PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA IN MIDDLE-AGED PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract. Myocardial ischemia is often asymptomatic in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) is frequently in an advanced stage when it becomes clinically manifested. Silent myocardial ischemia (SMI) is defined as objective evidence of myocardial ischemia in the absence of typical chest discomfort or other anginal equivalents.

Aim To test for LV function to assess the risk of silent myocardial ischemia(SMI) and to determine the relationship between abnormal perfusion tomography and the incidence of cardiac events in asymptomatic patients with middle-aged T2DM and to further evaluate the effectiveness of "aggressive" prevention strategies.

Metods. We retrospectively analysed medical records of 192 (110 male pts; 57.3%) chronologically consecutive asymptomatic middle-aged (≤60 years) patients with T2DM, who had undergone MPI subsequently followed by coronary angiography in case perfusion abnormalities were found. MPI was performed from 2010 to 2014 at a single outpatient care centre with nuclear medicine unit, according to the EANM procedural guidelines for stress-rest ECG gated SPECT one-day protocol using 99mTc-tetrofosmin (Verberne et al., 2015).

Results. Data confirm a relatively high prevalence of silent myocardial ischemia (SMI) in elderly patients with type 2 diabetes mellitus (T2DM), while no data are available regarding middle-aged subjects (≤60 years).

Medical records of 192 patients with T2DM aged ≤60 years (110 male patients; 57.3%), who had undergone myocardial perfusion imaging (MPI) between 2010 and 2014 followed by coronary angiography in case of abnormal result, were retrospectively analysed.

MPI was positive in 35 patients (18.2%); of those 31 (88.6%) had angiographically confirmed coronary stenosis. The positive predictive value of the MPI for predicting angiographic coronary stenosis in this age subgroup was 88.9%. Univariate analysis revealed post-stress LVEF drop ≥5% (p<0.03) and NT-proBNP levels detected in stress (p<0.05) to be associated with greater risk of ischemia in working-age T2DM patients. In multivariate analysis, LVEF drop ≥5% (p< 0.03) remained an independent predictor of SMI.

Prevalence of SMI in diabetic middle-aged patients was similar to that observed in studies of subjects over 65 years-old. Post-stress LVEF drop ≥5% and NT-proBNP levels can contribute to more precise identification of SMI. Our data suggest that "aggressive" management strategy should be implemented to reduce the risk of cardiac events in T2DM patients of middle age.

Conclusion. The presented data address only the prevalence, severity, and possible predictors of SMI at the time of enrolment into the study and suggest that advanced intervention procedures including "aggressive" drug management should be implemented to reduce the risk of cardiac events in forthcoming future. Follow-up evaluation should allow to define the relationship between abnormal perfusion imaging and the prevalence of cardiac events in asymptomatic middle-aged T2DM patients and to evaluate the effectiveness of "aggressive" preventive strategies.

Key words: *scintigraphy, silent myocardial ischemia, diabetes mellitus*

Поширеність безсимптомної ішемії міокарда у пацієнтів середнього віку, хворих на цукровий діабет типу 2.

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Резюме. *Вступ.* Ішемія міокарда часто має безсимптомний перебіг у пацієнтів із цукровим діабетом 2 типу (Т2ЦД) та ішемічною хворобою серця (ІХС) часто в запущеній стадії, коли вона проявляється клінічно. Безсимптомна ішемія міокарда (БІМ) визначається як об'єктивний доказ ішемії міокарда за відсутності типового дискомфорту в грудах або інших ангінальних еквівалентів.

Мета. Тестування функцій ЛШ із метою оцінки ризику ІПСШ та визначення взаємозв'язків між анормальною перфузійною томографією і поширеністю серцевих подій у безсимптомних пацієнтів із T2DM середнього віку та подальшою оцінкою ефективності «агресивних» профілактичних стратегій.

Матеріали та методи. Ми проаналізували ретроспективно медичну документацію 192 (110 чоловіків; 57,3%) хронологічно послідовних безсимптомних пацієнтів середнього віку (≤60 років) з Т2ЦД, які перенесли перфузійну візуалізацію міокарда, у разі виявлення порушень перфузії була здійснена коронарна ангіографія. БІМ був досліджений з 2010 по 2014 рік в єдиному амбулаторному центрі у відділенні ядерної медицини, згідно з процедурними рекомендаціями EANM для «stress-rest» ЕКГ, одноденний протокол SPECT із застосуванням 99mTc-тетрофосміна (Verberneta ін., 2015).

