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Cognitive-Behavioral Therapy for Panic Disorder in Patients with Stable Coronary Artery Disease: A Feasibility Study

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Abstract

Implementing cognitive-behavioral therapy (CBT), the first-line psychological treatment for panic disorder (PD), may be challenging in patients with comorbid coronary artery disease (CAD).This study aimed at assessing the feasibility and acceptability of a CBT for PD protocol that was adapted to patients suffering from comorbid CAD. It also aimed at evaluating the efficacy of the intervention to reduce PD symptomatology and psychological distress and improve quality of life. This was a single-case experimental design with pre-treatment, post-treatment and 6-month follow-up measures. Patients with PD and stable CAD received 14 to 17 individual, 1-h sessions of an adapted CBT for PD protocol. They completed interviews and questionnaires at pre-treatment, post-treatment and at a 6-month follow-up assessing intervention acceptability, PD symptomatology, psychological distress and quality of life. A total of 6 patients out of 7 completed the intervention and 6-month follow-up, indicating satisfactory feasibility. Acceptability was high (medians of ≥ 8.5 out of 9 and ≥ 80%) both at pre and post treatment. Remission rate was of 83% at post-treatment and 6-month follow-up. The intervention appeared to have positive effects on comorbid anxiety and depression symptoms and quality of life. The intervention appeared feasible and acceptable in patients with comorbid CAD. The effects of the adapted CBT protocol on PD symptoms, psychological distress and quality of life are promising and were maintained at the 6-month follow-up. Further studies should aim at replicating the present results in randomized-controlled trials

Keywords Panic disorder · Anxiety · Anxiety disorders · Cognitive-behavioral therapy · Coronary artery disease

Panic disorder (PD) is a severe anxiety disorder characterized by recurrent panic attacks, anticipation and worry about further panic attacks and their potential consequences as well as dysfunctional reassurance and avoidance behaviors aimed at preventing them (American Psychiatric Association[APA], 2013). Indeed, patients with PD tend to attribute the symptoms of a panic attack to a life-threatening condition such as coronary artery disease (CAD) (APA, 2013). While these catastrophic interpretations are generally unfounded in healthy individuals, CAD and PD do co-occur and such comorbidity represents a major public health concern (Celano et al., 2016; Jeejeebhoy et al., 2000). In fact, PD is associated with a 47% increased risk of developing CAD and a 40% increased risk of experiencing adverse cardiac events in previously healthy individuals (Tully et al., 2015). Inversely, the presence of CAD may increase the risk of developing PD through heightened fear of physical symptoms, catastrophic interpretations of physical sensations and a fear of dying (Meuret et al., 2017). Taken together, these data may explain why PD is 2.5 to 15 times more prevalent in patients with coronary artery disease (CAD) than in those without this condition (Fleet et al., 2000; Jeejeebhoy et al., 2000; Katerndahl, 2008; Kessler et al., 2006; Machado et al., 2017; Tully et al., 2014).

This is worrisome as, in patients with CAD, persistent and elevated anxiety has been associated with a wide range

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of adverse consequences, such as an increased risk of mortality and cardiac events, higher levels of psychological distress, increased healthcare utilization and a lowered quality of life (Celano et al., 2015; Kuhl et al., 2009; Martens et al., 2010; Moser, 2007; Moser et al., 2011; Roest et al., 2010; Roest et al., 2012; Shibeshi et al., 2007; Sowden & Huffman, 2009; Strik et al., 2003; Watkins et al., 2013).

Given its consequences, severity and chronicity when left untreated, early diagnosis and treatment of PD is very likely to improve the well-being of patients with comorbid CAD (Frasure-Smith & Lesperance, 2008; Grace et al., 2004; Huffman et al., 2010; Lane et al., 2002; Moser, 2007; Pogosova et al., 2015; Strik et al., 2003).

Recommended first-line treatments for PD include antidepressants, cognitive-behavioral therapy (CBT), or a combination of both (Katzman et al., 2014; National Institute for Health & Care Excellence, 2011). In patients with CAD, pharmacotherapy warrants caution as potential medical contraindications or harmful side effects must be managed (Celano et al., 2016; Yekehtaz et al., 2013). Moreover, psychotherapy has been shown to be at least as effective as pharmacotherapy for treating PD, while being more cost-effective and associated with higher maintenance of therapeutic gains (Katzman et al., 2014; McHugh et al., 2009). However, implementing CBT in patients with both PD and CAD may pose significant clinical challenges (Tremblay et al., 2020; Tully et al., 2016).

One of the main sources of concern is the considerable overlap between the symptoms of a panic attack and those of a cardiovascular event such as angina or an acute coronary syndrome (e.g., chest pain, dyspnea or nausea) (Abrignani et al., 2014; Meuret et al., 2017; Tremblay et al., 2020). Given the presence of a genuine medical risk related to the cardiac condition, clinicians and patients may feel uncomfortable or unsafe trying to differentiate such symptoms (Tremblay et al., 2020; Tully et al.). This represents a challenge for the success of CBT for PD as, at its core, the treatment aims at developing the patients' ability to tolerate and manage anxiety-related symptoms through gradual exposure (White & Barlow, 2002). Consequently, the right balance between interventions aiming at reducing the fear of physical symptoms and those promoting cardioprotective behaviors must be attained (Tremblay et al., 2020; Tully et al.; Tully et al., 2016).

To our knowledge, only one study has described an attempt at applying a cognitive-behavioral model to patients suffering from a cardiovascular disease and PD (Tully et al., 2016). This model describes several interesting strategies, such as CAD-related psychoeducation, suggestions to adapt therapeutic exercises to the presence of a cardiac condition and action plans for the management of chest pain (Tully et al., 2016). However, it was developed for patients suffering from heart failure and deviated considerably from a standard CBT for PD protocol in terms of number of sessions (8 instead of the 12 to 15 sessions generally recommended to treat PD), setting (both in-hospital and at-home) and the use of alternative exposure strategies (Katzman et al., 2014; National Institute for Health & Care Excellence, 2011; Tully et al., 2016). Such modifications were mainly implemented to promote patients' adherence, since some authors have suggested that cardiac patients may drop out early of psychotherapy (Tully et al., 2016). Consequently, the feasibility and acceptability of a minimally adapted full-length CBT for PD protocol in patients with CAD and the efficacy of such an intervention remain to be explored.

