Abstract

Objective: To research the myocardium stress dyskinesia as another possible cause of silent myocardium ischemia induced by exercise testing stress and to analyze the efficacy of the myocytic calcium blocker diltiazem for normalization of previously positive testing.

Method: In October 2004, ten patients without symptoms of coronary artery disease, presenting positive exercise testing, defined by ST segment depression, with neither precordial pain or arrhythmia during testing (six males (60%) and ages between 42 and 71 years old with mean of 58.2 years), were treated with 90 mg of diltiazem three times daily and re-studied five days after the first examination. Treadmill electrocardiography exercise testing was performed using the Bruce protocol.

Results: Diltiazem administration blocked the ST segment depression, both J point (mean 2.1 ± 0.3 mm in the control and 0.0 depression with treatment; p<0.001) and Y point (mean 1.65 ± 0.7 mm in the control and 0.0 depression with treatment; p<0.001). The Heart rate variations were not significant (p>0.05), with mean values of 156.1 ± 12.3 in the control, and 151.6 ± 23.4 beats per minute with treatment).

Conclusion: The administration of the myocytic calcium inhibitor diltiazem impeded the occurrence of the silent ST segment depression, previously induced by exercise stress testing in patients without symptoms of coronary arterial disease, confirming the involvement of the myocardium contraction dyskinesia in the phenomenon genesis.

Resumo

**Objetivo**: Pesquisando a discinesia de contração miocárdica como outra possibilidade causa da isquemia silenciosa de estresse, analisar a eficácia do cálcio inibidor miocítico diltiazem na normalização de testes ergométricos previamente positivos.

**Método**: Em outubro de 2004, dez pacientes, sem sintomas de doença arterial coronária, com teste ergométrico positivo definido por infradesnível de segmento ST, sem dor precordial nem arritmia durante os exames (Séis: 60% de sexo masculino; idades entre 42 e 71 anos, média de 58,2 anos), foram tratados com três doses diárias de 90mg de diltiazem e reestudados após período de cinco dias. Os exames foram realizados em esteira ergométrica, no protocolo de Bruce.

**Resultados**: O diltiazem impediu a depressão do segmento ST, tanto do ponto J (infradesnível médio e 2,1 ± 0,3mm, no controle, e 0,0 desnível com tratamento; \( p < 0,001 \)), quanto do ponto Y (infradesnível de 1,65 ± 0,7 mm, no controle, e 0,0 desnível com tratamento; \( p < 0,001 \)). A frequência cardíaca não aumentou significativamente (média de 156,1 ± 12,3 bpm, no controle, e 151,6 ± 23,4 bpm com tratamento/ \( p > 0,05 \)).

**Conclusão**: A administração do cálcio inibidor miocítico, diltiazem, impediu a depressão silenciosa do segmento ST previamente induzida por teste ergométrico em pacientes sem sintomas de doença arterial coronária, confirmando o envolvimento da discinesia da contração miocárdica na gênese do fenômeno.


INTRODUCTION

Since the studies of PARDEE in 1920 [1], alterations in electrocardiograms (ECG) of myocardial ischemia patients have been well defined, characterizing the relationship between the anomalous Q waves with inactive zones due to necrosis and consequent fibrosis, the ST segment deviated by the pre-necrotic ischemic lesion and T wave alterations by the establishment of ischemia in its earliest phases.

The advent and evolution of the diagnosis of coronary insufficiency by induced stress increased even more the importance of the analysis of ST segment deviations, not only because of the diagnostic specificity in itself, but also because of evidence of its almost immediate reversibility with the cessation of ischemia-inducing stress. Individual differences in the electrocardiographic responses to stress, with varying patterns of the ST deviation in individuals with normal coronary arteries, motivated the need of improvement in the criteria and the introduction of analysis of the J and Y points, which among other things facilitated the interpretation of descending and ascending ST designs (concave or convex). Even so there are still cases of induced ST variations diagnosed as false positive or false negative, that is, imprecise sensitivity and specificity.

It is also well known that individuals presenting with partial obstructive coronary disease, ventricular hypertrophy or significant overloads during stress, preserve the normal ST pattern, whilst others, without diagnosed heart disease, evolve with significant changes of the ST segment, specifically at point J, with maximum responses at higher heart rates. These patients, even with normal coronary arteries or with non-occlusive parietal alterations evidenced by scintigraphic or angiographic studies, generally present with a syndromic profile defined by atypical precordial or retrosternal pain reducing their physical capability and a horizontal depression of the ST segment, marked by a 2-millimeter depression or greater at point J and a normal point Y or one with less than one-millimeter of depression.

