Combination of myocardial perfusion imaging, left ventricle function parameters and coronary artery calcium score in risk evaluation in patients with diabetes mellitus

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Abstract

Objective: Myocardial perfusion imaging (MPI) can be challenging in some cases of multi vessel involvement. Our aim was to examine specific group of patients with diabetes mellitus (DM), who did not have significant reversible ischaemia diagnosed on perfusion study itself, and asses additional value of functional parameters obtained from gated acquisition and added information from coronary artery calcium score (CACS). **Subjects and Methods:** One hundred and seventy eight patients with a history of DM, with summed difference score (SDS)≤1, were included in the study. All patients underwent gated acquisition with recording of functional parameters and CACS evaluation. During the follow-up, cardiac events (CE) were recorded. **Results:** During the median follow-up of 20.3 months there were 23 CE encountered. Optimal cut-off value for CACS to predict CE was found at 1427, higher values were significantly related to CE (P<0.001). Low stress left ventricular ejection fraction (LVEF) <45% and induced stress LVEF drop for ≥5% were also more frequent in CE group (P=0.001, P=0.008). Multivariable Cox analysis revealed low stress LVEF (P=0.001, HR=4.48, 95%CI 1.79-11.22), stress induced LVEF drop (P=0.017, HR 3.13, 95%CI 1.22-8.01) and high CACS (P<0.001, HR 10.52, 95%CI 4.32-25.63) as significant predictors of CE. **Conclusion:** Low stress LVEF under 45%, post-stress LVEF drop for more than 5% and CACS more than or equal to 1427 are significant predictors of CE in patients with DM, who did not have reversible ischemia detected on MPI single photon emission computed tomography (SPECT).

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Introduction

Myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) is a well-established non-invasive diagnostic tool for the assessment of ischemia as well as prognosis. Conventional nuclear medicine procedure is based on the evaluation of regional inhomogeneities in perfusion distribution with added information from gated study regarding functional parameters of the left ventricle. In patients with multi vessel involvement, based on the principle of imaging with conventional method, the diagnosed extent of the ischaemia can be underestimated [1-3].

Coronary artery calcium deposits are morphological substrate of atherosclerosis, thus coronary artery calcium evaluation, as can be done with coronary artery calcium score (CACS) assessment, can reveal information about the epicardial vessel involvement [4, 5]. In our previous studies we found CACS to be a valuable adjunct to MPI SPECT in adverse outcome prediction [6, 7].

Diabetes mellitus (DM) is a metabolic disease with increased incidence [8]. Patients with DM are in the elevated risk of development of coronary artery disease (CAD). The primary cause of death in this patient's group is CAD and heart failure [9, 10]. Previous studies presented DM as an equivalent of coronary artery disease (CAD), however some recent investigations depict variability in this group and place an accent on the deeper risk stratification in this cohort [5, 11].

Our aim is to investigate group of patients with DM referred for MPI SPECT, without significant ischaemia diagnosed on perfusion study itself and asses additional value of functional parameters obtained from gated acquisition and added information from CACS.

Subjects and Methods

Study population

The study group consisted of 178 patients with a history of DM, referred for cardiac gated-SPECT imaging and without significant ischaemia diagnosed on MPI SPECT (i.e. without significant reversible defect detected, SDS 1).

The whole study group underwent MPI SPECT procedure with electrocardiographic (ECG) gating (gated-MPI SPECT) and CACS measurement. Informed consent was obtained from all individual participants included in the study.

Stress and rest testing

Patients were examined according to a one-day stress-rest protocol, or a two-day rest-stress protocol, the selection depended on the distance of the patient's residence from the laboratory. The stress test was done on a bicycle ergometer. Exercise was conducted until reaching 85% of the age-predicted maximal heart rate or the onset of angina pectoris, dyspnoea, fatigue, dizziness, frequent (>10 per minute) multifocal or paired ventricular extrasystoles, ST segment depression (>0.2mV), or when blood pressure decreased 10 Torr below the previous stage value.

