Topical Betablocker Use Can Result in Inconclusive Dobutamine Stress Echocardiography in Patients with Glaucoma

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Dobutamine stress echocardiography is a well-established method to assess coronary artery disease, of which sensitivity has been enhanced by adding atropine at the end of the protocol. Individuals with glaucoma, a disease with a high prevalence in patients with cardiac diseases older than 40 years, cannot benefit from the use of atropine as it is contraindicated for this group of patients. Additionally, these individuals are often treated with topical betablockers (eye drops), which can have systemic effects by decreasing cardiac frequency, blood pressure and pulmonary capacity. The aim of our study was to verify whether a possible systemic effect caused by the use of these eye drops, yielding a low chronotropic response, could result in inconclusive dobutamine stress echocardiography in patients with glaucoma.

Introduction

The dobutamine-atropine stress echocardiography is a broadly disseminated and well–established diagnostic method for coronary artery disease[1]. It is known that the use of systemic betablockers can interfere with the test result by decreasing the chronotropic response and reducing the diagnostic accuracy of the method[2]. The addition of atropine at the end of the dobutamine infusion protocol increases heart rate (HR) and consequently, the test sensitivity, especially in patients who use oral betablockers[3,4], and has been systematically used, except in patients with prostatism and closed-angle glaucoma, which are contraindications to its use[5].

Glaucoma is a disease with a high prevalence after 40 years of age; it is commonly observed in patients with cardiovascular disease and its treatment consists in the topic use of eye drops with several drugs, and among them betablockers, as their base[6]. Prior studies have reported that topic betablockers can have systemic effects, decreasing HR, blood pressure (BP) and pulmonary capacity, and that they are potentially capable of attenuating the stress-induced HR increase at the ergometric stress test (EST)[8,9]. To date, there have been no references regarding the influence of this drug on dobutamine-stress echocardiography.

The aim of our study was to verify whether the occurrence of a possible systemic effect of topic betablockers, resulting in low chronotropic response, could yield inconclusive results at the dobutamine-stress echocardiography in patients with glaucoma.

Key words

Dobutamine; echocardiography; adrenergic beta-antagonists; glaucoma.

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Methods

Forty-two patients who were submitted to pharmacological-stress echocardiography for diagnosis or evaluation of known coronary artery disease were studied. Of the 42 patients, 21 had glaucoma. The control group (CG) consisted of the other 21 patients. Among the 21 patients with glaucoma, 14 used topic betablocker (BB group) and 7 used eye drops based on other drugs (NB group). The patients were age-paired and none of them were using oral betablocker at the time of the examination. Those who had previously used this type of medication were advised to interrupt it 7 days before the test.

All of the patients were submitted to at-rest HR and BP assessment every three minutes during and after the infusion. According to the standardized norms, a complete echocardiography was carried out and a digital system captured images at rest and at the infusion peak [5]. Dobutamine was administered as a continuous infusion, in progressive doses of 10, 20, 30 up to 40 *u*g/kg/min. Atropine, however, was not administered to any of the patients. The aims of the examination were to attain submaximal HR (85% of the maximum HR) or the end of the protocol with the maximum dose of infusion, or the presence of ischemia observed by the alteration of the regional myocardial contractility.

The test was interrupted earlier in case of severe ventricular arrhythmia, presence of supra-unleveling of the ST segment > 2 mm at the electrocardiogram, increase of systolic pressure > 210 mmHg or diastolic pressure > 110 mmHg, or accentuated hypotension. The test was considered inconclusive when the target HR was not reached or when was premature interruption due to the presence of limiting side effects such as arrhythmia, hypertension and its consequences, such as headache, nausea and vomiting.

Statistical analysis - The qualitative variables were determined as absolute and relative frequency, whereas the quantitative variables were determined as means and standard deviation (SD). The comparisons between the groups were

performed by the chi-square test or Fisher's test. The ANOVA (analysis of variance) was used for homogenous variance. Tukey's test was used for multiple comparisons. Comparisons between the groups at different moments were carried out by univariate analysis. A value of $p < 0.05$ was considered to be statistically significant.

Results

There was no statistical difference between the groups regarding the demographical characteristics such as gender, presence of hypertension, diabetes, smoking, dyslipidemia and previous history of acute myocardial infarction (Table 1). All patients were paired by age.

The analysis of the systolic arterial pressure (SAP) showed that the groups presented similar SAP at rest and that the pressure increase at the infusion peak occurred equivalently, with no statistical difference among them (p=ns).

Table 1 - Demographical characteristics

Groups	BB (n=14)	NB (n=7)	CG (n=21)	p value
Age	65 ± 9	71 ± 7	63 ± 8	NS
Male	36%	14%	24%	NS
Hypertension	78%	71%	57%	NS
Diabetes mellitus	36%	14%	29%	NS
Dyslipidemia	64%	86%	52%	NS
Smoking	0	0	19%	NS
Previous AMI	21%	14%	14%	NS
EF>55%	64%	86%	81%	NS

AMI - acute myocardial infarction; EF - ejection fraction; NS - non-significant.

Although the BB group presented a higher diastolic arterial pressure (DAP) at rest, as well as at the peak when compared to the other groups, this difference was not statistically significant (p=ns).

