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THERAPEUTIC AND PROGNOSTIC VALUE  
OF SILENT MYOCARDIAL ISCHEMIA IN  
INTERMEDIATE AND HIGH RISK PATIENTS  
WITHOUT KNOWN CORONARY ARTERY  
DISEASE

**Correspondence to:**

**Dr Irena Peovska Mitevska**

University Cardiology Clinic  
Ul. Vodnjanska 17, 1000 Skopje,  
Macedonia  
Tel: +389 75 491 216  
E-mail: peovskai@yahoo.com

TERAPISKA I PROGNOTICKA VREDNOST  
ASIMPTOMATSKE MIKARDNE ISHEMIJE  
KOD PACIJENATA SA UMERENIM I  
VISOKIM KARDIOVASKULARNIM RIZIKOM  
BEZ POZNATE KORONARNE ARTERIJSKE  
BOLESTI

Irena Peovska Mitevska, Jelka Davceva Pavlovska,  
Elizabeta Srbinovska, Marijan Bosevski,  
Maja Zdravkovska, Marina Zdravevska

University Cardiology Clinic, Institute for Pathophysiology and Nuclear  
Medicine, Skopje, Macedonia

*Key words*

myocardial imaging, ischemia, coronary  
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*Ključne reči*

miokardna vizualizacija, ishemija,  
koronarna arterijska bolest

*Abstract*

**Aim:** To evaluate the presence of myocardial ischemia in asymptomatic patients with intermediate and high cardiovascular (CV) risk without previously known coronary artery disease (CAD) and the value of ischemia on therapeutic decision and prognosis.

**Materials and methods:** 75 asymptomatic patients (35 with intermediate and 40 patients with high CV risk-SCORE risk system), underwent SPECT myocardial perfusion imaging (MPI) for detection of suspected CAD. We used 17 segment model for scan perfusion and function analysis using perfusion scores. All patients have full blood laboratory analyses including lipid values, and presence of urine albuminuria. Patients were followed up for 18 months for cardiovascular events (new chest pain, hospitalization for acute coronary syndrome, revascularization, cardiac death). Logistic regression analysis was used to assess predictive parameters for myocardial ischemia and cardiovascular events.

**Results:** All patients have normal rest left ventricular function with EF >55%. SPECT MPI was performed in 60 patients. 12/60 patients (20%) had stress induced ischemia and 4 patients fixed defects. Mild ischemia was found in 6 patients - summed stress score (SDS) <4, moderate in 4 and severe ischemia in 2 patients. Severe ischemia was only related to the duration of diabetes. Stepwise logistic regression analysis for prediction of stress induced ischemia showed OR 2.4 (95% CI 1.7-3.6) for stress induced ECG changes, OR 2.8 for CAC >400 (95% CI 1.9-3.2) and OR 3.9 for presence of DM over 10y (95% CI 2.3-6.6). Patients with at least moderate ischemia were referred for coronary angiography.

**Conclusion:** SPECT myocardial perfusion imaging is valuable technique for detection of silent CAD in intermediate and high risk patients, which can risk stratify patients and guide management decision and.

*INTRODUCTION*

Despite significant improvement in the medical and invasive treatment, coronary artery disease (CAD) is still the leading cause of morbidity, mortality, and cost of management of high risk patients without known CAD. Acute myocardial infarction or sudden cardiac death are often the

first clinical presentation in asymptomatic patients due to the insufficient screening and proper management of CAD. The prevalence of silent ischemia in diabetic patients is between 22-51%. Diabetes is considered as CAD equivalent and diabetic patients are considered high risk patients. They have more extensive atherosclerosis with a higher prevalence of

multi-vessel CAD frequent silent myocardial ischaemia, and infarction with a higher cardiac event rate when compared with non-diabetic patients (1-3). Proposed strategies that may favourably affect CAD risk and outcomes in high risk asymptomatic population include identifying patients with subclinical disease at high risk of future cardiac events. Such subjects are likely to be good candidates for aggressive risk factor management. Current risk score models shows inferiority for individual risk stratification and ability to predict the presence of ischemia. Those models do not include family history of CAD, hypertriglyceridemia, diabetes, obesity, as well as the influence of ischemia on risk prediction. MPI with gated SPECT is a well-established and highly accepted test for the diagnostic and prognostic evaluation of patients with known or suspected coronary artery disease (CAD) (4-5). Many randomized and observational studies as well as meta-analyses confirmed the long term prognostic value of stress inducible ischemia by noninvasive imaging. However, it is important to emphasize that just because a certain variable is predictive of events does not mean that it is necessarily predictive for guiding therapy. The dilemma of the best diagnostic approach to asymptomatic patients with high CV risk in relation to the optimal therapeutic approach is still ongoing. Controversy arises regarding whether imaging based risk stratification improves patient's management and prognosis comparing to the traditional risk factor based stratification.