Objectives

The first objective of this study was to assess the feasibility and acceptability of a CBT for PD protocol which was adapted to patients suffering from stable CAD in terms of: (a) intervention acceptance and completion rates, (b) observance and (c) treatment credibility and expectancy. The underlying hypothesis was that the intervention would be both feasible and acceptable for patients. The second objective was to explore the efficacy of the adapted protocol on PD symptomatology, that is: (a) the presence of PD; (b) panic attacks frequency, (c) fear of anxiety-related physical sensations (i.e., anxiety sensitivity, cardiac anxiety, perceived aversiveness of panic attacks); (d) avoidance and reassurance behaviors and (e) anticipatory anxiety about further panic attacks. A third objective was to assess the effects of the adapted intervention on (a) the level of psychological distress (i.e., anxiety/depressive symptoms, presence of comorbid anxiety or mood disorders) and (b) health-related quality of life. The hypothesis related to the second and third objectives was that patients would improve on all measures and that this improvement would be maintained at the 6-month follow-up.

Methods

Design

This feasibility study is a series of single-case experimental AB designs (SCED) with pre, post and 6-month follow-up measures. While SCEDs can be useful and valid to gather preliminary data on the efficacy of an intervention that cannot be withdrawn or reversed (i.e., such as CBT), there are also several threats to their internal validity (e.g., maturation, history) (Michiels & Onghena, 2019; Morgan & Morgan, 2009; Rhoda et al., 2011). Randomized, non-concurrent multiple baselines is a proposed method to increase the internal validity of a SCED series by enabling some control

over the effects of time (Michiels & Onghena, 2019; Morgan & Morgan, 2009; Rhoda et al., 2011).

Participants

Participants were recruited in the cardiology outpatient clinic of the Centre intégré de santé et de services sociaux de Chaudière-Appalaches (CISSS-CA). To be eligible, patients had to: (1) be ≥ 18 years of age; (2) be able to provide free and informed consent; (3) read and speak French; (4) have a diagnosis of CAD (e.g., myocardial infarction, revascularization procedure, and/or a ≥ 50% coronary stenosis) according to standardized criteria and stable for at least three months and (5) present a primary PD diagnosis (most severe psychiatric disorder) as assessed with the *Anxiety and Related Disorders Interview Schedule for DSM-5* (ADIS-5) (Brown & Barlow, 2014). Patients were excluded if: (1) they were receiving psychotherapy for PD at the time of recruitment; (2) they presented a condition that could have interfered with study participation (e.g., psychotic state, major cognitive deficit) or (3) they suffered from a severe and/or unstable medical condition (e.g., chronic pulmonary obstructive disease, heart failure). Patients who were taking medication for anxiety at the time of recruitment were asked to maintain the same dosage until the end of treatment.

Procedure

Cardiologists from the clinic transferred the contact information of potentially eligible patients to the research team. These patients were contacted by phone to present the study and screen their eligibility (i.e., possible presence of PD). Those who screened positive for PD were then invited for an in-person interview during which written consent was obtained, PD diagnosis was confirmed and sociodemographic data was collected. After reviewing each eligible case with the research team, patients were contacted by phone to discuss the assessment results and, when eligible, they were invited to participate in the study. Upon acceptance, they were randomly assigned to a given waiting period (2, 3 or 4 weeks) by drawing a sealed opaque envelope. Baseline questionnaires were mailed to participants who were asked to fill them out during the week prior to their first treatment session. The intervention was then delivered on an individual basis, over 14 to 17 weeks, one hour per week. Patients filled out the intervention acceptability measure once at pre-treatment, after the psychoeducation and presentation of treatment rationale were completed (session 3) and once before the last treatment session. Observance to recommended therapeutic exercises was assessed by the therapist immediately after each session using a brief rating scale. Following the intervention and at a 6-month follow-up interview, the ADIS-5 and questionnaires were readministered. At each assessment point, PD and other related diagnoses were assessed by the main therapist (MAT) and then discussed with the project supervisor (GFB), an assessment procedure that led to excellent inter-rater agreements on the ADIS-5 diagnoses in our previous studies (Foldes-Busque et al., 2021; Foldes-Busque et al., 2018). Finally, during the waiting period and throughout the intervention, patients were invited to complete a daily panic symptom diary.

Adaptation of the Procedure Due to the Covid-19 Pandemic

In March 2020, the COVID-19 pandemic public health measures led to changes in the study procedure, as face-to-face interventions were no longer possible. At that time, two participants were in treatment, and one was completing the waiting period. After obtaining the authorization of the ethics committee of the (*masked for anonymousness)* and the participants' consent, one of the participants in treatment and the one in the waiting period received the intervention through videoconference (8 and 14 sessions, respectively). However, the case of the other participant in treatment was transferred to a health worker in the public system due to reluctance to videoconferencing. Three 6-month follow-up assessments were also done over the phone instead of in person.

Intervention

The intervention was delivered either by a trained doctoral student in psychology (supervised by a psychologist) or by an experienced psychologist. Weekly supervisions were implemented to discuss patients' progress and promote treatment integrity. The protocol was based on the CBT for PD protocol published by Marchand et al. (2018) (Marchand et al., 2018), which comprises the following empirically supported treatment components: psychoeducation on anxiety and panic, cognitive restructuring, interoceptive exposure, exposure to avoided activities/situations and maintenance of gains/prevention of relapse (Marchand et al., 2018; McHugh et al., 2009; Otto & Deveney, 2005; White & Barlow, 2004). Its efficacy in reducing PD symptomatology and improving quality of life has been previously established with excellent 2-year maintenance of therapeutic gains (Marchand et al., 2009; Roberge et al., 2005; Roberge et al., 2008). The intervention was adapted to address the main challenges of CBT for PD in patients with comorbid CAD. Like the original intervention, the adapted protocol comprised 14 one-hour individual sessions; however, one to three supplementary sessions could be added to further explore some of the techniques or strategies. As described in Table 1 and in Supporting Information (Table 1), the adaptations mainly consisted in adding psychoeducation concerning CAD and the role of anxiety as a cardiovascular risk factor, safe and functional

Table 1 Original CBT protocol for PD and CAD-specific adaptations

Sessions	Components of standard protocol	Adaptations
1–3	Psychoeducation Cognitive restructuring	Psychoeducation on CAD (i.e., development, prognosis, management) Modifiable and non-modifiable risk factors for CAD (including role of anxiety) Control over illness progression Differentiating the symptoms of a panic attack and a cardiac event Symptoms assessment/management plan (e.g., chest pain) Cardiac rehabilitation/health behaviors (advantages, barriers)
4–5	Interoceptive exposure Cognitive restructuring	Clearance from the cardiologist before starting Cognitive restructuring adapted to the presence of CAD Inclusion of difficulties encountered in cardiac rehabilitation
6	Exposure to natural activities	Clearance from the cardiologist before starting
7	Review of the strategies, challenges and progress	
8–11	Exposure to avoided situations	Clearance from the cardiologist before starting Role of physical exercise in the context of CAD and PD
12	Consolidation of therapeutic gains	
13–14	Maintenance of gains Relapse prevention	Observance to treatments for CAD and their relationship with PD Strategies to manage anxiety in the context of possible new cardiac events

symptom management strategies (both cardiac and anxiety-related), adapted cognitive restructuring exercises and promoting health behaviors. For instance, patients were encouraged to identify maladaptive thoughts (e.g., "I am going to die from a heart attack" while being short of breath during exercise) and to replace them with more realistic and constructive thoughts (e.g., "My cardiac condition is stable and my cardiac stress test showed that I can tolerate some physical effort"). Some adaptations were also based on our clinical experience with this population. The detailed adaptation process is described elsewhere (Tremblay et al., 2020). The intervention was manualized to promote treatment integrity.