Результати досліджень. Дані підтверджують відносно високу поширеність безсимптомна ішемії міокарда (БІМ) у літніх пацієнтів із цукровим діабетом 2 типу (Т2ЦД), поки немає даних про осіб середнього віку (≤60 років. БІМ був позитивним у 35 пацієнтів (18,2%); з них 31 (88,6%) мали ангіографічно підтверджений коронарний стеноз. Позитивне прогностичне значення перфузійну візуалізацію міокарда для прогнозування ангіографічного коронарного стенозу в цій віковій пкатегорії становило 88,9%. Уніваріантний аналіз показав, що після стресу зниження рівня LVEF ≥5% (p <0,03) та рівня NT-proBNP (мозковой натрійуретиний пропептид), виявлених при стресі (p <0,05), пов'язані з більшим ризиком ішемії у пацієнтів з T2DM працездатного віку. При багатофакторному аналізі падіння LVEF на ≥5% (p <0,03) залишалося незалежним предиктором БІМ. Поширеність БІМ у хворих на діабет середнього віку була подібною до тієї, що спостерігалась у дослідженнях осіб старше 65 років. Постстресовий LVEF на рівні ≥5% та рівень NT-proBNP (мозковой натрійуретиний пропептид)) можуть сприяти більш точній ідентифікації БІМ. Наші дані говорять про те, що «агресивна» стратегія менджементу повинна бути реалізована для зменшення ризику серцевих подій у пацієнтів середнього віку з Т2ЦД.

Висновки. Наведені дані стосуються лише поширеності, тяжкості та можливих прогнозів розвитку БІМ під час участі в дослідженні та пропонують застосовувати розширені процедури втручання, включаючи «агресивне» лікування наркотиками, щоб зменшити ризик серцевих подій у майбутньому. Подальше оцінювання повинно дати змогу визначити взаємозв'язок між анормальною перфузійною томографією та поширеністю серцевих подій у безсимптомних пацієнтів з T2DM середнього віку та оцінити ефективність «агресивних» профілактичних стратегій.

Ключові слова: сцинтиграфія, безсимптомна ішемія міокарда(БІМ), цукровий діабет

Introduction

Myocardial ischemia is often asymptomatic in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) is frequently in an advanced stage when it becomes clinically manifested. Silent myocardial ischemia (SMI) is defined as objective evidence of myocardial ischemia in the absence of typical chest discomfort or other anginal equivalents. It is a common, under-recognized marker of a significant underlying CAD associated with future cardiovascular events and poor prognosis. SMI is an important public health issue, and its early detection may prevent many episodes of sudden cardiac death annually (Cosson et al., 2005; Le Feuvre et al., 2011; Vasiliadis et al., 2014). Diabetic patients have a higher prevalence of SMI and recognised myocardial infarction than patients without diabetes (MacDonald et al., 2014). There are some data about the prevalence of SMI in T2DM patients in elderly at high risk for cardiovascular disease (Inoguchi et al., 2000; Faglia et al., 2002; Lima et al., 2004; Mohagheghie et al., 2011; Rawshani et al., 2017). However, data about the prevalence of SMI in middle-aged subgroup of the diabetic population remain limited.

Stress single-photon emission computed tomography (SPECT) is a validated imaging tool providing information on the physiological significance of flow-limitation and is also a cost-effective for risk assessment of the major adverse cardiac events in the general and diabetic populations. SPECT could accurately assess both myocardial perfusion and ventricular function in diabetic patients, providing important information for their management and is helpful in these situations (De Keyzer et al., 2011). Moreover, left ventricular (LV) function analysis in SPECT can enhances its prognostic and diagnostic ability, particularly in the prediction of SMI (Sharir et al., 1999). We sought to evaluate the prevalence of SMI detected by SPECT myocardial perfusion imaging (MPI) in association with some less recognised diagnostic predictors of it in T2DM asymptomatic patients of the middle age.

Purpose

LV functions Testing for to assess the risk of STIs and to determine the relationship between abnormal perfusion tomography and the incidence of cardiac events in asymptomatic patients with middle-aged T2DM and further evaluation of the effectiveness of "aggressive" prevention strategies.

