The Egyptian Heart Journal (2012) **64**, 1–6

Egyptian Society of Cardiology

The Egyptian Heart Journal

www.elsevier.com/locate/ehj
www.sciencedirect.com

ORIGINAL ARTICLE

Usefulness of atropine in patients with chronotropic incompetence and poor exercise capacity during treadmill stress testing

Mervat M. Khalaf [a,*], Ehab Ahmed Mohamed Taha [a], Gamal Hamed [a], Sherif Sabri [b]

[a] *Critical Care Medicine Department, Cairo University, Egypt*
[b] *Critical Care Department, Bani-Souif University, Egypt*

Received 10 January 2011; accepted 8 February 2011
Available online 14 October 2011

KEYWORDS

Atropine;
EST;
Borg scale;
Chronotropic incompetence

Abstract *Background:* Atropine, an anticholinergic agent, has been shown to increase heart rate and enhance the sensitivity of dobutamine stress echocardiography in the detection of CAD in patients with chronotropic incompetence; however, the addition of atropine to exercise stress testing EST, in these types of patients has not been well studied previously.
Objective: Investigating the usefulness and accuracy of atropine in decreasing the number of inconclusive results of EST in patients with chronotropic incompetence and poor exercise capacity.
Methods: Thirty patients (16 males and 14 females with the age range of 40:73 years with mean of 55 ± 8) out of 180 patients who preformed EST were chosen as having chronotropic incompetence or poor exercise capacity by Borg scale. Atropine was administered during the exercise phase in doses of 0.5 mg per minute until test conclusion or the maximum dose of 2 mg was reached. All patients were subjected to stress myocardial perfusion imaging SMPI to confirm accuracy.
Results: Conclusive test results were achieved in 29 patients (97%). Heart rate and blood pressure were markedly increased with statically highly significant difference (P value <0.001), patients on b-blocker treatment had lower maximum heart rate compared to other patients with significant difference. Twenty-three (79%) patients had negative test results and six (21%) patients had positive

* Corresponding author. Tel.: +20 144913787.
E-mail address: samasalma@yahoo.com (M.M. Khalaf).

Peer review under responsibility of Egyptian Society of Cardiology.
doi:10.1016/j.ehj.2011.08.016

test results, and if compared to SMPT results, EST was considered better positive than negative test, with higher specificity than sensitivity and accuracy.

Conclusions: Atropine injection during EST significantly reduced the inconclusive test results in patients with chronotropic incompetence and poor exercise capacity.

1. Introduction

Exercise stress test (EST) is one of the main diagnostic and prognostic tests for ischemic heart disease. Exercise testing remains the most widely used test in cardiology for predicting the likelihood and extent of coronary artery disease, assessing functional status, and predicting prognosis.[1,2]

Diagnostic accuracy of exercise testing is influenced by the degree of achievement of age-predicted target heart rate[3] then chronotropic incompetence and poor exercise capacity (an attenuated heart rate response to exercise) limits its utility. Both of these conditions have been associated with a poor long-term prognosis and have been shown to be independent predictors of mortality.[4–12]

Atropine, an anticholinergic agent, has been shown to increase heart rate and enhance the sensitivity of dobutamine stress echocardiography in the detection of CAD in patients with chronotropic incompetence.[13,14]

At the present time, when a patient is unable to achieve 85% of age-predicted heart rate during EST and has not demonstrated symptoms or electrocardiogram (ECG) changes suggestive of ischemia, the test is labeled as inconclusive. The patient is generally referred for a pharmacological stress test (e.g. dobutamine stress echocardiography, adenosine, or dipyridamole nuclear stress testing, cardiac catheterization), which adds to inconvenience and cost.

For standard exercise electrocardiography (ECG), there have been few data on atropine injection during or before physical exercise.[15,16] Little information has existed about how it might be used to decrease the number of inconclusive tests. It remains to be proven that atropine injection improves the diagnostic accuracy of standard exercise testing.[17]

The addition of atropine to standard treadmill testing, in the presence of chronotropic incompetence or poor exercise tolerance, has not been well studied previously.

Therefore, the aim of the study was to evaluate the potential role of atropine in reducing the number of treadmill stress tests with inconclusive results and minimizing the need for further diagnostic tests, also assessing its accuracy.

2. Patients and methods

A prospective, randomized clinical trial was conducted from September 2009 for a period of 8 months in Multidisciplinary Unit at the critical care department of Cairo University Hospital. Out of 180 patients who preformed stress ECG; only 30 patients met the inclusion criteria and enrolled into the study.