If the subjects did not fulfil the criteria for adequate exercise stressing, or were unable to exercise at all, they received a 4-minutes dipyridamole infusion at a standard dose of 0.56mg per kg of body weight or 0.4mg of regadenoson injection combined with a low level of exercise. Patients with the left bundle branch block were stressed by dipyridamole alone to avoid tachycardia and reduce the possibility of septal artefacts [12]. Pharmacological stress was conducted in 53 (29.8%) cases. The radiopharmaceuticals used were technetium-99m (^{99m}Tc) labelled sestamibi or tetrofosmin. The administered activity of the radiotracer for the reference patient (adult, 70kg) was 300MBq for the stress study. The dose for the rest study was 750MBq for the one-day protocol or 300MBq for two-day protocol. Administered activities of the radiopharmaceuticals were adjusted according to body weight.

Gated-SPECT acquisition and processing

Single photon emission computed tomography was acquired using a GE Discovery NM 630 or NM/CT 670 tomographic camera, equipped with low-energy high-resolution collimators in an L-mode (90°) configuration. Images were gated at eight frames per cardiac cycle. Acquired studies were processed and automatically evaluated using a 4-DM software application (INVIA, Ann Arbor, Michigan, USA) to calculate summed difference score (SDS), left ventricular (LV) ejection fraction (LVEF) in stress and rest.

Cut-off value from the gated study parameters was defined as a stress LVEF <45% and worsening of the LVEF after stress by more than 5% [13].

Coronary artery calcium scoring

Positron emission tomography/computed tomography (PET/CT) scanner Biograph mCT 40 (Siemens Healthineers, Erlangen, Germany) or hybrid tomographic camera GE Discovery NM/CT 670 (GE Healthcare, Chicago, Illinois, United States) were used with the standard vendor's software based on the Agatston method (cut-off: >130 Hounsfield units), to record and evaluate CACS values.

Follow-up

During the follow-up, the CE were recorded. The CE included those with angina pectoris requiring hospitalisation and coronary revascularization, a non-fatal myocardial infarction (MI), or cardiac death. Patients were categorized into two groups: having a CE (CE+) and not having a CE (CE-).

Statistical analysis

Continuous variables are expressed as the mean±standard deviation or median with interquartile range (IQR), and categorical variables are summarized by the count and percentages. Categorical variables were compared using Fisher-exact test, continuous variables were compared using the t-test or non-parametric tests (Mann-Whitney U test, median test), where appropriate. Receiver operating characteristic (ROC) analysis was performed to select the optimal CACS cut-off value to identify patients with a higher risk of CE. The optimal cut-off was determined by the value with the summed highest sensitivity and specificity. Odds ratios (OR) were calculated with 95% confidence intervals (95% CI).

Kaplan-Meier analysis with a Log-Rank test was used to describe the effect of the parameters on the survival time to CE.

Univariable and multivariable Cox proportional hazards models were used to determine whether evaluated variables predicted CE and to calculate an unadjusted and adjusted hazard ratios (HR) and 95% CI for selected predictors. The level of significance was set for all tests at $P<0.05$ (two-tailed). Statistical analysis was done using the jamovi project software package (Version 1.6, MAC OS).

Results

The mean age of the subjects included in the study was 65.3±10.2 years (range 36-100 years), 112 (62.9 %) were male. The median follow-up was 20.3 (IQR 11.2) months. During this period, there were 23 (12.9 %) patients with recorded CEs (7 cardiac deaths, 16 non-fatal MI or revascularizations).

In the CE+ group, there was significantly higher proportion of subjects with measured lower stress EF (<45%) and induced decrease of LV EF in stress (5%)-($P=0.001$, $P=0.008$). The median CACS was higher in CE+ group compared to CE- group, the proportions were different (CACS 1864, IQR 2719 vs. CACS 192, IQR 627, $P<0.001$). The male sex was significantly more frequent in CE+ group (82.6% vs. 60.0%, $P=0.039$). The groups did not differ in age significantly (64.7±9.6 vs. 65.4±10.3, $P=0.773$).

The optimal cut-off value for CACS to predict CE resulted from ROC analysis was at score of 1427, with sensitivity of 60.9%, specificity 90.3%, area under the curve (AUC) 77,5% (Figure 1). When analysing CACS as a dichotomous value, count of patients with CACS ≥1427 was significantly higher in CE+ patients (60.9% vs. 9.7%, $P<0.001$). Descriptive statistics are summarised in (Table 1).

