic attack; physical exercise

Introduction

Fear of a heart attack is a major concern among patients with panic disorder (PD). In fact, PD is a common diagnosis in patients presenting to emergency rooms (ERs) with non-cardiac chest pain,[1] with an odds ratio of 2.03 compared to the general population.[2] A widely accepted theory for this phenomenon explains PD patients' excessive health concerns as hypochondriacal fears, i.e., these patients would greatly misinterpret physical symptoms of anxiety as symptoms of heart disease.[3] On the other hand, Katerndahl[2] reported the concerning finding that, besides an increased ratio for PD diagnosis in non-cardiac chest pain patients, patients with an ER diagnosis of PD are at increased risk (odds ratio 1.25) of coronary heart disease when compared with the general population.

Going beyond ER studies, one comprehensive literature review concluded that there is considerable covariation between depression, anxiety, and anger/hostility and cardiovascular disease (CVD) in the general population.[4] PD patients, specifically, show increased incidence of cardiovascular risk for both coronary heart disease and cardiovascular-related sudden death when compared with the general population.[5]

The most extensively researched hypothesis proposed to explain the increased cardiovascular risk in patients with PD and depression is an autonomic dysfunction, in which a dominance of sympathetic over vagal control of heart rate might lead to arrhythmia and sudden death.[6] Alternatively, simpler explanations may have been overlooked. Aerobic exercise may be avoided by many PD patients[7] and sedentariness is known to be associated with increased cardiovascular risk.[8] In addition, exercise may induce acute panic attacks (PAs)[9,10] or increase subjective anxiety in patients with PD more than in other people.[11]

The understanding of why PD patients avoid exercise is linked to the extremely aversive nature of PAs. Spontaneous PAs seem to be a type of misreleased fear or, more likely, another brain-defense physiological function, which, according to Donald Klein,[12] would be a false alarm of suffocation. There are some marked differences between fear reactions and classic spontaneous panic; first, a PA is usually associated with marked air hunger, which is not characteristic of external danger-induced fear, and, more importantly, both clinical and challenge studies of PD did not elicit the emergency reaction of hypothalamic-pituitary-adrenal (HPA) axis releases.[13] Furthermore, situational PAs and inter-panic chronic anxiety share several components, i.e., conditioning.[14] In due course, bodily sensations such as palpitations, breathlessness, or dizziness can trigger PAs by increasing autonomic distress, sensitization to panic, and fear conditioning, thus leading to avoidance.[15]

It has been hypothesized that, rather than a generalized brain alarm system responsive to all dangers, diverse alarm mechanisms have evolved to deal with distinct dangers. PAs would be a form of brain alarm system dealing with the danger of suffocation, to quickly

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prevent anoxic brain damage. Hypersensitivity of this system to signals of possible suffocation could result in panic.[16,17] Accordingly, diverse substances and techniques can induce panic in patients with PD under controlled laboratory conditions.[18] On the other hand, most of these exposures, excluding lactate and CO_2, elicit substantial HPA axis activation, which is absent in spontaneous PAs.[19]

In the clinical setting, PD is a heterogeneous condition with diverse symptom patterns. Briggs et al.[20] reported a homogeneous subgroup of PD patients in which shortness of breath and increased respiratory effort were the preponderant symptoms. This was called respiratory subtype panic disorder (RPD). These findings were corroborated by both Broocks et al.[9] and by Onur et al.[21]

Due to the understanding that suffocation avoidance is a major mechanism in panic pathophysiology, it has been proposed that RPD would represent a more nuclear, homogeneous group of panic patients[22] and that hypersensitivity to CO_2 and/or lactate would be the etiological factor in RPD, as: 1) dyspnea is the main trigger for PAs in such patients[22]; 2) RPD patients have a lower resting end-tidal pCO_2;[23] and, finally, 3) RPD patients exhibit higher sensitivity to CO_2 inhalation.[24,25]

Patients with RPD may also experience more exercise-induced PAs due to intravascular lactate, which accumulates in subjects with low aerobic conditioning.[26] This phenomenon is of special relevance to the purposes of the present study.

