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Safety and efficacy of exercise testing with atropine in patients with recent uncomplicated ST elevation acute myocardial infarction

Research Article

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Abstract: Background: Exercise testing (ET) remains the most accessible and widely used technique for the detection of coronary artery disease (CAD) and for the assessment of its severity. Failure to reach 85% of maximal predicted heart rate (MPHR) during exercise may render an ET nondiagnostic for ischemia detection in patients with recent uncomplicated ST elevation acute myocardial infarction (STEMI). We sought to investigate the injection of atropine in patients who fail to achieve 85% of age-predicted heart rate during ET, defining its safety and efficacy to raise heart rate to adequate levels as well as to determine its effect on ET interpretation. Methods: Between January 2005 and December 2008, we studied 1150 consecutive patients with recent uncomplicated STEMI (850 men and 300 women, mean age 59 ± 8 years) who were referred to a single exercise testing laboratory, prior to beginning a physical training program. In 450 patients (398 males and 52 females, mean age 61 ± 7 years) with a non-diagnostic test, the ET was repeated 1-2 days later, and during the test, 1-2 mg of atropine was administered to patients who were unable to continue because of fatigue before reaching minimal heart rate (HR), without an ischemic response. Results: mean HR before atropine injection was 129.5 ± 13.6 beats per minute (bpm), and it increased up to 147.3 ± 13.5 bpm after drug administration, with an incremental of 17.8 ± 6.9 bpm ($p < 0.0001$). The mean percentage of age-related HR achieved was 86.5% ± 6.1%. In 378 of these patients (84%), more than 85% of their aged-related HR (89.9% ± 4.1%) was attained. No major adverse effects occurred. The maximal heart rate (147.3 ± 3.5 versus 129.5 ± 13.6) and the double product (29378.7 ± 6342.7 versus 25798.3 ± 5328.5) were significantly greater after atropine ($p < 0.0001$, respectively). The increase in the maximal HR improved the detection of the electrocardiographic signs of exercise-induced myocardial ischemia (sensibility increased from 82.1% to 89.2%, specificity from 52.3% to 68.2%, and prognostic accuracy from 77.2% to 86.1%). Conclusion: Atropine added to ET in patients who cannot achieve their 85% age-related HR is safe and well-tolerated, and improves the prognostic accuracy in patients with recent uncomplicated STEMI. The combination with atropine increases the utility and the cost-effectiveness of ET.

Keywords: *Atropine • Exercise testing • Maximal predicted heart rate • ST elevation acute myocardial infarction*

1. Introduction

Exercise stress testing is a vital non-invasive tool for determining the hemodynamic severity of coronary artery disease (CAD) in patients with recent uncomplicated STEMI.

For assessment during stress, exercise or pharmacologic stress is used [1]. Exercise stress is more physiologic, and some authors have found higher sensitivity and specificity for detection of CAD than pharmacologic stress [2]. For this reason, maximal subjective stress testing is encouraged whenever possible. However, if exercise capacity is poor, the study may be sub-optimal [3-6]. An exercise test result is considered sub-optimal if the patient does not have angina, fatigue, electrocardiographic (ECG) evidence of ischemia, arrhythmias,

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decrease in blood pressure, or signs of poor perfusion and does not achieve a minimal desirable heart rate [7]. Minimal heart rate is considered to be 85% of the patient's age – predicted heart rate (220 – Age) [8]. Unfortunately, a significant proportion of patients do not reach the minimal heart rate standard during exercise [9]. This is probably an increasing phenomenon, as the number of patients with established or suspected CAD shifts to a more aged, obese, and disabled population. A number of factors contribute to the failure to exercise adequately, including physical deconditioning, β – blockers, peripheral vascular disease, stroke, arthritis, orthopedic problems, and chronic pulmonary disease, as well as chronotropic incompetence related to depressed cardiac sympathetic tone [10-13].

Atropine is an anthicolinergic drug that causes a rapid increase in heart rate and has been commonly used as an adjunct to dobutamine in pharmacologic stress protocols [14-21]. However, atropine administration during exercise has not been extensively studied. We sought to investigate the injection of atropine in patients who fail to achieve 85% of age-predicted heart rate during exercise testing (ET), defining its safety and efficacy for raising heart rate to adequate levels as well as its effect on ET interpretation.