Kaplan-Meier analysis showed a significant association between the lower LV EF, stress induced LV EF decrease, higher CACS and the occurrence of CEs during follow-up

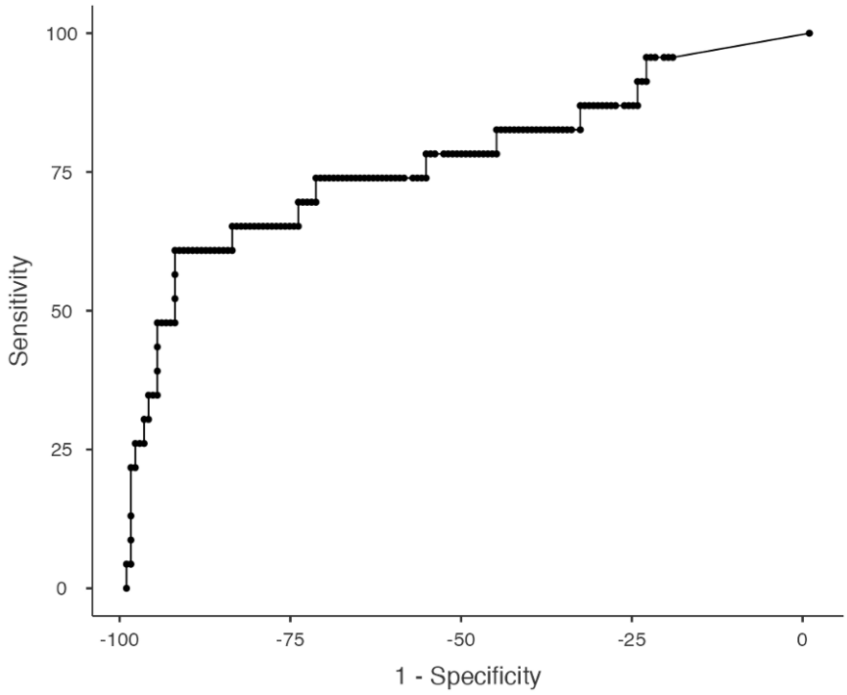

Figure 1. ROC curve of the CACS for the prediction of CE, AUC=0.775.

Table 1. *Summary characteristics of patients with and without cardiac events.*

	Global n=178	Cardiac events n=23	No cardiac event n=155	P value	OR	OR 95% CI
Age	65.3±10.2	64.7 ±9.6	65.4±10.3	0.773		
Male sex	112 (62.9%)	19 (82.6%)	93 (60.0%)	0.039*	3.17	1.03-9.75
Stress LVEF <45%	16 (9.0%)	7 (30.4%)	9 (5.8%)	0.001*	7.10	2.33-21.6
Decrease in stress LVEF ≥5%	21 (11.8%)	7 (30.4%)	14 (9.0%)	0.008*	4.41	1.55-12.50
CACS	225 (IQR 986)	1864 (IQR 2719)	192 (IQR 627)	<0.001*		
CACS ≥1427	29 (16.3%)	14 (60.9%)	15 (9.7%)	<0.001*	14.50	5.38-39.20

*Values given are the mean ± SD, median and IQR, or counts and percentage. * - significant P value.*

(P<0.001, P=0.012, P<0.001). The survival curves are expressed in Figure 2, Figure 3 and Figure 4 . There were 32 patients with zero CACS, only one of them encountered CE (3.1%). However, in this solitary case there was stress induced decrease of LVEF.

Univariable Cox hazards models revealed low stress EF (P<0.001, HR 5.57, 95% CI 2.27-13.66), induced decrease of LVEF in stress (P=0.016, HR 3.00, 95% CI 1.23-7.31) and CACS ≥1427 (P<0.001, HR 8.80, 95% CI 3.78-20.50) as parameters significantly associated with CE, whereas age and sex were not significant (P=0.977, P=0.059, Table 2).