Given the fact that PAs in patients with RPD may be closer in neurobiological terms to underlying defensive responses related to maintenance of respiration and pH homeostasis, and that PAs may be conditioned to concurrent situations,[10] such as exercise, we hypothesize that patients with PD (and those with RPD in particular) actively avoid physical activities and that this phenomenon leads to sedentariness and increased cardiovascular risk.

This hypothesis predicts that patients with PD would experience more exercise avoidance than controls and that this phenomenon would be more prominent in RPD. Hence, the aim of this study was to determine whether differences exist among subjects with RPD, subjects with non-respiratory panic disorder (NRPD), and healthy subjects (C) regarding exercise avoidance measures and performance during a cardiopulmonary exercise test.

Materials and methods

Ethics statement

All patients were fully aware of the objectives, methods, and potential risks and benefits of the experiment and provided written informed consent for participation. The study was approved on its scientific merit and methodological and ethical aspects by both the internal review board of the Department of Psychiatry of the School of Medicine, Universidade de São Paulo (USP), and the USP Research Ethics Committee (CAPPesq). The study was partially funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) grant number 06311-0. All patients received treatment and all volunteers were given a report of their cardiopulmonary exercise testing results.

Sample

Study subjects were recruited from three sources: 1) volunteers (controls), mostly students and staff of the Institute of Psychiatry, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), recruited through an internal ad and word of mouth (n=30). All were healthy, sedentary, and devoid of any psychiatric disorders (as assessed by the Mini International Neuropsychiatric Interview [MINI])[27]; 2) patients with PD, who were screened in the emergency department of the HC-FMUSP Institute of Cardiology (INCOR) (n=15); and 3) self-referrals for treatment at the Institute of Psychiatry Outpatient Anxiety Clinic, recruited through radio ads (n=23).

Thirty-eight patients with PD were initially selected for this trial. We were able to match 30 patients to controls in both age and gender. Eight patients were excluded from the study and were treated at the outpatient clinic. Thus, following the exclusions reported in Figure 1, 30 sedentary subjects aged 18 to 55 with a diagnosis of PDs, with or without agoraphobia, were enrolled. The MINI[27] interview was used for the diagnosis of PD.

Initially, 72 patients were enrolled and divided into two groups, control group and group NRPD + RPD. After assessment, 12 subjects were excluded: four from control group and eight from the NRPD + RPD group. The final sample thus comprised 30 subjects per group.

Procedures

Patients with PD were asked to complete the Body Sensations Questionnaire (BSQ)[28] for identification of their RPD subtype. The BSQ scale contains 17 items concerning the degree to which patients fear somatic symptoms commonly associated with PAs (e.g., heart palpitations, dizziness, etc.). Items are rated on a five-point scale ranging from 1 = not frightened or worried by this sensation to 5 = extremely frightened by this sensation. The total score therefore ranges from 17 to 85. Patients scoring five or more items as serious or very serious among the seven items that describe respiratory symptoms (2, 3, 4, 5, 6, 7, and 17) were characterized as having RPD. Otherwise, patients were characterized as having NRPD. There is no standard procedure for this characterization.

Bandelow's Panic and Agoraphobia Scale (PAS)[29] was used for assessment of panic symptom severity. The PAS assesses the severity of PD with or without agoraphobia on its five main symptom domains: PA severity, phobic avoidance, anticipatory anxiety and severity of dysfunction, and health preoccupations. There are separate forms for clinical observation and self-report. Each question is ranked from 0 to 4.

