Submaximal target heart rate and the detection of myocardial ischemia by stress myocardial perfusion imaging using the treadmill exercise Bruce protocol

Koşu bandı egzersiz Bruce protokolü ve stres miyokard perfüzyon görüntüleme ile submaksimal hedef kalp hızı ve miyokardiyal iskeminin saptanması

Ali Gholamrezanezhad[1, 2], Sahar Mirpour[1], Hadi Hajimohammadi[3], Aydin Pourmoslemi[3]

[1]Research Institute for Nuclear Medicine, Tehran University of Medical Sciences,
[2]Young Researchers Club, Azad University of Tehran,
[3]110 Nuclear Medicine Center, Tehran, Iran

ABSTRACT

Objective: It has been postulated that if patients fail to achieve their age-predicted target heart rate (THR: 85% of predicted maximal HR), the electrocardiographic changes following exercise treadmill test (ETT) and also scintigraphic results of this stress protocol for myocardial perfusion imaging (MPI) are unreliable. We decided to assess the ability of submaximal ETT in provoking ischemia as determined by MPI.

Methods: One hundred and nine patients (60 female, 49 male, mean age: 50.8±11.4, range: 32-76 years), were prospectively assessed with MPI after stress protocol of ETT. Forty-nine patients failed to attain THR. Myocardial perfusion imaging was performed based on the 1-day protocol, using Technetium-99m sestamibi (99mTc-MIBI).

Results: Sixty patients attained THR, of which 28 patients (46.7%) had normal myocardial perfusion pattern and 32 patients (53.3%) had scintigraphic evidence of ischemia. The remaining 49 patients had submaximal ETT, of which 15 patients (30.6%) had normal results and 34 patients (69.4%) had scintigraphic evidence of ischemia. Although ischemia was more common in those patients with submaximal ETT, however the difference was not statistically significant (p=0.088).

Conclusion: Ischemia is more common in patients who had performed a sub-maximal ETT. It could be a logical hypothesis that ischemic heart disease may limit the ability of patients to complete ETT and therefore, it would not be judged that submaximal ETT is always insufficient for MPI. In these settings, in patients who fail to attain the THR, it would be possible to proceed to the stress MPI test. *(Anadolu Kardiyol Derg 2008; 8: 192-6)*

Key words: Myocardial perfusion imaging, treadmill exercise, target heart rate, myocardial ischemia, 99mTc-MIBI

ÖZET

Amaç: Egzersiz stres test sırasında hastalar, yaşa bağlı tahmin edilen hedef kalp hızına (THR: 85% maksimum tahmin edilen kalp hızı) ulaşamazlar ise, egzersiz koşu bandı testi (ETT) sırasındaki elektrokardiyografik değişiklikler ile miyokard perfüzyon görüntüleme (MPI) stres protokolü sintigrafik sonuçlarının güvenilmez olduğu kabul edilmektedir. Biz, MPI tarafından belirlenmiş olan, iskemiyi provoke etmekte olan alt-azami ETT'nin yeteneğini değerlendirmeyi kararlaştırdık.

Yöntemler: Toplam 190 hasta (60 kadın 49 erkek, ortalama yaş: 50.8 ±-11.4 yıl, oran: 32-76 yaş), ETT'nin stres protokolünden sonra MPI ile ileriye dönük olarak değerlendirildi. Kırk dokuz hasta THR hedefine ulaşmakta başarısız oldu. Miyokard perfüzyon görüntüleme çalışması, 1 - gün protokolüne göre, Technetium-99m sestamibi (99mTc-MIBI) protokolü kullanılarak yapıldı.

Bulgular: Kalp hızı hedefine ulaşan 60 hastanın, 28'nde (46.7%) normal miyokard perfüzyon saptandı ve 32 hastada (53.3%) sintigrafide iskemi kanıtı vardı. Kalan 49 hasta submaksimal ETT ye ulaştı, bunların 15'nde (30.6%) normal perfüzyon mevcuttu ve 34 hastada (69.4%), iskemi kanıtı vardı. Submaksimal ETT ile birlikte bu hastalarda daha sık iskemi olmasına rağmen, yine de fark, istatistiksel yönden önemli değildi (p=0.088).