The horizontal depression of the ST segment has been interpreted (not rarely as a physiological response of tachycardia) as dependent on the heart beat [2], with DETRANO et al. [3] in 1986 and LACHTERMAN et al. [4] in 1990 studying the ST/TC stress induced index, as a diagnostic element in exercise stress testing. Even so, this interpretation has been contested, demonstrating that it does not have a greater diagnostic significance than the simple ST variations [5-8].

In 1984, PIC & BROUSTED [9] observed that the ST depression in isolation presents a sensitivity rate of 72.5% and a specificity rate of 62.5% in patients without previous infarction, an increase in the R-wave sensitivity 58.5% and specificity 67.5% (or of the QRS with 78% and 57.5%, respectively) and the pain 63% and 75%. The three together positively diagnosed in 100% of cases. The positivity of only one signal corresponds to normal coronary arteries in most cases. This difficulty in guaranteeing the electrocardiographic diagnosis to guide patients is continuously being highlighted in recent studies [10-12].

KURL et al. [13] in 2003 demonstrated a significant increase in cardiovascular death rate (3.5 times greater) and death due to brain strokes (2.2 times greater) in asymptomatic patients with a horizontal depression of the ST segment during exercise stress testing.

These results prove to be risk free only for patients where the basal ECG is normal and the TE normal. In all other circumstances, they seem to indicate the need of complementary angiographic, angiokinetic or scintigraphic studies with cineangiography being the most reliable for a definitive diagnosis.
Definitive studies that diagnose patients without coronary artery obstructions and alterations of the ST segment seen during exercise stress tests with sufficient precision over the long-term are still rare and relatively incomplete. However, there is already sufficient evidence to justify preventative treatment in these cases, so that the risks to which patients are exposed are not ignored [13].

The challenge includes a search for other etiopathogenic factors, as well as arriving at a consensus that silent myocardial ischemia depends only on coronary vascular disease.

Taking the classic pattern of ST segment with deviations of less than 1 mm as normal and considering additional deviations of the ST segment as ischemic, the possibility of an asymmetric response between the myocardial oxygen demand and the dynamics of the coronary reserve in these patients is acceptable, (a) by the intensity in the contraction produced being greater than that necessary for systolic outflow and for the existing peripheral demand, (b) by the inferior reflex vasodilation necessary for the existent contractile demand or (c) due to the atypical and heterogeneous pattern of the myocardial sectorial myofibrillar contraction. Under these conditions, the areas of less spastic contraction may act with a steal effect from the areas of more intense contraction.

An interpretation of the asymmetric intramural contractions corroborates with the results published by Lins [14], demonstrating the appearance of an intraventricular pressure gradient in the echocardiographic study using induced stress in a group of patients with positive exercise stress tests.

Accepting abnormal myocardial contractions as the main generator of the ischemic condition, highlights the role of adrenergic inotropic stimulants and Calcium\textsuperscript{++} dependents. Evidence that patients being treated for hypertension using beta-blockers also presented silent depression of the ST segment, the maximum VO\textsubscript{2} reached (mL/kg/min), heart rate (bpm), the double product (DP), the METs reached and the functional class (AHRA) were analyzed, using the following criteria: 1-excellent, 2-good, 3-normal (medium), 4-week and 5-very weak.

The Student t-test was employed to evaluate the statistical significance of differences between two parallel samples, with the level of significance was fixed with a p-value < 0.05. The EPIINFO version 6.04 computer program of the World Health Organization was used.

**RESULTS**

Table 1 presents the obtained results. It was confirmed that the administration of calcium-inhibitors impedes depression of the ST segment, both at point J (mean horizontal depression 2.1 ± 0.3 mm for controls, and 0.0 depression with treatment - p<0.001) and at point Y (horizontal depression of 1.65 ± 0.7 mm for controls, and 0.0 depression with treatment - p<0.001). The heart rate did not present with statistically significant variations (average 156.1 ± 12.3 bpm in the controls and 151.6 ± 23.4 bpm with treatment – p-value > 0.05). There was a statistically significant improvement in the functioning (p-value < 0.05) with the treatment (mean 2.6 ± 0.7 in controls and 1.9 ± 0.7 after treatment), without significante differences in the VO\textsubscript{2} or in the double product (p>0.05).

In two patients, the horizontal depression of the ST segment did not appear homogeneous in all complexes in each of the derivations analyzed, but the alterations were manifested progressively, with an appearance of claudication and pathologic complexes in with alternate anachronic and normal complexes on the same derivation (Figure 1).