The Physical Activity Readiness Questionnaire (PAR-Q)[30] was used for assessment of cardiovascular risk. The

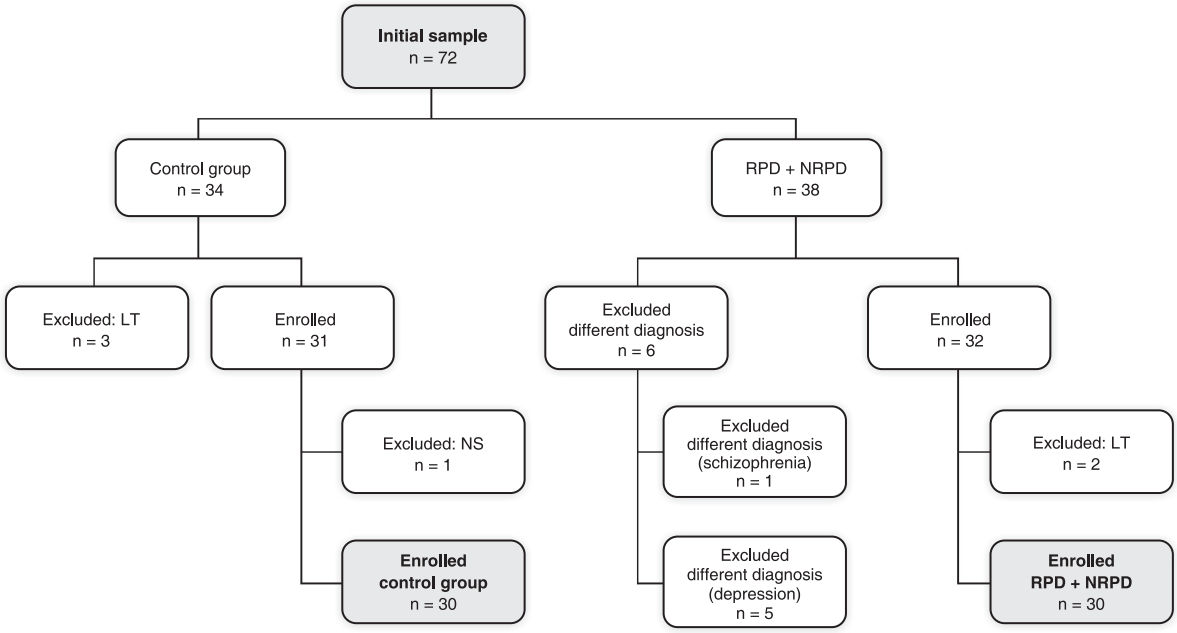


Figure 1 Sample recruitment and pre-screening. LT = lack of time; NA = non-sedentary; NRPD = non-respiratory panic disorder; RPD = respiratory panic disorder.

PAR-Q is a screening questionnaire that is widely used to investigate suitability to undertake physical activity programs.[31] It has 100% sensitivity and 80% specificity for detecting contraindications to physical activity, such as unstable angina.[30]

The Questionnaire for Assessment of Physical Activity Avoidance (QAPAA), a self-rated visual analog scale, was developed on the basis of the principles set forth by Bond & Lader.[32] Subjects are instructed to rate factors affecting their engagement in physical activities on two 10-cm lines, each with six anchor points. The first question quantifies the fear of physical activities, and the second one shows the avoidance of physical activity, i.e., being afraid of sensations or of its consequences. The questionnaire investigates and rates factors that influence exercise avoidance. A printable, English version of the scale is available online (http://www.amban.org.br/UserFiles/image/ImageBank/Escala%20de%20Esquiva%20de%20Atividade%20F%C3%ADsica.pdf).

Body weight and height were measured in kilograms (kg) and meters (m) respectively, and body mass index (BMI) was calculated by dividing the weight by the height squared (kg/m^2). Subjects were classified as normal weight if BMI was <25, overweight if BMI was 25-29.9, and obese if BMI was $\geqslant 30$, in accordance with U.S. National Heart, Lung, and Blood Institute guidelines.[33]

Quality of life was assessed with the Short Form (36) Health Survey (SF-36),[34] which was administered to all groups. The questionnaire includes 36 items (verbal scores range from 2 to 6) measuring eight dimensions of life quality: physical functioning (PF); role physical (RP); bodily pain (BP); general health (GH); vitality (VT); social functioning (SF); role emotional (RE); and mental health (MH); plus an item to evaluate perceived health conditions over the past year.

