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Noninvasive assessment of cardiac risk in type I diabetic patients being evaluated for combined pancreas-kidney transplantation using dipyridamole-MIBI perfusion

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Abstract This study was performed to determine the value of dipyridamole-^{99m}Tc-methoxy-isobutyl isonitrile perfusion (^{99m}TC-MIBI) tomographic scintigraphy in the assessment of cardiac risk in patients being evaluated prior to combined pancreas-kidney transplantation (PKT). We performed perfusion tomographic scintigraphy using single photon emission computed tomography (SPECT) on 77 patients. The tomographic images did not show clinically relevant findings in 65 patients. In the remaining 12 patients, coronary arteriography was performed: 2 showed normal results, 4 showed no stenosis, and 6 showed significant stenosis (≥ 70 %). Seventy-two patients underwent PKT. During the follow-up (6–48 months), there were seven cardiac events, 4 patients with significant stenosis, and 3 with nonsignificant stenosis upon coronary arteriography, and all had pathological tomographic images. ^{99m}Tc-MIBI tomographic scintigraphy may be useful in identifying patients at low risk of incurring cardiac events after PKT and may, in a large group of patients, obviate the need for routine coronary angiography.

Key words ^{99m}Tc-MIBI scintigraphy · Dipyridamole · Pancreas-kidney transplantation · Cardiac risk assessment · Diabetes mellitus

Abbreviations *^{99m}Tc* Technetium-99m · *^{99m}TC-MIBI* · ^{99m}Tc-methoxy-isobutyl isonitrile · *^{201}Tl* Thallium-201 · *CA* Coronary arteriography · *DMPTS* Dipyridamole-^{99m}TcMIBI perfusion tomographic scintigraphy · *LCXA* Left circumflex artery · *LDA* Left anterior descending coronary artery · *LVEF* Left ventricular ejection fraction · *NSS* Nonsignificant stenosis · *PKT* Pancreas-kidney transplantation · *PTCA* Percutaneous transluminal balloon angioplasty · *RCA* Right coronary artery · *SPECT* Single photon emission computed tomography

Introduction

Current data indicate the necessity of preventing cardiovascular death in combined pancreas-kidney transplantation [15, 21]. Numerous clinical and epidemiological studies have shown diabetes mellitus to be an independent risk factor for coronary artery disease [1], which plays a major role in determining survival after renal transplantation [3, 6]. Moreover, cardiovascular disease is the major cause of death after renal transplantation in this kind of patient [3].

With regard to patients undergoing vascular disease surgery, different studies have demonstrated that myocardial perfusion imaging using thallium-201 (^{201}Tl) can identify subgroups at low, intermediate, or high risk of incurring perioperative cardiac events with better accuracy than the conventional stress test [8, 13, 20]. In patients who are unable to perform treadmill exercise test-

Table 1 Clinical parameters in candidates for pancreas-kidney transplantation

	TOTAL	TOTAL (%)
Patients	77	
Men/women	50/27	
Cardiac symptoms	7	10
Nicotine consumption	25	32
Alcohol consumption	4	5.2
Hypertension	70	91
Dislipemia	41	53
Family history of cardiac disease	3	4
Duration of diabetes	23 ± 6 years	
Perotineal dialysis (n = 20)	8.6 ± 4.4 months	
Hemodialysis (n = 57)	9.9 ± 6.8 months	

ing for whatever reason, or in those who achieve only low, nondiagnostic exercise levels, dipyridamole myocardial perfusion imaging is the most thoroughly studied and well-validated pharmacological stress test [1]. The dipyridamole-^{201}Tl procedure is predictive of not only perioperative ischemic cardiac events but also of long-term outcome and late survival [4, 19]. After these publications, some authors studied the value of this procedure with regard to insulin-dependent diabetic patients being evaluated for PKT. The findings are in overall agreement with those noted in the vascular surgery series [5, 16, 18].