Measures

Clinician-Administered Measures

A phone screening interview, comprising questions covering the inclusion and exclusion criteria and the Panic Disorder module of the *Patient Health Questionnaire (*PHQ-PD), was administered to establish preliminary eligibility (Spitzer et al., 1999).

A brief interview created for the purpose of this study was used to document the baseline sociodemographic data of participants and their medical history. Items concerning the occurrence of cardiac events were administered at all assessment points.

PD and other psychiatric comorbidities were assessed using the ADIS-5 (Brown & Barlow, 2014). This standardized and semi-structured interview is one of the most recommended measures in research for diagnosing anxiety and mood disorders (Brown & Barlow, 2014; Shear & Maser, 1994; Tully et al., 2014).

An observance rating scale was created for the purpose of this study based on the work of Primakoff et al. (1986) (Primakoff et al., 1986). This scale comprises six possible observance ratings, that is: (1) The patient did not attempt the homework; (2) The patient attempted the homework but was unable to execute it for reasons such as lack of ability or extenuating circumstances; (3) The patient did a different homework than what was planned, but that can be considered relevant to the treatment goals; (4) The patient did a portion of the homework; (5) The patient did the homework and (6) The patient did more homework than planned (Primakoff et al., 1986).

Self-report Measures

To assess treatment acceptability, a French translation of the *Credibility and Expectancy Questionnaire* was used. This self-reported measure comprises six items on a Likert-type scale assessing credibility and expectancy prior to and following an intervention (Devilly & Borkovec, 2000).

PD severity was assessed using the validated French-Canadian version of the *Panic and Agoraphobia Scale* (PAS) (Bandelow, 1995; Roberge et al., 2003). This 13-item questionnaire comprises five subscales (panic attacks, avoidance, anticipatory anxiety, disability and health anxiety) while the total score reflects overall PD symptomatology (Bandelow, 1995; Roberge et al., 2003). The original and French versions present satisfactory internal consistency ($\alpha = .89$) and temporal stability ($r = .73$) (Bandelow, 1995; Roberge et al., 2003).

Anxiety sensitivity, defined as one's tendency to attribute negative consequences to anxiety symptoms, was evaluated

with the validated French-Canadian version of the *Anxiety Sensitivity Index* (ASI) (Reiss et al., 1986; Verreault et al., 2007). It comprises 16 items, with higher scores indicating more severe anxiety sensitivity, and has good internal consistency ($\alpha = .82–.91$) and temporal stability ($r = .71$) (Reiss et al., 1986; Verreault et al., 2007).

The validated French-Canadian version of the Cardiac Anxiety Questionnaire (CAQ-FR) was used to document the fear of cardiovascular sensations and their anticipated consequences (Bisson-Bernatchez et al., 2019; Eifert et al., 2000). A higher total score indicates higher levels of heart-focused anxiety, and the 15 items can also be divided into four subscales (fear, avoidance, attention and reassurance-seeking) (Bisson-Bernatchez et al., 2019). This self-report measure has good internal consistency ($\alpha = .88$) (Bisson-Bernatchez et al., 2019).

The GAD-7 and PHQ-9 were used as measures of psychological distress (anxiety and depressive symptoms, respectively) (Kroenke et al., 2001; Spitzer et al., 2006). Both instruments have excellent internal consistency ($\alpha = .86–.92$) (Kroenke et al., 2001; Spitzer et al., 2006).

Health-related quality of life was assessed using the validated French version of the *MacNew Heart Disease Health-Related Quality of Life*, a 27-item heart disease-specific measure that has good internal consistency ($\alpha = .75–.97$) and temporal stability ($r = .61–.97$) (Hofer et al., 2004; Pavy et al., 2015).

Finally, a panic symptom diary was used to document three aspects of PD symptomatology, that is: anticipatory anxiety, perceived aversiveness of panic attacks and number of panic attacks. In the morning, patients rated, using 11-point rating scales, their perceived expectancy of having a panic attack during the day (0 = I will not have a panic attack to 10 = I will definitely have a panic attack) and the expected aversiveness if it were to happen (0 = not bad at all to 10 = extremely bad) (de Beurs et al., 1997). At the end of each day, patients indicated the number of panic attacks that they experienced.

Statistical Analyses

The acceptation rate was conceptualized as the percentage of eligible participants who consented to participate in the study while the completion rate referred to the percentage of those participants who attended all planned sessions. Descriptive statistics were used to report data on the number of panic attacks across the study period and the remission rates for PD and other psychiatric comorbidities. Remission was defined as no longer meeting the DSM-5 diagnostic criteria for PD following the intervention. The percentage of sessions recorded in each observance category was calculated in relation to the total number of sessions during which homework was planned, which could vary between 10 and 13 for each patient. For the assessment of continuous outcomes related to treatment efficacy (questionnaires), Friedman's ANOVAs were conducted. Effect sizes were also calculated using the standardized mean differences between pre-treatment and post-treatment, and between post-treatment and 6-month follow-up. Hedge's correction was applied to Cohen's d due to the small sample size. These analyses were carried out with IBM SPSS Statistics for Mac 24.0 (Armonk, NY: IBM Corp.).

Data from the panic symptom diaries (anticipation and perceived aversiveness) was analysed using a dual method. First, a structured visual analysis based on the method proposed by Lane and Gast (2014) (Lane & Gast, 2014) was conducted. This analysis uses the split-middle method of trend estimation, which allows for an estimation of the direction of therapeutic change (improving/deteriorating) based on median values (Lane & Gast, 2014). This analysis was complemented with a non-parametric statistical method (Tau-U statistics) to assess changes between the baseline and treatment phases (Brossart et al., 2018; Lane & Gast, 2014). Tau-U statistics were computed using the online calculator available at www.singlecaseresearch.org.

