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ORIGINAL PAPER

The prognostic value of ultra low-dose thallium myocardial perfusion protocol using CZT SPECT

Veronika Bednárová[1,2] · Vladimír Kincl[1,2] · Milan Kamínek[2,3] · Jiří Vašina[2,4] · Roman Panovský[1,2] · Jan Máchal[5]

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Abstract

The purpose of this study was to assess the prognostic value of ultra-low dose thallium myocardial perfusion imaging. Three hundred and sixty-six patients (245 men) underwent ultra-low dose stress-redistribution imaging on CZT SPECT camera GE Discovery NM 530c. The stress test was performed by bicycle ergometry or regadenoson injection. The activity of 0.5 MBq (0.014 mCi) Tl-201 chloride per kilogram of body weight was administered. The stress images were acquired immediately and redistribution images were taken after 3 h. Patient follow-up was focused on combined end-point (death, myocardial infarction, unstable angina, revascularization and hospitalization for heart failure). Data analysis was performed from hospital database, with a mean period 23 months. Patients with revascularization within 1 month after SPECT was excluded as revascularization for diagnosis. Ischaemia on SPECT was found in 72 patients, 294 patients were without ischaemia. In patients with ischaemia there were 21 (29.2%) subjects with cardiac events, and 23 (7.9%) in patients without ischaemia (HR 4.15, 95% CI 2.30–7.51, $p < 0.0001$). Ultra-low dose thallium perfusion imaging using CZT camera provides very good prognostic results in assessment of myocardial ischaemia.

Keywords Myocardial perfusion · Thallium · Low-dose · CZT · SPECT · Prognostic value

Introduction

Assessment of myocardial ischaemia using nuclear cardiology methods is well and long-time established in clinical practice. One of the greatest progresses in both nuclear cardiology and general nuclear medicine was the introduction of cadmium-zinc-telluride (CZT) scanners. This technology uses semiconductor detectors with direct conversion of gamma radiation to electric signal. The increased sensitivity and multidetector geometry results in lower administered activity of radiopharmaceuticals and/or shortening of acquisition time. These parameters enable administration of lower activities of radiopharmaceuticals or shorter acquision time or combination of both these advantages. The majority of studies with CZT scanners was performed with Tc-99m labelled radiopharmaceuticals [1, 2], but these compounds have some disadvantages, particularly the extra-cardiac activity in the liver and bowel, that may cause artifacts and difficulties in perfusion assessment. The use of thallium Tl-201 can help to avoid these problems, thallium-201 has higher extraction fraction about 85% and it shows more ideal linear relation between the tracer uptake and myocardial blood flow after an intravenous administration. There are some disadvantages of thallium as well, e.g. the higher radiation burden due to longer half-life and lower energy of emitted radiation. These problems can be overcome using CZT scanners with three- to fivefold increase of photon sensitivity. The diagnostic and prognostic value of CZT scanners were described in several studies [3–5] but only Tc-99m or dual isotope Tl-201/ Tc-99m were used. The aim of our study was to assess the prognostic value of ultra-low

✉ Vladimír Kincl
vladimir.kincl@fnusa.cz

1 Department of Internal Medicine/Cardiology, St. Ann's University Hospital, Masaryk University, Brno, Czech Republic

2 International Clinical Research Center, St. Ann's University Hospital, Pekařská 53, 656 91 Brno, Czech Republic

3 Department of Nuclear Medicine, University Hospital Olomouc, Palacky University, Olomouc, Czech Republic

4 Department of Nuclear Medicine, Masaryk Memorial Cancer Center, Brno, Czech Republic

5 Department of Pathological Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

dose thallium stress-redistribution protocol on CZT SPECT camera.

Patients and methods

Our study comprised three hundred and sixty-six consecutive patients (245 men, 70%) who were referred to our nuclear cardiology lab for stress myocardial perfusion assessment during year 2015. The majority of patients (203, 55%) had known coronary artery disease, other clinical characteristics are listed in Table 1. Patients underwent one-day stress-redistribution protocol with ultra-low administered activity of thallium as we previously described [6]. Briefly, the stress test using bicycle ergometry was performed, in patients unable to exercise or with left bundle branch block an injection of 400 μg of regadenoson (Rapiscan®, Rapidscan pharma solutions, United Kingdom) was used. The Tl-201 chloride, 0.5 MBq (0.014 mCi) per kg of body weight was injected when at least 85% of predicted maximum heart rate was reached, or chest pain, or ST segment ≥ 1 mm deviation occured. If pharmacological stress was used, the tracer was injected 30–40 s after regadenoson administration. This study was approved by institutional ethics committee and all subjects gave their informed consent before enrollment to study.