The eight scales of SF-36 yielded two summary scales, namely, the physical component summary, combining PF, RP, BP, and GH; and the mental component summary, encompassing VT, SF, RE, and MH. Some of the dimensions, e.g., VT, GH, and SF, are present in both summary scores, and show correlations with both.[25]

Cardiopulmonary exercise testing, to assess cardiovascular capacity, was performed at the Movement Investigation Laboratory of the HC-FMUSP Institute of Orthopedics and Traumatology. The stress test was conducted on a medical-grade treadmill (Imbramed, ATL 10200, Amparo, Brazil) with variable speed (km/h) and slope (%). A modified version of the Heck stress test protocol was used with fixed speed and increasing slope increments at the rate of 2% per minute.[35] The speed was selected from those available (2.4, 3.6, 4.8, 6.0, 6.5, 7.2 km/h) based on lack of individual conditions after two pilot tests with different speeds.[36] Once speed had been selected, individuals remained for 1 minute at rest and shortly thereafter began the protocol at the previously chosen and tested speed. During the 3-minute recovery phase, beginning immediately, speed was decreased and maintained for 1 minute per decrement. Perceived exertion was evaluated by the patient at each stage of the exercise test on a 15-point linear scale (6-20) as described by Borg.[37]

Statistical analysis

Comparisons among groups (RPD, NRPD, and C) were done using ANOVA when the normality assumption was confirmed. Certain variables are represented by scores belonging to the natural numbers and we did not assume normality; therefore, we used nonparametric tests in these cases. The Mann-Whitney *U* post-hoc test with

Bonferroni correction was used to compare groups two by two, and the Kruskal-Wallis test was used to compare three groups otherwise.

The level of significance was set at $p \leqslant 0.05$ (two-tailed) for all analyses and 95% confidence intervals (95%CI) were used throughout the study. Statistical analyses were carried out in SPSS 14.0.

Results

The sociodemographic and clinical characteristics of the 30 patients (RPD and NRPD) and 30 controls (CG) are outlined in Tables 1 and 2, respectively. Both groups comprised young adults, with a mean (SD) age of 34.91 (7.96) years. Overall, 20 patients and 20 controls were females. No patients or controls were obese; six patients in the NRPD group were overweight. There were no overweight subjects in the control group. There were only four smokers: two patients (NRPD group) and two controls. The groups were fairly homogeneous, with no significant between-group differences ($p = 0.05$, chi-square test) in gender, age, educational attainment, occupational status, marital status, or smoking habit.

No patients were receiving antidepressant drugs at the start of the follow-up period.

Data on the differences in BSQ, PAS, QAPAA, and SF-36 scores and in maximal oxygen uptake (VO_2 max) among groups are shown in Table 3.

Diagnostic classification of patients as having either RPD or NRPD was based on BSQ results. Overall, 14 of the 30 patients with PD scored five or more items as serious or very serious among the seven items that describe respiratory symptoms and were classified as having RPD. As expected, the RPD group (n=14) showed higher scores on the BSQ when compared with the NRPD group (n=16) (Mann-Whitney, 95%CI 35.36±32.53 vs. 17.12±13.13; U = 0.500; $p < 0.001$, two-tailed).

Regarding the severity of panic/agoraphobia symptoms as measured by the PAS, there were no differences between the RPD and NRPD groups (Mann-Whitney, 95%CI 34.64±2.49 vs. 29.00±5.35; U = 66.500; p = 0.058), probably due to the small deviation in the RPD group and much larger deviation in the NRPD group. Even though there were no significant differences between RPD and NRPD subjects, the results approached significance, and, in our clinical impression, patients with RPD experienced homogenously more severe PD.