Methods

We retrospectively analysed medical records of 192 (110 male pts; 57.3%) chronologically consecutive asymptomatic middle-aged (≤60 years) patients with T2DM, who had undergone MPI subsequently followed by coronary

angiography in case perfusion abnormalities were found. MPI was performed from 2010 to 2014 at a single outpatient care centre with nuclear medicine unit, according to the EANM procedural guidelines for stress-rest ECG gated SPECT one-day protocol using 99mTc-tetrofosmin (Verberne et al., 2015). Perfusion images were judged blindly by two specialists independently using the 17-segment ASNC model, and SMI was diagnosed consensually as myocardial perfusion abnormalities without associated symptoms. Stress (cycle ergometry) and rest myocardial perfusion abnormalities were described as reversible (ischemia), fixed (scar), or mixed (scar and ischemia). The summed stress score (SSS) and summed rest score (SRS) were obtained, with the summed difference score (SDS) being the difference between the two. A mild ischemic defect was defined as showing the presence of a SDS ≥ 2. A moderate perfusion defect was defined as a SDS ≥ 2 in > 1 segment, and severe perfusion defect was defined as a SDS ≥ 3 in > 1 segment in stress images.

Calculation of left ventricular ejection fraction (LVEF) and ventricular volumes was performed by using quantitative software for endocardial and epicardial boundaries automatically tracing. Patients with abnormal MPI were referred for coronary angiography. Angiographic images were assessed blindly to the MPI data and significant stenosis was defined as ≥50% for LAD, and ≥75% for other coronary arteries.

LV dysfunction was defined as post-stress LVEF drop ≥5% and/or transient ischemic dilatation of LV in stress against rest. The levels of NT-proBNP were measured at rest and within 3 minutes in the early recovery stage of exercise testing.

All participants gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki. All patients were carefully assessed for classic coronary risk factors: age, sex, obesity, smoking, essential hypertension, dyslipidaemia, a family history of CAD, duration of diabetes, diabetic complications (Table 1).

Table 1

Clinical and laboratory characteristics of the subjects included in the study

Clinical and laboratory characteristics	Diabetic patients (n=192)
Age (years)	52.3 ± 6.7
Male (n/%)	110/57.3
Obesity (n/%)	151/78.6
Smoking (n/%)	3/1.56
Hypertension (n/%)	107/55.7
Dyslipidaemia (n/%)	140/72.9
Family history of CAD (n/%)	28/14.6
Duration of diabetes (years)	5.0 ± 3.2
Retinopathy (n/%)	20/10.4
Nephropathy (n/%)	13/6.8
Neuropathy (n/%)	7/3.6
Glucose (mmol/l)	7.8 ± 2.6
HbA1c (%)	7.2 ±1.3
High-sensitivity CRP (mg/l)	2.2 ±2.3
Total-C (mmol/l)	6.2 ± 3.5
HDL-C (mmol/l)	0.96 ± 0.4
LDL-C (mmol/l)	4.2 ± 1.8
Triglycerides (mmol/l)	3.9 ± 2.4

Data are expressed as the mean ± SD, number and percentage.

Continuous variables were expressed as mean values ± standard deviation, and frequencies as the number and percentage of patients. Between-group comparisons were made by means of non-parametric Mann–Whitney *U* test. Bivariate associations were tested using t test and Fisher's exact test. To identify the factors independently related with SMI univariate and multivariate analysis was performed. *P* values of <0.05 were considered statistically significant.

Statistical analyses were carried out using IBM SPSS Statistics V.19 software.

Results

MPI results showed that 157 (81,8%) patients had normal myocardial perfusion, while 35 (18.2%) patients showed perfusion defects on MPI (Table 2). In 33(17.2%) cases it was defined as reversible and in 2(1.0%) as mixed.

Table 2

MPI results

Result	MPI (n=192)
Negative (n/%)	157/81.8
Positive (n/%)	35/18.2

Data are expressed as number and percentage.

12 (33.4%) out of the 33 reversible perfusion defects were described as mild, 14 (42.4%) – moderate, and 7 (22.2%) – severe.

31 (88.6%) patients out of the 35 with abnormal MPI findings represented an abnormal coronary angiography. In 15(48.4%) out of the 31 patients it was defined as 1 vessel disease, in 10 (32.3%) – 2 vessels disease and in 6 (19.3%) – 3 vessels disease. 9 (29.0%) patients with positive angiographic results represented diffuse disease and vessel occlusion was detected in

2 (6.5%). Coronary anatomy did not allow any revascularisation procedure in 13 (41.9%) of the patients with abnormal coronary angiography.