Results

Characteristics of the Sample

Participants were seven white French-Canadians aged between 45 and 74 years old (mean age 57.8 ± 11.1 years) and 5 of them were men. Five participants completed 12 years or less (high school degree) of formal education, five had an annual income of $60,000 or less and five were married or in a common-law relationship. All participants had a history of myocardial infarction and revascularization procedure. Four participants met the diagnostic criteria for at least one psychiatric disorder other than PD (depression ($n = 3$), agoraphobia ($n = 2$), generalized anxiety disorder ($n = 1$), social phobia ($n = 1$)).

Treatment Feasibility

1. A total of 21 potential participants were referred to the research team. Among them, 10 screened positive for PD and were invited to the face-to-face interview. Seven patients were eligible to participate in the study and all of them consented (see Fig. 1 for flowchart).

Six participants out of seven (86%) completed treatment and completed the 6 month follow-up assessment. The remaining participant was referred elsewhere due to refusal of the change in the intervention format (i.e., videoconferencing) in the context of the COVID-19 pandemic public

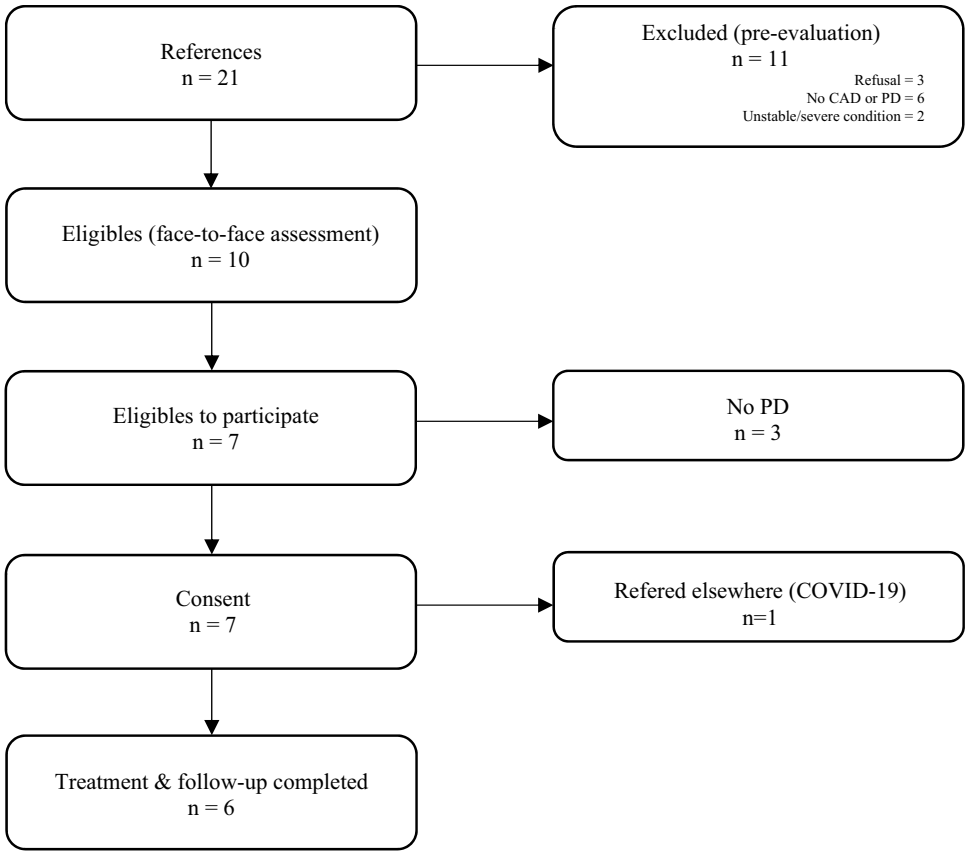


Fig. 1 Participants flowchart

health measures. Two participants received three additional sessions to address particularly strong dysfunctional beliefs about their physical symptoms through cognitive restructuring and planned at-home exposures. One participant considered dropping out in reaction to an exacerbation of PD symptomatology after attempting interoceptive exposure exercises at home. This situation was resolved through discussion and the participant resumed treatment after a 3-week interruption. None of the participants reported experiencing a cardiac event during the treatment phase and at the 6-month follow-up.

As can be seen in Table 2, the median credibility scores (questions 1–3) from the *Credibility and Expectancy Questionnaire* were initially of 8 out of 9 and increased to ≥ 8.5 out of 9 at post-treatment, indicating elevated treatment credibility at both assessment points. Expectancy scores (questions 4–6) were also elevated, with medians of 8 out of 9 and 80% at pre-treatment and post-treatment.

At-home CBT exercises were planned in 70 sessions out of 90 in total. Based on therapists' reports, participants did their homework as planned or more in 78.6% of cases (55/70 sessions), indicating excellent observance to CBT exercises. The remaining 15 sessions were either in the "attempted to do the homework" (2.9%; 2/70) or "did a portion of the homework" (18.6%; 13/70) categories. No sessions were recorded in the "The patient did not do the homework" category.

Treatment Efficacy: PD Remission and Severity

The remission rate of PD was of 83% ($n = 5/6$) at post-treatment and at the 6 month follow-up. Between pre-treatment and post-treatment, there was a significant reduction in the scores of the panic attack subscale of the PAS, the PD severity measure ($g = -1.3$, $p = .01$). Non-significant reductions of anxiety sensitivity (as measured with the ASI) and heart-focused anxiety (as measured with the CAQ-FR) levels were also observed, with moderate to large effect sizes ($g = -1.0$ and $-.7$, respectively, $p = .09$). The PAS avoidance subscale scores significantly decreased over time ($p = .03$), while a non-significant reduction in the scores of the CAQ-FR reassurance subscale was observed ($p = .06$), both with moderate effect sizes ($g = -.6$ and $g = -.7$, respectively). Anticipatory anxiety scores were also significantly reduced following the intervention, with a moderate effect size ($g = -.6$; $p = .03$). In all cases, therapeutic gains were maintained at the 6-month follow-up ($g = -.2$ to $.0$). These results are detailed in Table 3.

