Prevalence of Induced Ischemia by Mental Distress

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Abstract

Background: The myocardial radionuclide imaging with mental distress seems to induce ischemia through a particular physiopathology when compared to radionuclide imaging with physical or pharmacological distress.

Objective: To assess the prevalence of induced myocardial ischemia by mental distress in patients with thoracic pain and radionuclide imaging with normal conventional distress, with 99mTc-Sestamibi.

Methods: Twenty-two patients were admitted with thoracic pain at emergency or were referred to the nuclear medicine service of our institution, where myocardial radionuclide imaging of distress or rest without ischemic alterations was carried out. The patients were, then, invited to go through an additional phase with mental distress induced by color conflict (Strop Color Test) with the objective of detecting myocardial ischemia. Two cardiologists and nuclear physicians performed the blind analysis of perfusional data and consequent quantification through Summed Difference Score (SDS), punctuating the segments that were altered after mental distress and comparing it to the rest period image. The presence of myocardial ischemia was considered if SDS ≥ 3.

Results: The prevalence of mental distress-induced myocardial ischemia was 40% (9 positive patients). Among the 22 studied patients, there were no statistical differences with regard to the number of risk factors, mental distress-induced hemodynamic alterations, usage of medications, presented symptoms, presence or absence of coronary disease and variations of ejection fraction and final systolic volume of Gated SPECT.

Conclusion: In a selected sample of patients with thoracic pain and normal myocardial radionuclide imaging, the research of myocardial ischemia induced by mental distress through radionuclide imaging may be positive in up to 40% of cases. (Arq Bras Cardiol 2010; 94(3):301-307)

Key words: Myocardial ischemia; prevalence; stress disorders, traumatic.

Introduction

The myocardial perfusion radionuclide imaging has been applied in medical practice as an important tool for the diagnosis of myocardial ischemia. Is value on such diagnosis has been widely studied, which allows its utilization in patients admitted in emergency units and ambulatories[1]. However, a group of patients may relate thoracic pain in special situations without the utilization of the most commonly studied distress methods, like physical (through rolling mat) or pharmacological distress (adenosine, dipiridamol or dobutamine)[2]. Mental distress presents a relation to thoracic pain, and the physiopathological mechanisms responsible for this symptom seem to depend on the patient's endothelial function[3]. Several studies that aimed at inducing distress based on different protocols were conducted[3-5]. The association with image methods has added an additional value to clinical, electrocardiograph and hemodynamic findings obtained by mental distress induction. Researches that used echocardiogram and radioisotope ventriculography associated with mental distress showed that this is the responsible for alterations in ventricular function[5,6]. Studies that applied radionuclide imaging of myocardial perfusion during mental distress confirmed that the contraction alterations were induced by alterations in perfusion.

The necessity for myocardial ischemia diagnosis in patients with thoracic pain is extremely important for a better clinical handling, risk factor control and improvement of their life quality. In this decade, an acute syndrome, unleashed by mental distress and represented by thoracic pain, supraunevenness of ST segment at electrocardiogram, elevation of myocardial necrosis markers and peculiar alterations of myocardial contractility demonstrated in echocardiograph and ventriculograph findings, was described. The so called Takotsubo syndrome is characterized by a reduction in contractility of apical myocardial segments and hyper-contractility of basal segments of left ventricle[7]. Other

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epidemiological studies on natural catastrophes have showed a higher mortality rate by cardiac causes in comparison to other periods. Thus, patients submitted to chronic distress present a propensity to developing symptoms suggestive of myocardial ischemia with thoracic pain as well as coronary atherosclerotic disease[8]. Individuals with D-type personality, represented by a pattern of anxiety, depression and tendency on isolation and social inhibition, were studied in the 1990's. Such studies demonstrated the relation between this population and cardiac disease[9].

In clinical practice, there is a difficulty in incorporating such method for the investigation of myocardial ischemia. Very little is known about this individuals' response to distress induction and this lack of data limits the investigation of mental distress-induced ischemia in our sample. The assurance, reproducibility and prevalence of myocardial ischemia in these patients justify the conduction of stronger evidence. The present study aims at evaluating the prevalence of mental distress-induced myocardial ischemia (color conflict) in patients with thoracic pain and radionuclide imaging with physical (through rolling mat) or pharmacological distress (dipiridamol) with absence of myocardial ischemia.