However, although ^{201}Tl has excellent physiological characteristics for imaging myocardial perfusion and viability, its low energy (68–80 kev) is suboptimal for gamma camera imaging, and its relatively long half-life (73 h) is another disadvantage. To circumvent these limitations, investigators have developed different myocardial perfusion agents labelled with technetium-99 m (^{99m}Tc), an isotope with ideal physical properties for gamma camera imaging (mono-energeting gamma of 140 kev and 6 h half-life). Moreover, the high-quality images obtained hereby make it possible to perform the study synchronized with ECG, dividing the cardiac cycle into different images (gated single photon emission computed tomography (SPECT)). This technique was employed in the study of left ventricle wall thickening and wall motion, increasing the specificity of the SPECT to diagnose myocardial infarction [12] and elsewhere made it possible to obtain functional values and calculate the left ventricular ejection fraction (LVEF) [11]. Of the multiple technetium compounds, ^{99m}Tc methoxy-isobutyl isonitrile (^{99m}Tc-MIBI) was the first with favorable characteristics for myocardial perfusion imaging. Several experimental and clinical studies have demonstrated that the results of an appropriate ^{99m}Tc-MIBI imaging protocol provide similar information to those of a ^{201}Tl imaging protocol with respect to the detection of myocardial perfusion defects, assessment of the pattern of defect reversibility, overall detection of coronary artery disease, and detection in individual coronary arteries [7]. However, current data do not exist for SPECT using ^{99m}Tc-MIBI in the preoperative cardiac risk evaluation of diabetic patients. We therefore have examined the value of dipyridamole-^{99m}Tc-MIBI perfusion tomographic scintigraphy (DMPTS) in the noninvasive assessment of cardiac risk in type I diabetic patients being evaluated prior to combined PKT.

Patients and methods

Seventy-seven patients affected by type I diabetes mellitus were evaluated for PKT. The group consisted of 50 men and 27 women with a mean age of 37 ± 12 years. Informed consent was obtained from each patient prior to the examination, and the study was approved by the local ethics committee. A detailed history was taken, documenting the presence or absence of cardiac symptoms, nicotine and alcohol consumption, hypertension, dislipemia, hemodialysis or continuous ambulatory peritoneal dialysis and its duration, duration of diabetes, and family history of cardiac disease (Table 1).

All patients underwent DMPTS as part of their pretransplantation evaluation. The technique used has been previously described well and is a routine procedure [9]. While the patients were supine, dipyridamole (0.56 mg/kg body weight) was infused intravenously over a period of 4 min under the supervision of a cardiologist. Three ECG leads and blood pressure measurements were obtained at baseline and at 1-min intervals. Three to 4 min after the infusion, 20 mCi of MIBI (740 MBq) were administered intravenously. The patients were checked for an additional 5 min.

The pharmacological stress study was considered positive if there was at least 1 min of horizontal or downsloping ST segment depression 80 ms after the J point. If there was ST segment depression at rest, 1.00 mm of additional or downsloping ST depression was required.

The stress tomographic study was performed 60 min after radiotracer injection to avoid hepatobiliary and bowel activity. Data were acquired with a rotating gamma camera and a dedicated computer system (General Electric Medical Systems, Haifa, Israel) over 180° from the 45° right anterior to the 45° left posterior oblique position. Sixty projections were obtained in a 64 × 64 matrix over a 20-s period. The data were filtered and reoriented to obtain oblique angle tomograms parallel to the long axis and short axis of the left ventricle. The images obtained were divided into different segments and were classified depending on the myocardial wall of the left ventricle involved (Fig. 1). The reconstructed data were displayed as tomographic slices (and bull's eye maps). If there was a perfusion defect or any doubt in the stress images (according to the nuclear medicine physician's opinion), the rest study was done the day after (2-day protocol).

The rest study was only performed if the stress study showed abnormal or doubtful findings, and the characteristics (doses, image acquisition, and analysis) were the same as in the stress study, but synchronized with ECG (gated SPECT). The final images were interpreted by visual inspection and by consensus of three experienced observers (one cardiologist, two nuclear medicine physicians). Perfusion stress defects that were unchanged on the rest images were considered fixed. If rest images did not show wall thickening and wall motion in the gated SPECT images, myocardial infarction was diagnosed. On the other hand, defects which improved on the rest images were considered reversible. A global

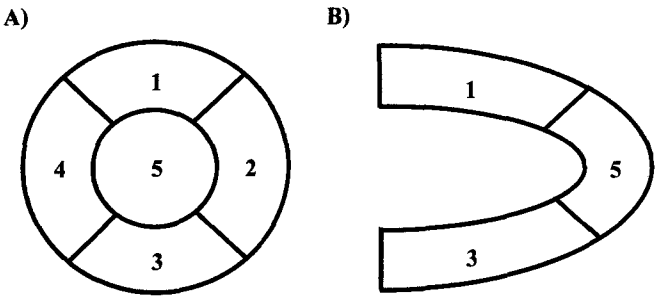

Fig. 1 Left ventricle segmentation using short (**A**) and long (**B**) axis dipyridamole-^{99m}Tc-MIBI perfusion tomographic scintigraphy images. *1* Anterior wall, *2* lateral wall, *3* inferior wall, *4* septum wall, *5* apex