## MATERIALS AND METHODS

### Study Population

Seventy-five consecutive asymptomatic patients (36 male, 24 female; age range  $63 \pm 15$  years), 35 with intermediate and 40 pts with high CV risk based on European Society of Cardiology SCORE risk stratification system (>5% risk for fatal cardiovascular event in the next 10 years) without previously known or established CAD were included in the study. All patients field WHO Rose Angina Questionnaire for confirmation of the asymptomatic status.

*Physical examination* of was done on pts regarding their blood pressure, weight, height, waist and body mass index (BMI). Patients risk factors were analyzed (hypertension, dyslipidaemia, diabetes mellitus type 2, peripheral artery disease, obesity, smoking, family history of CAD). Full blood laboratory analyses with lipid status, fasting glucose levels, HbA1C in diabetic patients, blood creatinine levels as well as albuminuria (30-300 mg/l) for patients with diabetes and hypertension was performed. Clinical and laboratory characteristics are shown in table 1 and 2.

*Exclusion criteria:* typical stable angina pectoris, previously know or established CAD (history of myocardial infarction, acute coronary syndromes, previous percutaneous intervention or coronary artery bypass surgery), LVEF <55% at rest, severe valvular disease, atrial fibrillation, presence of pace maker, severe chronic pulmonary disease.

The study adhered to the tenets of the Ethical Principles for Medical Research Involving Human Subjects in Declaration of Helsinki.

### Study protocol

All patients with established inclusion criteria underwent rest ECG and rest transthoracic echocardiography for assessment of systolic and diastolic left ventricular function by

transthoracic 2D echocardiography. All patients had preserved LV rest systolic function with left ventricular ejection fraction (LVEF >55%). All high risk patients had myocardial perfusion Single Photon Emission Computed Tomography (SPECT) imaging for detection of silent myocardial ischemia or silent myocardial infarction.

All patients were put on optimal medical treatment based on the latest ESC guidelines for CV prevention and management of stable CAD. Life style advices were given to all included patients. Patients were followed for 18 months for occurrence of new stable angina, hospitalization, acute coronary syndrome, coronary revascularization, new heart failure, cerebrovascular events, cardiovascular death.

### Myocardial perfusion SPECT imaging (MPI)

MPI SPECT imaging was performed using one day rest stress protocol with radiotracer Tc-99m sestamibi, using 15 mCi for the rest and 25 mCi for the stress study. We used single head gamma camera with commercially available quantitative gated and perfusion SPECT software package (4DM-SPECT). Patients were instructed to refrain from caffeine-containing beverages for at least 12 h, nitrates for 24 h, and beta-blockers for 48 h before the study. All patients underwent pharmacological stressing with Dipyridamole. We have used 17 segment model for quantitative Bull's eye analysis of regional myocardial perfusion and function. Myocardial perfusion was assessed by 5 point score system (0-normal radiotracer uptake; 1- mild, 2-moderate; 3- severe hypoperfusion; 4- absent uptake). Semiquantitative analysis of regional perfusion at rest and stress was performed using summed stress score (SSS), summed rest score (SRS) and summed differential score (SDS), aimed to assess the presence and extend of myocardial ischemia. Scan abnormalities were defined as follow: SSS <4 normal perfusion; 4-8 mild; 9-13 moderate; >13 severely abnormal scan. SDS <6 mild (<10% of LV); SDS 7-10 moderate (10-15% of LV); SDS >10 severe ischemia (>15% of LV). LV volumes, LVEF at rest and stress, presence of transit ischemic LV dilation (TID), visualization of right ventricle and lung uptake were also analyzed. Regional wall motion analysis was assess by 6 point scoring system at rest and stress (0-normal wall motion, 1-mild, 2- moderate; 3-severe hypokinesia, 4- akinesia, 5- dyskinesia) using wall motion score index (total wall motion score divided by 17).

### Coronary angiography

All patients with at least moderate myocardial ischemia (SDS >7) underwent coronary angiography. Invasive coronary angiograms were evaluated by consensus of 2 interventional cardiologists who were unaware of the SPECT and CAC imaging results. Segments were classified as normal, as having nonobstructive disease or as having significant stenosis (50% stenosis). Presence, localization, severity of coronary stenosis and number of vessels involved were analyzed. Percutaneous coronary intervention with stenting or coronary artery bypass surgery was performed according to the latest myocardial ESC revascularization guidelines.