Sonuç: İskemi submaksimal ETT'li olan hastalarda daha yaygındır. İskemik kalp hastalığının, ETT'i tamamlaması için hastaların yeteneğini sınırlayabildiği mantıklı bir hipotez olabilir ve bu yüzden, submaksimal ETT'in, her zaman MPI için yetersiz olduğu kararı doğru değildi. Bu şartlarda, THR hedefine ulaşmakta başarısız olan hastalarda, stres MPI testi yapmak mümkün olabilir. *(Anadolu Kardiyol Derg 2008; 8: 192-6)*

Anahtar kelimeler: Miyokard perfüzyon görüntüleme, koşu bandı egzersiz, hedef kalp hızı, miyokardiyal İskemi, 99mTc-MIBI

Address for Correspondence/Yazışma Adresi: Dr. Ali Gholamrezanezhad, Research Institute for Nuclear Medicine, Shariati hospital, Tehran University of Medical Sciences, Northern Kargar St., 14114 Tehran, Iran, Phone: +98 21 88633333, Fax: +98 21 88633039, E-mail: gholamrezanejhad@razi.tums.ac.ir

Anadolu Kardiyol Derg
2008; 8: 192-6

Gholamrezanezhad et al.
Target heart rate and myocardial ischemia 193

Introduction

Exercise test is one of the most helpful diagnostic tools in the field of cardiology. It has been used frequently as one of the main stress protocols and the best physiological stress technique for scintigraphic assessment of ischemia and myocardial perfusion imaging (MPI) (1). Numerous standardized exercise protocols for MPI exist (1). The most widely used protocol is the one designed by Bruce, exercise treadmill test (ETT), in which the subject starts out the test at 1.7 mph on a 10% grade (1). Subsequently, every 3 minutes the speed and grade of the treadmill are increased until the patient reaches a predefined end -point of exercise (1).

Percentage of the maximal heart rate is widely used to determine exercise intensities (2). It has been postulated that if patients fail to achieve their age-predicted target heart rate (THR: 85% of predicted maximal HR), the electrocardiographic changes following ETT stress and scintigraphic results of this stress protocol for MPI are unreliable (3). In fact, it has been hypothesized that the stress level achieved during exercise MPI may influence the sensitivity of the test for detecting coronary artery disease (CAD) (4-7). However, the effect of the level of exercise on the accuracy of technetium-99m methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) imaging has not been widely studied and controversial results exist (3, 8-21). We decided to assess the ability of submaximal ETT in provoking ischemia as determined by MPI.

Methods

As a cross-sectional study, all consecutive outpatients referred to our Nuclear Medicine Institute for a MPI SPECT test were assessed. Hence, one hundred and nine patients (60 female, 49 male) entered the study. The mean age of the participants was 50.8±11.4 years (age range: 32-76 years). Those patients who needed dipyridamole infusion for the stress protocol, due to in ability to exercise, degenerative joint disease of the lower extremities, respiratory failure etc, were excluded from the study. Patients who had any other known medical conditions affecting heart rate such as: thyroid function disorders, recent myocardial infarction (MI), unstable angina or consumption of any drug that could influence the response of heart rate to exercise were also excluded from the study. All patients included in this study were considered capable to complete the exercise stress test achieve the THR, and complete the MPI test.

The study was approved by the committee on ethics of the Research Institute for Nuclear Medicine, Medical sciences/Tehran University.

After obtaining verbal consent, as it was requested by the referring physician, all patients underwent the exercise stress test under the direct supervision of the cardiologist. The Bruce protocol with a Marquette Treadmill System (Marquette Electronics, Milwaukee, Wisc., U.S.A.) was used. A dose of 370 MBq of ^{99m}Tc-MIBI was injected for the stress study. The injection of ^{99m}Tc-MIBI was given at peak exercise, and patients were advised to continue the exercise for a minimum of 60-90 sec. In fact, ^{99m}Tc-MIBI was injected when the following end-points were reached: 85% of maximum predicted value for age, marked hypertensive or hypotensive response, ischemic

symptoms, severe fatigue and subsequent inability of the patient to continue the ETT. Immediately after the ETT and based on the maximal THR achieved during exercise, patients were categorized into a group of maximal ETT and a group of submaximal ETT. Subsequently, 30 min after the end of the exercise, MPI SPECT images were acquired. Few hours later, based on a one-day protocol, a dose of 1110 MBq 99mTc-MIBI was also injected for the rest study and SPECT mode acquisition was performed after 45-60 min. Two nuclear medicine physicians blinded to other clinical data and to the exercise test result, interpreted the MPI SPECT data as for any reversible myocardial perfusion abnormality (ischemia). Fixed (nonreversible) defects were not considered as positive MPI. Final diagnosis was reached by consensus.