Patients in both the RPD and NRPD groups showed more fear of physical exercise on the QAPAA scale than controls (Mann-Whitney, 95%CI: RPD vs. C, 6.71±2.20 vs. 0.46±0.32; U = 40.50; $p < 0.001$; NRPD vs. C, 5.50±1.71 vs. 0.46±0.32; U = 44.00; $p < 0.001$). Conversely, there was no difference between the RPD and NRPD groups (Mann-Whitney, 6.71±2.20 vs. 5.50±1.71; U = 84.00; p = 0.235).

Patients in both PD groups also showed more avoidance of physical exercise on the QAPAA scale than controls (Mann-Whitney, 95%CI: RPD vs. C, 6.00±1.69 vs. 1.40±0.62; U = 43.00; $p < 0.001$; NRPD vs. C, 5.50±1.53 vs. 1.40±0.62; U = 50.00; $p < 0.001$). Again, there was no difference between the RPD and NRPD groups (Mann-Whitney, 95%CI 6.00±1.69 vs. 5.50±1.53; U = 99.00; p = 0.581).

Both the RPD and NRPD groups showed a lower VO_2 max than their age- and gender-matched controls (Kruskal-Wallis, 95%CI: 26.85±2.05 and 26.28±2.32 vs. 33.97±2.29; chi-square = 25.80; $p < 0.001$) during the cardiopulmonary exercise test. Again, no difference was found between the RPD and NRPD groups (Mann-Whitney, 95%CI 26.85±2.05 vs. 26.28±2.32; U = 108.00; p = 0.868). All patients in both the RPD and NRPD groups voluntarily interrupted the cardiopulmonary exercise test at a submaximal heart rate. In contrast, all controls completed the test by reaching the preset maximum heart rate.

Furthermore, both the RPD and NRPD groups reported lower levels of PF as compared with controls on the physical symptoms component of the SF-36 (Kruskal-Wallis, 95%CI 60.62±10.77 and 65.59±8.62 vs.

Table 1 Sociodemographic profile

Characteristics	All groups n=60	NRPD n=16	RPD n=14	CG n=30
Sex				
Male	20 (33.3)	6 (37.5)	4 (28.6)	10 (33.3)
Female	40 (66.7)	10 (62.5)	10 (71.4)	20 (66.7)
Educational attainment				
Higher education	37 (61.7)	6 (37.5)	8 (57.1)	23 (76.7)
Less	23 (38.3)	10 (62.5)	6 (42.8)	7 (23.3)
Occupational status				
Working outside the home	54 (90.0)	16 (100)	10 (71.4)	28 (93.3)
Not working outside the home	6 (10.0)	0 (0.0)	4 (28.5)	2 (6.7)
Marital status				
Married	57 (95.0)	16 (100)	12 (85.7)	29 (96.7)
Unmarried	3 (5.0)	0 (0.0)	2 (14.2)	1 (3.3)
Age (years), mean ± SD	34.91±7.96	33.6±8.30	33.7±9.15	36.1±7.25

CG = control group; NRPD = non-respiratory panic disorder; RPD = respiratory panic disorder; SD = standard deviation.
All results are expressed as n (%), unless otherwise specified.
No significant ($p < 0.05$) between-group differences were found (chi-square test).

Table 2 Clinical profile

	All groups (n=60)		NRPD (n=16)		RPD (n=14)		CG (n=30)	
Variables	Mean (SD)	95%CI	Mean (SD)	95%CI	Mean (SD)	95%CI	Mean (SD)	95%CI
Weight, kg	72.78 (15.14)	68.80-76.76	77.06 (19.30)	66.77-87.34	67.57 (13.10)	60.00-75.13	72.93 (13.81)	67.77-78.09
Height, cm	169.35 (8.84)	167.06-171.63	169.50 (10.81)	163.73-175.26	165.07 (9.31)	159.69-170.45	171.26 (6.86)	168.70-173.83
BMI, kg/m^2	25.20 (4.14)	24.13-26.27	26.44 (4.21)	24.19-28.69	24.77 (4.50)	22.17-27.37	24.74 (3.93)	23.27-26.21
Abdominal circumference, cm	86.91 (12.09)	83.79-90.04	88.75 (16.61)	79.89-97.60	86.85 (12.03)	79.90-93.80	85.96 (9.33)	82.48-89.45
Resting heart rate, bpm*	83.11 (9.32)	80.70-85.52	85.43 (9.74)	80.24-90.62	84.28 (10.18)	78.40-90.16	81.33 (8.61)	78.11-84.55
Smokers, n (%)†	4 (6.67%)		2 (12.50%)		0 (0.00%)		2 (6.67%)	

