

# 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  $59 \pm 8$  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  $61 \pm 7$  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  $129.5 \pm 13.6$  beats per minute (bpm), and it increased up to  $147.3 \pm 13.5$  bpm after drug administration, with an incremental of  $17.8 \pm 6.9$  bpm ( $p < 0.0001$ ). The mean percentage of age-related HR achieved was  $86.5\% \pm 6.1\%$ . In 378 of these patients (84%), more than 85% of their aged-related HR ( $89.9\% \pm 4.1\%$ ) was attained. No major adverse effects occurred. The maximal heart rate ( $147.3 \pm 3.5$  versus  $129.5 \pm 13.6$ ) and the double product ( $29378.7 \pm 6342.7$  versus  $25798.3 \pm 5328.5$ ) 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 (sensitivity 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

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## 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 physi-

ologic, 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 ( $220 - \text{Age}$ ) [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,  $\beta$  – 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 anticholinergic 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  $59 \pm 8$  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.  $\beta$  – 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 exer-

cise, 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 ( $220 \text{ beats/min.} - \text{Age}$ ) 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  $\pm$  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  $59 \pm 8$  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.

<b>Patients (no.)</b>	<b>1150</b>
Age, years (mean $\pm$ SD)	59 $\pm$ 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)
<b>Infarct size (%)</b>	
Anterior	377 (32.8)
Inferior	521 (45.3)
Lateral	252 (21.9)
<b>Medications (%)</b>	
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  $61 \pm 7$  years) with a non-diagnostic test, mean HR in the ET without atropine was  $129.5 \pm 13.6$  beats per minute (bpm), increasing to  $147.3 \pm 13.5$  bpm after drug administration in the second ET, with an incremental increase in heart rate of  $17.8 \pm 6.9$  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

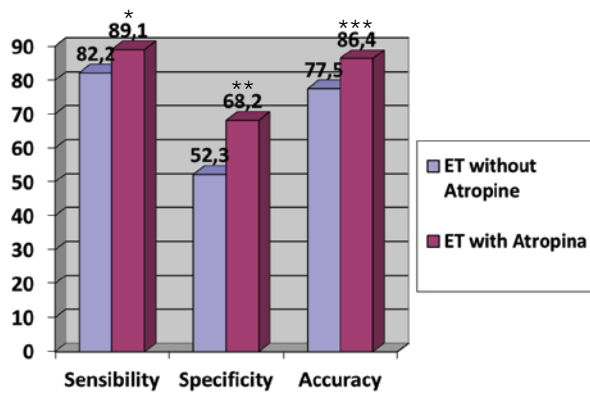
( $8.7 \pm 3.4$  bpm) was observed. The mean percentage of age-related HR achieved was  $86.5\% \pm 6.1\%$ . In 378 of these patients (84%) more than 85% of their age-related HR ( $89.9\% \pm 4.1\%$ ) was attained.

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  $0.4 \pm 1.1$  mm and  $0.8 \pm 1.2$  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
<b>Patients (n.)</b>	<b>450</b>	<b>450</b>		
Baseline HR (b.p.m.)	67.8 $\pm$ 12.0	69.7 $\pm$ 11.2	0.0143	0,38 to 3,41
Baseline SBP (mmHg)	128.5 $\pm$ 24.3	130.6 $\pm$ 22.6	0.1798	- 0,97 to 5,12
Baseline DBP (mmHg)	81.7 $\pm$ 13.5	82.2 $\pm$ 12.8	0.5687	- 1,22 to 2,22
Baseline RPP	9728.1 $\pm$ 2748.5	9635.2 $\pm$ 2878.3	0.6206	- 4,61 to 275,3
Maximal HR (bpm.)	129.5 $\pm$ 13.6	147.3 $\pm$ 13.5	< 0.0001	16,03 to 19,57
% ARHR	83.5 $\pm$ 8.1	91.8 $\pm$ 9.7	< 0.0001	7,13 to 9,47
Maximal RPP	25798.3 $\pm$ 5328.5	29378.7 $\pm$ 6342.7	< 0.0001	2813,99 to 4346,81
METs	7.8 $\pm$ 2.6	8.9 $\pm$ 2.9	< 0.0001	0,74 to 1,46
Maximal SBP (mmHg)	190.3 $\pm$ 35.4	195.3 $\pm$ 28.7	0.0202	0,78 to 9,22
Exercise duration (min)	9.8 $\pm$ 2.6	10.3 $\pm$ 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 $\pm$ 1.1	0.8 $\pm$ 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 thrombolytic 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 TI-201 images after submaximal exercise, 6 had myocardial ischemia detected by dipyridamole stress TI-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 addition 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 cannot 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 feasible, 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.