perfusion irregularity was considered as diabetic microangiopathy [2]. Perfusion abnormalities in the inferior, inferoapical, inferoseptal, and inferolateral segments were considered to reflect disease of the right coronary artery (RCA). Defects in the anterior, anteroseptal, septum, and anterolateral segments were considered to reflect disease of the left anterior descending coronary artery (LDA). The defects in the lateral segment reflected disease in the left circumflex artery (LCXA). Because of its varying vascular supply, the apex was not allocated to any involved territory. If the apex alone was involved, the LDA was considered to be the responsible coronary artery. Therefore, coronary arteriography (CA) was only done if there was a significant defect characteristic of coronary disease.

Selective CA was obtained using multiple left anterior oblique or right anterior oblique views and modifying cranial and caudal angulation when needed. The degree of stenosis was assessed using the definitions of the Coronary Artery Study Group, and the LVEF was also taken into account. The results were analyzed visually by two experienced cardiologists unaware of the tomographic results. Significant stenosis was defined as a reduction of 70% or more in the luminal diameter of at least one of the three major coronary arteries. All CA was performed within 3 months of the scintigraphic studies. With a positive CA, a therapeutic decision was made by the cardiologist regarding revascularization, percutaneous transluminal balloon angioplasty (PTCA), or conservative medical therapy. With a negative tomographic study or a CA with nonsignificant stenosis (NSS), the patients were referred to the waiting list and underwent PKT.

Results

There was no correlation between the presence or absence of cardiac symptoms, nicotine and alcohol consumption, hypertension, dislipemia, hemodialysis or continuos ambulatory peritoneal dialysis and its duration, duration of diabetes, and family history of cardiac disease, and the development of complications after surgery. Moreover, we did not find significant differences with regard to age, duration on dialysis, or smoking habits in the 14 patients with coronary abnormalities upon DMPTS compared to the rest of the patients.

Table 2 Results obtained in patients with pathological dipyridamole-^{99m}Tc-MIBI perfusion tomographic scintigraphy (DMTPS). (*CA* Coronary arteriography, *DA* LDA, *LCXA* left circumflex artery, *LDA* left anterior descending coronary artery, *LVEF* left ventricular ejection fraction, *N* normal, *NSS* Nonsignificant stenosis, *OM* DCA, distal circumflex artery, *P* pathological, *PKT* pancreas-kidney transplantation, *RCA* right coronary artery, *WT/WM* wall thickening/wall motion)

Patients who underwent PKT				
No	DMPTS	CA	LVEF (%)	Follow-up
1	Anterior ischemia	N	60	OK
2	Inferoapical ischemia	N	42	OK
3	Anteroseptal ischemia	NSS LDA 30%	54	Sudden cardiac death
4	Anteroseptal ischemia	NSS LDA and RCA 50%	66	OK
5	Anterolateral ischemia	NSS LDA 50%	43	Cardiac failure
6	Inferoapical ischemia	NSS LCXA and RCA 50%	46	Inferior wall infarction
7	Inferoapical ischemia	P RCA and LDA 80%		
	Anterior ischemia	(angioplasty)	59	OK
Contraindication of PKT				
No	DMPTS	CA	LVEF (%)	Follow-up
8	Anteroapical infarction (no WT/WM) Anterobasal ischemia	P DA 70%	64	OK
9	Anterolateral ischemia	P LCXA and RCA 80%	50	Angor pectoris
	Inferior ischemia	DA 90%		
10	Anterior ischemia	P LDA 90%	42	Sudden cardiac death
	Inferior infarction (no WT/WM)	RCA 100%		
11	Anterior ischemia	P OM 100%	44	Cardiac failure
	Inferior ischemia	DA 70%		
12	Inferolateral ischemia	P RCA 100%	50	Inferoseptal wall infarction