95%CI = 95% confidence interval; BMI = body mass index; CG = control group; NRPD = non-respiratory panic disorder, RPD = respiratory panic disorder; SD = standard deviation.
* Measured at the start of cardiopulmonary exercise testing.
† Individuals who smoke one or more cigarettes daily.

Table 3 Evaluations

	All groups (n=60)		NRPD (n=16)		RPD (n=14)		CG (n=30)	
Variables	Mean (SD)	95%CI	Mean (SD)	95%CI	Mean (SD)	95%CI	Mean (SD)	95%CI
BSQ	-	-	17.12 (3.99)	13.13-21.12	35.36 (2.82)	32.53-38.18	-	-
PAS	-	-	29.00 (10.05)	23.64-34.35	34.64 (4.32)	32.14-37.13	-	-
QAPAA								
Fear of physical exercise	3.26 (3.79)	2.28-4.24	5.50 (3.22)	3.78-7.21	6.71 (3.81)	4.51-8.91	0.46 (0.86)	0.14-0.78
Avoidance of physical exercise	3.56 (3.19)	2.74-4.39	5.50 (2.87)	3.96-7.03	6.00 (2.93)	4.30-7.69	1.40 (1.67)	0.77-2.02
VO_2 max	30.26 (6.34)	28.62-31.89	26.28 (4.35)	23.96-28.60	26.85 (3.56)	24.80-28.91	33.97 (6.14)	31.67-36.26
SF-36								
Physical symptoms component	74.87 (17.92)	70.24-79.50	65.59 (16.18)	56.97-74.21	60.62 (18.66)	49.85-71.40	86.47 (8.78)	83.19-89.75
Mental component	59.51 (23.82)	53.36-65.66	47.36 (17.82)	37.86-56.85	37.26 (19.91)	25.76-48.76	76.38 (14.04)	71.14-81.63

95%CI = 95% confidence interval; BSQ = Body Sensations Questionnaire; CG = control group; NRPD = non-respiratory panic disorder; PAS = Panic and Agoraphobia Scale; QAPAA = Questionnaire for Assessment of Physical Activity Avoidance; RPD = respiratory panic disorder; SD = standard deviation; SF-36= Short Form International Quality of Life Questionnaire; VO_2 max = maximal oxygen uptake.
The level of significance adopted was $\alpha \leqslant 0.05$. The Mann-Whitney *U* post-hoc test with Bonferroni correction was used to compare groups two by two, and the Kruskal-Wallis test to compare three groups otherwise.

86.47±3.27; chi-square = 31.67; $p < 0.001$). Again, there was no difference between the RPD and NRPD subtypes (Mann-Whitney, 95%CI 60.62±10.77 vs. 65.59±8.62; U = 104.00; p = 0.739).

Mental well-being scores were also lower in both the RPD and NRPD groups as compared with controls in the mental component of the SF-36 (Kruskal-Wallis, 95%CI 37.26±11.49 and 47.36±9.49 vs. 76.38±5.24; chi-square = 32.59; $p < 0.001$). No difference was found between the RPD and NRPD groups (Mann-Whitney, 95%CI 37.26±11.49 vs. 47.36±9.49; U = 85.00; p = 0.262).

Discussion

The primary objective of this study was to evaluate whether differences exist among individuals with RPD, individuals with NRPD, and healthy controls in relation to avoidance of physical exercise and performance during cardiopulmonary exercise testing.