Low stress LVEF, stress induced LVEF drop and dichotomous CACS variable were considered in multivariable Cox regression model. All these parameters were independent predictors of CE, stress LVEF <45% with a HR of 4.48 (95% CI 1.79-11.22, P=0.001) induced decrease of LVEF in stress with a HR of 3.13 (95% CI 1.22-8.01, P=0.017) and CACS ≥1427 with a HR of 10.52 (95% CI 4.32-25.63, P<0.001). The results of the analyses are summarised in Table 2 and Table 3.

Sensitivities, specificities, positive and negative predictive values for identification of CE were calculated for observed parameters. Relatively the highest sensitivity from observed values has CACS ≥1427 (60.9%). All the parameters showed specificity in range of 91.0%-94.2% (Table 4).

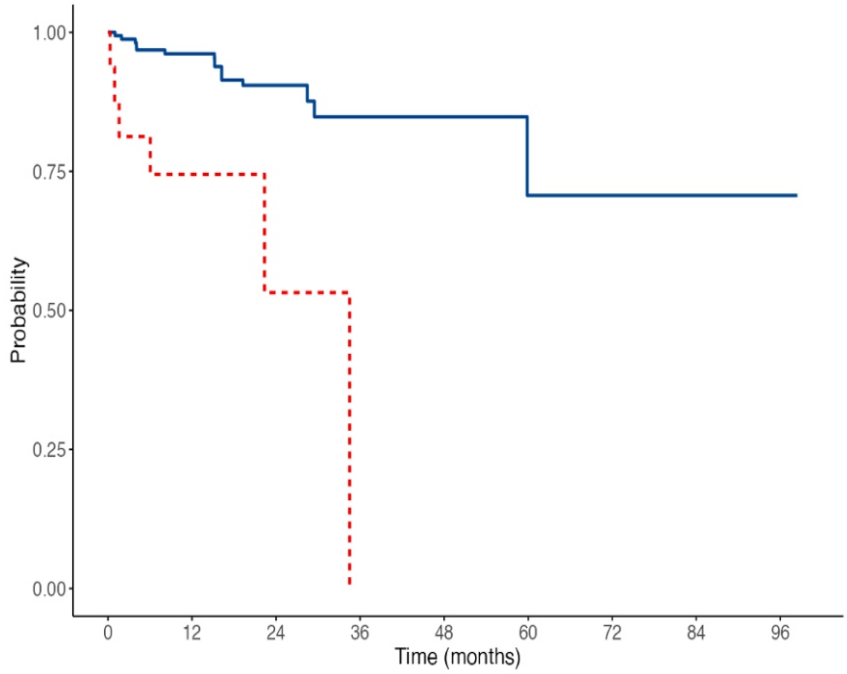

Figure 2. Kaplan-Meier survival curves: blue line-patients with stress LV EF ≥45%; red dotted line-patients with LVEF <45%. Patients with LVEF <45 had significantly poorer outcomes (P<0.001).