These results emphasize the incremental diagnostic value of MPI for evaluation of SMI in this specific subgroup of the diabetic population. MPI have showed a very good degree of specificity of the test (97.6%) with a positive predictive value of 88.9% for predicting angiographic coronary stenosis (Table3).

Table 3

Evaluation of MPI in predicting angiographic coronary stenosis

Statistic	Value	95% CI
Sensitivity (%)	69.5	61.5–82.6
Specificity (%)	97.6	79.9–99.3
PPV (%)	88.9	73.6–95.6
NPV (%)	50.6	48.9–52.3

PPV: positive predictive value; NPV: negative predictive value; CI: confidence intervals

We observed that retinopathy (OR 2.32; 95%-CI: 1.05–5.13; p>0.05), nephropathy (OR 2.12; 95%-CI: 1.0–6.13; p>0.5), and neuropathy (OR 1.70; 95%-CI, 1.07–2.71; p>0.05) were not associated with abnormal MPI.

Post-stress LVEF drop ≥5% was observed in 32 (91.4%) patients out of the 35 with abnormal MPI findings. In 29(82.9%) cases it was associated with post-stress transient ischemic dilatation of LV. Patients with LVEF drop ≥5% had higher SDS (p<0.01), but no significant difference in rest LV values (p >0.05) compared to patients without perfusion defects.

There was no significant difference between mean rest NT-proBNP level in MPI-negative against MPI-positive subgroups (182±80ng/l vs. 198±60ng/l, p>0.5), but patients with SMI had a significantly higher mean post-stress NT-proBNP level (889±92ng/l vs. 226±80ng/l; p<0.05).

Univariate analysis revealed post-stress LVEF drop ≥5% (p<0.03) and NT-proBNP level detected in early recovery stage of stress testing (p<0.05) to be associated with greater risk of ischemia in middle-aged T2DM pts. In multivariate analysis, LVEF drop ≥5% (p<0.03) remained to be an independent predictor of SMI.

Discussion

T2DM is a chronic metabolic disease, which results not only in significant direct medical costs but also in indirect productivity losses due to disability and early mortality in working age population. Almost 75% of diabetic decedents without clinical CAD have high-grade coronary atherosclerosis. Autopsy studies have identified a high prevalence of coronary atherosclerosis in patients with diabetes, even among those without clinical CAD (Goraya et al., 2002). The prevalence of SMI in the diabetic population is very variable in the different studies, ranging from 12% to almost 57%, and it is 3 to 6 fold higher than in asymptomatic non-diabetic population (Inoguchi et al., 2000; Wackers et al., 2004; Freeman, 2006; Le Feuvre et al., 2011). Several mechanisms are integrated in the SMI genesis. Endothelial dysfunction secondary to T2DM may play a role, leading to an inappropriate coronary flow response to increasing myocardial metabolic needs (coronary vascular tone abnormality). It is also due to an increased pain feeling threshold in diabetic patients, probably secondary to an elevated beta-endorphins rate. These two abnormalities are associated with an impaired autonomic nervous system.

The patients enrolled in the study were truly asymptomatic, working-age subjects with T2DM, free from known CAD. There were not typical clinical signs of angina at the time of referring patients for MPI. The patients were referred mostly from the clinics for diabetes and metabolic disorders or internal diseases. They were on contemporary medical treatment and were under reasonable metabolic control. Yet, 35 patients (18.2%) had evidence of SMI, including 21 with moderate-to-severe reversible perfusion abnormalities and 30 with stress-induced ST-segment changes. The prevalence of perfusion abnormalities in our study was somewhat lower than the 22% observed in the DIAD study (Wackers et al., 2004) but a bit greater than 15,7% obtained in an earlier study from France (Janand-Delenne et al., 1999). However, the lower prevalence reported in this earlier study likely reflects differences in patients selection. Subjects were of younger age, with T1DM and T2DM and perfusion abnormalities were assessed visually with somewhat less sensitive technique. Moreover, imagings were performed only if the initial exercise ECG stress test was abnormal or equivocal. Thus, patients who would have had perfusion abnormalities were likely missed. On the other hand, it should be noted that the prevalence of perfusion abnormalities in DIAD study is considerably higher than that reported in our study, reflecting the results of adenosine perfusion imaging in a slightly older sample of patients (50-75years).