SPECT imaging

Immediately after stress test, including about 5 min of camera setting and patient positionin, the patients went to image acquisition. The gated images in supine position were recorded for 10 min, then were acquired ungated prone images for 5 min for better assessment of inferior wall perfusion. Gated redistribution images were acquired after 3 h for 13 min. The prone images were finished 20–25 min after tracer injection, before the significant redistribution effect. The acquisition of images was performed on CZT SPECT camera Discovery NM 530c equipped with pinhole collimator (GE Healthcare, Haifa, Israel). This device has 19 solid state semiconductor detectors focused on the heart. The CZT pixel size was 2.46 × 2.46 mm, each detector contains 32 × 32 pixel large elements of 5 mm thickness. Reconstruction of images was performed on dedicated workstation (Xeleris 3.10, GE Healthcare), with iterative reconstruction. The images were reconstructed in standard axes, using 60 iterations and Butterworth postfilter 0.4/10 for both stress and rest images. No attenuation or scatter corrections were performed.

Table 1 Basic characteristics of patients cohort

Number of patients (men)	366 (245)
Patients with known CAD, N (%)	203 (55%)
Age, years (mean ± SD)	64 ± 10.4
Diabetes mellitus, N (%)	74 (20%)
Hyperlipoproteinaemia, N (%)	145 (39.6%)
Hypertension, N (%)	252 (68.9%)
Weight, kg (mean ± SD)	86.4 ± 15.8
Body mass index, (mean ± SD)	29 ± 4.4
Administerd activity of 201Tl chloride, MBq [mCi] (mean ± SD)	43.5 ± 8.5 [1.18 ± 0.23]
Effective dose, mSv (mean ± SD)	4.8 ± 0.9

CAD coronary artery disease, *SD* standard deviation

Image analysis

The reconstructed polar maps of left ventricle were divided into 17 segments, and the accumulation of tracer was assessed using five grade scale (0—normal, 1—equivocal, 2—mild, 3—severe, 4—absent of radiotracer uptake). The summed stress score, rest score and difference score were calculated and used for the assessment of ischaemia. In the case of borderline findings, a visual assessment of tomographic slices in all three axis was performed, and finally all patients were assessed as being with or without ischaemia. The reconstruction of polar maps, measurements of ejection fraction, end-diastolic and end-systolic volume were performed using software Corridor 4DM (Invia, Michigan, United States).

Follow-up

The clinical outcome of patients was followed-up using hospital database in patients visiting outpatient department of our hospital, or by contacting their attending physicians. A combined endpoint of cardiac death, myocardial infarction, unstable angina pectoris defined as need for urgent coronary angiography, revascularization and hospitalisation for heart failure was included in analysis. Revascularisations within one month after positive stress test were excluded from analysis as revascularization for diagnosis, not for prognosis. The mean follow-up period was 23 months.

Statistical analysis

Categorical variables are expressed as a percentage of the total count, continuous variables as mean ± standard deviation or median with lower–upper quartile in a case of distribution that is markedly different from Gaussian distribution. Two-tailed Fisher exact test and Mann–Whitney *U*-test were used to compare the ischaemic and non-ischaemic group. A multivariate Cox regression model was used for identification of risk parameters. The p-value below 0.05 was considered as statistically significant.

Results

There were 72 patients with positive test for ischaemia, other 294 were assessed as negative. The patients with ischaemia were significantly more frequent males, had a history of CAD, lower left ventricular ejection fraction and higher left ventricular end-diastolic and end-systolic volumes. No significant difference in age, body mass index or history of diabetes mellitus was found. The total number of cardiac events was 21 (29.2%) in ischaemia group and 23 (7.9%) in non-ischaemia group (< 0.001). Detail comparison of both groups is presented in Table 2. Numbers of patients with presence or absence of CAD or history of MI are presented in Table 3. The most of hard events were myocardial infarctions, there were two deaths. Kaplan–Meier curves of event-free survival are shown on Fig. 1. The Cox regression stepwise analysis confirmed ischaemia as a valid predictor of cardiac events in univariate model (HR 4.16; 95% CI 2.3–7.51; p < 0.001). The multivariate model of risk factor identified age, diabetes mellitus, history of CAD and ischaemia (HR 2.53; 95% CI 1.23–4.83; p = 0.005) as significant parameters for cardiac events (Table 4).