### Statistical analysis

We have used SPSS statistical package (version 18.0). Categorical values were expressed in percents, continued as mean value  $\pm$  SD. We have used Pearson method for corre-

lations assessment. Linear regression analysis was used to determine whether there was a correlation between the CAC score and perfusion abnormalities on SPECT. Multivariable regression analysis was built to identify factors associated independently with the presence of silent myocardial ischemia and CV events.  $p < 0.05$  was found as statistically significant for all statistical tests.

**RESULTS**

The prevalence of metabolic risk factors, laboratory findings and medical therapy are presented in tables 1 and 2. The average number of risk factor per patient was higher in patients with high CV risk.

**Table 1.** Basic characteristics of the study population

Variables	Patients n=75 (Intermediate risk pts n=35) (High risk patients n=40)
Age	65+/-9
Gender	45 m; 30 f
Diabetes	30 (40%)
Hypertension	38 (64%)
Dislipidaemia	28 (48%)
Obesity	23 (39%)
Peripheral artery disease	7 (12%)
HbA1C % in DM	7.9+/-7.2
Ejection fraction (%)	58+/-6%
Microalbuminuria	27 (45%)

DM-diabetes mellitus type 2

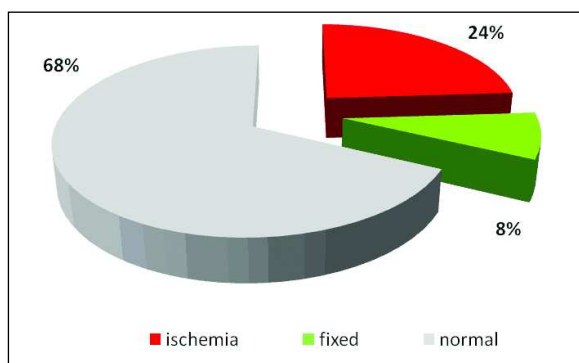
**Myocardial SPECT findings**

Myocardial perfusion imaging was performed in 50 asymptomatic patients (40 high risk and 10 moderate risk patients) and total of 850 segments were analyzed. All patients have normal rest left ventricular function with EF >55% assessed by Gated SPECT. Stress inducible ischemia was found in 12 pts (20%), from which 6 patients were diabetic. Fixed defects were found in 4 patients. Mildly abnormal scans were found in 6 patients - summed stress score (SSS) <8, moderately abnormal in 4 patients and severely abnormal scans in 2 patients- SSS <13 and SSS >13 (figures 1 and 2). Severe ischemia was only related to the duration of diabetes. 7 from 12 patients (58%) with ischemia findings were high risk patients. The example of patient with myocardial ischemia is showed in figure 3.

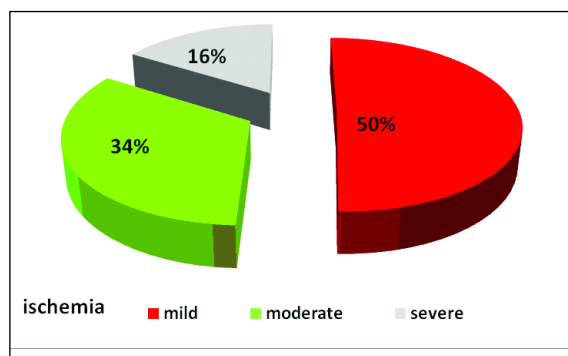
**Table 2.** Clinical characteristics of the study population

Variables	Values
Macroalbuminuria (>300mg/l)	3 (5%)
ACE/ARB	60 (100%)
Beta blocker	45 (75%)
Statins	49 (82%)
Aspirin	60 (100%)
Active smoker	15 (25%)
HDL (mmol/l)	0.9+/-0.4
LDL (mmol/l)	3.2+/-0.4
TGL (mmol/l)	2.3+/-0.6
Mean risk factors per patient	2+/-1

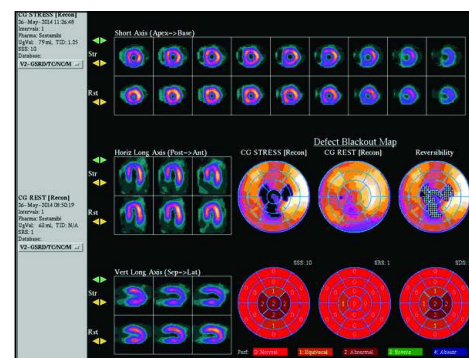
ACE-angiotensin receptors inhibitors, ABR- Angiotensin receptor inhibitors



**Fig. 1** Patients with abnormal scintigraphic findings



**Fig. 2** Severity of ischemia in study population



**Fig. 3** Myocardial perfusion scintigraphy patient scan with stress induced ischemia in the apex, apical inferior, apicoseptal and apicolateral segments

Pts with severe ischemia had fall of LVEF during stress study >5% and transit ischemic dilatation (TID). We found no correlation of traditional risk factors and albuminuria with the presence of myocardial ischemia (r=0,44 and r=0,39 respectively).

