Chest pain is a key symptom in acute coronary syndrome, one of the leading causes of death in the world. Therefore, it requires accurate investigation for rapid identification and early treatment. In contrast, patients at emergency room complaining of chest pain may present symptoms of anxiety and depression with no evidence of acute coronary syndrome. Panic disorder (PD) is a frequent diagnosis in this population. It was found that around 30% of patients experiencing chest pain had PD, 22% of them with no evidence of coronary artery disease (CAD).

As part of the multifactorial clinical picture known as mental stress (MS), PD is characterized by the occurrence of panic attacks (PAs), periods of intense fear accompanied by somatic symptoms, described as “respiratory symptoms,” which include choking and/or smothering sensations, shortness of breath, chest pain, and palpitation or accelerated heart rate (HR), all of them possibly present in acute coronary syndrome. Intriguingly, in addition to mimicking CAD, PD has also been identified as a risk factor for ischemic events. Several cases of PA triggering myocardial infarction have been reported. Of interest, acute stress has been linked to myocardial damage even in patients without any evidence of obstructive CAD. The aim of this study is to better assess chest pain present in PA, to exclude the presence of myocardial ischemia. To address this aim, we designed a clinical study in patients with PD and chest pain without known CAD. Here, we describe the preliminary results.

Methods

The present study was approved by the Institutional Ethics Committee, consistent with the terms of Declaration of Helsinki. Written informed consent was obtained from all patients. After testing, all patients were followed at regular outpatient PD treatment at our institution.

The patients met diagnostic criteria for PD after completing a structured interview based on the Diagnostic and Statistical Manual for Mental Disorders. The inclusion criterion was to have a minimum of 4 PAs, at least 1 of which was unanticipated, during the 4 weeks before the initiation of the evaluation. All patients also need to report chest pain, defined as chest pressure, pain, or discomfort, concomitantly with most of attacks. The exclusion criteria were CAD diagnosis, coronary risk factors, and use of cardiovascular, antipsychotic, antidepressant, regular benzodiazepine, or non-benzodiazepine anxiolytic medication.

To rule out myocardial ischemia induced by physical stress, the patients were subjected to a technetium-99m sestamibi single-photon emission computed tomography (sestamibi SPECT) investigation at rest and after maximum stress, the patients were subjected to a technetium-99m sestamibi single-photon emission computed tomography (sestamibi SPECT) investigation at rest and after maximum stress, the patients were subjected to a technetium-99m sestamibi single-photon emission computed tomography (sestamibi SPECT) investigation at rest and after maximum stress, the patients were subjected to a technetium-99m sestamibi single-photon emission computed tomography (sestamibi SPECT) investigation at rest and after maximum stress, the patients were subjected to a technetium-99m sestamibi single-photon emission computed tomography (sestamibi SPECT) investigation at rest and after maximum stress.
a sestamibi SPECT after a carbon dioxide (CO₂) panic challenge test. Patients with hypertensive response during treadmill exercise test were also excluded.

The CO₂ panic challenge consisted of 2 sequential vital capacity inhalations of a gas containing 35% CO₂ and 65% oxygen (O₂), delivered through a facial mask. Patients with PD are sensitive to small increases in CO₂, presenting sudden respiratory distress followed promptly by brief hyperventilation and PA similar to the spontaneous presentation that occurs outside the laboratory setting. 12

Immediately after second gas inhalation, technetium-99m sestamibi was injected as a marker of myocardial perfusion, regardless of whether patients presented a PA. SPECT acquisition was performed and independently interpreted by 2 nuclear cardiology specialists.

To record hemodynamic data, they were outfitted with a 12-lead electrocardiograph, a sphygmomanometer, and a pulse oximeter. A catheter was inserted for injection of the radioisotope. Patients rested for 10 minutes in a quiet room, while baseline HR, blood pressure (BP), oxygen saturation (PO₂), and electrocardiogram were recorded. After CO₂ challenge, HR, BP, PO₂, and electrocardiogram were sequentially recorded every 20 seconds for 4 minutes. The double product (DP), the result of multiplying the HR for systolic BP, is a hemodynamic parameter that mirrors the myocardial O₂ consumption and is directly implicated in states of myocardial ischemia. Patients were submitted to specific scales to measure anxiety and panic response13,14 before and after the CO₂ challenge.

Results

So far, 7 patients were studied in our lab, 4 women and 3 men, with ages ranging from 25 to 60 years. All had scores >8 in the subsection anxiety of the Hospital Anxiety and Depression Scale and the Mini International Neuropsychiatric Interview (MINI) diagnosis of PD. Only 1 patient had a score >8 for the Hospital Anxiety and Depression Scale for depression, with an MINI diagnosis of major depressive episode. Age, scores in each subscale of Hospital Anxiety and Depression Scale, and MINI diagnosis are described in Table 1.

After application of the inhalation test of CO₂, 57% of patients (4 of 7) showed symptoms and agreed they had a PA. When asked to compare the symptoms after the test with those in spontaneous attacks, 1 patient reported being
Inhalation of CO2.

1 minute after inhalation of CO2; D PT 4

Although the population studied is not large enough to discuss the results in terms of statistical significance, findings deserve some detailed comments.

Neither of the 2 patients who reported palpitations presented significant variations in HR. Tachycardia occurred in only 1 patient, which denied PA. The evolution of BP, both systolic and diastolic, showed no significant changes, except for patient 2 who showed a curve consistent with a hypertensive response after inhalation of CO2 and consequently the patient was the one who hit the DP of greater value (Tables 3 and 4). None of the 7 patients studied showed ischemic or any other electrocardiographic changes after inhalation of CO2.