Table 2 Pre-treatment and post-treatment scores—*Credibility and Expectancy Questionnaire* (Devilly & Borkovec, 2000)

	Mean (SD)	Median	Minimum Maximum	Range
Pre-treatment				
1. At this point, how logical does the therapy offered to you seem?	7.8 (.8)	8	7–9	1–9
2. At this point, how successful do you think this treatment will be in reducing your symptoms?	7.4 (1.5)	8	5–9	1–9
3. How confident would you be in recommending this treatment to a friend who experiences similar problems?	7.2 (1.6)	8	5–9	1–9
4. By the end of the therapy period, how much improvement in your difficulties do you think will occur?	78.0 (8.4)	80	70–90	0–100%
5. How much do you really *feel* that therapy will help you reduce your symptoms?	6.4 (3.1)	8	1–8	1–9
6. How much improvement in your symptoms do you really *feel* will occur?	76.0 (11.4)	80	60–90	0–100%
Post-treatment				
1. At this point, how logical did the therapy offered to you seem?	8.5 (.6)	8.5	8–9	1–9
2. At this point, how successful do you think this treatment was in reducing your symptoms?	8.3 (.8)	8.5	7–9	0–9
3. How confident would you be in recommending this treatment to a friend who experiences similar problems?	8.8 (.4)	9	8–9	0–9
4. How much improvement in your difficulties do you think occurred?	80.0 (15.5)	80	60–100	0–100%
5. How much do you really *feel* that therapy helped you reduce your symptoms?	8.0 (1.1)	8	7–9	0–9
6. How much improvement in your symptoms do you really *feel* occurred?	78.3 (17.2)	80	60–100	0–100%

Table 3 Measures of PD symptomatology

Measure	Pre-treatment	Post-treatment	6-month follow-up	Hedge's *g* pre-treatment/ post-treatment	Hedge's g post-treatment/ 6-month follow-up	*p* value
Anxiety Sensitivity Index	$\bar{x}$ 43.8 (5.9) $\tilde{x}$ 43.0 (10.0)	$\bar{x}$ 28.3 (14.1) $\tilde{x}$ 25.5 (24.0)	$\bar{x}$ 26.8 (11.8) $\tilde{x}$ 28.5 (23.0)	− 1.0	− .1	.09
CAQ-FR	$\bar{x}$ 39.0 (8.6) $\tilde{x}$ 42.0 (12.5)	$\bar{x}$ 24.0 (17.6) $\tilde{x}$ 23.0 (33.5)	$\bar{x}$ 22.0 (13.0) $\tilde{x}$ 21.0 (22.5)	− .7	− .1	.09
CAQ-FR—attention	$\bar{x}$ 11.2 (3.9) $\tilde{x}$ 13.0 (6.5)	$\bar{x}$ 7.5 (5.7) $\tilde{x}$ 7.0 (11.7)	$\bar{x}$ 7.2 (4.6) $\tilde{x}$ 6.5 (9.0)	− .4	− .1	.27
CAQ-FR—avoidance	$\bar{x}$ 10.4 (2.2) $\tilde{x}$ 11.0 (3.5)	$\bar{x}$ 6.2 (5.7) $\tilde{x}$ 4.5 (11.0)	$\bar{x}$ 5.7 (4.1) $\tilde{x}$ 4.5 (7.3)	− .6	− .1	.18
CAQ-FR—fear	$\bar{x}$ 10.0 (2.9) $\tilde{x}$ 11.0 (4.5)	$\bar{x}$ 6.0 (3.8) $\tilde{x}$ 6.5 (6.8)	$\bar{x}$ 5.3 (3.7) $\tilde{x}$ 6.0 (5.0)	− .9	− .2	.02
CAQ-FR—reassurance	$\bar{x}$ 7.4 (2.1) $\tilde{x}$ 7.0 (4.0)	$\bar{x}$ 4.3 (3.5) $\tilde{x}$ 3.5 (6.8)	$\bar{x}$ 3.8 (2.1) $\tilde{x}$ 4.5 (3.0)	− .7	− .1	.06
PAS—total	$\bar{x}$ 27.8 (9.3) $\tilde{x}$ 28.0 (15.5)	$\bar{x}$ 11.0 (11.1) $\tilde{x}$ 7.0 (12.0)	$\bar{x}$ 9.8 (11.5) $\tilde{x}$ 5.0 (18.8)	− 1.1	− .1	.01
PAS—panic attacks	$\bar{x}$ 7.0 (2.4) $\tilde{x}$ 6.0 (4.5)	$\bar{x}$ 2.0 (3.1) $\tilde{x}$ 1.0 (3.5)	$\bar{x}$ 1.7 (2.9) $\tilde{x}$ .0 (4.0)	− 1.3	− .1	.01
PAS—avoidance	$\bar{x}$ 5.4 (2.1) $\tilde{x}$ 5.0 (3.0)	$\bar{x}$ 3.3 (2.8) $\tilde{x}$ 3.5 (4.2)	$\bar{x}$ 2.5 (3.6) $\tilde{x}$ 1.0 (5.3)	− .6	− .2	.03
PAS—anticipatory anxiety	$\bar{x}$ 4.0 (1.6) $\tilde{x}$ 4.0 (3.0)	$\bar{x}$ 1.7 (2.3) $\tilde{x}$ 1.0 (3.0)	$\bar{x}$ 1.7 (2.0) $\tilde{x}$ 1.0 (4.0)	− .6	.0	.03
PAS—disability	$\bar{x}$ 6.0 (3.0) $\tilde{x}$ 7.0 (4.5)	$\bar{x}$ 1.5 (2.5) $\tilde{x}$ .0 (3.8)	$\bar{x}$ .5 (1.2) $\tilde{x}$ .0 (.8)	− 1.3	− .3	.01
PAS—health anxiety	$\bar{x}$ 5.4 (1.7) $\tilde{x}$ 5.0 (3.0)	$\bar{x}$ 2.5 (1.6) $\tilde{x}$ 2.5 (2.0)	$\bar{x}$ 2.7 (1.8) $\tilde{x}$ 2.5 (2.8)	− 1.4	.1	.01

Pre-treatment data missing for one participant

$\bar{x}$ = mean (standard deviation), $\tilde{x}$ = median (interquartile range)

Of note, the mean reported number of avoided situations, measured with the PAS, went from 4.6 (SD 5.3) to 2.2 (SD 2.4) between pre-treatment and post-treatment.

Treatment Efficacy: Psychological Distress and Health-Related Quality of Life

At post-treatment, remission from all cases of generalized anxiety disorder, social phobia and depression was observed. Remission from one of the two cases of agoraphobia was also observed at post-treatment and the other one was in remission at the 6-month follow-up. However, one participant met the diagnostic criteria for a new major depressive disorder at the 6-month follow-up.

Anxiety severity, as measured with the GAD-7, significantly decreased between pre-treatment and post-treatment, with a large effect size ($g = -1.1$, $p = .01$). Depressive symptoms, as assessed with the PHQ-9, also decreased over time although not significantly ($g = -.8$, $p = .18$). Both reductions were maintained at the 6-month follow-up ($g = -.2$). Health-related quality of life (*MacNew Heart Disease Health-Related Quality of Life*) improved between pre-treatment and post-treatment ($g = .8$, $p = .09$) and such improvement was maintained over a 6-month period ($g = .1$). Details results are presented in Table 4.