Methods

Twenty-two patients were prospectively selected (9 men) to participate in the study after going through myocardial radionuclide imaging for ischemia exclusion. Mean age among participators was 54,4 ± 14,9 years old. All patients presented complaint about thoracic pain and perfusion image of distress and normal rest. The exams were carried out from November 2005 to August 2008 after authorization of inclusion in a research protocol by means of na informed consent approved by the Ethics Committee of the institution. Data collected from patients were included in a database from Access software for statistical analysis.

Radionuclide imaging of myocardial perfusion was carried out with ^{99m}Tc-tetrofosmin in rest and under physical or pharmacological distress. All the acquired images were synchronized with electrocardiogram (gated). When the one-day protocol was accomplished in initial images, activities from 10 to 15 mCi and 35 to 40 mCi were utilized in late images. When the two-day protocol was accomplished, 25mCi were administered in each phase. Images were acquired in gamma camera e-Cam Duet (Siemens, Erlangen) with 1 inch NaI crystals around 45 to 90 minutes after the venous administration of the radiopharmaco. Acquisitions happened in two detectors configured in 90º, with 64x64 matrix, 64 projections of 25 seconds. There was synchronization of images with the electrocardiogram for the acquisition of gated images (gated SPECT) with an 8-interval division of cardiac cycle. The reconstruction of images was made by filtered retroprojection, by means of Butterworth filter with 0.5 cut and order of 5. Images were disposed in three axes: transversal short axis, vertical long axis and horizontal long axis. Tomography cuts were made with the division of myocardium in 17 segments[1].

The processing of the images from ventricular function was made through the software *Quantitative Gated SPECT* (QGS) with tridimensional reconstruction of left ventricle for the assessment of ventricle function, with analysis of ejection fraction, ventricle volumes, contractility and myocardial thickness. The quantification of the reversible defect was carried out through semi-quantitative analysis. The segmentation model of 17 seconds was employed. Each segment received a punctuation of 0 to 4 with regard to reduction of radiotracer catching: 0 = radiotracer normal catching; 1 = mistaken hypo-catching; 2 = moderate hypo-catching; 3 = radiotracer severe hypo-catching and 4 = absence of radiotracer detectable catching in certain segment[9]. The following scores were derived: the summed stress score (SSS), which is the sum of all 17 segments punctuation of distress exam; summed rest score (SRS) and summed difference score (SDS), which is the difference between SSS and SRS, as ≥ 3 was considered as positive for ischemia and < 3 negative for ischemia.

The utilized mental distress protocol was strop color test or (or color conflict), which consists of a continuum visual stimulus, as the direct attention is the cognitive mechanism applied, in which the individual must direct the attention, inhibit or stop an answer to say or do something else. In this test, successive screens are presented to the volunteers, who must say out loud the name of the color of the visualized character. It is possible to maintain a constant mental work through the manipulation of stimuli presentation velocity. For example: for the word "RED", "BLUE" must be said. The Strop Color Test is well accepted, has good reproducibility and execution. Associated with the test, an auditory stimulus was performed by means of a headphone, and the patient was followed-up with regard to the measurement of non-invasive continuum blood pressure, ECG and to the presence of symptoms. The test is limited by the necessity of a pervious peripheral venous access and continuum infusion of physiological solution.

The patient seats in front of the screen of a computer, in which the color conflict takes place. The test initiates after 4 minutes of seated rest. The conflict test lasts five minutes and the patients receive endovenous 99mTc-Sestamibi at 2.5 minutes. During the whole test, 12-derivation continuum electrocardiograph monitoring is made by digital electrocardiogram (ECG98®, HW, Brazil) and non-invasive cardiovascular hemodynamic monitoring is made by digital dynamometer version 1.22 (FMS BV®, Holanda). The dynamometer allows monitoring the hemodynamic parameters beat per beat. The maximum variations of cardiac frequency, systolic and diastolic blood pressure were used for the analysis. After accomplishing the distress, the phase of recovering for five additional minutes is initiated. The image is acquired within one or two hours after the sensorial distress is finished.