2. Materials and methods

Between January 2005 and December 2008, we studied 1150 consecutive patients with recent uncomplicated STEMI (850 men and 300 women, mean age 59 ± 8 years), 675 (58.7%) of whom were treated with thrombolysis and 475 (41.3%) of whom were treated with primary angioplasty of culprit lesion, and were referred to a single exercise testing laboratory, prior to beginning a physical training program.

The exclusion criteria were STEMI in the previous month, ejection fraction less than 45%, or inability to perform physical exercise. We also excluded patients with any formal contraindication for atropine, such as glaucoma, obstructive uropathy, or obstructive gastrointestinal disease. β – blockers or calcium antagonist therapy and apparent poor physical tolerance were non-exclusion criteria.

2.1 Exercise protocol

All of the patients performed maximal or symptom-limited treadmill exercise test according to the Bruce protocol (Marquette Max 1, Jupiter, FL, USA). Blood pressure and 12-lead electrocardiographic recording were obtained at rest, at the first and third minute of every stage of exercise, at the end of exercise, at the first and the third minute of the recovery period, and then every 3 minutes until the electrocardiogram returned to normal. During exercise, 12 leads were continuously monitored. The exercise test results were considered valid whenever the patient's maximal heart rate achieved was greater than or equal to 85% of the age – related target (220 heats/min. – Age) or any of the following symptoms developed: angina, ST depression > 0.2 mV, dyspnea, complex ventricular arrhythmias, a decrease in systolic blood pressure > 10 mmHg in two consecutive steps, and fatigue. The presence of angina or ST depression > 0.1 mV, measured at 80 ms from the J point, were considered as criteria of positivity. For patients who were unable to achieve 85% of age-predicted heart rate during the first ET because of fatigue and without an ischemic response, the stress test was repeated 1-2 days later, during which 1 mg of atropine was administered We monitored the heart rate response for the next minute and administered another 0.5 – 1 mg of atropine if the target heart rate was not reached. The maximal dose was 2 mg. After atropine administration, the load was maintained, and patients continued to exercise for at least 1 more minute. Severe adverse events due to atropine were recorded (we did not record minor adverse events such as palpitations or xerostomia). We compared these results with those of the first ET. Experienced staff cardiologists interpreted the exercise tests.

All patients gave written informed consent to undergo the study. The Human Studies Committee of the Buccheri La Ferla Fatebenefratelli Hospital approved this protocol.

2.2 Statistical analysis

Results are expressed as the mean ± standard deviation (SD). Data were analysed by the two-tailed T-test to identify differences intra-group. Nominal data were analysed by the Chi-square test. Sensitivity, specificity, and prognostic accuracy of ET were calculated using standard definitions. Differences were considered significant at a P-value < 0.05, the 95% confidential interval (95%CI) is also reported. All analyses were performed using the MedCalc Software Version 10.4.5.

3. Results

Baseline clinical characteristics are summarized in Table 1. Of 1150 patients, 850 (73.9%) were men and 300 (26.1%) women, mean age were 59 ± 8 years. Myocardial infarct size was anterior in 377 (32.8%) patients, inferior in 521 (45.3%) patients, and lateral in 252 (21.9%) patients.

Table 1. Baseline Clinical Characteristics.

Patients (no.)	**1150**
Age, years (mean ± SD)	59 ± 8
Male sex (%)	850 (79.3)
Diabetes (%)	527 (45.8)
Hypertension (%) a	894 (77.7)
Dyslipidemia (%) b	758 (65.9)
Cigarette smoking (%)	560 (48.7)
Family history of CAD (%)	327 (28.4)
Previous AMI (%)	270 (23.5)
History of PCI (%)	321 (27.9)
History of bypass surgery (%)	117 (10.2)
Infarct size (%)	
Anterior	377 (32.8)
Inferior	521 (45.3)
Lateral	252 (21.9)
Medications (%)	
B-blockers	807 (67.2)
Calcium antagonist	68 (27.2)
Amiodarone	96 (4.0)
ACE inhibitors	930 (80.8)
Statins	989 (86.0)
Antiplatelet agents	1085 (94.3)