Analysis of the Panic Diaries Outcomes

Among the six patients who completed the intervention, one did not return the panic diaries and those of another patient had too many missing data to allow for analyses (6 weeks missing). Data from the completed panic diaries ($n = 4$) indicated that all participants experienced panic attacks during the pre-treatment period, with weekly means ranging from .5 to 14 episodes. During the first half of the intervention, these weekly means decreased to .3 to 4.6 panic attacks and then further decreased to 0 to .6 during the second half of the intervention. Three out of 4 participants no longer experienced panic attacks after the first half of the intervention.

As depicted in Figs. 2 and 3, the severity of anticipation of further panic attacks followed an increasing trend for one participant, a decreasing trend for two participants and no trend for the last participant in the pre-treatment period. As for the level of perceived aversiveness of a panic attack, a decreasing trend was observed for three participants and no trend was observed for one participant in the pre-treatment period. No significant trend effects were detected during the pre-treatment period for three participants. For the remaining participant in whom significant trend effects were observed at baseline, analyses were conducted with the corrected trend. Replacing the corrected trend with the non-corrected one did not significantly alter the results.

During the intervention, a decreasing trend was observed in three participants with regard to the anticipation and in all four participants for the perceived aversiveness, indicating positive therapeutic effects of the intervention on these outcomes. The examination of the means, medians, as well as relative and absolute levels of change also supported these trends. Further details regarding the visual analyses can be found in Supporting Information (Tables 2, 3).

Significant differences were observed between the pre-treatment and intervention phases for both the level of anticipation (ES = −.47; 95% CI −.61, −.34; $p < .001$) and the level of perceived aversiveness of panic attacks (ES = −.67; 95%CI −.81, −.53; $p < .001$).

Discussion

The first objective of this study was to assess the feasibility and acceptability of an adapted CBT for PD in patients with comorbid CAD. The present results support

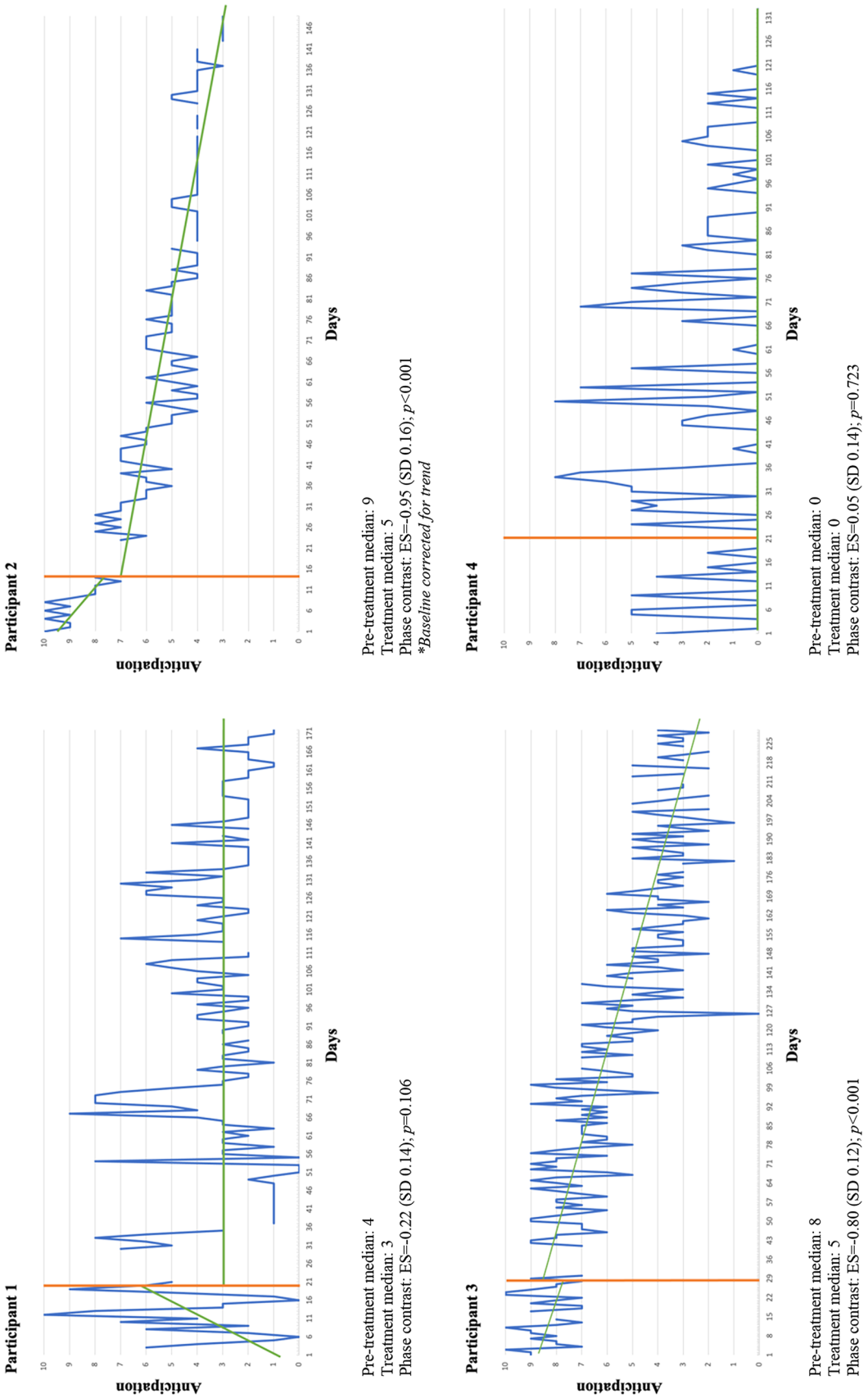
Table 4 Measures of psychological distress and quality of life

Measure	Pre-treatment	Post-treatment	6-month follow-up	Hedge's *g* pre-treatment/post-treatment	Hedge's g post-treatment/6-month follow-up	*p* value
GAD-7	$\bar{x}$ 13.8 (5.4) $\tilde{x}$ 14.0 (10.5)	$\bar{x}$ 5.0 (6.5) $\tilde{x}$ 3.0 (9.5)	$\bar{x}$ 3.7 (4.3) $\tilde{x}$ 2.5 (7.3)	− 1.1	− .2	.01
PHQ-9	$\bar{x}$ 12.6 (3.7) $\tilde{x}$ 13.0 (6.0)	$\bar{x}$ 6.0 (7.7) $\tilde{x}$ 3.0 (14.5)	$\bar{x}$ 4.7 (4.3) $\tilde{x}$ 3.0 (8.5)	− .8	− .2	.18
MacNew Heart Disease Health-Related Quality of Life	$\bar{x}$ 3.7 (.7) $\tilde{x}$ 3.6 (1.1)	$\bar{x}$ 5.2 (1.4) $\tilde{x}$ 5.6 (2.7)	$\bar{x}$ 5.3 (.9) $\tilde{x}$ 5.0 (1.8)	.8	.1	.09