**Predictors of Myocardial ischemia**

Stepwise logistic regression analysis for prediction of stress induced ischemia showed OR 2.4 (95% CI 1.7-3.6) for stress induced ECG changes, OR 2.8 for ST segment

depression on stress study >400 (95% CI 1.9-3.2) and OR 3.9 for presence of DM over 10y (95% CI 2.3-6.6) which is shown in table 3.

**Table 3.** Stepwise logistic regression analysis for predictors of stress induced ischemia

	B	S.E.	Wald	df	Sign	OR	95% CI	
<b>DM &gt;10y</b>	1,965	0,321	5,360	1	0,000	3,932	2,398	6,147
<b>ECG stress</b>	1,032	0,523	6,579	1	0,000	2,446	1,734	3,567
<b>ST depression</b>	1,367	1,497	7,323	1	0,003	2,867	1,956	3,268

DM- diabetes mellitus type 2; CAC- coronary calcium score

### Cardiovascular events

During the follow up period 6 pts with moderate and severe ischemia had percutaneous coronary revascularization (PCI) with stenting. Two patients had PCI to RCA, 3 patients had PCI to LAD and 1 patient had PCI to LAD and LCx. Patients with mild ischemia (SDS <7) and normal MPI findings were put on intensive medical therapy and advices for life style modification. There were no events in patients with normal MPS study or mild ischemia (<10% of LV myocardium). One patient has been hospitalized due to acute coronary syndrome. He had two vessel diseases (LAD and LCx) with moderate myocardial ischemia and recommendation for intensive medical treatment. No other cardiovascular events were registered during the follow up period.

### DISCUSSION

Our study showed diabetes duration, ST segment depression and coronary calcium score as predictors of myocardial ischemia in both patients with intermediate and high risk asymptomatic patients. The dilemma on how should we screen asymptomatic patients, who to screen and how to screen is still ongoing. Screening for silent coronary artery disease in high CV risk patients is aimed to detect the disease in an early stage in order to initiate early appropriate treatment, having in mind that in up to 60% of male and 42% of female patients the first initial presentation of CAD is acute myocardial infarction and around in 40% sudden cardiac death (1,2). Consequently, there is a strong argument for using atherosclerosis imaging to evaluate the risk of incident CAD (3).

The diagnostic and prognostic value of functional imaging of CAD with MPI SPECT is well established, although there are less data for the asymptomatic high risk patients. Meta-analysis involving patients with normal MPI SPECT demonstrated that the median annual rate of cardiac death or non fatal myocardial infarction is much smaller in non diabetic patients (0.6%) than in diabetic populations, in whom published rates have ranged from 1.6 to 3.3% (6). This highly variable prevalence, together with the fact that a normal MPI SPECT is associated with a greater cardiovascular risk in diabetic patients, points to the need for additional clinical or imaging data to select the patients who will actually benefit from a screening procedure for occult CAD (7,8). The European and American guidelines recommend screening asymptomatic high risk patients, which includes diabetic patients with evidence of peripheral or carotid occlusive arterial disease, microvascular disease (proliferative

retinopathy, nephropathy), or at least two cardiovascular risk factors (diabetic dyslipidemia, hypertension, smoking, family history of premature CAD) (9). Recommended risk stratification models (SCORE, FRAMINGHAM, PROCAM), have evident inferiorities, which do not include many additional risk factors such as diabetes, family history, obesity and leaves many patients with residual risk. These models do not predict the presence of myocardial ischemia which has prognostic information.