Image acquisition was performed with a rotating, single head gamma camera (Siemens, Germany), equipped with a low energy, high resolution parallel hole, collimator with step and shoot mode, elliptical orbits, matrix size of 64 x 64 x 16, and using a roving 38.0 cm^2 detector mask. A 20% window around the 140 KeV energy peak of ^{99m}Tc- was used. Patients were lying at the supine position. Thirty-two 30 sec projections at the low dose stress study and 20 sec at the high dose rest study were obtained over a 180° orbit (45° right anterior oblique to 45° left posterior oblique). The projection data sets were prefiltered with a two-dimensional Butterworth filter (cut-off 0.40, order 5.0), reconstructed with filtered back-projection and there was no attenuation correction. Patients were instructed to fast for at least 4 h and all ,-blocking drugs, diltiazem and verapamil were discontinued 48 h before the ETT.

Statistical analysis

Quantitative data are expressed as mean ± SD. We performed the Chi-squared test for contingency tables of qualitative variables, and Student t test for comparison of quantitative variables between groups. All reported P values are two-tailed and p< 0.05 was considered to be statistically significant. The SPSS for Windows (Release 11.5.0, Chicago, IL, U.S.A) software was used for statistical analysis.

Results

The difference in baseline heart rate between those who achieved the THR and those who did not achieve was not statistically significant (p>0.05).

Sixty patients attained THR (93.3%±9.7%), of which 28 patients (46.7%) had negative MPI and 32 patients (53.3%) had scintigraphic evidence of ischemia. The remaining 49 patients had submaximal ETT (THR - 72.6%±6.3%), of which 15 patients (30.6%) had negative MPI and 34 patients (69.4%) had scintigraphic evidence of ischemia. Although ischemia was more common in those patients with submaximal ETT, however the difference was not statistically significant (p=0.088).

Table 1. Distribution of patients according with ETT and MPI results

	Negative MPI	Ischemia	
Maximal ETT	28	32	60
Subaximal ETT	15	34	49
	43	66	109

ETT- exercise treadmill test, MPI- myocardial perfusion imaging

194 Gholamrezanezhad et al.
Target heart rate and myocardial ischemia

Anadolu Kardiyol Derg
2008; 8: 192-6

Table 1 summarizes the results of the two groups. The mean age of patients who achieved THR was 52.7±11.1 years and of those who did not achieve THR was 48.8±10.1 years (p=0.57). There was only weak correlation between the extension of perfusion abnormality and the percentage of age corrected-heart rate (r=-0.24, P=0.01). The clinical characteristics of patients groups are summarized in Table 2 and the characteristics of ETT and extension of perfusion defect on MPI for both groups are presented in Table 3.

The reasons for the termination of ETT were: Extreme fatigue and inability to continue to exercise in six patients, chest pain in nine patients, vertigo in seven patients and drop in blood pressure in six patients. The prevalence of incomplete exercise was significantly higher in women (p<0.01).

Discussion

The precise analysis of the patients' characteristics (Table 2) showed that as compared to the maximal ETT patients, more submaximal ETT patients were on beta-blockers and calcium channel blockers at baseline and despite the 48 hour proscription on drug administration prior to testing, residual drug effects might have been expected to have some effect on blunting heart rate responses. However, despite of the higher prevalence of drug consumption (as a possible- not exclusive- explanation of submaximal ETT) in submaximal ETT patients, ischemia was more common in these patients. Thus, one can logically hypothesize that since patients with non-cardiac pathologic conditions were excluded and since the mean age of the two groups of our patients did not differ statistically, submaximal ETT (even induced by residual effects of drugs or hypertension) can be able to provoke myocardial ischemia on the MPI. In these settings, it is possible to administer the radiopharmaceutical in the peak heart rate even if patients fail to attain the maximum THR according to age. In fact, based on our study (due to limited number of patients studied), it is impossible to determine whether the main cause of submaximal ETT is recent drug consumption/hypertension of the patients or the underlying ischemic heart disease. Hence, future studies should be conducted on larger number of patients in order to make possible performing regression analysis. On the other hand, it can be logically expectable that both these factors to be involved in preventing the heart rate to reach the targeted value.

