Journal of Psychosomatic Research 76 (2014) 41–45

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

# A study of myocardial perfusion in patients with panic disorder and low risk coronary artery disease after 35% $CO_2$ challenge

Richard Fleet [a,b,*], Guillaume Foldes-Busque [b,c], Jean Grégoire [c,d,e], François Harel [d,e], Catherine Laurin [f,g], Denis Burelle [d,f], Kim Lavoie [d,g,h,i]

[a] Department of Family Medicine Emergency Medicine, Université Laval, Quebec, Canada
[b] Research Chair in Emergency Medicine, Université Laval-Hôtel-Dieu de Lévis, Quebec, Canada
[c] School of Psychology, Université Laval, Quebec, Canada
[d] Research Centre, Montreal Heart Institute, affiliated with Université de Montréal, Montreal, Canada
[e] Nuclear Medicine Service, Montreal Heart Institute, Montreal, Canada
[f] Department of Medicine, Montreal Heart Institute, Montreal, Canada
[g] Montreal Behavioural Medicine Centre, Research Centre, Department of Chest Medicine, Hôpital du Sacré-Cœur de Montréal, affiliated with Université de Montréal, Montreal, Canada
[h] Department of Psychology, Université du Québec à Montréal (UQAM), Montreal, Canada
[i] Department of Psychology, University of Calgary, Alberta, Canada

ARTICLE INFO

*Article history:*
Received 9 May 2013
Received in revised form 2 August 2013
Accepted 3 August 2013

*Keywords:*
Panic disorder
Panic attacks
Myocardial ischemia
Exercise stress test
Myocardial perfusion defects
Coronary artery disease

ABSTRACT

*Background:* We have previously reported that 35% $CO_2$ challenge induced myocardial ischemia in 81% of coronary artery disease (CAD) patients with comorbid panic disorder (PD) and previous positive nuclear exercise stress tests. However, it is yet unclear whether this is the case among CAD patients with PD and normal nuclear exercise stress test results. We hypothesized that a potent mental stressor such as a panic challenge among CAD patients with PD would also induce ischemia in patients with normal exercise stress tests.
*Methods:* Forty-one coronary artery disease patients with normal nuclear exercise stress tests (21 patients with PD and 20 without PD) were submitted to a well-established panic challenge test (with 1 vital capacity inhalation of a gas mixture containing 35% $CO_2$ and 65% $O_2$) and injected with Tc-99m-tetrofosmin (Myoview), upon inhalation. Single photon emission computed tomography imaging was used to assess per-panic challenge reversible myocardial ischemia and HR, BP, and a 12 lead ECG was continuously measured during the procedure.
*Results:* Fifty-eight percent of panic disorder patients (12/21) had a panic attack during the panic challenge vs 15% (3/20) of controls ($p = 0.005$). Only 10% of patients in each group displayed myocardial ischemia per panic challenge.
*Conclusions:* These findings suggest that panic attacks among panic disorder patients with lower-risk coronary artery disease may not confer a risk for myocardial ischemia.



## Introduction

Panic disorder (PD) is a common, disabling anxiety disorder that has a lifetime prevalence of approximately 5% [1]. In addition, close to 22% of individuals suffer from panic attacks without meeting the full DSM-IV diagnostic criteria for PD [1,2]. Six out of the 13 possible symptoms of DSM-IV panic attacks mimic those of coronary artery disease (CAD) [2]. One of the greatest fears of individuals with PD is dying from a heart attack, which often leads to repetitive medical consultations and significant health care costs [3–5].

PD has been found to be one of the leading diagnoses associated with non-cardiac chest pain in both the emergency department and outpatient cardiology settings [6–8]. Community-based studies have found that PD and panic-like anxiety are associated with an increased risk of incident CAD, myocardial infarction (MI) and cardiovascular mortality, even after adjusting for traditional risk factors [9,10]. A high rate of comorbidity (10–30%) between PD and CAD has also been observed [11,12]. The exact mechanisms linking the two illnesses are unclear. One hypothesis is that panic attacks, a potent emotional stressor, have effects on the myocardium similar to the effects of mental stress [13]. In fact, laboratory mental stress challenges induce myocardial ischemia, i.e. reduced blood flow to the heart (a condition that increases risk for myocardial infarction and death) in 30 to 70% of patients with CAD [14–16] and have been shown to confer a three-fold increased risk of death at 5 years in these patients [17]. Although somewhat debatable, laboratory "mental stress tests" are viewed as simulations of daily life stress and may not be personally relevant to all patients. However, panic attacks in patients with PD are arguably highly relevant and potent stressors that can be safely and reliably reproduced in the

* Corresponding author at: Research Chair in Emergency Medicine, 143 Wolfe Street, Lévis, Quebec G6V 3Z1 Canada. Tel.: +1 418 835 7121x3173.
*E-mail address:* rfleet@videotron.ca (R. Fleet).

0022-3999/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychores.2013.08.003

laboratory [18–21]. This offers the possibility to study their impact on myocardial ischemia.

We have previously reported that panic attacks induced in the laboratory through inhalation of a mixture of 35% $CO_2$ and 65% $O_2$ are associated with myocardial ischemia, as measured using single photon emission computed tomography (SPECT), in 80% of patients with established PD and CAD [11]. However, this previous study exclusively focused on CAD patients with recent exercise-inducible ischemia, who may be considered "high risk". As such, the association between panic attacks and myocardial ischemia in more "low-risk" PD/CAD patients remains unexplored. The current study sought to determine the association between induced panic attacks and myocardial ischemia in patients with comorbid PD and CAD as well as recent *normal* exercise stress tests. Determining the answer to this question is vital for the provision of accurate prognostic information to patients with comorbid PD and CAD, particularly in light of recent population-based studies associating PD with increased risk of MI and mortality [9,10].

