Myocardial Perfusion Imaging Study of CO_2-Induced Panic Attack

Gastão L.F. Soares-Filho, MD, PhD[a,b,*], Sergio Machado, PhD[a,c,d], Oscar Arias-Carrión, MD, PhD[e], Gaetano Santulli, MD, PhD[f,g], Claudio T. Mesquita, MD, PhD[h,i], Fiammetta Cosci, MD, PhD[j], Adriana C. Silva, PhD[a], and Antonio E. Nardi, MD, PhD[a]

Chest pain is often seen alongside with panic attacks. Moreover, panic disorder has been suggested as a risk factor for cardiovascular disease and even a trigger for acute coronary syndrome. Patients with coronary artery disease may have myocardial ischemia in response to mental stress, in which panic attack is a strong component, by an increase in coronary vasomotor tone or sympathetic hyperactivity setting off an increase in myocardial oxygen consumption. Indeed, coronary artery spasm was presumed to be present in cases of cardiac ischemia linked to panic disorder. These findings correlating panic disorder with coronary artery disease lead us to raise questions about the favorable prognosis of chest pain in panic attack. To investigate whether myocardial ischemia is the genesis of chest pain in panic attacks, we developed a myocardial perfusion study through research by myocardial scintigraphy in patients with panic attacks induced in the laboratory by inhalation of 35% carbon dioxide. In conclusion, from the data obtained, some hypotheses are discussed from the viewpoint of endothelial dysfunction and microvascular disease present in mental stress response. **(Am J Cardiol 2014;113:384−388)**

Chest pain is a key symptom in acute coronary syndrome, one of the leading causes of death in the world.[1] 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.[2] Panic disorder (PD) is a frequent diagnosis in this population.[3] It was found that around 30% of patients experiencing chest pain had PD, 22% of them with no evidence of coronary artery disease (CAD).[4] 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,"[5] 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.[6] Intriguingly, in addition to mimicking CAD, PD has also been identified as a risk factor for ischemic events.[7] Several cases of PA triggering myocardial infarction have been reported.[8,9] Of interest, acute stress has been linked to myocardial damage even in patients without any evidence of obstructive CAD.[10] 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.[11] 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 performance during a treadmill exercise test. Those with negative ischemic response were invited to undergo

[a]Panic and Respiration Laboratory, Institute of Psychiatry, Federal University of Rio de Janeiro, INCT—Translational Medicine (CNPq), Rio de Janeiro, Brazil; [b]Medical School, Department of Psychiatry, Severino Sombra University, Vassouras, Rio de Janeiro, Brazil; [c]Physical Activity Neuroscience, Physical Activity Postgraduate Program, Salgado de Oliveira University (UNIVERSO), Niterói, Rio de Janeiro, Brazil; [d]Quiropraxia Program of Faculty of Health Sciences, Central University, Santiago, Chile; [e]Movement Disorders and Transcranial Magnetic Stimulation Unit, Hospital General Dr. Manuel Gea González, Secretaría de Salud, México DF, México; [f]Department of Advanced Biomedical Sciences, "Federico II" University of Naples, Naples, Italy; [g]Columbia University Medical Center, New York, New York; [h]Department of Nuclear Medicine, Pró-Cardíaco Hospital/PROCEP, Rio de Janeiro, Brazil; [i]Cardiology Department, Federal Fluminense University, Rio de Janeiro, Brazil; and [j]Department of Psychology, University of Florence, Florence, Italy. Manuscript received June 10, 2013; revised manuscript received and accepted September 17, 2013.

See page 387 for disclosure information.

*Corresponding author: Tel: (+55) 21-2103-1500; fax: (+55) 21-2579-3713.

E-mail address: galufo@gmail.com (G.L.F. Soares-Filho).

0002-9149/13/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2013.09.035

Table 1
Age, scores in each subscale of Hospital Anxiety and Depression Scale (HADS), and Mini International Neuropsychiatric Interview (MINI) diagnostic

Patient	Age (yrs)	HADS-A	HADS-D	MINI
1	60	15	4	PD
2	55	10	1	PD/Ag
3	37	13	4	PD/Ag
4	34	10	11	PD + MDD
5	51	14	5	PD + Ag
6	25	12	6	PD/Ag + PTSD
7	50	15	3	PD/Ag

Ag = agoraphobia; MDD = major depressive disorder; PTSD = post-traumatic stress disorder.

a sestamibi SPECT after a carbon dioxide (CO_2) panic challenge test. Patients with hypertensive response during treadmill exercise test were also excluded.