In a recent study of silent CAD detection in a cohort of 102 asymptomatic T2DM subjects (57±7years), attending 5 Italian outpatient clinics, a significant higher prevalence of silent CAD was observed in subjects with abnormal vs. normal ECG (23 vs. 4%; P=0.004), but not in subjects with high vs. low pre-test silent CAD risk (14 vs. 9%; p=0.472). An abnormal ECG was defined to be a strong, independent predictor of silent CAD (OR 8.9; CI 1.27-62.5; p=0.028) in T2DM (Vigili de Kreutzenberg et al., 2017).

Our second goal was to identify predictors of MPI abnormalities. Demographics, traditional cardiac risk factors, diabetes complications, and biomarkers were analysed. Overall predictors of SMI in working-age cohort of T2DM patients were post-stress LVEF drop ≥5% and NT-proBNP levels detected in stress. In univariate analysis, only post-stress LVEF drop ≥5% was the factor associated with moderate-to-large perfusion defects abnormalities that raise substantial clinical concern. In working-age patients with diabetes, post-stress LVEF drop showed to be an independent predictor of stress-induced ischemia and increases the risk of subsequent cardiac events in T2DM patients. However, a fall in LVEF is detectable also in patients with normal myocardial perfusion. These findings suggest that a post-stress LVEF drop may be related to a specific diabetic cardiomyopathy in the absence of myocardial perfusion abnormalities. Diabetic complications such as retinopathy, nephropathy and neuropathy showed not to be significantly associated with either test abnormality or marked perfusion defects. In addition, traditional cardiac risk factors (male gender, hypertension, smoking and family history, or dyslipidaemia), previously reported as risk factors for CAD and poor outcome (De Keyzer et al., 2011) were not associated with SMI in middle-aged T2DM patients.

Conclusions

Prevalence of T2DM in middle-aged population is high and still rising in Europe. Both diabetes and pre-diabetic states are risk factors for CAD. Their emergence starts many years before clinical events appear, developing silently, in parallel with the progression from pre-diabetic status to T2DM (Alegria-Barrero, 2014). Our study

suggests that 18.2% of asymptomatic middle-aged patients with T2DM have SMI. More importantly, 13.7% of them have markedly abnormal (moderate-to-severe) myocardial perfusion abnormalities. This justifies screening for SMI by non-invasive and cost-effective technique such as SPECT MPI in subpopulation of T2DM patients of the middle age. LV function testing may have an important role in the SMI risk assessment because of the association shown in the present study between LVEF drop ≥5%, NT-proBNP levels detected in stress and perfusion defects occur-

ring. The presented data address only the prevalence, severity, and possible predictors of SMI at the time of enrolment into the study and suggest that advanced intervention procedures including "aggressive" drug management should be implemented to reduce the risk of cardiac events in forthcoming future. Follow-up evaluation should allow to define the relationship between abnormal perfusion imaging and the prevalence of cardiac events in asymptomatic middle-aged T2DM patients and to evaluate the effectiveness of "aggressive" preventive strategies.

REFERENCES

1. Alegria-Barrero, A., 2014. New insights regarding management of diabetes. An article from the E-journal of the ESC Council for Cardiology Practice, vol. 12, no. 11. Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-12/New-insights-regarding-management-of-diabetes

2. Cosson, E., Attali, J.R. and Valensi, P., 2005. Markers for silent myocardial ischemia in diabetes. Are they helpful? Diabetes Metab., vol. 31, no. 2, pp.205-213.

3. De Keyzer, E., Kerkhove, D., Van Camp, G., De Sutter, J., Achtergael, W., Keymeulen, B. and Weytjens, C., 2011. Screening for silent myocardial ischaemia in patients with type 2 diabetes mellitus: a quest to improve selection of the target screening population. Acta Cardiol., vol. 66, no. 6, pp. 715-720.

4. Faglia, E., Favales, F., Calia, P., Paleari, F., Segalini, G., Gamba, P.L., Rocca, A., Musacchio, N., Mastropasqua, A., Testori, G., et al., 2002. Milan Study on Atherosclerosis and Diabetes (Mi SAD). Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). Diabetes Care, vol. 25, no. 11, pp. 2032-2036.