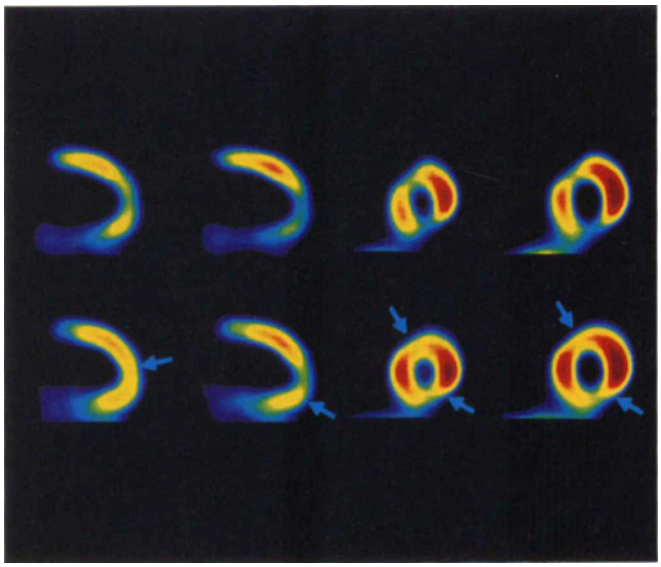

Fig. 2 Dipyridamole-^{99m}Tc-MIBI perfusion tomographic scintigraphy shows partially reversible anterior and inferior defects suggestive of ischemia. The arteriography found nonsignificant lesions (left circumflex artery and right coronary artery 50%). This patient was submitted to pancreas-kidney transplantation and suffered an inferior wall infarction 10 months after transplantation

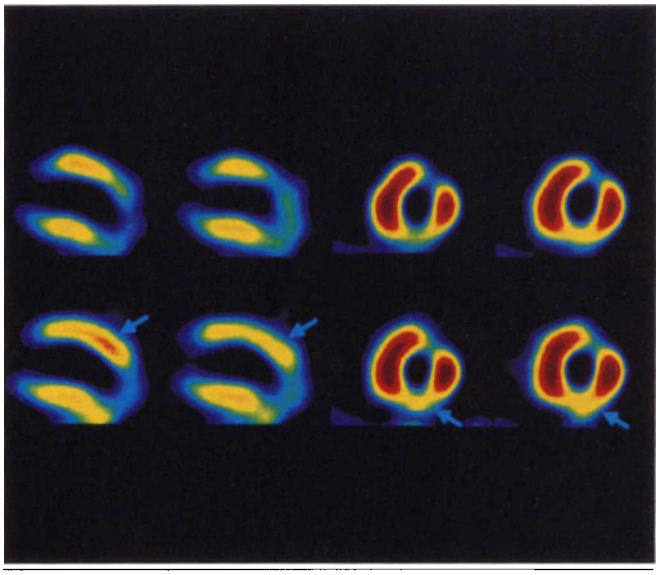

Fig. 3 Dipyridamole-^{99m}Tc-MIBI perfusion tomographic scintigraphy shows an anterior reversible defect suggestive of ischemia and an inferior fixed defect suggestive of infarction. The arteriography found a significant lesion in the left anterior descending coronary artery (90%) and right coronary artery (100%).This patient was not admitted to pancreas-kidney transplantation and suffered a sudden cardiac death 15 months after the arteriography

The DMPTS was well tolerated. Of the 77 patients who underwent DMPTS testing prior to transplantation, only one had a positive pharmacologic stress study (angor pectoris) showing inferolateral ischemia upon DMPTS (RCA: 100% in CA), and PKT was contraindicated. As shown in Table 2 (patient 12), the patient suffered an inferoseptal wall infarction 2 months after CA. The overall scintigraphic image quality was quite good. None of the patients had to be excluded from the study because of low image quality.

Thirty patients showed normal stress tomographic studies. For the remaining patients, rest tomograhic studies were also performed. Therefore the total number of scintigraphies was 124 (77 stress studies and 47 rest studies). Tomographic images were normal or without clinical relevance in 65 patients (84.4%). Of the remaining 12 patients (15.6%), all showed reversible defects, and in two of these patients there were also fixed defects with no wall thickening in gated SPECT images, correlating well with CA findings as probable myocardial infarctions (Table 2, patients 8 and 10). CA was performed on all patients with stress tomographic defects. The results showed that two were normal, that four had NSS, and that six had significant lesions. The LVEF was in the range of 42–66% (Table 2). Of the six patients with positive CA, only one was considered for PTCA. This patient was later referred to the waiting list and underwent PKT with a correct evolution. The remaining five patients were treated with a conservative medical therapy and were excluded from PKT. Therefore, 72 patients were referred to the waiting list and underwent PKT.

After PKT, there were no perioperative cardiac events. During the follow-up (6–48 months) after PKT, seven of the 77 patients (10%) had cardiac events, all being patients with pathologic DMPTS (Table 2). The remaining 70 patients were free of cardiac events. Of the six patients that were either normal or had NSS upon CA, one suffered sudden cardiac death (44 months after PKT), one had a myocardial infarction in the inferior wall (10 months after PKT) (Fig. 2), and one developed cardiac failure (Table 2). Of the six patients with significant stenosis upon CA, one suffered sudden cardiac death (15 months after CA) (Fig. 3), one had a myocardial infarction in the inferoseptal wall (2 months after CA), one developed cardiac failure, and one was affected by multiple episodes of angor pectoris within 7–14 months after CA.

