

Prognostic value of myocardial perfusion abnormalities for long-term prognosis in patients after coronary artery bypass grafting

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ABSTRACT

Aims: The objective was to evaluate the prognostic value of exercise myocardial perfusion scintigraphy (MPS) in patients who underwent coronary artery bypass grafting (CABG). **Subjects and Methods:** A retrospective, one-center study of 361 patients with multivessel coronary artery disease was carried out. All the patients underwent MPS after CABG due to worsened health status. MPS was performed at 4.5 years standard deviation (SD: 0.2), based on symptoms. MPS was carried out using Tc-99m methoxy isobutyl isonitrile and following a 1-day protocol (stress-rest). The end points were analyzed at 6.5 years (SD: 3.3) after MPS, on the average. **Statistical Analysis Used:** SPSS software for Windows, version 13.0. The *t*-test or the χ^2 -test was used. Survival times were calculated. A multivariate Cox proportional hazards model was developed. **Results:** During the follow-up, death occurred in 54 patients, and 37 patients experienced major adverse cardiovascular events (MACE). In the multivariate analysis, advanced age hazard ratio (HR: 1.45; 95% confidence interval [CI]: 1.4–2.02; *P* = 0.027), previous myocardial infarction (HR: 3.17; 95% CI: 1.22–8.2; *P* = 0.018), left ventricular ejection fraction of <40% (HR: 2.16; 95% CI: 1.2–3.89; *P* = 0.01), and the summed stress score (SSS) of ≥ 4 (HR: 1.87; 95% CI: 1.02–3.41; *P* = 0.04) were independent predictors of all-cause death. The summed difference score (SDS) was the only independent predictor of MACE (HR: 1.26; 95% CI: 1.06–1.48; *P* = 0.034). **Conclusions:** The parameters of MPS were found to have prognostic value in the long-term period after CABG. Advanced age, previous myocardial infarction, decreased left ventricular ejection fraction, and the abnormal SSS were associated with an increased risk of all-cause death. The SDS was found to be the only significant risk factor for MACE.

Keywords: Long-term prognosis, myocardial perfusion scintigraphy, myocardial revascularization

INTRODUCTION

Ischemic heart disease is the leading course of death in the most countries of the world. In spite of multiple preventive measures, the number of cardiac attacks increases, leading to the increasing number of interventions. The surgical approach is very effective treatment method; however, 41–50% of patients experience recurrent ischemic symptoms 5–10 years after surgery.^[1,2] During

the postoperative period, a different treatment strategy depending on the risk of new major adverse cardiovascular events (MACE) should be applied to this polymorphic contingent.^[3] Myocardial perfusion scintigraphy (MPS) is one of the most suitable noninvasive methods to assess the status of patients after revascularization.^[2,4–6]

The aim of this study was to evaluate the prognostic value of MPS data for long-term all-cause death and the development of new MACE in patients who underwent coronary artery bypass grafting (CABG).

SUBJECTS AND METHODS

This was a retrospective, one-center study that included 361 consecutive patients with ischemic heart disease, who

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underwent CABG due to multivessel coronary artery disease during 1998-2004. During the follow-up after the surgical treatment, when the patients experienced dyspnea, arrhythmias, recurrent, or worsened angina, there were all referred for exercise MPS. The patients underwent MPS at a different time points after the CABG based on clinical symptoms. The mean time period between CABG and MPS was 4.5 years standard deviation (SD: 2.4). Endpoints and outcomes were analyzed in 2012, that is, at 6.5 years (SD: 3.3) after MPS, on the average. A prognostic value of clinical markers was assessed in two aspects: All-cause death and the development of new MACE such as myocardial infarction, percutaneous coronary interventions, and repeat CABG. For this purpose, the data acquired with the help of a standardized questionnaire (by mail or phone) from the database of the Hospital Heart Center, and the data and information from the residents' register service were used.