Although the emerging evidence supports the appropriateness of testing patients with vascular disease, recent studies have reported a similar frequency of abnormal MPI SPECT studies in asymptomatic diabetic patients with and without two or more cardiovascular risk factors (10). In pooled studies including both diabetic and non-diabetic patients and symptomatic as well as asymptomatic patients, an unequivocally normal stress MPI has been associated with a cardiac event rate of <1% per year (12-14). With abnormal stress MPI studies, the extent and severity of myocardial ischaemia strongly predicts short and long-term risks of coronary events. At least eight subsequent studies have confirmed that event rates vary with the size of perfusion defect (10,12). Kang et al. showed that hard cardiac event rates in diabetics with mild, moderate, and severe perfusion defects were 1-2, 3-4, and 7% per year, respectively (11). De Lorenzo et al showed that an abnormal MPI significantly increased the annual incidence of hard cardiovascular events (9%) when compared with a normal MPI (2%). Furthermore, in this study, established risk factors were related neither to the extent of abnormalities on MPI nor to the cardiovascular events (13). The only large prospectively designed study of asymptomatic ischaemia in unselected type 2 diabetics (DIAD) with no prior CAD, found 22% prevalence of an abnormal MPI study, with marked perfusion abnormalities occurring in 6% of patients. This study also demonstrated that traditional cardiovascular risk factors and novel biomarkers were not predictive of abnormal myocardial perfusion (5). In comparison, male gender, duration of diabetes, and the presence of cardiac autonomic dysfunction were strong predictors of ischaemia (5). DIAD 2 trial confirmed that myocardial ischemia can be reduced by intensive medical treatment and risk factors control.

Our study showed the presence of silent ischemia in 20% of the evaluated patients. The differences in the prevalence of silent ischemia in the literature might be due to the differences in the evaluated population, risk factor duration and risk factors control in the different parts of the world, stress test methodology, imaging techniques and interpretation definitions. There was a long debate concerning the best screening approach in asymptomatic patient with high CV risk. European guidelines on CV prevention and treatment of stable CAD as well as American guidelines on screening for CAD in asymptomatic adults indicates that imaging of atherosclerosis and functional imaging of CAD have a place and can be used in this population. It is important to know the predictors of myocardial ischemia in high risk population in order to properly select patients for noninvasive functional imaging (9).

## CONCLUSION

The presence of silent myocardial ischemia in asymptomatic patients with increased cardiovascular risk is high, especially in patients with long standing diabetes. SPECT MPI is valuable method for detection of myocardial ischemia, which improves risk stratification and guide management decision. Aggressive risk factor control and coro-

nary revascularization in patients with minimum moderate ischemia could modify the natural history of the disease and improve prognosis.

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## Sažetak

Cilj rada: Procena prisustva miokardne ishemije kod asimptomatskih pacijenata sa srednjim i visokim kardiovaskularnim rizikom, bez poznate koronarne arterijske bolesti (KAB) i uticaj ishemije na terapijske odluke i prognozu.

Materijal i metode: U radu je uključeno 75 asimptomatskih pacijenata (35 sa umerenim i 40 sa visokim kardiovaskularnim rizikom- SCORE rizik sistem procena), kod kojih je izvedena SPECT miokardna perfuziona scintigrafija (MPS) u cilju detekcije suspektne KAB. Koristili smo 17 segmentni model za analizu miokardne perfuzije i funkcije pomoću perfuzionih i funkcionalnih skorova. Kod svih pacijenata uradjena je laboratorijska analiza koja je uključila lipidni profil, degradacione produkte, a kod visoko rizičnih pacijenata analizovana je i 24 časovna albuminurija. Pacijenti su praćeni 18 meseci za kardiovaskularne neželjene posledice (nova pojava grudne boli, hospitalizacija zbog revaskularizacije ili akutnog koronarnog sindroma, srčani udar, srčana smrt). Logistička regresiona analiza je korišćena za procenu prediktivnih parametara za miokardnu ishemiju i kardiovaskularne atake.

Rezultati: Svi pacijenti su imali normalnu levo komornu funkciju, sa ejectionom frakcijom >55%. 15/75 (20%) pacijenata imali su stres induciranu ishemiju. Laka ishemija je nadjena kod 6 pacijenata – sumiran stres skor (SSS) <4, umerena ishemija (SSS 4-8) kod 4 i teška ishemija (SSS>8) kod 2 pacijenata. Teška ishemija je korelirala sa trajanjem dijabetesa. Logistička regresiona analiza za predikciju stres inducirane ishemije je pokazala OR 2.4 (95% CI 1.7-3.6) za pad ejectione frakcije >5% pri opterećenju, OR 2.8 za ST segment stresom inducirane promene (95% CI 1.9-3.2) i OR 3.9 za prisustvo dijabetesa nad 10 godina (95% CI 2.3-6.6). Pacijenti najmanje sa umerenom ishemijom (n=6) su upućeni na koronarnu angiografiju i invazivno lečenje.

Zaključak: SPECT miokardna perfuziona scintigrafija je korisna neinvazivna metoda za detekciju asimptomatske miokardne ishemije kod pacijenata sa umerenim i visokim kardiovaskularnim rizikom, što utiče na stratifikaciju rizika pacijenata i terapijsku odluku.

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