Discussion

In the guidelines for the clinical use of cardiac radionuclide imaging, it is said that dipyridamole scintigraphy may be useful in selected patients who are thought to be at high cardiac risk and require other major surgery. In renal transplant recipients the second-most common

cause of death, after infections, is cardiovascular disease [14], whereas myocardial infarction is the main cause in diabetic patients. Moreover, diabetes mellitus is a particularly strong risk factor for mortality from coronary heart disease in young adults [1]. In this study, the overall graft survival did not vary significantly between recipients with diabetic and nondiabetic renal disease, but the overall patient survival was significantly lower in patients with diabetes [3]. Of the first 45 pancreatic/renal transplant recipients – from February 1983 to February 1992 – for whom no rigorous cardiac evaluation was done, two (4.4%) died at 3 and 10 days after transplantation, with myocardial infarction being the cause of death. The data therefore emphasize the necessity that cardiovascular death be prevented in connection with kidney transplantation or PKT by means of a more rigorous pretransplantation cardiac assessment and treatment before acceptance for transplantation [21]. However, in diabetic patients CA should not be carried out routinely due to an associated risk of acute renal failure [21]. Thus, ^{201}Tl perfusion studies could be an alternative for these patients [15, 21] since this technique increases the accuracy of the conventional stress test and may obviate the need for CA with the result of a normal DMPTS [21].

The development of dipyridamole ^{201}Tl perfusion studies has been a major advance in preoperative testing of patients unable to exercise. Peripheral vascular or neurologic disease frequently limits the ability to perform maximal exercise. Such patients may benefit from alternative forms like the dipyridamole-^{201}Tl procedure. Since patients with renal disease may not achieve an adequate heart rate response during exercise stress testing, pharmacologic stress with dipyridamole was preferred as an alternative [1].

Although some studies such as that by Vanderberg et al. [17] conclude that ^{201}Tl does not have a high predictive value in the assessment of these patients it is well accepted that a normal dipyridamole ^{201}Tl perfusion scan predicts a good cardiovascular outcome for at least 24 months following the test [13]. It is therefore not only useful in predicting preoperative myocardial infarction or death, but also provides long-term prognosis information. However, comparable data do not exist for DMPTS of this kind of patient.

Screening of cardiopathy with radionuclide testing has also been studied in asymptomatic candidates for liver transplantation [7]. Stress myocardial perfusion imaging seems to be useless for preoperative cardiac risk assessment in these patients because most do not show any abnormalities suggestive of ischemic disease and most have a favorable outcome after liver transplantation.

In our study, no patients with a normal DMPTS had a cardiac event within the perioperative period or during the follow-up. Taking this into account, this protocol could also be useful for the pretransplantation cardiac assessment of diabetic patients, obviating unnecessary routine CA and also reducing costs.

Our results correspond with those of Mistry et al. [10] inasmuch as none of the patients with a fixed defect and none with normal CA or NSS upon CA had a perioperative event, but they do not correlate with respect to late cardiac events such as myocardial infarction and cardiac death during follow-up. Moreover, a fixed defect could not only represent a severe ischemia but an infarction as well.

As has been described with ^{201}Tl, a reversible defect is probably a major factor predictor of cardiac disease in these kinds of patients without a history of myocardial infarction [10]. Perhaps the most important prognostic predicting is found in the extent of perfusion abnormality [13], which provides prognostic information on a patient's risk for subsequent cardiac events [8]. Compared to ^{201}Tl scintigraphy, DMPTS provides additional information when acquired SPECT images are synchronized with ECG (gated SPECT) since this technique enables the assessment of myocardial infarction [12] (as in patients 8 and 10) and the possibility of obtaining the LVEF with demonstrated viability results [11]. Determining LVEF with this noninvasive, cost-free, and time-saving technique may be another important prognostic factor in these patients, especially in controlling the development of cardiac failure. In our group, two patients with a normal LVEF before PKT developed cardiac failure reaching LVEF values of 42 and 43%, suggesting the necessity of follow-up to ensure a correct cardiac function in their evolution.

We conclude that ^{99m}Tc-MIBI tomographic scintigraphy may be useful in identifying patients at low risk for incurring cardiac events after PKT and may, for a large group of patients, obviate the need for routine CA. However, studies performed on a larger group of patients may be necessary to confirm our results.

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