Table 2 Comparison of groups of patients with and without ischaemia

Parameter	Ischaemia	No ischaemia	p-value[§]
n	72	294	
Age (years)	64.2 ± 9.6	63.9 ± 10.6	0.92
Sex (men/women) (%)	86.1%/13.9%	62.2%/37.8%	< 0.001
BMI (kg m^{-2})	29.8 ± 4.8	28.9 ± 4.2	0.20
LV EF (%)	50 ± 13	58 ± 10	< 0.001
LV EDV (ml)[a]	115 (100–148)	92 (72–114)	< 0.001
LV ESV (ml)[a]	58 (42–80)	38 (26–56)	< 0.001
SPECT SSS[a]	7 (4–14)	0 (0–1)	< 0.001
SPECT SDS[a]	5 (3–7)	0 (0–0)	< 0.001
Diabetes (%)	22.2%	19.7%	0.63
Endpoint reached N (%)	21 [29.2%]	23 [7.9%]	< 0.001
History of CAD (%)	86.1%	48.0%	< 0.001

BMI body mass index, *LV* left ventricular, *EF* ejection fraction, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SSS* summed stress score, *SDS* summed difference score

[a]Categorical variables are expressed as a percentage of total count, continuous variables as mean ± standard deviation or median (lower–upper quartile)

[§]Unadjusted p-value

Discussion

The use of Tl-201 in nuclear cardiology has decreased over the last two decades due to its higher radiation burden and lower energy of emitted radiation that may cause some attenuation artifacts. Since the introduction of CZT SPECT scanners into clinical practice, number of studies with thallium has grown [7–9]. Thallium has some advantages in comparison with technetium radiopharmaceuticals, e.g. better myocardial perfusion characteristics with a higher extraction fraction, depicting myocardial blood flow more accurately. Furthermore, the extracardiac activity from bowel and gall bladder is not commonly present in thallium studies due to renal excretion of thallium. Validation of myocardial perfusion protocols has been made by several ways. There is not always sufficient to compare it with coronary angiography, because comparison of anatomic and funtional imaging method may be sometimes misleading. Some papers about using fractional flow reserve (FFR) were published to validate results of myocardial perfusion studies. Mouden et al. [10] examined 100 patients with intermediate stenosis by Tc tetrofosmin SPECT on CZT scanner and invasive FFR measurements. They found concorance between these two

Table 3 The number of patients in subgroups according to presence of coronary artery disease (CAD) or myocardial infarction (MI)

	Known CAD				No known CAD	
	Previous MI		No MI		Ischaemia	No ischaemia
	Ischaemia	No ischaemia	Ischaemia	No ischaemia		
Number	32	68	30	68	10	158
Death			2			
MI	2	5	2			1
Unstable angina	2	2	2	3	1	1
Hospitalisation for heart failure		2				
revascularisation	7	4	3	5		
Hard events	2	5	4			1
Total events	11	13	9	8	1	2

Hard events = death or MI, total events = death, MI, unstable angina, hospitalisation for heart failure, revascularisation

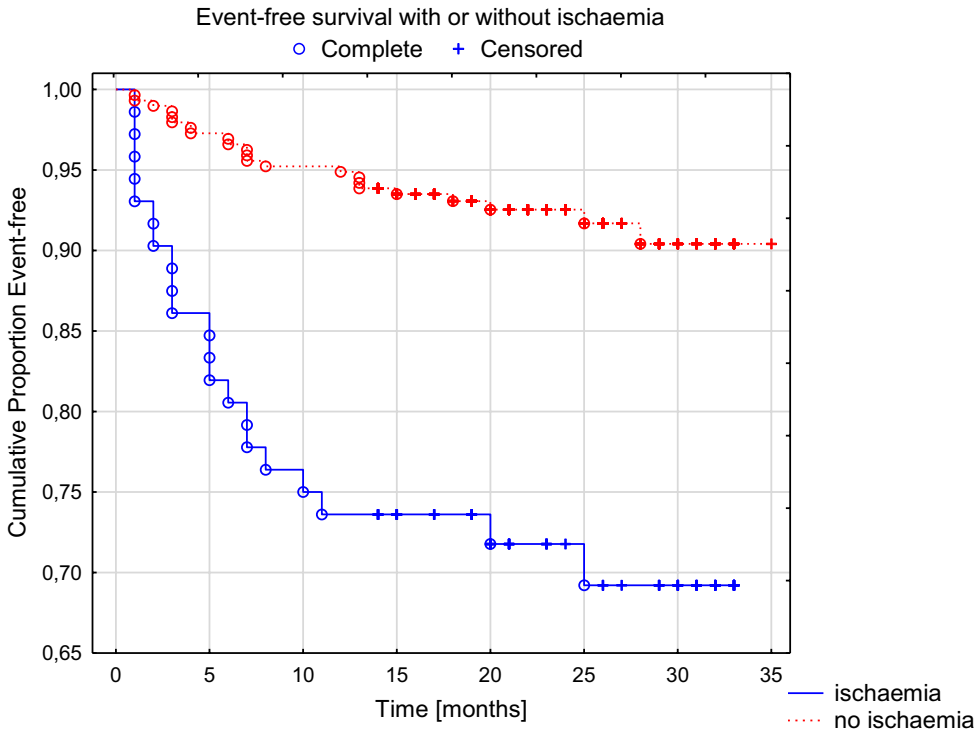

Fig. 1 Kaplan–Meier analysis of event-free survival in groups with and without ischaemia, log rank test $p < 0.0001$

