Effect of intravenous atropine on treadmill stress test results in patients with poor exercise capacity or chronotropic incompetence

Samad Ghaffari, MD, Bahram Sohrabi, MD.

ABSTRACT

Objective: Exercise stress test (EST) is one of the main diagnostic and prognostic tests for ischemic heart disease. However, its usefulness depends on achieving target heart rate, then chronotropic incompetence and poor exercise capacity limits its utility. We evaluated the usefulness of atropine administration during the EST to decrease the number of tests with inconclusive results in these patients.

Methods: We carried out this study in Shahid Madani Heart Center, Tabriz, Iran from September 2003 to December 2004 and comprised of 210 patients undergoing EST. In subjects experiencing fatigue when they achieved 50-75% of target heart rate (THR), or those who failed to achieve their THR, atropine was administered in doses of 0.5 mg per minute until the test conclusion (positive test results or target heart rate achieved) or until a maximum dose of 2 mg was administered.

Results: Forty-one (19.5%) of the 210 patients required atropine (mean dose: 1.1 mg) during the study. Among patients who received atropine, conclusive test was achieved in 38 cases (92.7%). Atropine administration resulted in a mean increase in heart rate of 38 beats/min (range 8-71 beat/min). Atropine injection resulted in a trend towards more positive results of EST in comparison to non-atropine group (31.7% versus 18.3%, p=0.053). There was no difference in response to atropine in subjects with chronotropic incompetence or poor exercise capacity (p=0.5).

Conclusion: Use of atropine as an adjunct to standard EST can help decrease the number of inconclusive tests. Larger studies are necessary to define the role of atropine in EST and also to evaluate the accuracy of conclusive EST after atropine administration

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Exercise stress testing (EST) remains the most widely used testing in cardiology for predicting the likelihood and extent of coronary artery disease (CAD), assessment of prognosis and functional capacity.[1] The sensitivity and specificity of EST for the diagnosis of CAD primarily depends on the pretest probability of CAD, the severity of CAD and the degree of achievement of age-predicted target heart rate (THR).[2] Patients may not achieve their THR due to poor exercise capacity or chronotropic incompetence. Chronotropic incompetence is failure to achieve 85% of the age-predicted maximum heart rate at maximum exercise capacity during EST.[3] Poor exercise capacity (inability to reach an exercise level of at least 6 metabolic equivalents or METS), likewise limits the utility of the exercise testing.[4] In routine practice, when a patient is unable to achieve THR during EST and has not demonstrated symptoms or

From the Department of Cardiology, Madani Heart Hospital, Tabriz University of Medical Sciences, Tabriz, *Iran*.

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Address correspondence and reprint request to: Dr. Samad Ghaffari, Department of Cardiology, Madani Heart Hospital, Tabriz, *Iran*. Tel. +98 (411) 3357771. Fax. +98 (411) 3344021. E-mail: ghafaris@gmail.com

electrocardiographic changes indicative of ischemia or has poor exercise capacity, the test is reported as inconclusive EST and usually, we referred the patient for dipyridamole nuclear stress testing or dobutamine stress echocardiography which adds to cost.[2] Atropine has been shown to increase the overall diagnostic sensitivity of dobutamine stress echocardiography.[5] Dipyridamole has also been combined with atropine for stress testing, but addition of atropine to EST, due to poor exercise capacity or chronotropic incompetence, has not been well studied previously.[2] Therefore, we decided to evaluate the potential role and incremental value of atropine in reducing the number of inconclusive EST.