The CO_2 panic challenge consisted of 2 sequential vital capacity inhalations of a gas containing 35% CO_2 and 65% oxygen (O_2), delivered through a facial mask. Patients with PD are sensitive to small increases in CO_2, 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 (PO_2), and electrocardiogram were recorded. After CO_2 challenge, HR, BP, PO_2, 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 O_2 consumption and is directly implicated in states of myocardial ischemia. Patients were submitted to specific scales to measure anxiety and panic response[13,14] before and after the CO_2 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 CO_2, 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

Table 2
The presence and intensity of symptoms after inhalation of carbon dioxide (CO_2)

Patient	Nausea	Derealization	Paresthesia	Waves	Chest Pain	Fear of Dying	Fear of Loosing Control	Breathlessness	Vertigo	Palpitations	Tremble	Sweating	Suffocation
1	0	0	0	0	0	0	0	0	0	0	0	0	2
2	0	2	0	0	2	0	0	0	2	1	0	0	0
3	0	3	0	0	3	4	4	3	4	4	2	0	3
4	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	3	3	0	3	4	4	3	2	4	3	0	3
6	0	2	0	0	2	0	1	3	2	0	0	0	0
7	0	2	0	0	2	4	4	4	4	0	0	0	4

Table 3
Hemodynamic data of patients after inhalation of carbon dioxide (CO_2)

Patient	HR				SBP				DBP			
	ΔT 0	ΔT 20 seconds	ΔT 1 minute	ΔT 4 minutes	ΔT 0	ΔT 20 seconds	ΔT 1 minute	ΔT 4 minutes	ΔT 0	ΔT 20 seconds	ΔT 1 minute	ΔT 4 minutes
1	83	87	77	88	130	130	110	130	70	70	70	88
2	78	89	83	77	140	160	190	160	90	90	100	100
3	76	101	79	72	120	120	120	140	80	80	80	90
4	87	107	118	77	130	130	130	140	80	80	80	80
5	81	103	84	69	130	130	130	140	80	80	80	80
6	62	84	69	63	120	110	110	120	80	80	80	80
7	85	97	72	61	110	110	130	100	80	80	80	70

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 4
Double product (DP) (HR × systolic BP)

Patient	DP T0	DP T 20	DP T1	DP T4
1	10,790	11,310	8,470	11,440
2	10,920	14,240	15,770	12,320
3	9,120	12,120	9,480	10,080
4	11,310	13,910	15,340	10,780
5	10,530	13,390	10,920	9,660
6	7,440	9,240	7,590	7,560
7	9,350	10,670	9,360	6,100

DP T0 = double product before inhalation of CO_2; DP T 20 = double product 20 seconds after inhalation of CO_2; DP T1 = double product 1 minute after inhalation of CO_2; DP T4 = double product 4 minutes after inhalation of CO_2.

less intense than the spontaneous, 2 patients reported similar intensity, and 1 patient reported symptoms of greater intensity. Analyzing symptoms presented after CO_2 test, derealization, chest pain, fear of losing control, dizziness, and shortness of breath (hyperventilation) were present in all 4 patients with positive PA. Chest pain was moderate in 2 patients and severe in the other 2 ones. The presence and intensity of symptoms after inhalation of CO_2 are summarized in Table 2. 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 CO_2 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 CO_2.

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 CO_2.

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 PO_2 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 CO_2 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[15] documented induced myocardial perfusion defects using CO_2 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,[16] 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.[17] Furthermore, patients with positive hyperventilation test result are likely to have life-threatening arrhythmias and multivessel spasms.[18] In our results, all 4 patients who had a PA after CO_2 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,[19] as happened in the case 2 reported. It may be present through