The rationale for this investigation was our assumption that exercise avoidance might underlie the increased mortality observed in patients with PD due to cardiovascular morbidity.[6] Hypothetically, exercise avoidance occurs due to fear conditioning of physical symptoms of arousal such as dyspnea. In the long term, this leads to sedentariness and increased cardiovascular risk. This model predicts that PD patients would report more avoidance and fear of physical exercise than controls, a finding corroborated by the present study. On the other hand, contrary to predictions, there were no differences between patients with the RPD and NRPD subtypes regarding exercise avoidance.

One possibility is that the small sample size might conceal clinically relevant differences due to lack of power. This hypothesis may explain the finding that patients in the RPD group experienced more severe panic/agoraphobia symptoms as measured by the PAS. The difference was very close to significance (p = 0.054), and was probably attributable to a very high deviation in NRPD group symptom severity scores (29.00±10.06) as compared with the RPD group, which had much more homogeneous symptom severity scores (34.64±4.33).The lack of differences in symptom severity between RPD and NRPD patients is also in contrast with the previous literature.[21,24]

On the other hand, on most other measures, some differences that have been reported in the literature – such as the fact that RPD patients do fear and avoid exercise more than patients with other forms of panic (e.g., CO_2 hypersensitivity, anxiety sensitivity) – were clearly not observed in the present study. The differences were very small and would not reach significance with a larger sample (p = 0.235 and p = 0.581 respectively).

Some methodological differences might explain the discrepancies between the results of the present study and those reported elsewhere in the literature. Onur et al.[21] found that patients with RPD had higher mean total scores on the Anxiety Sensitivity Index (ASI) and PAS than patients with NRPD. Furthermore, patients with RPD attained higher scores than patients with NRPD on four domains of the PAS (panic-like symptoms, agoraphobia, separation sensitivity, and reassurance seeking). The significant discriminating factors of the RPD and NRPD groups were the panic-like symptoms, agoraphobia, separation sensitivity, and reassurance seeking domains. This study suggests that anxiety sensitivity and panic-agoraphobic spectrum symptoms might be particularly relevant to understanding subtypes of PD. Bibber et al.[24] also reported different results; patients in the RPD group were significantly more sensitive to CO_2 than those in the NRPD group. The respiratory group also had higher scores on the PAS and had a longer duration of illness; both of these factors can be indicators of illness severity, but we did not find this difference to be significant. Conversely, we only observed differences between the PD and C groups.

The results of cardiopulmonary exercise testing corroborated our premise of a lower level of physical conditioning in patients with PD. The main difference observed between patients with PD (RPD and NRPD) and controls was in the VO_2 max, which was higher in the control group (sedentary but healthy subjects). On the other hand, contrary to our premises, there was no difference in VO_2 max between patients with RPD and patients with NRPD. These results would also be unlikely to change with a larger sample (p = 0.951). Further corroborating the lack of difference is the more qualitative finding that all patients in both the RPD and NRPD groups – and none in the control group – interrupted the cardiopulmonary exercise test at a sub-maximal heart rate.

Previous studies investigating cardiovascular functioning in patients with PD pointed out that these patients exhibit poor cardiorespiratory fitness and report more effort during physical exercise than healthy subjects. Patients with PD reached the target heart rate (HR) and ventilatory threshold earlier and exhibited lower oxygen consumption, higher HR, and lower within-subject standard deviations of HR (a measure of cardiac variability). Exertion was also greater, and there was a significant correlation between respiratory rate, tidal volume, and HR.[38] On the other hand, patients with RPD had not yet been investigated in terms of their cardiovascular performance compared with NRPD patients.