Methods. The study was carried out in Shahid Madani Heart Center, Tabriz, Iran from September 2003 to December 2004. A total of 216 patients, undergoing Treadmill EST were enrolled in the study. Exclusion criteria included conditions that precluded the use of atropine (myasthenia gravis, obstructive uropathy and a narrow angle glaucoma). Informed consent was obtained from all subjects. An intravenous (IV) line was established in all patients before the test and patients underwent continuous electrocardiogram (ECG) monitoring. Blood pressure measurement was performed every minute during EST and every 3 minutes during the recovery phase. A physician was present at the test site as part of our protocol. Two criteria were established for atropine injection: First, a heart rate range of 50-70% of THR in subjects experiencing fatigue at submaximal test. A patient with <50% of THR at the time of near fatigue was not expected to reach a THR even with atropine. Likewise, a patient with >70% of THR at the time of near-fatigue was likely to achieve THR before the termination of the test without atropine. Second, patients who had symptoms but did not meat the usual criteria for termination of the EST (achievement of >85% of THR, patients request to stop the test, severe chest pain, marked ST-Segment depression, development of ST-Segment elevation, hypotension, complex arrhythmia, dyspnea or fatigue). Atropine was administered as 0.5 mg IV injection at 1-minute intervals until the THR or a maximum dose of 2 mg or a positive EST result was achieved. Patients were monitored for about 15 minutes after the test for possible complications. Demographic parameters, drug history, test indications and results and atropine doses were recorded for analysis with SPSS statistical software and a p value of <0.05 was considered to be significant.

Results. A total of 210 patients were enrolled in the study (**Table 1**). We did not received informed consent in 6 eligible patients to participate in the study. There was no patient with contraindication for atropine injection. Mean age (±SD) of patients was 50.5±10.6 years and 67% were male. The test indications included: atypical chest pain in most patients (54%), post infarction evaluation or stable CAD (34%), post-percutaneous coronary intervention and post-coronary artery bypass grafting status in 12%. Patients in atropine group had a low mean resting heart rate (80±16 versus 91±15 beats/min, p=0.01). Forty-one (19.5%) of the 210 patients received atropine resulting from poor exercise capacity (9 [22%]) or chronotropic incompetence (32 [78%]). The average change in maximum heart rate was 38±19 beats/min (range: 8-71 beats/min). The average dose of administered atropine was 1.12±0.55mg. Beta blocker, and calcium channel blockers usage were not significantly different in atropine group versus non-atropine group (17.1% versus 26%, p=0.056 for beta blockers and 4.9% versus 5.3%, p=0.3 for calcium blockers). Among 47 patients who were taking beta-blockers atropine was injected in 8 cases (17%) at the time of EST and resulted in conclusive test in all of them. Mean blood pressure was 167/80 mm Hg in atropine group and 165/80 mm Hg in those without atropine injection (p=0.53). **Figure 1** is a flow diagram showing the results of EST in subjects receiving atropine, versus subjects not receiving atropine. Among patients who received atropine, conclusive test results were achieved in 38 patients (92.7%): 61% negative and 31.7% positive. Therefore, atropine injection resulted in a significant decrease in inconclusive test results (p=0.01). 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 2 patients with chronotropic incompetence, p value was not significant). The positive EST result was reported in 13 (31.7%) patients with atropine injection and 31 (18.3%) patients without it (p=0.05). No adverse reaction related to atropine administration was reported during and after the EST.

Discussion. Chronotropic incompetence has been reported to occur in 11-23% of cases and to be an independent predictor of poor outcome.[6] 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.[4] After 6 METs, an increase in each MET of exercise capacity is associated with a 20-25% decrease in adverse cardiac outcomes.[7]

Table 1 - Characteristics of study patients.

Characteriestics	Atropine group n=41	No atropine group n=169	*p*-value
Age (years)	50.4 ± 9.6	50.5 ± 11.1	NS
Male (%)	60.1	68	NS
Resting HR (min-1)	80 ± 16	91 ± 15	0.01
Exercise BP (mm Hg)	167 / 80	165 / 80	NS
Risk factor			
Diabetes	12.2	9.5	NS
Hypertension	34.1	27.8	NS
Smoking	17	19.5	NS
Medications (%)			
Beta-blocker	17.1	26	0.05
Ca-blocker	4.9	5.3	NS
Aspirin	52	58	NS
EST indication			
Atypical chest pain	48.7	55.6	NS
Post MI or CSA	36.5	33.1	NS
Post PCI or CABG	14.6	19	NS

