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

Irena Milvidaite, Ilona Kulakiene¹, Jone Vencloviene, Sarunas Kinduris, Nemira Jurkiene¹, Vytautas Grizas, Ramun Navickas, Rimvydas Slapikas²

Institute of Cardiology, ¹Departments of Nuclear Medicine and ²Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

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 χ²-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
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 ≥85% of predicted maximum heart rate, angina, dyspnea, fatigue, leg weakness, ≥2-mm ST-segment depression, severe arrhythmias, and hypotension or hypertension of ≥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 ≥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 χ² 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,
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 \( \geq 4 \) (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 underwent percutaneous coronary interventions. Of note, 10 patients

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

| Variable                                      | HR     | 95% CI          | \( \mathbf{P} \) |
|-----------------------------------------------|--------|-----------------|-----------------|
| Unadjusted predictors of all-cause death      |        |                 |                 |
| 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. \( \geq 100 \) 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 \( \geq 4 \) points       | 2.54   | 1.44–4.48       | 0.002 (vs. 0-3) |
| 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. \( \geq 100 \) 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 \( \geq 4 \) points       | 1.87   | 1.02–3.41       | 0.043 (vs. 0-3) |

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.
**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. 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. 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.

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. 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. 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 in small, which limited more detailed risk stratification.

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 (≥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.

REFERENCES

1. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501-55.

2. Zellweger MJ, Lewin HC, Lai S, Dubois EA, Friedman JD, Germano G, et al. When to stress patients after coronary artery bypass surgery? Risk stratification in patients early and late post-CABG using stress myocardial perfusion SPECT: Implications of appropriate clinical strategies. J Am Coll Cardiol 2001;37:144-52.

3. Acampa W, Petretta MP, Daniele S, Perrone-Filardi P, Petretta M, Cuocolo A. Myocardial perfusion imaging after coronary revascularization: A clinical appraisal. Eur J Nucl Med Mol Imaging 2013;40:1275-82.

4. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pollikka PA, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 2009;53:2201-29.

5. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171-85.

6. Al Aoual B, Mbi M, Adabag S, Garetta S, Thai H, Goldman S, et al. Utility of nuclear stress imaging for detecting coronary artery bypass graft disease. BMC Cardiovasc Disord 2012;12:62.

7. Gibbons RJ, Balady GJ, Brierer JT, Chairman 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;106:1883-92.

8. Fazzan-Far A, Phillips HR, Shaw LK, Sturr AZ, Fiazzat M, O’Connor CM, et al. Ischemia change in stable coronary artery disease is an independent predictor of death and myocardial infarction. JACC Cardiovasc Imaging 2012;5:715-24.

9. Kim YH, Ahn JM, Park DW, Song HG, Lee JY, Kim WJ, et al. Impact of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary disease. J Am Coll Cardiol 2012;60:181-90.

10. Gimelli A, Rossi G, Landi P, Marzuolo P, Iervasi G, L’abbate A, et al. Stress/rest myocardial perfusion abnormalities by Gated SPECT: Still the best predictor of cardiac events in stable ischemic heart disease. J Nucl Med 2009;50:546-53.

11. Shaw LJ, Cerqueira MD, Brooks MM, Althouse AD, Sansing VV, Beller GA, et al. Impact of left ventricular function and the extent of ischemia and scar by stress myocardial perfusion imaging on prognosis and therapeutic risk reduction in diabetic patients with coronary artery disease: Results from the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial. J Nucl Cardiol 2012;19:658-69.

12. Elhendy A, Schinkel AF, van Domburg RT, Bax JJ, Vakilema R, Poldermans D. Prediction of all-cause mortality in women with known or suspected coronary artery disease by stress technetium-99m tetrofosmin myocardial perfusion imaging. Am J Cardiol 2004;93:450-2.

13. Marcassa C, Bax JJ, Bengel F, Hesse B, Petersen CL, Reyes E, et al. Clinical value, cost-effectiveness, and safety of myocardial perfusion scintigraphy: A position statement. Eur Heart J 2008;29:557-63.

14. Sciagrà R, Pellegri M, Pupi A, Bolognese L, Bisi G, Carnovale V, et al. Prognostic implications of Tc-99m sestamibi viability imaging and subsequent therapeutic strategy in patients with chronic coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol 2000;36:739-45.

15. Adamu U, Knollmann D, Almutairi B, Alrawashdeh W, Deserno V, Vogt F, et al. Stress/rest myocardial perfusion scintigraphy in patients without significant coronary artery disease. J Nucl Cardiol 2010;17:38-44.

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