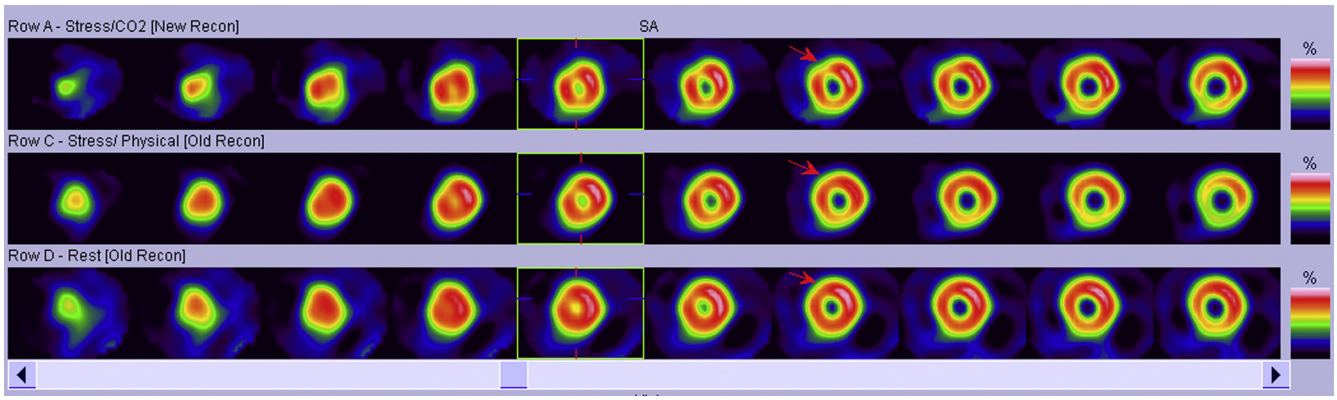

Figure 1. Reversible perfusional defect in midanteroseptal segment (pointed by the *red arrows*) suggesting myocardial ischemia after CO_2 challenge, not present in images taken during physical stress and rest.

means of an increase in HR, BP, and myocardial contractility, leading to an increase in DP and myocardial oxygen demand.[20] More precisely, HR elevations during laboratory MS are relatively small, contrasting with a relevant BP elevation, as presented in patient 2.[21] Although the value of the DP for induction of ischemia during CO_2 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 contraction factors occurs.[22] So, with intact endothelium, MS normally induces coronary artery vasodilation as a response to sympathetic stimulus. Harris[23] has documented a 64% average increase in flow-mediated vasodilator in this population.

This vasodilation in normal arteries appears to be mediated by the stimulation of β2-adrenoceptors, which initiate the formation of cyclic adenosine monophosphate and smooth muscle relaxation by the inhibition of myosin light-chain kinase that is responsible for phosphorylating smooth muscle myosin, thereby producing less contractile force and vascular relaxation.[24] In patients with CAD, endothelial injury blunts these events enabling MS to trigger coronary vasoconstriction and myocardial oxygen offer and/or demand imbalance.[25] Some reports showed that coronary microcirculation fails to dilate during MS.[26] 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.[27]

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.[28] 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.[29] Possibly CO_2 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[15] found that about 50% of controls who did not develop a PA showed perfusion defects with the challenge of CO_2, proposing 3 possible explanations: a startle response inducing perfusion defect, a redistribution of blood flow secondary to a CO_2-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,[30] an integrated application of innovative tools, clinical methods, and technologies to improve the understanding of health problems and the use of CO_2 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.

1. Okrainec K, Banerjee DK, Eisenberg MJ. Coronary artery disease in the developing world. *Am Heart J* 2004;148:7−15.
2. Soares-Filho GL, Freire RC, Biancha K, Pacheco T, Volschan A, Valença AM, Nardi AE. Use of the hospital anxiety and depression scale (HADS) in a cardiac emergency room-chest pain unit. *Clinics* 2009;64:209−214.
3. Steptoe A, Kivimäki M. Stress and cardiovascular disease. *Nat Rev Cardiol* 2012;9:360−370.
4. Lynch P, Galbraith KM. Panic in the emergency room. *Can J Psychiatry* 2003;48:361−366.
5. Freire RC, Valença AM, Nascimento I, Lopes F, Mezzasalma MA, Zin WA, Nardi AE. Clinical features of respiratory and nocturnal panic disorder subtypes. *Psychiatry Res* 2007;152:287−291.
6. Bellemain-Appaix A, O'Connor SA, Silvain J, Cucherat M, Beygui F, Barthélémy O, Collet JP, Jacq L, Bernasconi F, Montalescot G; ACTION Group. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients

undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *JAMA* 2012;308:2507−2516.
7. Smoller JW, Pollack MH, Wassertheil-Smoller S, Jackson RD, Oberman A, Wong ND, Sheps D. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. *Arch Gen Psychiatry* 2007;64: 1153−1160.
8. Biyik I, Yagtu V, Ergene O. Acute myocardial infarction triggered by acute intense stress in a patient with panic disorder. *Turk KardiyolDern Ars* 2008;36:111−115.
9. Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, Willett WC. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation* 1994;89:1992−1997.
10. Soares-Filho GL, Felix RC, Azevedo JC, Mesquita CT, Mesquita ET, Valenca AM, Nardi AE. Broken heart or takotsubo syndrome: support for the neurohumoral hypothesis of stress cardiomyopathy. *Prog-Neuropsychopharmacol Biol Psychiatry* 2009;34:247−249.
11. American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders. 4th edition. Washington, DC: American Psychiatric Press, 1994.
12. Klein DF. False suffocation alarms, spontaneous panics and related conditions: on integrative hypothesis. *Arch Gen Psychiatry* 1993;50: 306−317.
13. Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatr Scand* 1986;73(Suppl 326):1−37.
14. Shear MK, Brown TA, Barlow DH, Money R, Sholomskas DE, Woods SW, Gorman JM, Papp LA. Multicenter collaborative panic disorder severity scale. *Am J Psychiatry* 1997;154:1571−1575.
15. Fleet R, Lespérance F, Arsenault A, Grégoire J, Lavoie K, Laurin C, Harel F, Burelle D, Lambert J, Beitman B, Frasure-Smith N. Myocardial perfusion study of panic attacks in patients with coronary artery disease. *Am J Cardiol* 2005;96:1064−1068.
16. Huffman JC, Pollack MH, Stern TA. Panic disorder and chest pain: mechanisms, morbidity, and management. *Prim Care Companion J Clin Psychiatry* 2002;4:54−62.
17. Fujii H, Yasue H, Okumura K, Matsuyama K, Morikami Y, Miyagi H, Ogawa H. Hyperventilation-induced simultaneous multivessel coronary spasm in patients with variant angina: an echocardiographic and arteriographic study. *J Am Coll Cardiol* 1988;12:1184−1192.
18. Nakao K, Ohgushi M, Yoshimura M, Morooka K, Okumura K, Ogawa H, Kugiyama K, Oike Y, Fujimoto K, Yasue H. Hyperventilation as a specific test for diagnosis of coronary artery spasm. *Am J Cardiol* 1997;80:545−549.
19. Noel Bairey C, Krantz DS, Rozanski A. Mental stress as an acute trigger of ischemic left ventricular dysfunction and blood pressure elevation in coronary artery disease. *Am J Cardiol* 1990;66:28−31.
20. L'abbate A, Simonetti I, Carpeggiani C, Michelassi C. Coronary dynamics and mental arithmetic stress in humans. *Circulation* 1991;83(Suppl. 2):94−99.
21. Rozanski A, Bairey CN, Krantz DS, Friedman J, Resser KJ, Morell M, Hilton-Chalfen S, Hestrin L, Bietendorf J, Berman DS. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. *N Engl J Med* 1988;318:1005−1012.
22. Santulli G, Cipolletta E, Sorriento D, Del Giudice C, Anastasio A, Monaco S, Maione AS, Condorelli G, Puca A, Trimarco B, Illario M, Iaccarino G. CaMK4 gene deletion induces hypertension. *J Am Heart Assoc* 2012;1:e001081.
23. Harris CW. Effects of mental stress on brachial artery flow-mediated vasodilation in healthy normal individuals. *Am Heart J* 2000;139: 405−411.
24. Klabunde RE. Cardiovascular Physiology Concepts. Second Edition. Philadelphia: Lippincott Williams & Wilkins, 2011.
25. Blumenthal JA, Jiang W, Waugh RA, Frid DJ, Morris JJ, Coleman RE, Hanson M, Babyak M, Thyrum ET, Krantz DS. Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life: association and hemodynamic features. *Circulation* 1995;92: 2102−2108.
26. Dakak N, Quyyumi AA, Eisenhofer G, Goldstein DS, Cannon RO III. Sympathetically mediated effects of mental stress on the cardiac microcirculation of patients with coronary artery disease. *Am J Cardiol* 1995;76:125−130.
27. Fuchs LC, Landas SK, Johnson AK. Behavioral stress alters coronary vascular reactivity in borderline hypertensive rats. *J Hypertens* 1997;15:301−307.
28. Yeung AC, Vekshtein VI, Krantz DS, Vita JA, Ryan TJ Jr, Ganz P, Selwyn AP. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. *N Engl J Med* 1991;325:1551−1556.
29. Ramachandruni S, Fillingim RB, McGorray SP, Schmalfuss CM, Cooper GR, Schofield RS, Sheps DS. Mental stress provokes ischemia in coronary artery disease subjects without exercise or adenosine-induced ischemia. *J Am Coll Cardiol* 2006;47:987−991.
30. Hallak JEC, Crippa JAS, Quevedo J, Roesler R, Schröder N, Nardi AE, Kapczinski F. National Science and Technology Institute for Translational Medicine (INCT-TM): advancing the field of translational medicine and mental health. *Rev Bras Psiquiatr* 2010;32:83−90.