The images were blindly assessed by experienced nuclear physicians. The results of radionuclide imaging were available for the physicians who were in charge of the patients' treatment. For the purpose of this study, the images were characterized as positive or negative for myocardial ischemia. Studies that demonstrated perfusion defects with SDS ≥ 3 were considered as positive. All other studies were considered[7]. Patients with previous infarction or coronary

atherosclerotic disease history were not excluded. Mean time period between the accomplishment of conventional and mental distress was 32 days.

The analysis of both mental SDS subgroups was carried out (≥ 3 and < 3) under the point of view of test delta concerning systolic pressure (Delta SP), diastolic pressure (Delta DP) and cardiac frequency (Delta CF) for the assessment of the association between hemodynamic alterations occurred during mental distress and ischemia.

For the comparison of numeric data, the non-parametric Mann-Whitney test was employed, and for proportion comparisons (categorical data) the Fisher's Exact test was applied. The non-parametric method was used for the variables did not present normal distribution (Gaussian distribution) due to data dispersion and to the sample's size. The adopted criteria for determining the significance level was 5%. Statistical analysis was processed by the statistical software SAS® System, version 6.04.

Results

Twenty-two patients with thoracic pain referred to our service by the emergency room or ambulatory of Hospital Pró-Cardíaco were assessed, and all of them presented thoracic pain and radionuclide imaging with physical (20 patients) or pharmacological distress (2 patients), and absence of ischemia from November 2005 to August 2008. Patients were invited to go through the radionuclide imaging with mental distress in comparison to the rest image. Hemodynamic variables of conventional and mental distress were analyzed and described in Table 5.

All patients presented thoracic pain; however, they were characterized with regard to pain characteristic, such as typical, atypical and non-coronary. Other symptoms reported by the patients are described in Table 2:

Analysis of risk factors and its association with ischemia

With the objective of identifying the population with higher probability of presenting positive mental distress, the frequency (n) and the percentage (%) of coronary factors were assessed according to mental SDS (≥ 3 and < 3) and respective descriptive level (p-value) from Fisher's Exact test, as shown in Table 3.

Analysis of radionuclide imaging results

The semi-quantitative analysis of myocardial perfusion by scores had the following values: the mean of scores summed after mental distress (SSS) was 3.4 ± 4; mean of rest score was 0.2 ± 0.7; and mean of differential score (SDS) was 3.2 ± 4. From the 22 studied patients, 8 (40.1%) presented mental distress image positive for ischemia (SDS ≥ 3). According to the presence of ischemia during mental distress, the number of risk factors and left ventricle ejection fraction variation were assessed between mental distress and rest periods (Δ EF), as well as the variation of final systolic volume (Δ FSV) through Gated SPECT. These variables did not present significant differences when compared according to SDS, as shown in Table 4.

Analysis of hemodynamic data from mental distress

Patients showed hemodynamic responses that were measurable at mental distress. Delta values correspond to the maximum variations between measures of rest and during distress, as gauged beat per beat by means of the dynamometer. Table 5 shows the mean and standard deviation (SD) of hemodynamic variations (delta) the test according to mental SDS (≥ 3 and < 3), as well as the significance level.

To illustrate the merit if such technique, the radionuclide images of one of the studied patients are herein demonstrated. 67-year-old female patient presenting oppressive retroesternal discomfort associated with dizziness at the moment of admittance in the emergency room. The patient was hypertensive, diabetic, dyslipidemic, sedentary and under treatment for panic syndrome. She went through distress myocardial radionuclide imaging with dipiridamol, which was negative for ischemia (Figure 1). She was submitted to radionuclide imaging with mental distress 3 days after the first procedure, demonstrating an extended area of reversible defect on the interventricular septum, on the anterior

Table 1 – Frequency of main clinical characteristics

Clinical characteristics	n	%
Male	9	40.9
Aged	6	27.3
SAH	16	72.7
DM	4	18.2
Dyslipidemia	16	72.7
Sedentarism	17	77.3
Obesity	10	45.5
Menopause	5	22.7
Previous CAD	6	36.6

SAH - Systemic arterial hypertension; DM - Diabetes mellitus; CAD - Coronary artery disease.