2.1. Inclusion criteria

Thirty patients with chronotropic incompetence and poor exercise capacity during treadmill stress testing; two criteria were chosen for the administration of atropine during the test:

(1) Patients who had symptoms and an exertion score < 7 but do not meet the criteria for termination of the TMST; we used the non-linear Borg scale for perceived exertion, with scores ranging from 0 (no exertion at all) to 10 (very strong exertion).
(2) A heart rate range of 50–75% of the maximum predicted heart rate (MPHR).

2.2. Exclusion criteria

Included standard contraindications for TMST, and conditions that precluded the use of atropine for which each subject was checked before the test.

All included patients were subjected to the following: full clinical evaluation; including history and physical examination with special emphasis on medications and risk factors.

2.3. Study protocol

Treadmill testing was performed according to the modified Bruce protocol with continuous 12-lead ECG monitoring. Patients fasted for at least 4 h before the test, and their regular medications were not withheld. A patent peripheral intravenous (IV) line was established in all patients before the study.

During TMST, patients underwent continuous ECG monitoring and blood pressure measurements every phase during exercise and every 3 min during the recovery period. Patients were also questioned every minute during the stress test for symptoms of chest pain, fatigue, dyspnea, and claudication. Atropine was administered in doses of 0.5 mg per minute until the test conclusion (positive test results or target heart rate is achieved) or until a maximum dose of 2 mg is administered in the same setting. Patients receiving atropine are monitored for adverse effects (e.g. irritation at the injection site, dryness of mouth, tachycardia and palpitations).

All patients were subjected to stress myocardial perfusion imaging to confirm accuracy.

2.4. Statistical analysis

Patients' data were tabulated and processed using SPSS (15.0) statistical package for Windows XP.

Description of quantitative variables as mean, SD and range.
Description of qualitative variables as number and percentage.
Chi-square test was used to compare qualitative variables between groups.
Unpaired *t*-test was used to compare quantitative variables, in parametric data (SD $<$ 50% mean).
Paired *t*-test used to compare quantitative variable in the same group.

Sensitivity = true ve + /true + ve + false − ve
= ability of the test to detect + ve cases
Specificity = true − ve/true − ve + false + ve
= ability of the test to exclude negative cases
PPV (positive predictive value) = true + /true + ve + false + ve
= % of true + ve cases to all positive
NPV = true − /true − ve + false − ve
= % of the true − ve to all negative cases

Accuracy: true +ve + true −ve/total.
P value >0.05 insignificant.
P < 0.05 significant.
P < 0.01 highly significant.

3. Results

Thirty patients out of 180 were enrolled in the study to take atropine during stress test as they had an exertion score more than 7 according to the Borg scale or the MPHR was ranging from 50% to 75%.

3.1. Demographic data and risk factors

The age range was 40:73 years with mean of 55 ± 8, they were 16 males and 14 females, 60% of them were non-smokers, 63.3% were diabetic and other risk factors' distribution is seen in Table 1.

3.2. Medications

Twenty-two patients (73%) of the studied cases were on BB therapy, while 10% of them were on nitrates.

3.3. Test indications

Twenty-two patients (73%) of the studied cases were presented for chest pain evaluation, 23% for follow up after percutaneous coronary intervention and post-coronary artery bypass grafting status and 3% for preoperative evaluation.

Table 1 Demographic data and risk factors.

Variables	Mean ± SD	Range
Age (years)	55 ± 8	40–73
Gender		
Male	16	53.3%
Female	14	46.7%
Smoking		
Smoker	3	10%
Ex-smoker	9	30%
Non-smoker	18	60%
DM	19	63.3%
HTN	11	36.7%
Abnormal cholesterol	14	46.7%
Obesity	9	30%

3.4. Atropine dose

The average dose of administered atropine was 0.76 ± 0.34 mg (18 patients received 0.5 mg, nine patients received 1 mg and three patients received 1.5 mg). Among study group, more than 66% of the studied cases (20 patients) had poor physical fitness, while 33% (10 patients) had chronotropic incompetence.

3.5. Test outcomes

The heart rate and blood pressure were markedly increased with statistically highly significant difference in between the stages of stress.

ECG (at rest, just before atropine injection and at peak exercise), the average change in HR between maximum HR and HR at the start of injection of atropine was 37% which has highly significant difference, also the heart rate declined in recovery with statistically highly significant difference in comparison to maximum heart rate by using paired *t*-test (Table 2).

The heart rate increased gradually with atropine dose with statically highly significant difference in between the stages by using paired *t*-test, the average change in maximum heart rate was 86% of the resting heart rate (Table 3).

The HR was markedly increased among BB group from resting until maximum with statistically highly significant difference in between by using paired *t*-test. The average change in maximum heart rate was 90.7% of resting heart rate (Table 4).