**COMMENTS**

The consensus that deviations of the ST segment are more reliable to confirm myocardial ischemia during exercise stress testing compared to other hemodynamic or.
The current universal consensus of a relationship between induced stress ischemia, evidenced by silent depression of the ST segment, with coronary artery perviousness does not adequately explain cases of normal coronary arteries, nor does it offer perspectives of therapeutic options for the patients involved. When considering another possible cardiovascular nosologic entity responsible for the ST segment depression in patients without organic coronary lesions and without defined heart disease, the following physiopathologic factors are especially interesting: the physiologic mechanism of supply-demand in the myocardial metabolism and interactive physiopathology of the ischemic degenerative alterations (with electrocardiographic and pharmacokinetic signs) of the transmembrane activation/inhibition of myocardial contraction and angiokinesis.

Mechanism of supply-demand in the myocardial metabolism

The preservation of the myocardial integrity depends basically on the relation between the supply and demand of essential metabolic substrates, with the coronary arterial blood flow as the factor responsible for cellular supply. In adverse circumstances, the cellular mechanisms of the coronary reserve and ischemic adaptation are determinants which respond to the myocardial survival capacity.

The phenomenon of coronary reserve can be demonstrated in flowmetry by the reactive hyperemia that follows occlusion of a coronary artery at an interval of ten seconds. Even occlusions of only one second cause reperfusion at an increased flow rate, estimated as normal hyperflow when levels are five times the basal rate, that is, from 250 mL to 1250 mL/min, or from 0.9 mL/g of myocardium to 4.5 mL/g [16]. Coronary artery diseases, including endothelial dysfunction and alterations in the extra-vascular resistance factor, can significantly alter the coronary reserve.

Ischemic adaptation is the resource by which the myocardium is able to present sensitive changes in its electrocardiographic variables (arrhythmia, Q wave or R wave alterations) is well known [15].

Table 1. Re-synchronism of the myocardial contraction-perfusion by diltiazem

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Fig. 1 – Ischemic claudication (arrows) presenting with normal between pathologic complexes

GOMES, OM ET AL - Myocardium stress diskinesia disease


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Basic knowledge of myocardial ischemia

1 - cytoplasmatic hypoxia with a reduction in the pH, reduction of the ionic pumping activity resulting from the transmembrane potential. It is notable that the ECG can remain unaltered even in situations of complete inactivation of the myocardial contraction, even in mechanical uncoupling, which is reproducible in the laboratory using drugs. With this limitation always in view, is it possible to make a correlation between the biochemical and histopathologic phases of ischemia and alterations on the ECG? 

2 - horizontal depression of the ST segment, depletion of PTA, enzyme release (CK-MB, troponin), production of lactic acid and free radicals, apoptosis, ultra-structural injury, infarction area, the incidence of arrhythmia, nosyoming remodeling, activation of leukocytes, hospitalization, with reduction of mortality and protection of the endothelium during reperfusion.

Although a simple episode of transitory ischemia can produce heart protection, repetitive episodes of brief periods of occlusion, if they are frequent, can cause trachyphylaxy resulting in myocardial injury.

Any expression of the proprieties of adaptation/ischemic resistance will depend on the evolution of the myocardial ischemia for the conditions of integral recovery, necrosis, stunning or hibernation. Stunning, which is the maximum reversible ultrastructural lesion and hibernation representing the condition of tissue survival with optimized minimum flow, by the maximum ischemic adaptation capacity or minimum sustainable metabolic reserve?

Electrocardiographic signal of myocardial ischemia

The correlation between the evolution of acute myocardial ischemia and the pattern of electrocardiographic register is sufficiently defined, with the T wave altered at the start of ischemia, the ST segment showing the progression of cellular degeneration and the Q wave diagnosing the definitive establishment of necrosis. All these signs are intimately linked to variations in the ionic flow of the cellular membrane and modifications resulting from the transmembrane potential. It is notable that the ECG can remain unaltered even in situations of complete inactivation of the myocardial contraction, even in mechanical uncoupling, which is reproducible in the laboratory using drugs. With this limitation always in view, is it possible to make a correlation between the biochemical and histopathologic phases of ischemia and alterations on the ECG? 