3.1 Atropine Effects

In 450 patients (398 males and 52 females, mean age 61 ± 7 years) with a non-diagnostic test, mean HR in the ET without atropine was 129.5 ± 13.6 beats per minute (bpm), increasing to 147.3 ± 13.5 bpm after drug administration in the second ET, with an incremental increase in heart rateof 17.8 ± 6.9 bpm (p < 0.0001; 95% CI = 16,03 – 19,57). The usual atropine dose was 1.0 mg. Only 57 patients (12.6%) who did not respond to this initial dose, received a higher dose of atropine up to a maximum of 2 mg, and an extra increment in HR (8.7 ± 3.4 bpm) was observed. The mean percentage of age-related HR achieved was 86.5% ± 6.1%. In 378 of these patients (84%) more than 85% of their aged-related HR (89.9% ± 4.1%) was attained.

After administration of atropine, arrhythmias were observed in 21 patients (4.7%), 7 (1.5%) with isolated premature ventricular contraction and 13 (2.9%) with premature atrial contraction. Ventricular tachycardia or ventricular fibrillation did not occur. One patient with a history of paroxysmal supraventricular tachycardia, had this arrhythmias developed after atropine injection. The patient had no hemodynamic impairment and reverted to sinus rhythm, after administration of verapamil, during the recovery period. Dry mouth was reported by 129 patients (28.7%) and was attributed to atropine effect.

There were significant differences between the two stress tests (with and without atropine) regarding peak HR, peak systolic blood pressure, rate pressure product, percentage of age-related HR, metabolic equivalents achieved, and total exercise time (Table 2). There were also significant differences in the development of chest pain: 48 patients (10.7%) in the first ET without atropine, and 77 patients (17.1%) during the second ET with atropine (p = 0.0074; 95% CI = 1,74 – 11,06), and in ECG change: mean ST-segment depression was 0.4 ± 1.1 mm and 0.8 ± 1.2 mm respectively (p < 0.0001; 95% CI = 0,25 – 0,55). The increase of the maximal HR improved the detection of the electrocardiographic signs of exercise-induced myocardial ischemia, sensibility increased from 82.1% to 89.2% (p = 0.0033; 95% CI = 2,38 – 11,82), specificity from 52.3% to 68.2% (p < 0.0001; 95% CI = 9,38 – 22,28), and prognostic accuracy from 77,2% to 86,1% (p = 0.008; 95% CI = 3,7 – 14,06) (Figure 1).

Table 2. Baseline and Maximal Clinical, Electrocardiographic, and Hemodynamic Parameters.

	ET without Atropine	ET with Atropine	P Value	95% CI
Patients (n.)	**450**	**450**		
Baseline HR (b.p.m.)	67.8 ± 12.0	69.7 ± 11.2	0.0143	0,38 to 3,41
Baseline SBP (mmHg)	128.5 ± 24.3	130.6 ± 22.6	0.1798	- 0,97 to 5,12
Baseline DBP (mmHg)	81.7 ± 13.5	82.2 ± 12.8	0.5687	- 1,22 to 2,22
Baseline RPP	9728.1 ± 2748.5	9635.2 ± 2878.3	0.6206	- 4,61 to 275,3
Maximal HR (bpm.)	129.5 ± 13.6	147.3 ± 13.5	< 0.0001	16,03 to 19,57
% ARHR	83.5 ± 8.1	91.8 ± 9.7	< 0.0001	7,13 to 9,47
Maximal RPP	25798.3 ± 5328.5	29378.7 ± 6342.7	< 0.0001	2813,99 to 4346,81
METs	7.8 ± 2.6	8.9 ± 2.9	< 0.0001	0,74 to 1,46
Maximal SBP (mmHg)	190.3 ± 35.4	195.3 ± 28.7	0.0202	0,78 to 9,22
Exercise duration (min)	9.8 ± 2.6	10.3 ± 2.3	0.0023	0,18 to 0,82
Chest pain developed (%)	48 (10.7)	77 (17.1)	0.0074	1,74 to 11,06
ST-segment depression (mm)	0.4 ± 1.1	0.8 ± 1.2	< 0.0001	0,25 to 0,55