5. Freeman, M., 2006. Myocardial perfusion imaging in diabetes mellitus. Can J Cardiol., vol.22, suppl. A, pp. 22-25.

6. Goraya, T.Y., Leibson, C.L., Palumbo, P.J., Weston, S.A., Killian, J.M., Pfeifer, E.A., Jacobsen, S.J., Frye, R.L. and Roger, V.L., 2002. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. J Am Coll Cardiol., vol. 40, no. 5, pp. 946-953.

7. Janand-Delenne, B., Savin, B., Habib, G., Bory, M., Vague, P. and Lassmann-Vague, V., 1999. Silent myocardial ischemia in patients with diabetes: who to screen. Diabetes Care, vol. 22, no. 9, pp. 1396-1400.

8. Inoguchi, T., Yamashita, T., Umeda, F., Mihara, H., Nakagaki, O., Takada, K., Kawano, T., Murao, H., Doi, T. and Nawata, H., 2000. High incidence of silent myocardial ischemia in elderly patients with non insulin-dependent diabetes mellitus. Diabetes Res Clin Pract., vol. 47, no. 1, pp. 37-44.

9. Le Feuvre, C., Jacqueminet, S. and Barthelemy O., 2011. Myocardial ischemia: a silent epidemic in Type 2 diabetes patients. Future Cardiol., vol. 7, no. 2, pp. 183-190.

10. Lima, R.S., De Lorenzo, A., Pantoja, M.R. and Siqueira, A., 2004. Incremental Prognostic value of myocardial perfusion 99m-technetium-sestamibi SPECT in the elderly. Int J Cardiol., vol. 93, no. 2-3, pp. 137-143.

11. MacDonald, M.R., Petrie, M.C., Home, P.D., Komajda, M., Jones, N.P., Beck-Nielsen, H., Gomis, R., Hanefeld, M., Pocock, S.J., Curtis, P.S., et al., 2011. Incidence and prevalence of u n r e c o g n i z e d myocardial infarction in people with diabetes: a substudy of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study. Diabetes Care, vol.34, no. 6, pp. 1394-1396.

12. Mohagheghie, A., Ahmadabadi, M.N., Hedayat, D.K., Pourbehi, M.R. and Assadi, M., 2011.

13. Myocardial perfusion imaging using technetium-99m sestamibi in asymptomatic diabetic patients. Nuklearmedicine, vol. 50, no. 1, pp. 3-8.

14. Rawshani, A., Franzén, S., Eliasson, B., Svensson, A.M., Miftaraj, M., McGuire, D.K., Sattar, N., Rosengren, A. and Gudbjörnsdottir, S., 2017. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med., vol. 13, no. 15, pp. 1407-1418.

15. Sharir, T., Germano, G., Kavanagh, P.B., Lai, S., Cohen, I., Lewin, H.C., Friedman, J.D., Zellweger, M.J. and Berman, D.S., 1999. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation, vol. 100, no. 10, pp. 1035-1042.
16. Vasiliadis, I., Kolovou, G., Mavrogeni, S., Nair, D.R. and Mikhailidis, D.P., 2014. Sudden cardiac death and diabetes mellitus. J Diabetes Complications, vol. 28, no. 4, pp. 573-579.
17. Verberne, H.J., Acampa, W., Anagnostopoulos, C., Ballinger, J., Bengel, F., De Bondt, P., Buechel, R.R., Cuocolo, A., van Eck-Smit, B.L., Flotats, A., et al., 2015. European Association of Nuclear Medicine (EANM). EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. Eur J Nucl Med Mol Imaging, vol. 42, no. 12, pp. 1929-1940.
18. Vigili de Kreutzenberg, S.,Solini, A., Vitolo, E., Boi, A., Bacci, S., Cocozza, S., Nappo, R., Rivellese, A., Avogaro, A. and Baroni, M.G., 2017. Silent coronary heart disease in patients with type 2 diabetes: application of a screening approach in a follow-up study. J Diabetes Complications, vol. 32, no. 17, pp. 30111-30113.
19. Wackers, F.J., Young L.H., Inzucchi, S.E., Chyun, D.A., Davey, J.A., Barrett, E.J., Taillefer, R., Wittlin, S.D., Heller, G.V., Filipchuk, N., et al., 2004. Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care, vol. 27, no. 8, pp. 1954-1961.