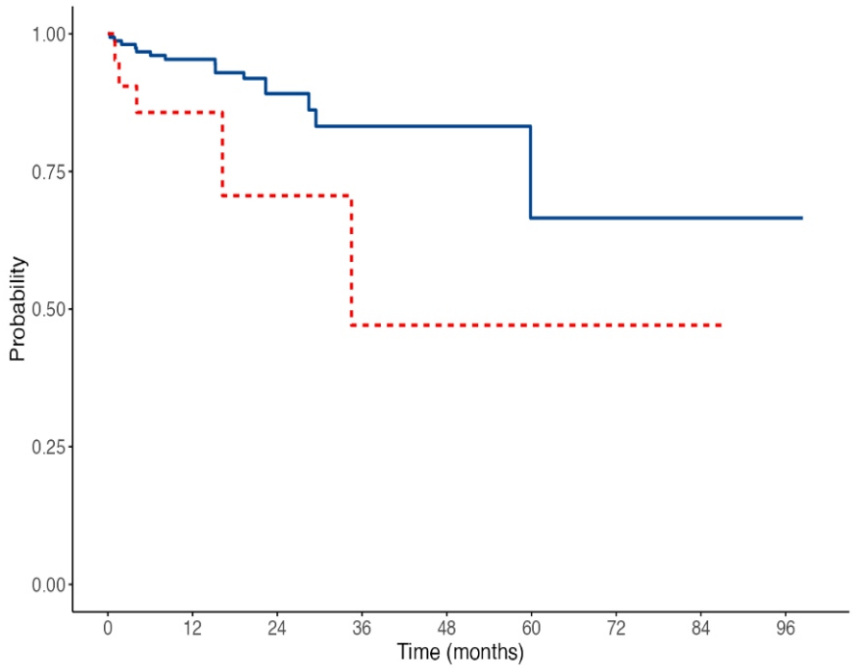

Figure 3. Kaplan-Meier survival curves: blue line - patients without stress induced LV EF drop for ≥5%; red dotted line-patients with stress induced LV EF drop for ≥5%. Patients with stress induced LV EF drop for ≥5% had significantly poorer outcomes (P=0.012).

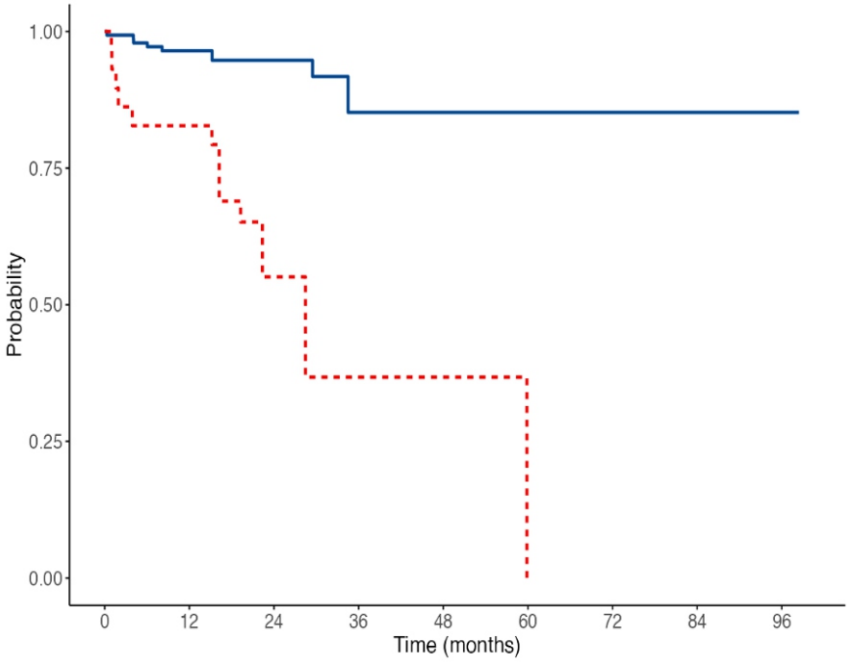

Figure 4. Kaplan-Meier survival curves: blue line-patients with CACS <1427, red dotted line patients with CACS ≥1427. Patients with CACS ≥1427 had significantly poorer outcomes (P<0.001).

Table 2. *Univariable hazard ratios (HR) with 95% CI in observed parameters.*

	P value	HR	HR 95% CI
Age	0.977	1.00	0.96-1.04
Male sex	0.059	2.82	0.96-8.30
Stress LVEF <45%	<0.001*	5.57	2.27-13.66
Decrease in stress LVEF ≥5%	0.016*	3.00	1.23-7.31
CACS ≥1427	<0.001*	8.80	3.78-20.50

** - significant P value.*

Table 3. *Adjusted multivariable hazard ratios (HR) with 95% CI for low stress LVEF, induced stress LVEF drop and CACS ≥1427.*

	P value	HR	HR 95% CI
Stress LVEF <45%	0.001*	4.48	1.79-11.22
Decrease in stress LVEF ≥5%	0.017*	3.13	1.22-8.01
CACS ≥1427	<0.001*	10.52	4.32-25.63

** - significant P value*

Table 4. *Sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV) of observed parameters.*

	Sensitivity	Specificity	PPV	NPV
Stress LVEF <45%	30.4%	94.2%	43.8%	90.1%
Decrease in stress LVEF ≥5%	30.4%	91.0%	33.3%	89.8%
CACS ≥1427	60.9%	90.3%	48.3%	94.0%

Discussion

Diabetes mellitus is strong and independent risk factor of CAD [14]. Previous studies supported performing risk assessment of such patients with MPI SPECT [11, 15]. Patients with DM have often silent coronary artery disease and such asymptomatic course can lead to advanced stages when detected [16]. Autopsy and angiography reveal higher incidence of left main coronary artery lesion, multivessel disease and diffuse CAD in patients with DM [17].