Basically, the following phases can be considered for myocardial ischemia: 1 - cytoplasmatic hypoxia with a reduction in the pH, reduction of the ionic pumping activity and the start of the formation of oxygen free radicals; 2 - Edema and vacuolization of mitochondrias; 3 - Rupture of mitochondrias and of the myofibrils; 4 - karyolysis and 5 - Fibrosis of substitution. The first and the second phases are rapidly induced and reversible; the second generally appears after 5-10 minutes of ischemia and the third phase marks the start of necrosis, which generally occurs after 15-20 minutes of normothermic ischemia, with reversibility depending of the extension of the injured area and capacity of viable sustentation of the myocardium [18-22]. The myocardial ischemic stunning can be between phases 2 and 3 with most lesions reversible.

Physiopathology of ischemia with silent depression of the ST segment

The etiopathological correlation of the transmembrane disorder of calcium flow, as a marker of silent stress ischemia without coronary arterial disease, has clinical proof of cause and effect in electrocardiographic alterations present in the surgical post-cardioplegia myocardial reperfusion, in patients presenting with hyperpotassemia (K+ > 7 mEq/L) and hypocalcaemia (Ca ++ < 7 mg/dL): the electrocardiogram presents ST horizontal depression with the T wave negative, similar to the “Pardee Complex” of acute infarction, progressively corrected until complete normalization is achieved by the endovenous use of calcium gluconate and renal depuration of the potassium [23, 24]. Such solid physiopathologic evidence justified the hypothesis of treatment of the disorder using a calcium inhibitor.

The initial results so far (shown in Table 1), confirmed this physiopathologic and pharmacokinetic evidence. Note that treatment with diltiazem normalized the response to exercise stress test.

It is notable, in respect to the data, that maintenance of heart frequency was possible without the ischemic signs seen in the control group and without therapeutic stabilization.

On the other hand, myocardial disease with diskinetik contraction-perfusion, as it is related to the progressive functional response of the heart muscle, presupposes the possibility of installation and progressive regional extension of the contraction-perfusion asymmetry. This is a fact not infrequently observed in these patients, with the initial...
The social aspect of the problem, in some studies, is similar to incidence of hypertension, with possible significant regional variations [26-28], as the positive exercise stress test in asymptomatic patients includes from 0.6 to 15% of the studied population (eight studies). In a maximum of 0.06 to 1.6% cases this is associated with significant arterial disease (narrowing of 50% or more of the epicardial coronary artery), suggesting that stress myocardial dyskinesia is a disease occurring in 0.54 to 13.4% of the asymptomatic population [29]. KURL et al. [13], in 2003, demonstrated a significant increase in cardiovascular death (3.5 times greater) and of strokes (2.2 times greater) in asymptomatic individuals with horizontal depression of the ST segment evidenced during exercise stress testing.

The ideal situation is that all patients with stress myocardial dyskinesia without coronary arterial disease, a condition which defines the nosology, are completely studied in respect to the normality of the coronary arteries. However, the condition of public health system is complex, because the number of positive cases is relatively small and the negative cases high. On the other hand the evidence shows that the disease increases considerably the morbidity-mortality of individuals, thus it requires special preventive treatment.

The initial experience of our institution, supporting the use of 90-120 mg diltiazem three times daily, highlights another significant aspect of the study. Re-synchronization of the myocardial contraction/perfusion by the drug appears to be a diagnostic test option to improve the criterion of the indication of complementary studies of coronary perviousness. As Antônio Felipe Simão and Maurício Nunes assure us there are no drugs, in acceptable clinical doses, able to normalize exercise stress testing in patients with significant coronary obstructions. Moreover, the use of diltiazem increases the safety in the initial period of rehabilitation, until effective myocardial conditioning, allowing a faster improvement of the functional performance, as occurred in previously treated patients, providing psychological and functional benefits of motivation and adherence.

Recent research suggests, without sufficient proof of cause, the occurrence of myocardial perfusion disorders of the microcirculation in the postoperative period of coronary revascularization [30]. From this it can be inferred that dyskinesia of myocardial contraction may also influence the direction of intramyocardial flow patterns, determining postoperative ventricular functional alterations. There are no studies yet comparing the evolution of these patients.

In a general analysis, the results obtained in the current investigation, without similar results reported in the literature, indicate a disorder of the myocardial contraction synchronism is another factor of silent ischemia induced by exercise stress, efficiently treated using diltiazem calcium inhibitor.
As frequently in preliminary clinical research, the small sample size, notwithstanding its absolute statistical significance and the restricted number of parameters analyzed, suggest the necessity of further investigations to provide an uncontestable scientific definition of the phenomenon observed.

BIBLIOGRAPHIC REFERENCES