The first group of previous studies in this regard consists of those studies, which are in agreement with our hypothesis and in fact are those stating submaximal ETT was able to induce ischemia on the MPI test (3). In a study similar to ours, 101 patients referred for suspected CAD, underwent ETT and MPI. It was found that ischemia was twice as common in those patients who had performed a sub-maximal, than in those who had a maximal ETT. Patients with maximal ETT, had 84% normal MPI studies (3). These authors assumed that patients with CAD are

Table 2. The clinical characteristics of patients

Characteristics	Maximal ETT			Submaximal ETT			p
	Normal MPI	Ischemic MPI	p	Normal MPI	Ischemic MPI	p	
Diabetes mellitus	2/28	12/32	<0.01	0/15	9/34	0.04	0.64
Hypertension	1/28	12/32	0.001	5/15	19/34	0.22	<0.01
Hyperlipidemia	8/28	10/32	1.0	2/15	21/34	<0.01	0.08
Cigarette smoking	9/28	7/32	0.40	2/15	12/34	0.17	0.83
History of MI	0/28	2/32	0.49	0/15	4/34	0.30	0.41
History of revascularization	0/28	2/32	0.49	0/15	9/34	0.04	0.01
Recent consumption of β-blockers or CCBs*	1/28	12/32	<0.01	5/15	21/34	0.21	<0.01

* The number of patients in each group for whom ,-blockers and calcium channel blockers needed to be withheld.
Data are represented as proportions, Chi-square test
CCB- calcium channel blocker, ETT- exercise treadmill test, MI - myocardial infarction, MPI- myocardial perfusion imaging

Table 3. The characteristics of ETT and extension of perfusion defect on MPI for both groups

Characteristics	Maximal ETT			Submaximal ETT			p
	Normal MPI	Ischemic MPI	p	Normal MPI	Ischemic MPI	p	
Duration of ETT	7.46±2.19	6.36±2	0.04	6.09±1.97	4.41±1.33	0.001	<0.001
Maximum heart rate	157.32±7.51	150.87±12.78	0.02	141±10.88	127.64±6.54	<0.001	<0.001
Extension of perfusion abnormality*	0	1.15±0.51	<0.001	0	1.35±0.59	<0.001	0.02

* Based on the number of walls (anterior, inferior, lateral, septal and apical) suffered from the abnormal perfusion, extension of the perfusion abnormality was graded from 0 (normal myocardial perfusion) to 5 (myocardial perfusion abnormality involving all 5 walls- which actually was seen in no patient).
Data are represented as mean±SD and proportions
Student t test and Chi-square test
ETT - exercise treadmill test, MPI - myocardial perfusion imaging

Anadolu Kardiyol Derg
2008; 8: 192-6

Gholamrezanezhad et al.
Target heart rate and myocardial ischemia   **195**

often unable to complete the exercise test because of a compromised coronary circulation. Hence, they recommended that ETT should not be discontinued prior to radiopharmaceutical administration if patients fail to attain the THR (3). In another report, in 22 patients with angiographically-confirmed CAD, the effect of submaximal and of maximal exercise on the size and the location of MPI Thallium-201 defects was compared (8). Submaximal exercise resulted in reversible defects in 91% of patients, however, the size of the ischemic area and the degree of ischemia were significantly reduced by both qualitative and quantitative criteria (8). Conversely, in our study (Table 3), the extension of perfusion abnormality was more severe in those patients with submaximal ETT (although an important confounding factor in this regard is higher prevalence of previous revascularization or known coronary artery disease in this group).

The first report in this area relates to our findings and shows that the overall prevalence of perfusion defects remains the same for all levels of effort (9). Brown and Rowen (17), in 261 patients have also found that there is no significant relationship between the cardiac event and any stress index, including Bruce stage, peak heart rate or percent maximal predicted heart rate achieved. The risk of cardiac death or nonfatal myocardial infarction in patients with a normal exercise 201Tl is low and is not affected by the degree of THR achieved, which again confirms our study findings (17). It has been emphasized that in men with abnormal scans, impaired myocardial perfusion alters the relationship between exercise duration and age (18). The well-designed study of Stratmann et al (4) in 250 patients with angiographically-confirmed CAD was also undertaken to assess the effects of exercise level on sensitivity of MPI in unmasking CAD. No significant differences were found in sensitivities of an abnormal MIBI scan or the reversibility of the myocardial defect, between 102 patients reaching 85% of age predicted heart rate and 148 others who did not (82 vs. 89% and 66 vs. 70%, respectively, p>0.05). Interestingly and similar to our findings, the authors concluded that the sensitivity of the stress MPI for identifying CAD is relatively independent of the peak heart rate achieved (4).