Atropine acted effectively on both groups (BB group and non-BB group) with no significant difference in between both groups except at a stage of maximum exercise, *P* value <0.05 (Table 5).

Conclusive test results were achieved in 29 patients (97%), only one patient had inconclusive test results 3%. Therefore, atropine injection resulted in a significant decrease in inconclusive test results.

Twenty-three patients (79%) had negative stress test and six patients (21%) had positive exercise stress test.

Comparison between thallium and stress ECG results among the studied cases revealed statistically significant association between thallium and stress test results by using chi-square test, *P* value <0.05 (Table 6).

Stress ECG was considered better positive than negative test when its results were validated to thallium results specially in 22 patients coming for chest pain evaluation, with higher specificity (100%) than sensitivity (43%) and accuracy (62%) as the PPV was 100% and NPV was 83% (Table 7).

Follow-up angiographic data were available in only 3 of the 6 patients with positive ECG test results after atropine administration. The three patients had significant CAD. Likewise, only 1 of the 8 patients with negative stress ECG test results and positive thallium underwent angiography at our facility which revealed insignificant LAD and LCX.

3.6. Adverse outcomes of atropine

Ten percent (three patients) of the studied cases had complications which were prolonged recovery in two patients and ventricular tachycardia with hemodynamic stability in the third

Table 2 Changes in HR and blood pressure at rest and at peak exercise.

Variables	HR at Start of atropine	Maximum	% of change	*t*	*P* value
HR (bpm) at start of atropine/max	109 ± 9.5	148 ± 9.8	37	3.9	<0.001 HS
HR (bpm) resting/max	79 ± 13	148 ± 9.8	86	27	<0.001 HS
HR (bpm) recovery/max	129 ± 12	147 ± 9	13	11	<0.001 HS
SBP (mmhg)	133 ± 11	162 ± 21	22	7	<0.001 HS
DBP (mmhg)	84 ± 8	91 ± 8	8.3	3	<0.001 HS

Table 3 Changes in HR at every dose of atropine and at peak exercise.

Variables	Mean ± SD	% of change	*t*	*P* value
Resting HR	79 ± 13	–	–	–
Atropine 0.5	109 ± 9.5	38	13	<0.001
Atropine 1	122 ± 12	54	12	<0.001
Atropine 1.5	127 ± 9	61	10	<0.001
Maximum HR	148 ± 9.8	86	27	<0.001

Table 4 Changes in HR from resting and after atropine intake among BB group.

Variables	Mean ± SD	% of change	*t*	*P* value
Resting HR	76 ± 12		–	–
Atropine 0.5	109 ± 10.5	18	3	<0.001
Atropine 1	121 ± 13	60	6	<0.001
Atropine 1.5	121 ± 0	59	8	<0.001
Maximum HR	145 ± 10	90.7	12	<0.001

Table 5 Comparison between BB and non-BB group as regards changes in HR from resting and after atropine intake.

Variables	BB group	Non-BB group	*t*	*P* value
Resting HR	76 ± 12	86 ± 11	1.9	>0.05
Atropine 0.5	109 ± 10.5	108 ± 6.6	0.6	>0.05
Atropine 1	121 ± 13	125 ± 7	0.45	>0.05
Atropine 1.5	121 ± 0	–	–	–
Maximum HR	145 ± 10	153 ± 7	2.2	<0.05

Table 6 Comparison between thallium and stress ECG among the studied cases.

Stress ECG	Negative thallium	Positive thallium	χ^2	*P*
Negative	15 (93.8%)	8 (61.5%)	5.5	<0.05 S
Positive	1 (6.3%)	5 (38.5%)		

patient. None of the previous complications needed hospital admission; however, they needed 20 min observation.

Palpitation and dry mouth were the most frequent side effects of atropine which occurred in two patients (6.7%) and five patients (16.7%), respectively.

Table 7 Validity of stress ECG in relation to thallium among the studied cases and in patients coming for chest pain evaluation.

Validity	% in all studied patients (n = 30)	% in chest pain evaluation (N = 22)
Sensitivity	40	43
Specificity	94	100
PPV	83	100
NPV	65	83
Accuracy	68	62

4. Discussion

Chronotropic incompetence is defined as a failure to achieve 85% of the age-predicted maximum heart rate at maximum exercise capacity during stress testing. This phenomenon has been reported to occur in 11–23% of cases and to be an independent predictor of poor outcome.[5,15,18]

Poor exercise capacity (inability to achieve a moderate level of exercise), likewise limits the utility of the exercise testing and is a powerful modifiable predictor of adverse outcomes. After six METs, an increase in each MET of exercise capacity is associated with a 20–25% decrease in adverse cardiac outcome.[13]

The timing of atropine administration in conjunction with stress testing can be either before the test, as in Variola et al.[15] studies with TMST, or during the test, as in this study.