After analyzing sestamibi SPECT images from the 7 patients, we found that patient 2 demonstrated a reversible myocardial perfusion defect in mid anteroseptal segment consistent with myocardial ischemia (Figure 1), which was not present in both the stress tests previously performed during rest and exercise. Although presented moderate derealization, vertigo, chest pain, and mild palpitation, this patient denied having had PA, but he was the one who showed greater hypertensive response and highest DP, 1 minute after inhaling CO2.

In the prechallenge phase, his HR was 78 beats/min. At 20 seconds, it increased to 89 beats/min, decreasing to 83 beats/min at minute 1. His baseline BP was 140/90 mm Hg. This value has changed in 20 seconds, increasing to 160/90 mm Hg, up to 190/100 mm Hg in 1 minute, when his DP reached the peak value of 15,770 beats/min × mm Hg. It is noteworthy that this hypertensive response was not present during the exercise test, justifying the fact that the patient was not excluded from the study. The PO2 did not change after the test. It is important to report that although he has had the highest DP at studied sample, during treadmill exercise test peak effort, he experienced values much greater than that presented in the CO2 challenge test (32,550 beats/min × mm Hg vs 15,770 beats/min × mm Hg), with no evidence of ischemia on electrocardiogram or perfusion deficit on sestamibi SPECT.

### Discussion

To the best of our knowledge, this is the first time myocardial ischemia is studied through PA laboratory in patients free of diagnosis or risk factor for CAD. In a previous study, Fleet et al documented induced myocardial perfusion defects using CO2 panic challenge. However, this population had CAD diagnosis and was under full cardiovascular medication.

PAs can cause chest pain by way of several cardiac and noncardiac mechanisms, often involving the presence of hyperventilation. It is established that increases in respiratory rate, inducing an alkalotic state, can trigger intracellular influx of calcium ions and provoke coronary vasospasm and myocardial ischemia. Furthermore, patients with positive hyperventilation test result are likely to have life-threatening arrhythmias and multivessel spasms. In our results, all 4 patients who had a PA after CO2 test presented hyperventilation; 3 classified it as moderate and 1 as severe. None of them presented any perfusion deficit. The only one who presented myocardial perfusion defect did not report any respiratory distress, forcing us to seek a further understanding to the results that do not pass through mechanisms involving hyperventilation. Myocardial ischemia during MS response in patients with CAD may clarify the comprehension of our results.

Myocardial ischemia induced by MS is often silent, as happened in the case 2 reported. It may be present through...
means of an increase in HR, BP, and myocardial contractility, leading to an increase in DP and myocardial oxygen demand. More precisely, HR elevations during laboratory MS are relatively small, contrasting with a relevant BP elevation, as presented in patient 2. Although the value of the DP for induction of ischemia during CO2 test was significantly lower than that presented in the exercise testing. So, other mechanisms as an increase in coronary vasomotor tone (vasospasm) and shortening coronary blood flow, from the perspective of endothelial dysfunction and microvascular disease, might also be involved.

In normal conditions, the endothelial tissue acts as a barrier between the intravascular space and arterial smooth muscle, where the production of vascular relaxing and/or a barrier between the intravascular space and arterial smooth muscle, myosin, thereby producing less contractile force and chain kinase that is responsible for phosphorylating smooth muscle myosin, thereby producing less contractile force and vascular relaxation. In patients with CAD, endothelial injury blunts these events enabling MS to trigger coronary vasoconstriction and myocardial oxygen offer and/or demand imbalance. Some reports showed that coronary microcirculation fails to dilate during MS. Interesting to note that in our report, patient 2 was the one who reached the highest BP values. In an animal model study, borderline hypertensive rats exposed to stress displayed impaired arterial dilation in response to acetylcholine.

Indeed, angiography has documented a peculiar coronary response at the site of atherosclerosis during the arithmetic performance test. Segments with stenosis have suffered constriction, whereas the segments without atherosclerotic disease have not changed significantly or showed vasodilation, indicating that atherosclerosis disturbs the vasomotor response typical of large coronary arteries. Reinforcing this view, myocardial perfusion deficits after MS have been documented in subjects with CAD with previous normal exercise or chemical nuclear stress test results. Possibly CO2 challenge test could trigger myocardial ischemia by the same mechanisms. What that calls attention in our series is that the patient who denied having a PA came to present perfusion deficit in myocardial scintigraphy, and after testing, the patient complained of weak symptoms such as mild chest pain, palpitations, dizziness, and no panic. Hemodynamic data however showed increases in systolic BP and HR, suggesting hyperadrenergic activity. Fleet et al. found that about 50% of controls who did not develop a PA showed perfusion defects with the challenge of CO2, proposing 3 possible explanations: a startle response inducing perfusion defect, a redistribution of blood flow secondary to a CO2-induced vasodilatation in certain coronary vessels, and a tendency of patients in the control group to deny panic symptoms.

PA has the ability to act as a powerful mental stressor. Based on translational medicine goals, an integrated application of innovative tools, clinical methods, and technologies to improve the understanding of health problems and the use of CO2 challenge followed by sestamibi SPECT represents a useful diagnostic method to investigate chest pain in patients with PD.

Disclosures

The authors have no conflicts of interest to disclose.