On the contrary, the second group of previous studies consists of those, which have found that heart rate and probably metabolic work create the conditions necessary for subendocardial ischemia (14) and in fact they concluded that heart rate was related to ischemia. Therefore it has been postulated that if patients fail to achieve their age-predicted THR, the electrocardiographic changes following ETT and scintigraphic results of this stress protocol for MPI are unreliable (3, 14). Indolfi and Ross stated that heart rate is a major factor influencing transmural blood flow distribution and regional function, because when coronary vasodilatation is maximal there is an inverse relation between the level of heart rate and subendocardial perfusion (15). Thus, it was hypothesized that in experimental regional ischemia, increasing heart rate reduces subendocardial flow and contraction, whereas slowing of heart rate causes improvement of contraction associated with increased subendocardial blood flow, accompanied by a decrease in outer wall blood flow. The authors concluded that exercise-induced regional ischemia in the presence of coronary stenosis will be attenuated when heart rate is slowed using a beta-blocking agent, a specific rate-slowing drug or other causes of submaximal

exercise (15). In the investigation of Huang et al, the same conclusions were made for scintigraphic studies (5). In this study exercise SPECT showed significantly more perfusion abnormalities in group 1 patients (ischemic ST-segment depression or >85% of maximal predicted heart rate) than in group 2 patients (who did not met the above-mentioned criteria) (96% vs 75%, p<0.001) (5). These authors concluded that the sensitivity of the test is affected by the level of exercise. Other studies also confirmed that the level of exercise affects the results of SPECT thallium imaging in the detection of ischemia (6, 7). These concerns about low sensitivity of submaximal exercise have led to some interventions such as dobutamine or dipyridamole infusion or administration of atropine to unmask ischemia in symptomatic patients with non-diagnostic thallium-201 scans using submaximal ETT (7, 10, 13). However, in our study, such relationship was statistically weak.

Finally it should be noted that converting to pharmacologic (primarily vasodilator) stress testing when it appears that the patient will not be able to achieve a maximal heart rate response, is a routine alternative procedure; But there are some concerns about this alternative (eg. cost, time, effects on image quality). With the increasingly common addition of low-level exercise to vasodilator stress testing, however, concerns regarding drug side effects and image artifacts are minimized. Regarding the acknowledged potential for underestimation of degree of ischemia, converting to the widely accepted and well-validated option of pharmacologic stress, in such patients seems to be logical. However, according to our study findings, whenever cost, time or any other problem (such as underlying disease- e.g. asthma) prevents pharmacologic stress addition, this submaximal ETT may be considered adequate to unmask the presence of underlying CAD.

Study limitations

Patients with known ischemic heart disease are more likely to be on beta-blocker or calcium channel blockers treatment. The finding of more perfusion abnormalities in the former group would be possibly primarily related to the bias in patient assignment. Given the above considerations, it would be important to repeat the study on a group of patients with known CAD, which are reasonably balanced between the two groups.

It should be emphasized that there are some other limitations in our study: lack of attenuation correction, nonrandomization of patients entered in the study, and lack of gold standard for CAD (such as angiographic analysis of patients) are the main drawbacks of the study. Hence, these drawbacks make our study only an observational investigation, which simply should serve to generate hypotheses for more rigorous future studies.

Conclusion

Our study confirms that submaximal ETT in current practice is not always insufficient for performing the MPI test. We suggest that it is possible to administer the radiopharmaceutical at the peak heart rate even if the patient fails to attain the THR, except if heart rate is reduced by a beta-blocking or other bradycardia inducing drug or by abnormal heart conditions causing bradycardia. This may be, but not necessarily, considered adequate to unmask the presence of underlying CAD in some situations.

196 Gholamrezanezhad et al.
Target heart rate and myocardial ischemia

Anadolu Kardiyol Derg
2008; 8: 192-6

References

1. Wackers FJTh. Myocardial perfusion imaging. In: Sandler MP, Coleman RE, Pattonn JA, Wackers FJTh, Gottschalk A, editors. Diagnostic Nuclear Medicine. 4th edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2003. p. 273-317.