Pre-test administration of atropine has also been shown to be useful in exercise echocardiography by increasing peak heart rate and facilitating better acquisition of post-exercise images.[13]

In our study, we administered atropine during EST on the basis of the patient's subjective symptoms of near-fatigue so that we might decrease the incidence of inconclusive test results and obviate the need for the second stress test used in the study by Variola et al.[15] in his study.

Twenty-five patients who had inconclusive EST results had the test repeated with pre-test administration of 1–2 mg of atropine, 80% of the patients (n = 20) proceeded to have conclusive test results. While in our study conclusive test results were achieved in 29 of the 30 patients (97%) (n = 23), 79% were negative and (n = 6) 21% were positive. More than two-third of patients were undergoing the test for evaluation of chest pain.

In the study conducted by Munagala et al.,[17] conclusive test results were achieved in 23 of the 33 patients (70%): (n = 17) 74% negative and (n = 6) 26% positive. Ghaffari et al.

conclusive test results were achieved in 38 of the 41 patients (92%) ($n = 25$) 65% negative and ($n = 13$) 35% positive.

In the present study, 30 patients received atropine due to poor exercise capacity (20 patients; 66%) or chronotropic incompetence (10 patients; 33%) There were no statistically significant differences between subjects with poor exercise capacity or chronotropic incompetence regarding demographic data or B blocker usage (P value was not significant).

In the study of Munagala et al.,[17] 33 required atropine due to poor exercise capacity (six patients; 18%) or chronotropic incompetence (27 patients; 82%) Atropine administration resulted in conclusive tests more often in subjects with poor chronotropic response than in subjects with poor exercise capacity (78% versus 33%, $P = 0.001$).

In Ghaffari et al. [18] 41 patients received atropine due to poor exercise capacity (nine patients; 22%) or chronotropic incompetence (32 patients; 78%). There were no differences in response to atropine in subjects with poor exercise capacity or chronotropic incompetence. (Inconclusive EST was found in one patient with poor exercise capacity and two patients with chronotropic incompetence, P value was not significant).

Higher degree of HR increase in our study after atropine injection (69 beats/min versus 25 beats/min in Munagala et al.[17] study, and 38 beats/min in Ghaffari et al.[18] study) that resulted in more conclusive test results with a lower rate of atropine injection 0.76 ± 0.34 mg despite highest percentage of B blocker, may be related to lower resting HR in Munagala et al.[17] study (68 beats/min versus 79 in our study), also higher incidence of patient with poor physical fitness. We used modified Bruce protocol instead of Bruce protocol unlike previous studies as to try to diminish the contribution of test in exhaustion for the patient, which might be the cause for high percentage of patients with poor physical fitness. In addition, 30% of study group was obese, this limiting factor was not commented upon in previous studies. In addition, the percentage of diabetic patients was the highest in our study group we had highest mean age.

Myocardial perfusion images were available for all patients in the study. Angiographic data from only 3 of the 6 patients with positive ECG test results after atropine administration were available for review. The three patients had significant CAD. Likewise, only 1 of the 8 patients with negative stress ECG test results and positive thallium underwent angiography at our facility which revealed insignificant LAD and LCX.

Regarding accuracy of atropine in relation to TMST which was not studied before the present study, it revealed a mean sensitivity of 40%, mean specificity of 94% and positive predictive value of 83%. Moreover, if patients with known ischemic heart disease were excluded, it demonstrated a mean sensitivity of 43%, mean specificity of 100% and positive predictive value of 100%. These results show that stress ECG is considered better positive than negative test, with higher specificity than sensitivity and accuracy. Thus, the use of stress ECG as a screening test is limited by its low sensitivity. However, if the result is negative it needs an extra confirmatory test where these results can be explained by the fact that the study group consisted of patients with poor exercise capacity and chronotropic incompetence which in itself is a risk factor.

The addition of atropine administration to TMST would involve an increase in costs related to establishment of an IV line, additional personnel for atropine injection, and the cost of the agent. But considering the higher cost of nuclear imaging, dobutamine echocardiography or coronary angiography, it will be a negligible amount.

Even in patients without pre-established IV lines who come for TMST, we believe the cost and inconvenience of an IV line may be justified in selected patients for 2 reasons:

(a) It helps avoid the necessity of a second test performed at a later time.

(b) It affords additional safety for dealing swiftly with rare complications of TMST.

Conclusion

Atropine injection during EST significantly reduced the inconclusive test results in patients with chronotropic incompetence and poor exercise capacity. Stress ECG is considered better negative than positive test, with higher specificity than sensitivity and accuracy. Side effects and complication of atropine use were minor and did not need hospital admission.

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