Stress test

All the patients underwent the bicycle exercise stress test with the stepwise increments of 50 W every 3 min. Cuff blood pressure measurements were obtained at rest and every 3 min during exercise; a standard 12-lead electrocardiogram (ECG) was continuously recorded until the end of the recovery phase. The end points of exercise were $\geq 85\%$ of predicted maximum heart rate, angina, dyspnea, fatigue, leg weakness, ≥ 2 -mm ST-segment depression, severe arrhythmias, and hypotension or hypertension of $\geq 230/115$ mm Hg. At the end of the stress test, 270-330 MBq of Tc-99m methoxy isobutyl isonitrile (MIBI) was injected intravenously, while the patient continued exercising for an additional minute. The normal exercise test was defined according to the guidelines for exercise testing.^[7] The ECG response to exercise was classified as ischemic (≥ 1 mm horizontal or downsloping or 1.5 mm upsloping ST-segment depression at 80 ms after the J point, or typical angina), borderline (equivocal changes on the exercise ECG), and nondiagnostic (patients did not achieve an optimal target [$\geq 85\%$ of maximum] heart rate, and there were no signs of ischemia on the ECG).

Myocardial perfusion scintigraphy

Myocardial perfusion scintigraphy was performed following the 1-day stress-rest protocol. A stress scan was acquired 30-45 min after an injection of 270-330 MBq of Tc-99m MIBI. A rest scan was acquired 45-60 min after an injection of 500-550 MBq of Tc-99m MIBI, allowing at least a 3-h period between the two injections. All myocardial perfusion studies were performed as gated single-photon emission computed tomography with a low-energy collimated dual-head gamma camera Siemens E. CAM. The camera was rotated in an 180° circular orbit in a step- and-shot mode about the patient's chest from a 45° right anterior oblique view to a 45° left posterior oblique view. A total of 64 projections of 30 s each was acquired with a zoom factor of 1.45 and a 64 × 64 matrix. The acquired raw scintigraphic data were processed through a Butterworth filter with a cut off 0.6 cm^{-1} . Then, the reconstructions of the short axis and the vertical and horizontal long axes were acquired.

The left ventricle (LV) was divided into 20 segments, and myocardial perfusion was evaluated in each segment using a 5-point (0-4) scoring system. A summed stress score (SSS) and summed rest score (SRS) were derived from stress and rest scans, respectively. Myocardial perfusion was interpreted as normal when the SSS ranged from 0 to 3. Myocardial perfusion was interpreted as abnormal if the SSS was ≥ 4 . The summed difference score (SDS) indicating myocardial ischemia was calculated as the difference between the SSS and the SRS.

All the patients gave signed written informed consent to perform MPS.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics, version 13.0. Values were expressed as mean (SD) and number or percentage. Using the *t*-test (for continuous variables) or the χ^2 test (for categorical variables), patients' baseline characteristics that were significantly associated with outcomes were identified. Survival times were calculated by calculating the time (in days) from MPS to MACE and all-cause death or the last date the patient was known to be alive. The multivariate Cox proportional hazards model was developed by a backward stepwise method, entering informative clinical variables, in order to evaluate the risk of all-cause death or MACE after CABG. $P < 0.05$ was considered to be statistically significant.

RESULTS

For the period of the study, 307 patients survived out of 361, death occurred in 54 patients. Table 1 shows the demographic and clinical characteristics of these patients. The groups were matched by age and sex. A previous myocardial infarction and Canadian Cardiovascular Society Class III Angina were significantly more common in the group of patients who died ($P < 0.05$). The exercise stress test was discontinued due to dyspnea more frequently in the patients who died than their counterparts who survived ($P < 0.05$); there were no significant differences in other parameters of the exercise stress test between the groups. During the follow-up, decreased LV ejection fraction and increased LV mass index were detected significantly more often in patients who died had when compared to the survivors ($P < 0.05$). The evaluation of MPS data revealed that abnormal myocardial perfusion was significantly more common among the deceased patients than the survivors ($P < 0.05$). Moreover, the mean SSS was significantly higher in the group of deceased patients than that of survivors ($P < 0.05$). The mean SDS was higher in this group as well, but the difference was not significant.