Table 2 – Frequency of symptoms in the studied sample

Symptoms	n	%
Typical TD	5	22.7
Atypical TD	14	63.6
Non-coronary TD	3	13.6
Dyspnea	1	4.5
Tiredness	6	27.3
Palpitations	6	27.3

TP - Thoracic pain

wall, on the inferior wall and on the apex of left ventricle (Figure 2). The patient was referred to the accomplishment of cinecoronariography, which revealed a 40% lesion on the anterior descendent artery in its medium portion.

Discussion

Our study demonstrated a prevalence of perfusion alterations induced by sensorial distress in 40% of the cases from a sample of patients with episodes of thoracic pain in rest and with perfusion radionuclide imaging negative for conventional methods.

The presence of myocardial ischemia induced by sensorial distress was not isolately or conjunctly associated with any risk factor, as well as was not correlated to hemodynamic or electrocardiographic alterations observed during sensorial distress. Though the number of cases had been relatively limited, these findings are in accordance to Kop et al[10] study and, in conjunct, the results suggest that the insertion of this technique in clinical practice may be useful in the determination of a subgroup of patients with non-detectable myocardial ischemia through habitual investigation techniques.

The detection of myocardial ischemia through radionuclide imaging with physical or pharmacological distress has solid confirmation of value based on literature data. In a recent review on the theme, myocardial radionuclide imaging was considered with a 90% sensibility and 89% specificity for the detection of obstructive coronary disease. Its prognostic value is even more relevant, for in an analysis of 16 studies, with a total of 20,983 patients with normal radionuclide imaging and a mean follow-up of 28 months, a 0.7% rate of infarction or cardiac obit per year was observed, a value that is similar to the asymptomatic population[11]. Despite the excellent exactness of myocardial perfusion radionuclide imaging, some patients with established coronary disease

Table 3 – Distribution of risk factors according to the presence of ischemia during mental distress

Risk factor	Mental SDS ≥3		Mental SDS <3		p-value
	n	%	n	%	
Male	4	50.0	5	35.7	0.41
Age ≥ 65 years old	3	37.5	3	21.4	0.36
SAH	5	62.5	11	78.6	0.36
DM	1	12.5	3	21.4	0.53
Dyslipidemia	7	87.5	9	64.3	0.25
Obesity	2	25.0	8	57.1	0.15
Menopause	3	37.5	2	14.3	0.23
Smoking	0	0.0	1	7.1	-

SAH - Systemic arterial hypertension; DM - diabetes mellitus; SDS - summed difference score.

Table 4 – Distribution of age, risk factors and left ventricle functional data according to the presence of ischemia during mental distress

Variable	Mental SDS	n	Mean	SD	p-value
Age	≥3	8	52.1	21.1	0.86
	< 3	14	55.6	10.8	
Number of RF	≥3	8	3.6	1.6	0.80
	< 3	14	3.9	1.5	
Delta EF	≥3	8	-2.6	4.8	0.56
	< 3	14	-1.2	5.9	
Delta FSV	≥3	8	-0.4	3.7	0.63
	< 3	14	-0.8	3.9	

RF - risk factors; SDS - summed difference score; Delta EF - variation of left ventricle ejection fraction at the phase post-distress to rest; Delta FSV - variation of left ventricle final systolic volume at the phase post-distress to rest; SD - standard deviation.

may present ischemia only during sensorial distress. Ramachandruni et al[12] demonstrated that sensorial distress was capable of unleashing ischemia in 29% of patients with CAD and negative distress radionuclide[1]. Hassan et al[13] found a lower prevalence of ischemia during sensorial distress (19%), however, their criteria for ischemia were more rigid (SDS >4) than those of other studies[11]. Comparing the current study to the abovementioned ones, we observe that there is a higher prevalence of ischemia in our sample. The reasons for such prevalence are: (1) only patients with thoracic pain were included in our study, while other authors included asymptomatic patients; (2) patients with previous DAC were not excluded; (3) a more sensitive criterion was employed for mental distress-induced ischemia (SDS ≥ 3), for even authors who employ more rigid criteria, like Hassan et al[13], agree that lower limitations should be employed in clinical practice due to the less magnitude of mental distress-induced ischemia[11].