At least one unaffected coronary artery is needed for accurate interpretation of perfusion data processed on conventional MPI SPECT, due to its principle based on the assessment of relative radiopharmaceutical distribution [1, 3]. Myocardial perfusion imaging can by false-negative due to left main or three-vessel disease causing "balanced ischemia" [18]. This can be the case in the examined study group as well.

Diabetes mellitus cause the development of related cardiomyopathy, which leads to heart failure. This means that the heart involvement in DM is not caused only through atherosclerosis and hypertension [9, 19].

Functional parameters obtained from gated-MPI SPECT study can bring additional diagnostic and prognostic value to perfusion study itself. Combined assessment of left ventricular function with perfusion enhances the sensitivity for detection of high-risk variables such as defects in multiple vascular territories [2]. Coronary artery calcium deposits reflect morphoanatomical changes in atherosclerosis. Coronary artery calcification is affected by age, gender, and race, and represents prognostic factor [20, 21]. The CACS adds value to the Framingham risk score and to other methods, the CACS is also an independent predictor of the risk of major cardiovascular events [22].

In our specific study population of patients with DM, who have not reversible perfusion deficit indicating for ischemia, the incidence of CE during the follow-up was not negligible (12.9%). This emphasises the role of additional techniques to identify such cases. Functional parameters are thought as a manifestation of induced ischaemic stunning of the myocardium, which can lead to decrease of LVEF, and possibly dilatation of LV. Post-stress LVEF <45% and ESV >70mL have generally incremental prognostic values and provide risk stratification [23]. Absolute low Stress LVEF as well as induced decrease of stress LVEF by more than 5% was more frequent in CE patients in our study, too. Stress induced LVEF drop associated with increased risk of CE in patients with DM was observed in study of Ferro et al. (2013), their findings suggested that such functional changes of the left ventricle can be associated with a specific diabetic cardiomyopathy, even in the absence of perfusion abnormalities [24]. Such results are thought to be relative to post stress myocardial stunning, but some authors discuss other possibilities for such stress induced changes on gated-MPI SPECT. Emmett et al. (2012) reported interesting observation, when comparing results from gated-MPI SPECT and echocardiographic measurements of LV. In patients with a significant decrease of post-stress LVEF and increase of volumes on gated-MPI SPECT they did not find concordant results on echocardiography. This suggests that such changes on gated-MPI SPECT are not related to true myocardial stunning, but they reflect the subendocardial hypoperfusion and is more likely the reflection of the severity of coronary flow reserve impairment [25].

Observed parameters in our study showed relatively higher negative predictive values, resulted from the low prevalence. However, the specificities 90% and more can have potential to rule-in the subjects with potential CE. Considering all the parameters combined, at least one of them was positive in 18/23 (78.2 %) CE.

Surprisingly, there were significantly more males with CE, but in the univariable regression model the male sex was not significant predictor for CE in this group. Becker et al. (2003) found different risk of CE associated with type 2 DM between the sexes, it was considerably higher in women than in men [26].

The European guidelines on cardiovascular disease prevention in clinical practice note that a higher cardiovascular risk is associated with a CACS over 300 [27]. The median CACS in our CE+ group was 1724, with a quite wide range from 0 to 5095, the observed cut-off value for CE+ prediction was higher, too. Generally, our higher value may be due to the study population with possible higher atherosclerosis burden and related calcium deposits.

Adjusted hazard for CACS ≥1427 was 10.52 times higher than for patients with lower values. Additional prognostic value of CACS to MPI SPECT was also found in our previous studies, in patients in end-stage renal disease and in patients who are in higher risk of multi vessel coronary disease [6, 7].

There was only single case of CE in the cohort of patients with CACS=0. Valenti et al. (2016) in the study evaluated 9715

subjects during long term follow-up (median 14.7 years), they confirmed that zero CACS is associated with reduced risk of death, but for diabetic patients with a CACS=0, there is only a temporal relationship, with increased risk of mortality after 5 years [28]. However, our study can't support these results because of the shorter follow-up period. Contrary, some authors suggest, that higher CACS can lead to plaque stabilisation, with a lower risk compared to plaques without calcifications [29].