Pre-treatment data missing for one participant

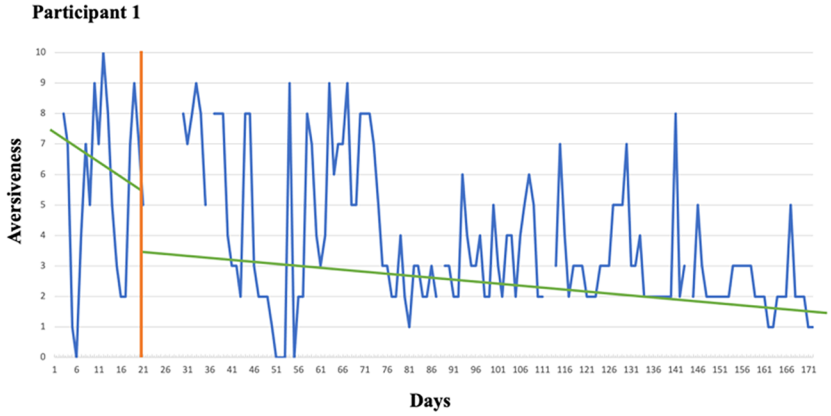
$\bar{x}$ = mean (standard deviation) $\tilde{x}$ = median (interquartile range)

For the MacNew Heart Disease Health-Related Quality of Life, higher scores indicate better quality of life

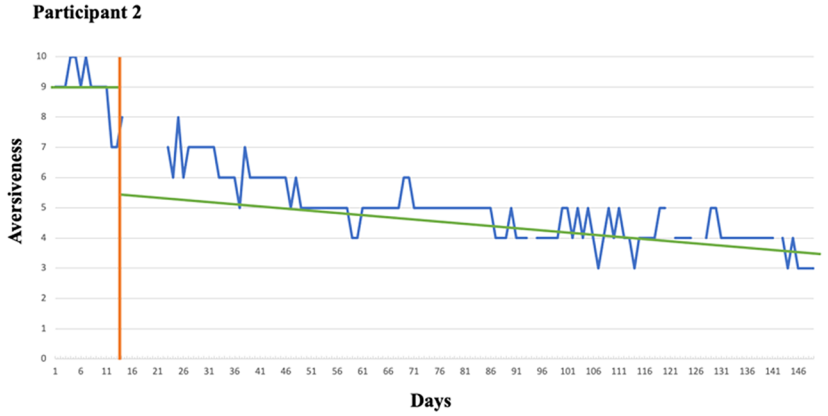


The orange line separates the pre-treatment and treatment periods
ES: effect size; SD: standard deviation

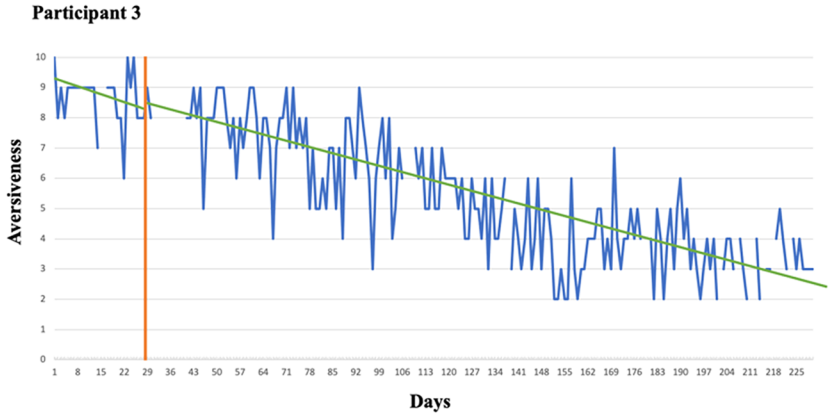
Fig. 2 Level of anticipation of panic attacks



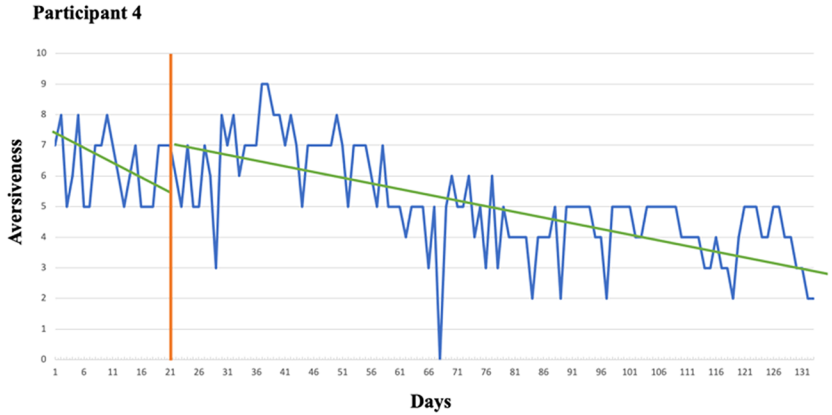
Pre-treatment median: 7
Treatment median: 3
Phase contrast: ES=-0.40 (SD 0.14); p=0.004



Pre-treatment median: 9
Treatment median: 5
Phase contrast: ES=-0.97 (SD 0.16); $p<0.001$
**Baseline corrected for trend*



Pre-treatment median: 9
Treatment median: 5
Phase contrast: ES=-0.85 (SD 0.12); $p<0.001$



Pre-treatment median: 7
Treatment median: 5
Phase contrast: ES=-0.48 (SD 0.14); $p<0.001$

The orange line separates the pre-treatment and treatment periods
ES: effect size; SD: standard deviation

Fig. 3 Level of perceived aversiveness of panic attacks

the hypothesis that the intervention would be both feasible and acceptable. First, the fact that all eligible participants accepted to participate and that all but one completed the intervention is encouraging. In comparison, in a pilot study of patients suffering from comorbid PD and asthma, 50% of participants dropped out of an adapted 14-session CBT protocol, but that rate decreased to 17% after its length was reduced to 8 sessions (Lehrer et al., 2008). The highest dropout rates were observed before and during the interoceptive exposure sessions (Lehrer et al., 2008). In line with these findings, in the present study, the participant who considered dropping out did so during the interoceptive exposure phase of the intervention. Together, these data suggest that, in the context of a comorbid medical illness such as CAD, it may be necessary to pay extra attention to the perceived acceptability of this technique to ensure that patients fully participate. In addition, Tully et al. (2016) also suggest a 8-session protocol to treat panic in patients with heart failure, based on data indicating that cardiac patients tend to drop out of psychotherapy early due to the fact that these patients do not consider themselves as "psychiatric patients" (Tully et al., 2016). However, results from the present study indicate that a CBT protocol comprising 14 to 17 sessions can have excellent completion rates and acceptability in patients with CAD, which suggests that the first-line psychological treatment for PD can be successfully delivered in this population, provided that minimal adaptations are implemented. In the present study, it is likely that the adapted psychoeducation and cognitive restructuring exercises contributed significantly to the fact that all participants were able to complete the interoceptive exposure exercises successfully, both during sessions and at home, and to complete at least 14 sessions of intervention, and even 17 in 2 cases. Therefore, this suggests that a full-length treatment may not only be feasible and acceptable but necessary to fully address PD symptomatology in patients with comorbid CAD. Moreover, no cardiac event was reported by patients during the study.