Table 2 summarizes the predictors of all-cause death. In the univariate Cox regression analysis, advanced age, previous myocardial infarction, class III angina, low-peak workload (< 100 W), reduced peak systolic blood pressure, LV mass index, and end-diastolic diameter, LV ejection fraction of $< 40\%$, and the SSS of ≥ 4 were informative predictors of all-cause death. In the multivariate Cox regression analysis,

Table 1: Baseline demographic and clinical characteristics of survivors and patients who died due to all-cause death

Baseline characteristic	Survivors (n=307)	Patients who died (n=54)	P
Age, mean (SD), years	63.49 (9.11)	65.87 (8.47)	NS
Men	74.9	85.2	NS
Previous myocardial infarction	66.6	90.7	<0.005
Diabetes	14.3	14.7	NS
Angina			
Functional capacity (CCS)			
Class I	1.0	1.9	NS
Class II	57.0	35.2	<0.05
Class III	17.9	40.7	<0.05
Clinical classification			
Typical	40.4	51.9	NS
Atypical	35.5	25.9	NS
Noncardiac	14.3	9.3	NS
No pain	9.8	12.9	NS
Workload, mean (SD), W	100.9 (36.8)	87.04 (32.8)	<0.01
Reason of exercise termination			
Angina and/or ST-segment depression	11.1	12.9	NS
Dyspnea	32.9	50.0	<0.05
Target heart rate	20.8	16.7	NS
Assessment of exercise test			
Pathological	17.3	16.7	NS
Normal	8.5	1.9	NS
Borderline	17.6	12.9	NS
Nondiagnostic	56.6	68.5	NS
Echocardiography data			
LV ejection fraction, mean (SD)	44.8 (8.78)	36.11 (11.01)	<0.001
LV ejection fraction <40%	23.8	55.6	<0.001
LVEDD, mean (SD)	49.44 (6.7)	54.63 (8.68)	NS
LV mass index, mean (SD)	112.65 (26.62)	131.49 (32.97)	<0.01
Myocardial perfusion scintigraphy			
Normal	52.8	33.4	<0.01
Abnormal	47.2	66.6	<0.01
Fixed defect	24.8	33.3	NS
Reversible defects	22.4	33.3	NS
SSS, mean (SD)	6.26 (8.07)	9.44 (10.1)	<0.05
SDS, mean (SD)	1.47 (2.04)	1.64 (2.58)	NS

Values are percentage unless otherwise stated. CCS: Canadian Cardiovascular Society, LVEDD: Left ventricular end-diastolic diameter, LV: Left ventricular, SSS: Summed stress score, SDS: Summed difference score, SD: Standard deviation, NS: Not significant

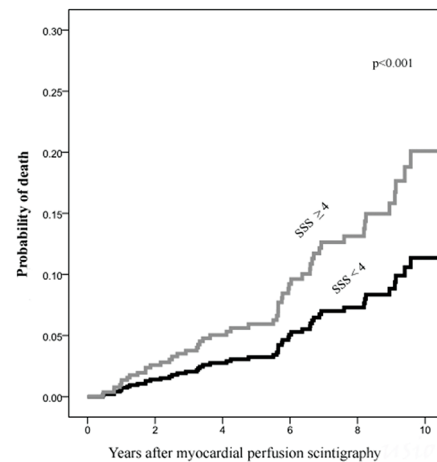
advanced age hazard ratio (HR: 1.45; 95% confidence interval [CI]: 1.04–2.02; $P = 0.027$), previous myocardial infarction (HR: 3.17; 95% CI: 1.22–8.20; $P = 0.018$), LV ejection fraction of <40% (HR: 2.16; 95% CI: 1.20–3.89; $P = 0.010$), and the SSS of ≥ 4 (HR: 1.87; 95% CI: 1.02–3.41; $P = 0.043$) remained to be evaluating by proportional hazard model significantly associated with an increased risk of all-cause death. Figure 1 shows the probability of death, evaluating by proportional hazard model in patient with both normal and abnormal SSS values.