Methods evaluating myocardial blood flow (MBF) or coronary flow reserve (CFR) present additional diagnostic and prognostic information compared to conventional SPECT based on relative perfusion distribution [30-32]. The semiconductor SPECT cameras based on cadmium-zinc-telluride detectors (CZT) technology and dedicated geometry of the gantry optimised for myocardial imaging are available, the studies obtained by such systems can be utilised for such purposes. Bailly at al (2021). showed a significant correlation of CFR with SCORE-estimated risk and also with prediction of lesions diagnosed during angiography, they suggest that MFR evaluation should be added to SPECT in high- and very-high-risk patients [33]. Considering the CACS evaluation, most of dedicated CZT SPECT cameras are not equipped with CT scanner [34]. Thus, obtaining CACS on such imaging system should not be as effective as it can be possible on hybrid camera during single examination.

The limitation of the study is the possible influence of the prognosis during the follow-up by the therapeutic approach that was indicated according to the results of previous diagnostic tests. Another limitation can be the possible heterogeneity of study from the meaning of type of DM, we did not specifically discriminate subjects with type 1 and 2 DM.

In conclusion, low stress LVEF under 45%, post-stress LVEF drop by more than 5% and CACS more than or equal to 1427 are significant predictors of CE in patients with DM, who do not have significant reversible ischemia detected on MPI SPECT. These parameters should be considered in risk stratification of patients with a history of DM, who underwent gated-MPI SPECT study.

Bibliography

1. Melikian N, De Bondt P, Tonino P et al. Fractional Flow Reserve and Myocardial Perfusion Imaging in Patients With Angiographic Multivessel Coronary Artery Disease. *JACC Cardiovasc Interv* 2010; 3(3): 307-14.
2. Lima RS., Watson DD, Goode AR et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. *J Am Coll Cardiol* 2003; 42(1): 64-70.
3. Ragosta M, Bishop AH, Lipson LC et al. Comparison Between Angiography and Fractional Flow Reserve Versus Single-Photon Emission Computed Tomographic Myocardial Perfusion Imaging for Determining Lesion Significance in Patients With Multivessel Coronary Disease. *Am J Cardiol* 2007; 99(7): 896-902.
4. Dharampal AS, de Feyter PJ. Coronary artery calcification: does it predict obstructive coronary artery disease? *Netherlands Hear J* 2013; 21(7-8): 344-6.
5. Malik S, Zhao Y, Budoff M et al. Coronary Artery Calcium Score for Long-term Risk Classification in Individuals With Type 2 Diabetes and Metabolic Syndrome From the Multi-Ethnic Study of Atherosclerosis. *JAMA Cardiol* 2017; 2(12): 1332.
6. Havel M, Koranda P, Kincl V et al. Additional value of the coronary artery calcium score in patients for whom myocardial perfusion imaging is challenging. *Kardiol Pol* 2019; 77(4): 458-64.
7. Havel M, Kaminek M, Metelkova I et al. Prognostic value of myocardial perfusion imaging and coronary artery calcium measurements in patients with end-stage renal disease. *Hell J Nucl Med* 2015; 18(3): 199-206.
8. Lin X, Xu Y, Pan X et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* 2020; 10(1): 14790.
9. Leon BM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015; 6(13): 1246.
10. Aronson D, Edelman ER. Coronary Artery Disease and Diabetes Mellitus. *Cardiol Clin* 2014; 32(3): 439-55.
11. Budoff MJ, Raggi P, Beller GA et al. Noninvasive Cardiovascular Risk Assessment of the Asymptomatic Diabetic Patient. *JACC Cardiovasc Imaging* 2016; 9(2): 176-92.
12. Burrell S, MacDonald A. Artifacts and pitfalls in myocardial perfusion imaging. *J Nucl Med Technol* 2006; 34(4): 193-211.
13. Verberne HJ, Acampa W, Anagnostopoulos C et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. *Eur J Nucl Med Mol Imaging* 2015; 42(12): 1929-40.
14. Stamler J, Vaccaro O, Neaton JD et al. Diabetes, Other Risk Factors, and 12-Yr Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16(2): 434-44.
15. Hajar R. Diabetes as "coronary artery disease risk equivalent": A historical perspective. *Hear Views* 2017; 18(1): 34.
16. Wackers FJT, Young LH, Inzucchi SE et al. Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects: The DIAD study. *Diabetes Care* 2004; 27(8): 1954-61.
17. Flaherty JD. Diabetes and Coronary Revascularization. *JAMA* 2005; 293(12): 1501.
18. Yokota S, Ottervanger JP, Mouden M et al. Prevalence, location, and extent of significant coronary artery disease in patients with normal myocardial perfusion imaging. *J Nucl Cardiol* 2014; 21(2): 284-90.
19. Asghar O, Al-Sunni A, Khavandi K et al. Diabetic cardiomyopathy. *Clin Sci* 2009; 116(10): 741-60.
20. Hoff JA, Chomka EV., Krainik AJ et al. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol* 2001; 87(12): 1335-9.
21. McClelland RL, Chung H, Detrano R et al. Distribution of Coronary Artery Calcium by Race, Gender, and Age: Results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005; 113(1): 30-7.
22. Neves PO, Andrade J, Monção H. Coronary artery calcium score: current status. *Radiol Bras* 2017; 50(3): 182-9.
23. Sharir T, Germano G, Kavanagh PB et al. Incremental Prognostic Value of Post-Stress Left Ventricular Ejection Fraction and Volume by Gated Myocardial Perfusion Single Photon Emission Computed Tomography. *Circulation* 1999; 100(10): 1035-42.
24. Ferro A, Petretta M, Acampa W et al. Post-stress left ventricular ejection fraction drop in patients with diabetes: a gated myocardial perfusion imaging study. *BMC Cardiovasc Disord* 2013; 13(1): 99.
25. Emmett L, Ng A, Ha L et al. Comparative assessment of rest and post-stress left ventricular volumes and left ventricular ejection fraction on gated myocardial perfusion imaging (MPI) and echocardiography in patients with transient ischaemic dilation on adenosine MPI: Myocardial stun. *J Nucl Cardiol* 2012; 19(4): 735-42.
26. Becker A. Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals without and with prior cardiovascular disease 10-year follow-up of the Hoorn Study. *Eur Heart J* 2003; 24(15): 1406-13.

