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Prognostic value of inducible myocardial ischemia in predicting cardiovascular events after renal transplantation

Bertrand Dussol, Jean-Louis Bonnet, Jerome Sampol, Bernard Savin, Catherine De La Forte, Olivier Mundler, Gilbert Habib, Sophie Morange, Karine Barrau, Anderson Loundoun, Henri Vacher-Coponat, and Yvon Berland

Service de Néphrologie et Hémodialyse, Hôpital de la Conception, Marseille, France; Centre d'Investigation Clinique, APHM-INSERM, Marseille, France; Service de Cardiologie A, Hôpital de la Timone, Marseille, France; Service de Médecine Nucléaire, Hôpital de la Timone, Marseille, France; Service de Cardiologie B, Hôpital de la Timone, Marseille, France; and Unité d'Epidémiologie Prévention et Santé Publique, Faculté Timone, Marseille, France

Prognostic value of inducible myocardial ischemia in predicting cardiovascular events after renal transplantation.

Background. The aims of the present study were to determine the prevalence of inducible myocardial ischemia (IMI) in renal transplant recipients (RTR) more than 50 years old, to identify predictors of IMI, and to search for its prognostic value.

Methods. Among the 377 renal transplantations performed between 1989 and 1998 in a single institution, 120 were done in patients ≥50 years old, and 97 were recruited for the study. During the last quarter of 1998, all of them underwent an exercise test (EST), an exercise-thallium 201 single photon emission computed tomography coupled with dipyridamole (SPECT), and 81% of them had a dobutamine stress echocardiography (DSE). Patients with IMI subsequently underwent coronary angiography to detect coronary stenosis.

Results. IMI was present in 12 of the 97 patients (10%). The diagnosis was evidenced by EST in four cases, by SPECT in 11 cases, and DSE in three cases. Five of these 12 patients (42%) had significant coronary artery stenosis (≥50%). Multivariate analysis of several pre- and post-transplant variables evidenced acute rejection and left ventricular hypertrophy as significant correlates of IMI (both $P < 0.03$). Patients were prospectively followed-up for 48 months for the occurrence of major cardiovascular events. Kaplan-Meier analysis revealed a significant increase in cardiovascular events in the IMI group ($P < 0.0001$). In addition, the Cox proportional hazards model revealed that IMI and diabetes mellitus had an independent significant effect on the occurrence of major cardiovascular events.

Conclusion. IMI was present in 10% of RTR aged ≥50 years, and was predicted by acute rejection and left ventricular hypertrophy. IMI had a strong effect on major cardiovascular events in this population.

Key words: inducible myocardial ischemia, coronary artery disease, noninvasive stress tests, coronary angiography, renal transplantation, multivariate analysis, Cox model.

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Cardiovascular disease (CVD) is the leading cause of death in renal transplant recipients (RTR) [1, 2]. Death due to cardiovascular disease with a functional transplant is the first cause of transplant loss [3, 4]. It not only accounts for the increased mortality of these patients, but it is also a major cause of morbidity [5]. The high incidence of cardiovascular events in RTR is associated with an increased prevalence of traditional risk factors, such as diabetes, hypertension, and dyslipidemia [6–9]. Hyperhomocysteinemia and renal failure are also involved [10–12]. Finally, factors directly linked to the transplantation also play significant roles, such as toxic effects of immunosuppression [13], rejection, and infections [14, 15].

Coronary artery disease is the main cause of myocardial ischemia in RTR [16], and coronary angiography is still the gold standard for assessing the diagnosis. But this procedure is invasive and costly. Actually, to detect myocardial ischemia, most centers rely on noninvasive cardiac stress testing, usually performed before the transplantation [17]. Moreover, in 30% of RTR, myocardial ischemia is not related to a significant stenosis of the coronary artery and may be due to a microangiopathy in relation with diabetes, left ventricular hypertrophy, calcium deposits, and endothelial dysfunction [18].

Cohn [19] has estimated that up to 4% of apparently healthy asymptomatic middle-aged men have inducible myocardial ischemia (IMI). In asymptomatic men with two or more major coronary risk factors, the prevalence reaches 10% [20, 21]. The prevalence is from 15% to 30% in patients with previous myocardial infarction [22]. In hemodialyzed patients, the prevalence increases to 40% [23].