An alternative explanation for the lack of differences between the RPD and NRPD groups on cardiopulmonary exercise testing is that there might be other subtypes of PD, which also develop aversion to bodily sensations associated with exercise (i.e., tachycardia), among the NRPD group. The clinical relevance of this profile of symptoms may have been overlooked in the literature. Indeed, cognitive psychology proposes that biases towards catastrophic misinterpretation of diverse bodily sensations as much more dangerous than they really are, leading to increased avoidance of situations associated with these bodily sensations, may lead to a PA.[39] Another finding that supports cognitive biases underlying susceptibility to panic/agoraphobia is the fact that subjects with PD perceive symptoms as more embarrassing than controls.[40] Furthermore, the more catastrophically a symptom is interpreted, the more intense will the agoraphobic avoidance be.[41]

Lower quality of life in patients with PD as compared with healthy controls, as measured by the SF-36 in this study, has been reported previously in the literature.[42]

Our results suggest that patients with RPD seem not to avoid exercise and have worse cardiovascular performance than other PD patients. Despite our negative results, there are evidences that RPD may be more closely related to the core clinical features of PD. Compared to NRPD patients, RPD patients experience more spontaneous PAs and respond more selectively to imipramine than to alprazolam.[20] RPD has been shown to be more associated with an increased familial risk of PD and with longer duration and greater severity of illness.[24] RPD patients also experience higher anxiety sensitivity, a core PD feature.[43] Also in consonance with the relevance of respiratory physiology to PD is the finding that brain structures associated with the pathophysiology of PD, such as the serotonergic midbrain raphe neurons, are CO_2/H+ sensitive,[44] which led Serveson et al.[45] to suggest that brain acid-base homeostasis may be related to PD pathophysiology.

Accordingly, midbrain serotonergic neurons with rostral projections may be implicated in complex behaviors that are responses to respiratory acidosis, such as increased arousal and panic reactions.[45] Furthermore, acid-sensing (CO_2/H+) ion channels (ASIC 1a) are abundantly expressed in the amygdala and appear to mediate fear conditioning in mice. Fear conditioning is the most important neurobiological process underlying symptom progression to agoraphobia in PD.[46] Taken together, these evidences point to the understanding that PAs experimentally induced by CO_2 and lactate in the laboratory may be closer in pathophysiology to those spontaneously experienced by PD patients, or, at least, by a more nuclear subgroup of patients, such as those with RPD.

The present study results are also fully consistent with those reported by Sardinha et al.[47] in a systematic review, where they proposed that the underlying mechanisms of increased cardiac risk in PD patients would reflect the direct and indirect effects of autonomic dysfunction, as well as behavioral risk factors associated with an unhealthy lifestyle, which may be associated with exercise avoidance.[47]

There are limitations to generalizing the results of the present study and stating that PD is a risk factor for cardiovascular disease due to sedentary lifestyle. The most important is that the possibility that general distress and unspecified stress-related metabolic changes may underlie a common etiological factor shared by these conditions cannot be ruled out.[48] Indeed, PD, depression, and other conditions associated with high perceived stress present with metabolic changes. These unspecific changes, in turn, are known to be associated with elevated cardiovascular risk.

Finally, as it is clear that all PD patients avoid physical activity, exercise should be prescribed to this patient population. In addition to its effects on cardiovascular risk reduction, anxiolytic effects of aerobic exercise have been described (e.g., by Long & Satvel,[49] in healthy volunteers). Moreover, case reports[50] and two clinical studies have suggested that exercise training may be of therapeutic use in patients with anxiety neurosis[51] and PD.[52]

In summary, the present study found that patients with PD do indeed avoid physical activity and exhibit lower cardiovascular fitness as compared with healthy controls. Taken together, these factors may contribute to the increased cardiovascular risk observed in this patient population.

On the other hand, contradicting our hypothesis, patients with the RPD subtype did not avoid physical activity more and did not have worse cardiovascular performance than patients with NRPD. This suggests that other clusters of symptoms besides respiratory symptoms (i.e., cardiovascular) may also be aversely conditioned by PAs. This hypothesis warrants further investigation.

There is still a lack of evidence in the literature to endorse physical exercise as an adjunct to PD treatment. Theoretically, aerobic exercises could be a way of eliciting bodily symptoms in PD patients in a playful context and thus could be used therapeutically as exposure-based therapy for bodily symptoms of arousal, thus reducing anxiety sensitivity. Any reduction in cardiovascular risk would be a welcome added benefit.

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Disclosure

The authors report no conflicts of interest.

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