It was hypothesized that a greater proportion of CAD patients with PD would display reversible myocardial perfusion defects in response to the challenge, compared to CAD patients without PD.

## Methods

The internal ethics and review board of the Montreal Heart Institute approved this project. Informed consent was obtained from all patients and their cardiologists.

### *Recruitment procedure*

Consecutive patients aged 18 to 70 years who were referred for exercise SPECT imaging were recruited to complete an initial sociodemographic and medical history interview on the day of their exercise stress test. This was followed by a brief psychiatric screening interview (Primary Care Evaluation of Mental Disorders, PRIME-MD) [22] for probable PD and the Anxiety Sensitivity Index (ASI) [23,24] and the Beck Depression Inventory-II (BDI-II) [25,26]. CAD was defined as having a documented history of either MI, Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Graft surgery (CABG), or a past angiogram indicating at least a 50% stenosis in 1 or more major coronary arteries. To be eligible for further participation, patients had to have demonstrated an *absence* of reversible myocardial perfusion defects on their exercise SPECT. Patients who had recently (<2 months) had an MI or major cardiac event/procedure (e.g., CABG, PCI) or who had a diagnosis of congestive heart failure, unstable angina, serious arrhythmias, acute or chronic pulmonary disease, history of stroke, history of substance abuse disorder, or cognitive/neurological deficits, were excluded from further participation.

All potentially eligible patients were then contacted by a graduate student in clinical psychology who conducted the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) [27,28] to confirm eligibility for the control or the panic group. Graduate students received one day training in the ADIS-IV administration. Interviews were supervised and every potential study subject's evaluation was reviewed by senior clinical psychologists (RF and KL). Patients meeting criteria for primary PD and those with no current or lifetime history for any psychiatric disorder (including panic attacks), with no current or recent (<1 month) daily use of psychotropic medications, were invited to take part in the panic challenge procedure. Consenting patients were scheduled for a laboratory panic challenge within 1 month of their exercise SPECT investigation.

Over a 12-month period, a total of 1897 patients were referred for exercise stress SPECT imaging, of which 1675 (88%) consented to participate in the screening interview. Patients with probable PD and those patients without a current or lifetime history of a psychiatric disorder who met all other eligibility criteria (n = 172) were contacted by phone to undergo the structured psychiatric interview to verify psychiatric status (i.e., PD diagnosis or no diagnosis). A total of 154 (90%) patients consented to undergo this interview. Eligible patients (n = 50) meeting diagnostic criteria for the primary PD (PD group) or with no current or lifetime history of a psychiatric disorder (control group) were invited to undergo the panic challenge procedure, and 41 (82%) accepted (21 with PD and 20 controls).

### *Nuclear medicine investigations*

Patients underwent 3 SPECT imaging studies: 1) at rest; 2) at maximum exercise performance during a treadmill exercise test using a standard Ramp protocol (BRUCE) [29]; and 3) during a laboratory panic challenge. Patients were maintained on their usual cardiac medications for all 3 studies. A quantity of 0.42 mCi/kg of Tc-99m-tetrofosmin (Myoview, Amersham Health, Princeton, NJ) was used as a marker of myocardial perfusion, and SPECT acquisition was performed 1 to 2 h after injection according to a standard protocol [30,31].

### *$CO_2$ inhalation procedure*

Within 1 month of their exercise stress tests, patients presented to the Nuclear Medicine Department of the Montreal Heart Institute and met with the research assistant who administered the baseline Panic Symptom Scale (PSS) in an interview format [32]. The PSS asks subjects to rate the intensity (absent, mild, moderate, severe, extremely severe) of 13 panic symptoms derived from the DSM-IV-TR and 5 nonspecific symptoms to control for patients' over endorsement of somatic symptoms in general. All patients responded to the PSS before and after the $CO_2$ challenge. Following the baseline PSS, patients were instrumented with a 12-lead ECG and an automated sphygmomanometer, and a catheter was inserted in the non-dominant arm for the injection of the radioactive tracer. Patients rested for 15 min in a supine position while their heart rate (HR) and systolic and diastolic blood pressure (SBP, DBP) were recorded every 60 s. The average of the 3 last measures was used as a baseline value.

Just prior to the $CO_2$ inhalation, patients were fitted with a mask connected to a respirometer, and their vital capacity was measured by asking them to empty their lungs and then inhale the maximal amount of air possible (measured in liters) in 1 inhalation. Patients then took 1 vital capacity inhalation of a gas containing 35% $CO_2$ and 65% $O_2$ delivered through the mask. If the patient inhaled at least 80% of his previously assessed vital capacity, the radioactive tracer was injected. All patients who completed the procedure were able to do this on their first attempt. Patients were asked to signal the beginning and end of panic attacks by raising their hand. These times were noted with a stop watch, and the difference in seconds was taken as the duration of the attack. When patients did signal/report symptoms, the PSS was administered immediately after symptom cessation; otherwise, the PSS was re-administered 2 min after inhalation. Patients were classified as having had a panic attack if their symptoms met DSM-IV-TR criteria. SBP, DBP, and HR were continuously recorded throughout the procedure.

### *SPECT image analyses*

SPECT images were interpreted independently by 2 nuclear cardiology specialists who were blind to patient group and response to panic challenge. The myocardium was divided into 20 regions, and perfusion defects were rated from 0 (no perfusion defect) to 4 (absence of perfusion, i.e., no blood flow). Reversible perfusion defect scores, measuring overall ischemia in the exercise and panic conditions, were calculated by subtracting the total resting perfusion defect score from the total exercise and total panic challenge scores. All cases were discussed, and discordances were resolved by consensus.