A second objective of this study was to explore the efficacy of the intervention regarding the reduction of PD symptomatology in terms of presence of PD according to the DSM-5 criteria, number of panic attacks, fear of anxiety-related symptoms, avoidance and reassurance behaviors and anticipatory anxiety. Improvements were observed for all these outcomes, a result that is in line with those of previous studies in which the original version of Marchand et al.'s CBT protocol was used in patients with PD but without a cardiac condition (Marchand et al., 2009; Roberge et al., 2008). In addition, the observed remission rate of 83% in the present study is promising as it is higher than the one reported in a recent meta-analysis of remissions rates of PD after CBT in adults (48–58%) (Springer et al., 2018). This observation should however be interpreted with caution, as studies with small sample sizes tend to yield optimistic results (Cuijpers & Cristea, 2016).

Despite the considerable improvement in anxiety sensitivity and heart-focused anxiety following the intervention, relatively elevated levels of both were observed at post-treatment and 6-month follow-up. More precisely, the level of anxiety sensitivity reported by participants following the intervention (mean score, 26.8) was higher than that of patients with PD but without CAD who received the original CBT protocol (mean score, 20.5) and also higher than normative data in the general population (mean scores, 14.2 to 22.5) (Marchand et al., 2009; Vereault et al., 2007). This may be a source of concern, given that anxiety sensitivity and heart-focused anxiety are both closely related to the development and maintenance of PD (Eifert et al., 2000; Reiss et al., 1986). One possibility is that changes related to these outcomes may take longer to take effect. This hypothesis is supported by results from Marchand et al.'s study (2008) which reported that anxiety sensitivity levels significantly decrease in the year following CBT for PD. Further studies with longer follow-up times may help determine if further adaptations are required to address these highly relevant clinical targets more thoroughly.

The third and final objective of this study was to explore the effects of the intervention on psychological distress and quality of life. The intervention appeared to have a positive impact on comorbid anxiety and mood disorders as well as anxiety and depressive symptoms. These findings are consistent with those of a previous study which suggested that comorbid anxiety and depressive symptoms do not impede the treatment of PD and may in fact improve throughout the course of the intervention (Allen et al., 2010). Reductions in anxiety and depressive symptoms, measured with the same instruments (i.e., GAD-7 and PHQ-9), were also observed in (Tully et al. 2016) study in patients with heart failure. Among the possible hypotheses to explain these results, it is likely that this improvement either reflects that anxiety and depressive symptoms were a consequence of PD and thus were indirectly alleviated by the intervention, or that patients were able to generalize some of their newly acquired skills to other emotional difficulties. In addition, at pre-treatment, the health-related quality of life of patients from the present study (mean score, 3.7) was similar to that of patients with heart failure and clinically significant anxiety (mean score, 3.9) (Höfer et al., 2008). Following the intervention, quality of life (mean score, 5.2) was comparable to the normative reference data for patients with angina pectoris (mean score, 5.0), myocardial infarction (mean score, 5.3) and heart failure without clinically significant anxiety (mean score, 4.8) (Hofer et al., 2016; Höfer et al., 2008).

One interesting finding is that the intervention also appears acceptable and effective through videoconference. Indeed, due to the COVID-19 pandemic and the associated confinement measures, two participants received most or all of the intervention through this modality. Both were in remission from PD at post-treatment and at the 6-month follow-up. These results are consistent with a recent meta-analysis that indicates that remote CBT for PD is effective and is associated with large effect sizes (Efron & Wootton, 2021). However, one participant in the present study was reluctant to videoconferencing and had to be referred elsewhere. This illustrates that, while remote interventions may be useful and effective, they require careful patient assessment and, in some cases, cannot be a substitute for face-to-face interventions.

Strengths and Limitations of the Study

Strengths of this study include the use of a recommended measure to establish the presence of PD and related disorders and of multiple validated instruments to assess outcomes. In addition, our adapted protocol was in line with the recommended duration and format of CBT for PD (Katzman et al., 2014; National Institute for Health & Care Excellence, 2011). Finally, the use of several analytic methods (descriptive, visual and statistic) to interpret the results represents another strength of this study.

Limitations of this feasibility study include the small sample size which limits the generalization of our study results to the entire population of adult patients suffering from both CAD and PD and the presence of missing data (pre-treatment data for one participant and two panic diaries). In addition, the study population was recruited from a single site and may thus have been prone to selection and referral biases. Moreover, most assessments were conducted by the therapist who delivered the intervention, which could have led to selection bias. However, this bias is unlikely to have had significant impacts since all cases were discussed with another assessor and data from the self-report questionnaires was consistent with that of the standardized clinical interviews at all assessment points. Finally, longer term outcomes (beyond 6 months) were not assessed, thus the durability of the intervention effects compared to the general population remain to be explored.

Conclusion

A parsimonious adaptation of a CBT for PD protocol appears feasible and acceptable in patients with stable CAD. The intervention appears effective in reducing PD symptomatology and psychological distress and improving quality of life in this sample. Further research should aim at replicating these results in larger controlled studies to further establish the efficacy of this promising intervention and assess its impacts on cardiovascular outcomes (e.g., mortality, adverse cardiac events).

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Data Availability The data that support the findings of this study are available from the corresponding author upon request.

Code Availability N/A.

Declarations

Conflict of interest Marie-Andrée Tremblay, Isabelle Denis, Stéphane Turcotte, Michel DeGrâce, Phillip J. Tully and Guillaume Foldes-Busque declare that they have no conflict of interest.

Ethical Approval This research project was approved by the Ethics Board of the Centre intégré de santé et de services sociaux de Chaudière-Appalaches (2018-464).

Human and Animal Rights All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of the Centre de recherche du Centre intégré de santé et de Services Sociaux de Chaudière-Appalaches (project 2018-464).

Consent to Participate Written consent was obtained from all study participants.

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