Thirty-seven patients in the survivors group experienced MACE. Myocardial infarction occurred in six patients, three patients underwent CABG, and the remaining 28 patients underwent percutaneous coronary interventions. Of note, 10 patients

Table 2: Predictors of all-cause death using univariate and multivariate cox regression analysis

Variable	HR	95% CI	P
Univariate predictors of all-cause death Unadjusted			
Age (per 10 years)	1.51	1.10-2.06	0.01
Previous myocardial infarction (vs. no infarction)	4.48	1.79-11.3	0.001
Class III angina (vs. class I-II)	2.09	1.14-3.85	0.018
Peak workload < 100 W (vs. ≥ 100 W)	2.15	1.26-3.67	0.005
Peak systolic blood pressure (decrease per 10 units)	1.16	1.06-1.27	0.001
LV mass index (per unit)	1.02	1.01-1.03	<0.001
LV end-diastolic diameter (per unit)	1.10	1.06-1.14	<0.001
LV ejection fraction < 40% (vs. $\geq 40\%$)	3.39	1.98-5.81	<0.001
Summed stress score ≥ 4 points (vs. 0-3)	2.54	1.44-4.48	0.002
Summed difference score (per unit)	1.12	0.98-1.29	0.092
Reversible defects (vs. without reversible defects)	1.60	0.91-2.82	0.104
Multivariate predictors of all-cause death adjusted			
Age (per 10 years)	1.45	1.04-2.02	0.027
Myocardial infarction (vs. without infarction)	3.17	1.22-8.20	0.018
Peak workload < 100 W (vs. ≥ 100 W)	1.55	0.86-2.79	0.147
LV ejection fraction < 40% (vs. $\geq 40\%$)	2.16	1.20-3.89	0.010
Summed stress score ≥ 4 points (vs. 0-3)	1.87	1.02-3.41	0.043

HR: Hazard ratio, CI: Confidence interval, LV: Left ventricular

**Figure 1:** The probability of death, evaluated by proportional hazard model, in patient with both normal and abnormal summed stress score values

underwent percutaneous coronary interventions based on the results of MPS. The demographic and clinical characteristics of the patients who experienced MACE are presented in Table 3. As the results show, there were no significant differences between the groups regarding demographic, clinical, echocardiographic, and MPS data, except the mean SDS value, a parameter reflecting myocardial ischemia that was significantly higher in the group of patients who experienced MACE ($P < 0.05$).

Table 4 summarizes the predictors of MACE. The SDS was the only informative risk factor for MACE in the univariate Cox regression analysis (HR: 1.23; 95% CI: 1.05-1.45; $P = 0.012$) and remained to be associated with an increased risk of MACE in the

Table 3: Baseline demographic and clinical characteristics of survivors with and without major adverse cardiovascular events

Baseline characteristic	Survivors without MACE (n=270)	Survivors with MACE (n=37)	P
Age, mean (SD), years	63.47 (9.30)	65.59 (7.73)	NS
Men	74.0	81.1	NS
Previous myocardial infarction	66.3	67.6	NS
Diabetes	13.5	18.9	NS
Angina			
Functional capacity (CCS)			
Class I	0.7	2.7	NS
Class II	56.3	62.2	NS
Class III	18.1	16.2	NS
Clinical classification			
Typical	41.1	35.1	NS
Atypical	34.1	46.0	NS
Noncardiac	15.2	8.1	NS
No pain	9.6	10.8	NS
Workload, mean (SD), W	99.35 (36.03)	112.16 (41.09)	NS
Reason of exercise termination			
Angina and/or ST-segment depression	11.1	10.8	NS
Dyspnea	32.2	37.8	NS
Target heart rate	21.1	18.9	NS
Assessment of exercise test			
Pathological	17.0	18.9	NS
Normal	8.2	10.8	NS
Borderline	17.4	18.9	NS
Nondiagnostic	57.4	51.4	NS
Echocardiography data, mean (SD)			
LV ejection fraction	44.59 (8.9)	46.41 (7.74)	NS
LVEDD	49.34 (6.79)	50.15 (6.11)	NS
LV mass index	111.49 (26.53)	120.11 (26.39)	NS
Myocardial perfusion scintigraphy			
Normal	52.6	54.1	NS
Abnormal	47.4	45.9	NS
Fixed defects	25.6	18.9	NS
Reversible defects	21.8	27.0	NS
SSS, mean (SD)	6.18 (8.13)	6.89 (7.75)	NS
SDS, mean (SD)	1.33 (1.81)	2.53 (3.20)	<0.05