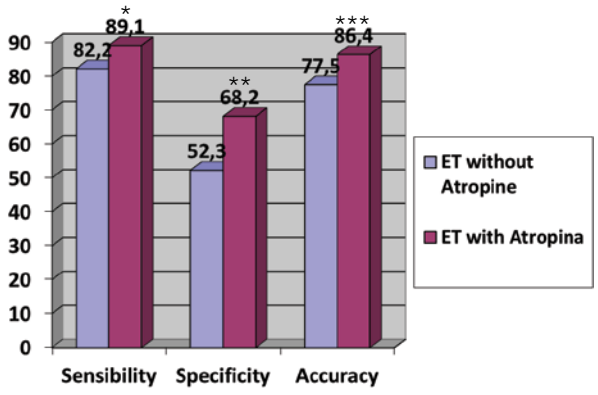

Figure 1. Sensibility, specificity and prognostic accuracy of ET with and without atropine in 450 patients.
* p = 0.0033, ** p < 0.0001, and *** p = 0.008 versus ET without atropine, respectively.

The majority of positive tests were in patients treated only with thronmbolytic therapy (88%) versus those treated with primary percutaneous coronary intervention (12%).

4. Discussion

The maximal heart frequency (HF) and the percentage of the maximal predicted HR achieved, in the absence of any other endpoint such as arrhythmias, symptoms, ST changes, or hypotension, are the most frequently used variables to quantify the exercise level.

Failure to achieve an adequate HF during exercise may render a ET non-diagnostic for detection and risk stratification of CAD in absence of clinical or electrocardiographic signs of ischemia [8]. HR control during exercise is the result of a number of influences mediated by the autonomic nervous system. Some patients have an attenuated HR response to exercise and are unable to reach their normal predicted HR. This phenomenon has been called “chronotropic incompetence” and has been correlated with higher rates of total mortality and incidence of coronary artery disease in follow-up [9,12,22,23]. The physiologic mechanism of this response is unclear. Some authors have explained this chronotropic incompetence as a form of sick sinus syndrome. Recently, it has been postulated that this could represent an individual adaptation to exercise through compensatory parasympathetic hyperactivity [13]. The limitations of submaximal exercise have been reported in several small studies. Verzijlbergen *et al.* [4] observed that of 15 patients with normal planar Tl-201 images after submaximal exercise, 6 had myocardial ischemia detected by dipyridamole stress Tl-201. Similar results described by McLaughlin *et al.* [5] reported fewer perfusion defects after low-level exercise compared with maximal exercise in patients with angiographically documented CAD undergoing planar TL-201 myocardial perfusion imaging. These observations were confirmed by Manganelli *et al.* [6], whom described the extent and severity of ischemia detected by SPECT images was significantly reduced in patients after submaximal exercise (placebo group) compared with those patients in an atropine group. Because patients with low HR response during exercise may have either false-negative scans or an underestimated defect extent, and because the presence and extent of stress myocardial perfusion defects are strong determinants of cardiac events and of the need for subsequent cardiac catheterization [24,25], inappropriate patient management may result. The use of atropine to increase HR during exercise to at least 85% of maximal predicted HR may overcome these problems and avoid non-diagnostic ET studies or reduce the need for repeated exercise or the use of pharmacologic stress as a substitute. Atropine is an excellent drug for achieving a rapid increase in HR through parasympathetic blockade. Given intravenously, atropine decreases sinus node recovery time and improves conduction through the atrioventricular node, resulting in an increase in HR. There is extensive experience in the use of atropine with dobutamine in stress SPECT and in stress echocardiography to increase the heart rate, with a good safety profile, including a consecutive series of more than 6000 patients [17,18,26,27]. The addition of atropine during dobutamine infusion results in a higher diagnostic sensitivity for the diagnosis of coronary stenosis and better prognostic data compared with dobutamine alone [28]. Atropine has also been added to pharmacologic echocardiographic stress in different types of patients; it is usually well tolerated, and the diagnostic ability of the test improves. In our previous studies [14,29], we used atropine added to dobutamine stress echocardiography and in stress SPECT to increase the HR response, improving the sensitivity of the tests without losing specificity and without severe adverse effects. However, atropine use during exercise has not been extensively studied. Atropine injection results in sufficient stress to accurately evaluate myocardial ischemia not only because of the increase in HR (as HR is one of the major determinants of myocardial oxygen demand) but also because of the increase in the rate pressure product (which correlates fairly well with oxygen consumption during exercise) [30]. In our study, the fact that the majority of positive tests were obtained in patients treated with thrombolysis is due to the non-completed revascularization of the culprit lesion on behalf of the medical therapy versus primary PCI. To our knowledge, this is the first study based on “head-to-head” direct comparison between the same patient