27. Piepoli MF, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016; 37(29): 2315-81.
28. Valenti V, Hartaigh B ó, Cho I et al. Absence of Coronary Artery Calcium Identifies Asymptomatic Diabetic Individuals at Low Near-Term But Not Long-Term Risk of Mortality. *Circ Cardiovasc Imaging* 2016; 9(2): e003528.
29. Thomas IC, Forbang NI, Criqui MH. The evolving view of coronary artery calcium and cardiovascular disease risk. *Clin Cardiol* 2018; 41(1): 144-50.
30. Camici PG, Rimoldi OE. The Clinical Value of Myocardial Blood Flow Measurement. *J Nucl Med* 2009; 50(7): 1076-87.
31. Valenta I, Dilsizian V, Quercioli A et al. Quantitative PET/CT Measures of Myocardial Flow Reserve and Atherosclerosis for Cardiac Risk Assessment and Predicting Adverse Patient Outcomes. *Curr Cardiol Rep* 2013; 15(3): 344.
32. Herzog BA, Husmann L, Valenta I et al. Long-Term Prognostic Value of ^{13}N-Ammonia Myocardial Perfusion Positron Emission Tomography. *J Am Coll Cardiol* 2009; 54(2): 150-6.
33. Bailly M, Thibault F, Courtehoux M et al. Myocardial Flow Reserve Measurement During CZT-SPECT Perfusion Imaging for Coronary Artery Disease Screening: Correlation With Clinical Findings and Invasive Coronary Angiography-The CFR-OR Study. *Front Med* 2021; 8: 691893.
34. Bailly M, Thibault F, Courtehoux M et al. Impact of attenuation correction for CZT-SPECT measurement of myocardial blood flow. *J Nucl Cardiol* 2021; 28(6): 2560-8.