HR - heart rate, BP - blood pressure, Ca - calcium,
EST - exercise stress test, MI - myocardial infarction,
CSA - chronic stable angina,
CABG - coronary artery bypass grafting,
PCI - percutaneous coronary intervention, NS - not significant

Atropine is generally a safe drug when used in selected patients and has become part of standard dobutamine stress echocardiography.[5] The timing of atropine administration with stress testing can be either before the test, as in previous studies with EST, or during the test, as in dobutamine stress echocardiography. Variola et al[8] reported an increased sensitivity and specificity of EST for detection of CAD with pre-test atropine administration in patients with chronotropic incompetence demonstrated on previous EST.[2] 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, compared with 92.7% of subjects in our study. 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.[8] Physiologically, at the onset of exercise, an abrupt increase in heart rate occurs, and this has been attributed to the loss of vagal tone; further increases in heart rate are felt to be sympathetic-drive mediated. The increase in heart rate seen in our study with atropine administration 4-5 minutes into exercise suggests that parasympathetic tone plays a role even in the latter part of exercise. In

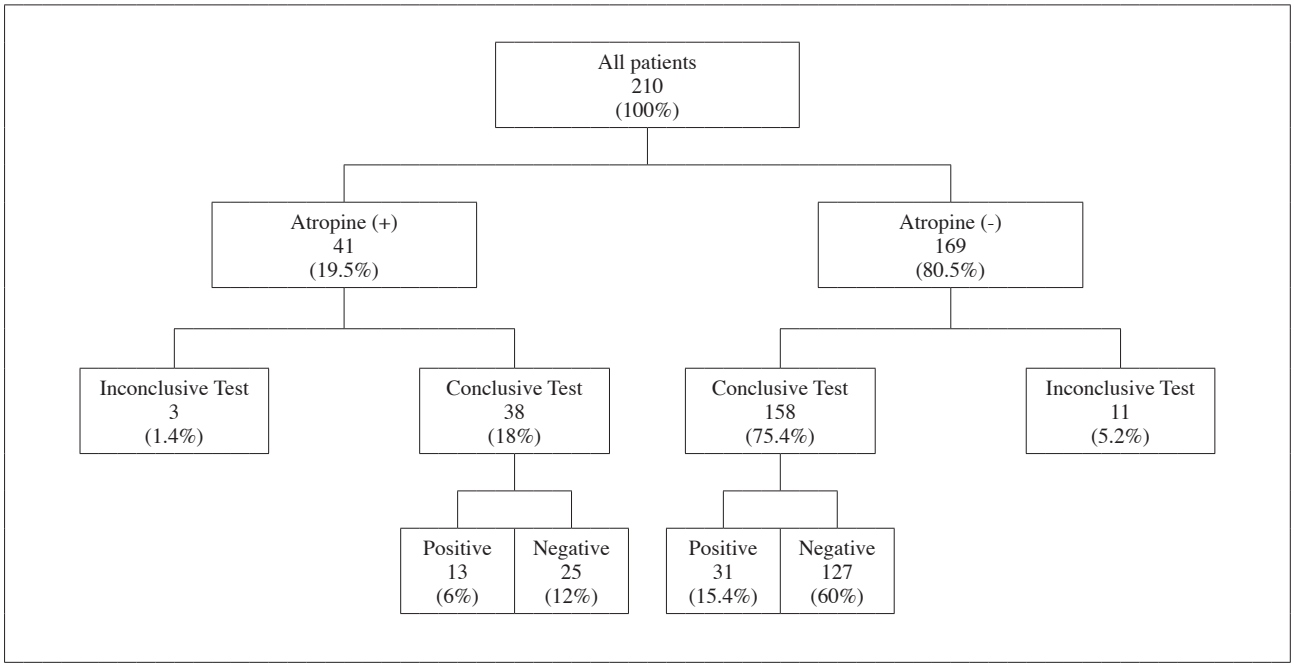

Figure 1 - Flow diagram of results of exercise stress test in subjects receiving atropine and in subjects not requiring atropine.