population undergoing exercise stress testing with and without atropine, suggesting that the chronotropic response in the "active" arm was induced by the addiction of atropine. In this study, the increase in HR and systolic blood pressure after atropine resulted in a mean rate-pressure product that is similar to that of a maximal exercise test. The atropine used during the exercise test reduced the number of non-diagnostic ET and increased the sensibility, specificity and prognostic accuracy of ET (Figure 1). Another advantage of atropine ET is that this method may avoid pharmacologic stress in patients who have only partial limitations to exercise. The relatively long duration of atropine effects (30-60 minutes) [31] is a potential drawback of its use when compared with vasodilators stress, particularly with adenosine. In this study atropine injection was well tolerated. There was a moderate frequency of non-life-threatening arrhythmias, and a brief episode of paroxysmal supraventricular tachycardia, which resolved after administration of verapamil. In addition, other side effects from the medication were very uncommon. Our results are similar with those of previous studies showing a low incidence of adverse effects [6,29,32,33].

4.1 Limitations

The population we studied was made up of mostly males and patients with high prevalence to coronary artery disease. Results canot be generalized to all groups of patients, because the sample population represents a general estimation of coronary angiography at a cardiology department showing in general a fair indication of coronary angiographic examination chart, In fact, the greater interest of such a method of stress testing is its ability to diagnose myocardial ischemia in a population with a lower prevalence of coronary artery disease. This will certainly be useful to evaluate the exercise test with atropine in female patients and / or non-specific alterations of end-stage surface ECG. The exercise test with atropine also, like all pharmacological tests will be used to induce myocardial ischemia, playing a non-physiological situation.

Another limit was the difference in baseline characteristics of the patients. Unfortunately, patients with sub-maximal exercise often received more beta-blocker treatment because of previous history of AMI. Beta-blocker therapy probably was the major factor for high incidence of sub-maximal exercise test and not reaching 85% age predicted heart rate.

5. Conclusions

Survivors of AMI constitute a large, readily identifiable subset of patients in whom prognosis ultimately depends on the extent of residual ischemia, left ventricular dysfunction and presence of myocardial viability. Patients with either overt heart failure or ongoing myocardial ischemia have an adverse outcome and should be managed with an aggressive diagnostic and therapeutic approach. In the vast majority of patients who are asymptomatic after AMI, an early functional evaluation with stressing procedures is mandatory. This study supports the idea that atropine may extend the opportunity to achieve target heart rate in patients whose exercise heart rate would otherwise be submaximal. In our study, atropine administration was feasibile, safe and well- tolerated during exercise stress testing. Moreover, in this "head-to-head" study, as there was direct comparison in the same group of patients studied on 2 occasions, with and without atropine (patients not able to reach the minimal target HR, nor any other exercise stress test endpoint), we can conclude that there are differences in the diagnostic capacity between the two groups with the use of atropine. We believe that this is the first study that establishes the clinical utility of atropine associated with exercise in patients with recent uncomplicated AMI, because the recognition of myocardial ischemia is important for predicting harder prognostic end point.

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Conflict of interest

All authors declare no conflict of interest.

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