In patients with thoracic pain related to mental distress, the endothelial dysfunction seems to be the main present factor[14]. Epicardial vasoconstriction and microvascular dysfunction of the coronary artery have been suggested as basis mechanisms for sensorial distress-induced ischemia[15]. The hemodynamic responses to sensorial distress are associated with paradox vasoconstriction of damaged coronary vases, but nor necessarily with significant obstructive lesions. Kop et al[16] demonstrated the vasoconstriction of epicardial coronary arteries during sensorial distress, and such vasoconstriction did not present any relation to conventional risk factors, such as dyslipidemia or hypertension, a finding that is similar to those of our study[16]. The combination of increase in double product with a reduction in the offer of oxygen to the myocardium is determinant for ischemia in this subgroup of patients.

The adverse prognostic value of sensorial distress-induced ischemia is documented in recently published

Table 5 - Behavior of hemodynamic variables according to the presence of ischemia during mental distress

Variable	Mental SDS	n	Mean	SD	p-value
Delta SP	≥3	8	35.3	13.1	0.27
	< 3	14	41.9	16.7	
Delta DP	≥3	8	23.5	8.9	0.26
	< 3	14	27.5	8.7	
Delta CF	≥3	8	19.5	7.9	0.56
	< 3	14	20.0	17.8	

SDS - summed difference score; Delta SP - variation of systolic arterial pressure during distress; Delta DP - variation of diastolic arterial pressure during distress; Delta CF - variation of cardiac frequency during distress; SD - standard deviation.

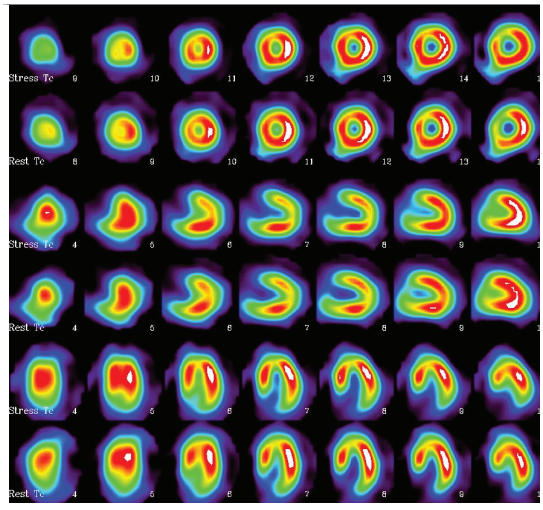

Figure 1 – *Rest and distress myocardial radionuclide imaging with dipiridamol. A homogeneous distribution of the radiotracer on the myocardium in both phases is observed.*

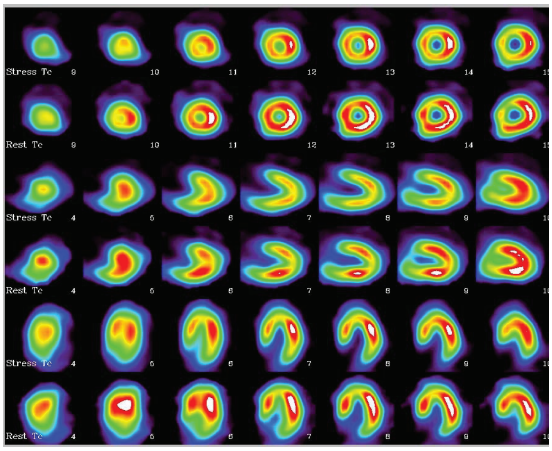

Figure 2 - *Rest and distress myocardial radionuclide imaging with strop color test. Unlikely Figure 1, there is an extended perfusion defect in distress phase that comprises the interventricular septum, the anterior wall, the inferior wall and the left ventricle apex. SDS quantification was 14.*