On the other hand, the heart rate (HR) at rest was similar in all groups (p=ns), but it was significantly lower in the BB group at the infusion peak when compared to the other groups ($p<0.05$). This result confirms the systemic effect of the betablocker on the dobutamine-induced HR increment. The data on pressure and HR are summarized in Table 2.

All of the tests from the NB and CG groups were conclusive. However, only 3 tests were conclusive among the 14 patients from the BB group. Eleven patients presented inconclusive tests due to the lack of isolated chronotropic response (n=1) and/or associated to limiting side effects such as hypertension and headache (n=8) or ventricular arrhythmia (n=2) (Table 2).

The ejection fraction (EF) was equivalent in the three groups, with no statistical difference among them (p=ns) (Table 1). Among the 31 conclusive tests, 11 were positive and 20 were negative for ischemia. Of the 11 positive tests, 7 were from the CG, 3 from the NG group and 1 was from the BB group (p=ns) (Table 2).

Discussion

Our results show that the use of topic betablockers in patients with glaucoma can interfere with the results of the dobutamine-stress echocardiography test, resulting in an ineffective chronotropic response and, consequently, in inconclusive tests. This effect had been previously observed by authors who used the ergometric test as the stressor agent[8,9]. However, there are no studies indicating the same effect in patients submitted to pharmacological-stress echocardiography.

It is known that the use of systemic betablockers can interfere with the results of the pharmacological-stress

Table 2 - Hemodynamic variables at rest and dobutamine-stress echocardiography results in the different groups

Groups	BB (n=14)	NB (n=7)	CG (n=21)	p values
HR at rest	69 ± 2	70 ± 3	71 ± 2	NS
Peak HR	72 ± 2	130 ± 10	133 ± 12	< 0.001
Diastolic BP r	90.7 ± 9	87.1 ± 7.6	86.2 ± 6.7	NS
Diastolic BP p	95 ± 11.6	87.1 ± 13.8	88.6 ± 7.3	NS
Systolic BP r	152 ± 20.4	159 ± 22	142 ± 16	NS
Systolic BP p	171 ± 36	161 ± 17	155 ± 22	NS
Dob 40ug/Kg/min	29%	29%	33%	NS
Inconclusive tests	11 (79%)	0	0	< 0.001
Conclusive tests	3 (21.4%)	7 (100%)	21 (100%)	< 0.001
Positive tests	1 (33%)	3 (40%)	7 (33%)	NS
Side effects	10 (71%)	1 (14%)	3 (14%)	< 0.001

HR - heart rate; BP - blood pressure; r - at rest; p - at peak of dobutamine infusion; Dob - dose of infused dobutamine; p< 0.05 significant; NS - non-significant. Values expressed in percentages refer to the number of patients in each group that used the maximum dose of dobutamine.

echocardiography by preventing HR increase, causing arterial hypertension and headache during the test[2]. The addition of atropine to the dobutamine infusion protocol decreased the number of inconclusive tests and is now currently performed as early as possible[10]. However, since the proposal of its inclusion in the original protocol and the establishment of its contraindications, there have been no reports in the literature on the results of pharmacological-stress echocardiography in patients with glaucoma, who could not benefit from the use of atropine. This is probably due to the fact that many patients with cardiac disease and glaucoma are submitted to this test under the use of oral betablocker, and the lack of chronotropic response is attributed to the oral medication, instead of the topic presentation. The present study was only possible because the use of betablockers was systematically withdrawn, excluding any possibility of sample "contamination".

Clinical significance - Although the coexistence of respiratory or cardiovascular disease is a contraindication to the use of topical betablockers, cardiologists do not commonly take these effects into account in clinical practice and do not pay special attention to the possible drug interactions between these eye drops and other pharmaceuticals. The use of this kind of eye drops is very disseminated in our country due to its low cost. Therefore, the choice of treatment for these patients' cardiopathy should be considered with caution, considering the type of eye drops used by these patients.

Additionally, other diagnostic tests for coronary artery disease can possibly present inconclusive results, increasing the cost of treatment. Another question to be considered is the contraindication of atropine for patients with closed-angle glaucoma, exclusively. In our country, patients frequently do not know what type of glaucoma they have and the communication with the ophthalmologist does not take place. To our knowledge, atropine is systematically contraindicated for patients with any type of glaucoma in echocardiography laboratories. We do not know whether further knowledge about this affection would prevent the contraindication of atropine, which is so useful for the effective test performance. Additionally, it is necessary to study the possibility of withdrawing the topic betablocker before carrying out the stress echocardiography and possibly any diagnostic test during which it is necessary to increase heart rate.

Study limitations - The present study sample size is small and thus, it is not possible to establish whether the deleterious effect of the topic betablocker is dose-dependent and/or time-dependent. Furthermore, due to the study design, we do not know whether this drug withdrawal would be indicated during the performance of dobutamine stress echocardiography. The coexistence of glaucoma and coronary artery disease at older age ranges is a relevant fact that justifies further research. Therefore, it is necessary to increase the sample size and to consider the substitution of the topic betablocker for other types of medication.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association with Graduate Work

This study is not associated with any graduation program.

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