## References

- [1] Gibbons RJ, Balady GJ, Timothy Bricker J, Chaitman BR, Fletcher GF, Froelicher VF *et al.* ACC/AHA 2002 Guideline Update for Exercise Testing: Summary Article. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines), *Circulation* 2002; 106: 1883-1892
- [2] Primeau M, Taillefer R, Essiambre R, Lambert R, Honos G. Technetium 99m Sestamibi myocardial perfusion imaging: comparison between treadmill, dipyridamole and trans-oesophageal atrial pacing "stress" tests in normal subjects, *Eur J Nucl Med* 1991; 18: 247-251
- [3] Brown KA, Rowen M. Impact of antianginal medications, peak heart rate and stress level on the prognostic value of a normal exercise myocardial perfusion imaging study, *J Nucl Med* 1993; 34: 1467-1471
- [4] Verzijlbergen JF, Vermeersch PHMJ, Laarman G, Ascoop CAPL. Inadequate exercise leads to suboptimal imaging. Thallium-201 myocardial perfusion imaging after dipyridamole combined with low-level exercise unmasks ischemia in symptomatic patients with non diagnostic thallium-201 scan who exercise submaximally, *J Nucl Med* 1991; 32: 2071-2078
- [5] McLaughlin PR, Martin RP, Doherty P *et al.* Reproducibility of thallium-201 myocardial imaging, *Circulation* 1977; 55: 497-503
- [6] Manganelli F, Spadafora M, Varrella P *et al.* Addition of atropine to submaximal exercise stress testing in patients evaluated for suspected ischemia with SPECT imaging: a randomized placebo-controlled trial, *Eur J Nucl Med Mol Imaging* 2011; 38: 245-251
- [7] Gibbons RJ, Balady GJ, Beasley JW *et al.* ACC/AHA guidelines for exercise testing, *J Am Coll Cardiol* 1997; 30: 260-3111
- [8] Iskandrian AS, Heo J, Kong B, Lyons E. The effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients, *J Am Coll Cardiol* 1989; 14: 1477-1486
- [9] Gauri AJ, Raxwal VK, Roux L *et al.* Effects of chronotropic incompetence and beta-blocker use on the exercise treadmill test in men, *Am Heart J* 2001; 142: 136-141
- [10] White MP. Pharmacologic stress testing: understanding the options, *J Nucl Cardiol* 1999; 6: 672-675
- [11] Roche F, Pichot V, Da Costa A *et al.* Chronotropic incompetence response to exercise in congestive heart failure, relationship with the cardiac autonomic status, *Clin Physiol* 2001; 21: 335-342
- [12] Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart Study, *Circulation* 1996; 93: 1520-1526
- [13] Ellestad MH. Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?), *Circulation* 1996; 93: 1485-1487
- [14] Sarullo FM, Schicchi R, Schirò M *et al.* Comparative evaluation of dobutamine-atropine stress echocardiography with exercise testing for detection of coronary artery disease [in Italian], *G Ital Cardiol* 1996; 26: 1279-1290
- [15] McNeill AJ, Fioretti PM, el-Said SM *et al.* Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography, *Am J Cardiol* 1992; 70: 41-46
- [16] Secknus MA, Marwick TH. Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3011 studies over 5 years, *J Am Coll Cardiol* 1997; 29: 1234-1240
- [17] Geleijnse ML, Elhendy A, van Domburg RT *et al.* Cardiac imaging for risk stratification with dobutamine –atropine stress testing in patients with chest pain: echocardiography, perfusion scintigraphy, or both?, *Circulation* 1997; 96: 137-147
- [18] Elhendy A, Valkema R, van Domburg RT *et al.* Safety of dobutamine-atropine stress myocardial perfusion scintigraphy, *J Nucl Med* 1998; 39: 1662-1666
- [19] Elhendy A, van Domburg RT, Bax JJ *et al.* The functional significance of chronotropic incompetence during dobutamine stress test, *Heart* 1999; 81: 398-403
- [20] Geleijnse ML, Elhendy A, Fioretti PM, Roelandt JRTC. Dobutamine stress myocardial perfusion imaging, *Am Coll Cardiol* 2000; 36: 2017-2027
- [21] Elhendy A, van Domburg RT, Bax JJ *et al.* Safety , hemodynamic profile, and feasibility of dobutamine stress technetium myocardial perfusion single-photon emission CT imaging for evaluation of coronary artery disease in the elderly, *Chest* 2000; 117: 649-656

- [22] Ellestad MH, Wan MK. Predictive implications of stress testing : follow-up of 2700 subjects after maximum treadmill stress testing, *Circulation* 1975; 51: 363-369
- [23] Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing, *N Engl J Med* 2002; 354: 793-801
- [24] Ledenheim ML, Pollock BH, Rozanski A et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease, *J Am Coll Cardiol* 1986; 7: 464-471
- [25] Hachamovitch R, Berman DS, Kiat H et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease. Incremental prognostic value and use in risk stratification, *Circulation* 1996; 93: 905-914
- [26] Schinkel AF, Elhendy A, van Domburg RT. Prognostic value of dobutamine-atropine stress (99m) Tc-tetrofosmin myocardial perfusion SPECT in patients with known or suspected coronary artery disease, *J Nucl Med* 2002; 43: 767-772
- [27] Tsutsui JM, Osorio AFF, Lario FC et al. Comparison of safety and efficacy of the early injection of atropine during dobutamine stress echocardiography with the conventional protocol, *Am J Cardiol* 2004; 94: 1367-1372
- [28] Caner B, Karanfil A, Uysal U. Effect of an additional atropine injection during dobutamine infusion for myocardial SPECT, *Nucl Med Commun* 1997; 18: 567-573
- [29] Sarullo FM, Ventimiglia C, Taormina A et al. Safety and feasibility of atropine added in patients with sub-maximal heart rate during exercise myocardial perfusion SPECT, *Int J Cardiovasc Imaging* 2007; 23: 511-518
- [30] David D, Lang RM, Borow KM. Clinical utility of exercise, pacing, and pharmacologic stress testing for the noninvasive determination of myocardial contractility and reserve, *Am Heart J* 1988; 116: 235-247
- [31] Katzung BG. Basic and clinical pharmacology, New York: Lange Medical, McGraw-Hill; 2001 p. 115
- [32] Variola A, Albiero R, Dander B, Buonanno C. Exercise testing with atropine [in Italian], *G Ital Cardiol* 1997; 27: 255-262
- [33] Munagala VK, Guduguntla V, Kasravi B, Cummings G, Gardin JM. Use of atropine in patients with chronotropic incompetence and poor exercise capacity during treadmill stress testing, *Am Heart J* 2003; 145: 1046-1050