articles[17]. Patients with established coronary disease and sensorial distress-induced ischemic alterations have up to 3 times more cardiac events than coronary patients that do not demonstrate alterations during mental distress[18]. Specchia et al followed up, for 51 months, 61 patients with mental distress-induced ischemia and 211 without ischemia induced by mental distress. The groups did not present differences in CAD severity or in left ventricle function. At the end of follow-up, 65% of the patients with positive mental distress went through revascularization and were compared to only 38% of control patients[19]. More recently, the follow-up of PIMI study patients[20] was published, and demonstrated a 16% rate of adverse events among patients with mental distress-induced ischemia in comparison to only 6% of patients without ischemia induced by mental distress. There are no prognostic data available on the impact of mental distress-induced ischemia in patients without CAD up till now. Besides the unique characteristics associated with sensorial distress, it seems that patients with ischemia induced by such mechanism benefit from individualized approaches for treatment. Blumenthal et al[21] assessed patients with myocardial ischemia during mental distress and concluded that physical activities and cognitive therapy for reduction of emotional stress were superior to the isolate pharmacological treatment concerning the improvement of coronary risk markers.

Endothelial dysfunction is one of the most important mechanisms involved in ischemia secondary to mental distress. The coronary vascular endothelium is the mediator of vasodilatation secondary to nitric oxide liberation after sympathetic stimulation. The individuals who present endothelial dysfunction have loss of this vasodilator capability during an acute adrenergic discharge (acute distress) as much as in chronic distress situations[19]. Distress is associated with a reduction in the nitric oxide (NO) synthesis, increasing NO degradation, LDL catching, formation of reactive 02 forms, expression of vascular adhesion molecules 1 (VCAM-1), intracellular adhesion molecules 1 (ICAM-1), chemo-attractors 1 (MCP-1), cytokines (TNF-α, interleukin-6) and pro-thrombotic molecules secretion[21]. Associated with functional alterations, distress affects the endothelial cytoskeleton, provoking permanent structural changes on cells. Such structure alterations combined with endothelial cell apoptosis, also provoked by distress, unleash a higher endothelial permeability for circulation LDL and inflammatory cells (monocytes, T-lymphocytes and mastocytes). The blood stagnation posteriorly found in the regions of reduced blood flow makes easy the infiltration of LDL and inflammatory cells in the inner layer vase[12].

The development of tensional distress is identified by many mechanic-receptors, such as integrin, ionic channels, receptor tyrosine kinase and G proteins. These substances work as a trigger that unleashes a series of events with signaling molecules that result in the activation of NF-κB or AP-1. This transcription is associated with elements that are sensitive to distress and placed in many proatherogenic genes, causing them up-regulation. These genes stimulate the liberation of potential vasoconstrictors like endoteline-1 (ET-1), adhesion molecules (VCAM-1 and ICAM-1), chemo-attractors and cytokines, oxidative enzymes, NADPH, xanthine oxidase, growth factor derived from platelets (PDGF) and matritial degradation enzymes. Elevated ET may cause direct endothelial injury, increasing the endothelial permeability to LDL and circulating inflammatory mediators[21].

The present study was not designed to define the population with higher propensity to develop mental distress-induced ischemia, but to assess the frequency of individuals with thoracic pain and normal previous exams that may respond with mental distress-induced ischemia. Previous studies demonstrate the difficulty in defining how patients respond to distress[2,13]. This limitation may be related to social factors or to natural alterations of the individual concerning his intrinsic capability of reacting to stress. It was recently demonstrated that certain types of polymorphisms of β-receptor are associated with abnormal hemodynamic and vasodilator responses when these individuals are submitted to mental distress[10,14-16]. Once patients with positive mental distress must be individually treated, as suggested by Blumenthal et al[21], it is possible to speculate that the accomplishment of tests which may detect the presence of mental distress-induced ischemia may be employed whenever there is a suspicion on this condition, specially in carriers of previous CAD, even in the presence of myocardial radionuclide imaging with negative conventional distress[19,21].

In conclusion, the prevalence of radionuclide imaging with 99mTc-Tetrofosmin in rest with sensorial distress in patients with thoracic pain episode was herein analyzed for a research on myocardial ischemia. It was observed that approximately 40% of the patients developed ischemia only after mental distress induction.

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