2. Wonisch M, Hofmann P, Fruhwald FM, Kraxner W, Hödl R, Pokan R, et al. Influence of beta-blocker use on percentage of target heart rate exercise prescription. Eur J Cardiovasc Prev Rehabil 2003; 10: 296-301.

3. Elmegadmi AH, Randall C, Garvie NW. Treadmill exercise and myocardial perfusion imaging: the relationship between target rate and ischaemia. 34th Annual Meeting of the British Nuclear Medicine Society, MICC, Manchester, 27-29th March, 2006. Nucl Med Commun 2006; 27: 281 (abstract).

4. Stratmann HG, Younis LT, Wittry MD, Amato M, Mark AL, Miller DD. Effect of the stress level achieved during symptom-limited exercise technetium-99m sestamibi myocardial tomography on the detection of coronary artery disease. Clin Cardiol 1996; 19: 787-92.

5. Huang PJ, Chieng PU, Lee YT, Chiang FT, Tseng YZ, Liau CS, et al. Exercise thallium-201 tomographic scintigraphy in the diagnosis of coronary artery disease: emphasis on the effect of exercise level. J Formos Med Assoc 1992; 91: 1096-101.

6. Iskandrian AS, Heo J, Kong B, Lyons E. 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: 1477-86.

7. Verzijlbergen JF, Vermeersch PH, Laarman GJ, Ascoop CA. et al. 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 scans who exercise submaximally. J Nucl Med 1991; 32: 2071-8.

8. Heller GV, Ahmed I, Tilkemeier PL, Barbour MM, Garber CE. Influence of exercise intensity on the presence, distribution, and size of thallium-201 defects. Am Heart J 1992; 123: 909-6.

9. Esquivel L, Pollock SG, Beller GA, Gibson RS, Watson DD, Kaul S. Effect of the degree of effort on the sensitivity of the exercise thallium-201 stress test in symptomatic coronary artery disease. Am J Cardiol 1989; 63: 160-5.

10. De Lorenzo A, Foerster J, Sciammarella MG, Suey C, Hayes SW, Friedman JD, et al. Use of atropine in patients with submaximal heart rate during exercise myocardial perfusion SPECT. J Nucl Cardiol 2003; 10: 51-5.

11. Adragao P, Aleixo A, Gomes RS. Diagnostic value of the submaximal treadmill exercise test in the subacute phase of myocardial infarct. Rev Port Cardiol 1989; 8: 359-65.

12. Stewart RE, Kander N, Juni JE, Ellis SG, O'Neill WW, Schork MA, et al. Submaximal exercise thallium-201 SPECT for assessment of interventional therapy in patients with acute myocardial infarction. Am Heart J 1991; 121: 1033-41.

13. Levy M, Pornin M, Languillat N, Charles JP, Angelard T, Sarkhis A, et al. Quantitative thallium myocardial tomoscintigraphy. Value of intravenous infusion of dipyridamole after negative submaximal exercise test. Arch Mal Coeur Vaiss 1992; 85: 187-91.

14. MacLeod RS, Punske B, Yilmaz B, Shome S, Taccardi B. The role of heart rate in myocardial ischemia from restricted coronary perfusion. J Electrocardiol 2001; 34: 43-51.

15. Indolfi C, Ross J Jr. The role of heart rate in myocardial ischemia and infarction: implications of myocardial perfusion-contraction matching. Prog Cardiovasc Dis 1993; 36: 61-74.

16. Powles AC, Sutton JR, Wicks JR, Oldridge NB, Jones NL. Reduced heart rate response to exercise in ischemic heart disease: the fallacy of the target heart rate in exercise testing. Med Sci Sports 1979; 11: 227-33.

17. 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: 1467-71.

18. Schechter D, Sapoznikov D, Luria MH, Mendelson S, Bocher M, Chisin R. Heart rate variability as a marker of myocardial perfusion. Cardiology 1998; 90: 239-43.

19. Milvidaite I, Kulakiene I, Linoniene L, Gugiene L, Rusakeviciene E, Pauliute J. When can normal stress myocardial perfusion scans be observed in patients with chest pain and known or suspected coronary artery disease? Medicina (Kaunas) 2004; 40: 627-32.

20. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I, Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol 2004; 44: 423-30.

21. Kim YH, Lee KH, Chang HJ, Lee EJ, Chung HW, Choi JY, et al. Depressed heart rate response to vasodilator stress for myocardial SPECT predicts mortality in patients after myocardial infarction. Int J Cardiovasc Imag 2006; 22: 663-70.