the study of Munagala et al,[2] 33 of the 126 patients (26%) required atropine (mean dose, 1 mg) during the study; 23 of the 33 patients (70%) proceeded to achieve their target heart rate (n=17) or positive test results (n=6). The mean increase in heart rate after atropine administration was 25 beats/min (range 3-53 beats/min). Atropine was required in 39% of patients receiving beta-blockers, versus 21% of patients not receiving beta-blockers (p=0.02). Among patients receiving atropine, they achieved a conclusive test significantly more often in patients not receiving beta-blockers (94% versus 46%, p=0.01). 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).[2] In our study, 41 (19.5%) of the 210 patients received atropine due to poor exercise capacity (9 patients; 22%) or chronotropic incompetence (32 patients; 78%). The average change in maximum heart rate was 38±19 beats/min (range: 8-71 beats/min). The average dose of administered atropine was 1.12±0.55mg. Higher degree of HR increase in our study after atropine injection (38±19 beats/min versus 25 beats/min in Munagala et al[2] study) with a lower rate of atropine injection in patients taking beta blockers in our study (17.1% versus 45% in Munagala et al[2] study) may be related to lower dose of administered beta-blockers in our patients. A valuable clue to this hypothesis comes from lower resting HR in Munagala et al[2] study (68 in atropine group and 76.2 in non atropine group versus 80±16 and 91±15 in our study). Positive test result was seen in 31.7% of patients in atropine group versus 18.3% in non-atropine group (p=0.05). Considering the equal amount of maximal BP that has been reported only in our study (mean BP=167/80 in atropine group and 165/80 mmHg in no atropine group p=0.53) this may indicate to higher rate of false positive results with atropine and needs to be confirmed with the myocardial perfusion study, dobutamine stress echocardiography or coronary angiography. In contrast to Munagala et al study that showed conclusive tests more often in subjects with poor chronotropic response than in subjects with poor exercise capacity (78% versus 33%, p=0.001), in our study the conclusive EST result was seen in 93.7% of the first and 88.8% of second group (p value was not significant). Again, this may be related to the higher rate of patients taking beta–blocker in Munagala et al[2] study (45% versus 17.1% in our study). However, at least 50% of patients taking beta-blockers have good response to atropine in both studies. The conclusive EST result was achieved in 92.7% of our patients compared with 70% in the study of Munagala et al.[2] Considering the relatively equal amount of administered atropine, it seems that higher rate of prescribed beta-blockers and calcium channel blockers in Munagala group (42.1% versus 29.5% in our study) is responsible for this different result. In both studies, no adverse events were reported with the use of atropine. And in both studies, a lower resting heart rate was a predictor of incomplete EST and needed for atropine. The addition of atropine administration to EST would involve an increase in costs related to establishment of an intravenous (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. Before we can recommend the use of atropine injection in exercise electrocardiogram (ECG) in our daily practice, further study of the diagnostic accuracy of atropine exercise ECG is needed. It must be compared with the standard exercise ECG and pharmacologic stress testing in patients with poor exercise capacity, beta-blocker therapy, known chronotropic incompetence, or sick sinus syndrome. The major limitation of our study is the lack of any gold standard test to evaluate the sensitivity and specificity of conclusive EST results. Also, the exercise duration after atropine administration is unknown and this may interfere in interpretation of atropine effects.

In conclusion, the use of atropine as an adjunct to standard EST can help decrease the number of inconclusive tests, even in patients taking beta-blockers without any significant side effect. This effect is similar for both groups of patients; those with chronotropic incompetence or poor exercise capacity. Larger studies are warranted to further define the role of atropine in diagnostic EST and also to evaluate the accuracy of conclusive EST after atropine administration.

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