Table 4 The Cox model with risk factors of CAD

	Chi square	p-value	95% lower CI	95% upper CI	HR	95% HR lower CI	95% HR upper CI
Age	7.577	**0.006**	−0.08	−0.01	0.952	0.920	0.986
BMI	0.445	0.505	−0.047	0.096	1.024	0.954	1.101
EF	0.019	0.890	−0.031	0.027	0.997	0.969	1.027
Presence of ischaemia	6.221	**0.012**	0.186	1.552	2.385	1.205	4.721
Diabetes	6.161	**0.013**	0.189	1.606	2.453	1.208	4.983
Hyperlipoproteinaemia	0.962	0.327	−0.346	1.040	1.415	0.707	0.829
Hypertension	0.026	0.871	−0.805	0.682	0.941	0.447	1.978
History of CAD	7.011	**0.008**	0.330	2.211	3.563	1.391	9.127

Bold values indicate the statistically significant p-values

BMI body mass index, *EF* left ventricular ejection fraction, *CAD* coronary artery disease, *HR* hazard ratio, *CI* confidence interval

methods 73% on a per-patient basis and 79% on a per-vessel basis. The 27 discordant fingings consisted of 19% positive SPECT with FFR ≥ 0.75 and 8% of negative SPECT with abnormal FFR < 0.75. However, from the 100 patients, only 31% had ischaemia on SPECT and only 20% had abnormal FFR. A large study by Engbers et al. [5], used follow-up of patients with positive and negative findings of ischaemia on CZT SPECT. They assessed cohort of 4057 stable patients without history of CAD for primary (nonfatal myocardial infarction and cardiac mortality) and secondary outcomes (late revascularization [> 90 days after scanning] and primary outcome). The median follow-up period was 2.4 years. The annual event rates were low in patients with negative SPECT (0.2% primary outcome and 0.6% for secondary outcome). Patients with moderate or large perfusion defects had these event rates 1.2% and 4.3% respectively. Multivariate analysis showed hazard ratio 4.0, 95% CI 1.5–10.5 and 12.1, 95% CI 7.2–20.2, for primary and secondary outcomes, respectively. Our study showed higher event rates, in group with ischaemia 29.2% during mean follow-up period of 23 months and 7.9% in group without ischaemia. However, our population of patients had high proportion of CAD history. In groups with positive and negative perfusion study it was 86.1% and 48.0% respectively. The low-dose protocols were described in several papers, but mostly with use of technetium radiopharmaceticals [4, 11]. Thallium low-dose protocol was tested as a part of dual isotope protocol [12], with mean administered activity 52 ± 5 MBq

(1.4 ± 0.14 mCi) and mean effective dose of 8.3 mSv for full stress-rest imaging. Single tracer thallium low-dose protocol was described by Songy et al. [13]. They used 1.1 MBq/kg and estimated effective dose was below 12 mSv. Our ultra-low dose protocol with 0.5 MBq/kg (i.e. approximately 1 mCi for 70 kg patient) of thallium proved reliable quality of images [6], and this study also provided very good prognostic results with estimated effective dose about 4.5 mSv for complete stress-redistribution test. Our results give comparable prognostic value with previous studies [14, 15]. The main advantage of our protocol is lower radiation exposure with preserving benefits of thallium as a perfusion tracer.

Our study have several limitations. First, the number of subjects is relatively small, larger studies are needed for more accurate results of diagnostic and prognostic value in different groups of patients (with and without presence of CAD, history of MI). Another disadvantage is absence of control assessment of myocardial ischaemia by another method like FFR or perfusion MRI study. Only the prognostic effect of presence of myocardial ischaemia was evaluated.

In conclusion, our pilot results with ultra-low-dose thallium perfusion protocol showed very good prognostic information with significantly lower cardiac event rate in patients with normal myocardial perfusion. The CZT technology allows use of thallium with its advantages as a perfusion tracer and with minimizing disadvantages, particurarly the higher radiation burden for patients.

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Compliance with ethical standards

Conflict of interest All authors declare none conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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