Values are percentage unless otherwise stated. MACE: Major adverse cardiovascular events, CCS: Canadian Cardiovascular Society, LVEDD: Left ventricular end-diastolic diameter, LV: Left ventricular, SSS: Summed stress score, SDS: Summed difference score, SD: Standard deviation, NS: Not significant

Table 4: Predictors of major adverse cardiac events in survivors using univariate and multivariate Cox regression analysis

Variable	HR	95% CI	P
Univariate predictors of all-cause death	Unadjusted		
Summed stress score ≥ 4 points (vs. 0–3)	1.15	0.60–2.20	0.672
Summed difference score (per unit)	1.23	1.05–1.45	0.012
Reversible defects (vs. without reversible defects)	1.33	0.64–2.75	0.441
Multivariate predictors of all-cause death	Adjusted		
Summed difference score (per unit)	1.26	1.06–1.48	0.034

HR: Hazard ratio, CI: Confidence interval

multivariate Cox regression model (HR: 1.26; 95% CI: 1.06–1.48; $P = 0.034$).

DISCUSSION

This retrospective, one-center study aimed at evaluating the value of MPS data for the long-term prognosis of symptomatic patients who underwent CABG. The major findings of our study are as follows: (1) MPS data were independent risk factors for both all-cause death (SSS) and development of new MACE (SDS) during the long-term period after CABG; (2) only few independent informative predictors, especially of new MACE, in patients after CABG were identified.

There are numerous literature data reporting the prognostic value of MPS in revascularized patients. A study by Farzaneh-Far *et al.* demonstrated that deterioration of perfusion abnormalities identified on MPS repeated in 1 year, was an independent risk factor of death or myocardial infarction irrespective of the treatment applied (medical therapy alone, percutaneous coronary intervention, or CABG) during the 5.8 years of the follow-up period.^[8] There are published data that myocardial revascularization performed based on MPS data (ischemia-guided revascularization) reduced the risk of repeat revascularization and MACE in patients with multivessel coronary artery disease during the 5-year period.^[9] Other authors pointed out that MPS had a sufficient sensitivity for detecting graft disease in patients with an optimal exercise heart rate response at 1 year after CABG.^[6]

Our results showed that advanced age, previous myocardial infarction, reduced LV ejection fraction, and abnormal myocardial perfusion ($SSS \geq 4$) were independent predictors for higher risk of all-cause death during the long-term period after CABG. These data are in line with those of other authors who reported the similar markers to be informative in the prognosis of survival.^[2,10–12] Some studies have suggested that the markers of LV dysfunction are more informative for the prediction of death, whereas the indicators of ischemia are better predictors of MACE.^[13,14] In our study, the SDS, a score reflecting ischemic changes, was found to be an independent prognostic parameter of MACE as well. However, we failed to identify more predictors identifying an increased risk of MACE. We think that a low number of the prognostic markers of MACE were influenced by the following reasons: The group of the patients with MACE was relatively small, that is, only 37 patients, and the two groups compared, that is, survivors with MACE and without MACE, were identical regarding demographic, clinical, and MPS data [Table 3]. Such homogeneity of the study population made risk stratification more difficult, and this is emphasized by other authors as well.^[15]

To sum up, myocardial perfusion abnormalities, detected at mean of 4.5 years following CABG, are one of the main factors that help predict the long-term course and prognosis of the disease in such patients, even though the target heart rate during the exercise stress test has not been achieved.

Limitations

First, our study was retrospective, and the sample size was relatively small, which limited more detailed risk stratification

during the long-term period after CABG. Second, although all our patients could perform the bicycle exercise stress test, the vast majority of them did not achieve the optimal heart rate ($\geq 85\%$ of maximum), and this suggests that myocardial perfusion abnormalities would be more significant, and their prognostic value would be greater in case of the optimal heart rate achieved. On the other hand, in clinical practice, such patients (after CABG, with a history myocardial infarction, and having LV dysfunction) rarely achieve the optimal heart rate due to nonspecific reasons of exercise intolerance and administered medications, including beta-blockers. A stress test with pharmacological agents would be more beneficial for these patients, but there were no possibilities to perform this test in our clinic at that time.

Despite all the above limitations, we think that our experience will be useful for specialists in other centers in evaluating the value of stress MPS for the prognosis of patients who underwent CABG.

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