The aims of this study were to determine the prevalence of IMI in a large group of RTR over 50 years of age. In addition, we looked for correlates for IMI. After testing, patients were followed-up for four years to determine

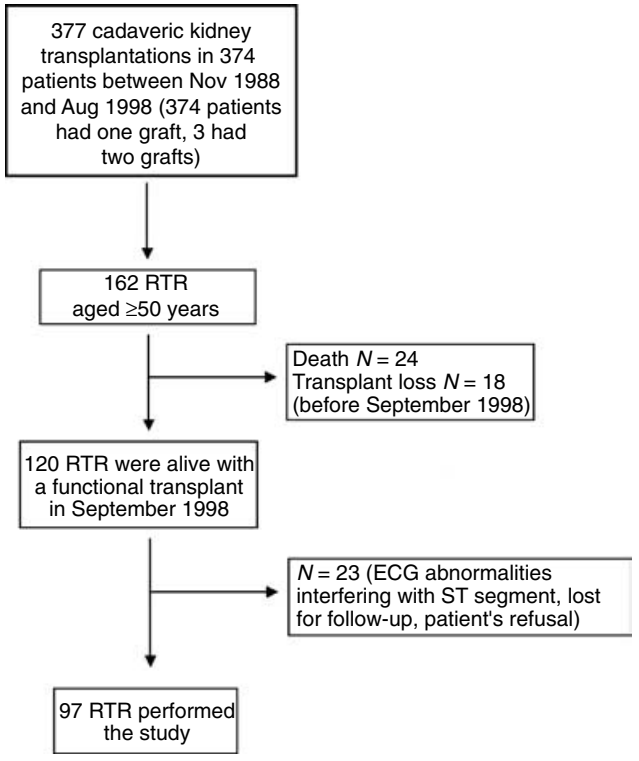

Fig. 1. Profile of the study.

the incidence of cardiovascular events in patients with or without IMI.

METHODS

Study population

We analyzed the records of all cadaveric kidney transplantations ($N = 377$) performed between November 1988 and August 1998 in a single center. Since 1988, all patient data have been recorded on a microcomputer with a specific database management program. Among the 374 renal transplants recipients, 162 were ≥50 years old. At the time of the study, 120 patients were alive with a functional transplant. Twenty-three patients were excluded from the study either because of ECG abnormalities interfering with exercise ST-segment interpretation (major left ventricular hypertrophy, left bundle branch block, pre-excitation, atrial fibrillation) or because they declined to participate in the study or were lost to follow-up. Thus, 97 patients performed the study (Fig. 1). The characteristics of the patients who did not participate did not differ from those in the study population (data not shown). None of the patients had suffered from myocardial infarction or undergone bypass surgery or percutaneous revascularization during the previous year. Ten patients had previous coronary artery disease two or more years before the start of the study. Among these 10 patients, two had myocardial infarction and eight had acute coronary syndrome necessitating percutaneous revascularization. All patients gave their informed consent to participate in the study.

All the patients were treated by hemodialysis before transplantation. After transplantation, they all received the same quadruple sequential therapy with thymoglobulins 1 amp/10 kg/day (Thymoglobulins; Institut Mérieux, France) for seven days, prednisone 1 mg/kg/day tapered to 0.25 mg/kg/day from D15 to D30, and azathioprine 3 mg/kg/day secondarily adjusted to white cell count. Cyclosporine (6 mg/kg/day) was started at D5. The target whole blood levels were 200 to 300 ng/mL during the first three months and then 150 to 250 ng/mL afterwards. During the follow up, immunosuppressive treatments were modified according to clinical events. The diagnosis of acute rejection was based on standard clinical and pathologic criteria [24]. Antirejection therapy was either methylprednisolone pulses or monoclonal antibodies to CD3, according to the severity of the rejection.

Detection of inducible myocardial ischemia and coronary angiography

Before IMI detection, patients underwent a clinical screening that included a detailed history and a resting electrocardiography. Detection tests were performed after complete discontinuation of medications that have potential antianginal effects: two days for β-blockers, and one to three days for calcium-channel blockers. Screening tests and coronarographies were performed by the same cardiologist (B.S. for exercise test, B.S. and O.M. for scintigraphy, G.H. for dobutamine stress echocardiography, J.L.B. for coronarography). All the patients were referred to exercise test and scintigraphy. Dobutamine echocardiography was optional but recommended, and coronarography was indicated in case of IMI detection.

Exercise test (EST)

Exercise electrocardiography was performed on a cycloergometer through a protocol starting at a workload of 30 watts, with increments of 30 watts every 3 minutes and a 12-lead ECG analysis system (Marquette CASE 16; Marquette Electronics, Milwaukee, WI, USA). The criteria for interruption of exercise were fatigue, chest pain, dyspnea, decreased systolic blood pressure, exertional blood pressure above 250/120 mm Hg, congestive heart failure, and severe ventricular or supraventricular arrythmias. The test was considered negative if no significant ECG abnormalities were observed upon reaching or exceeding at least 85% of the maximal predicted heart rate as calculated by the Astrand formula (220-age). The test was considered positive when horizontal or downsloping ST-segment depression ≥1 mm was observed 80 milliseconds after the J point.

Dipyridamole-exercise coupled with thallium-201 single photon emission tomography (SPECT)

The test started with dipyridamole infusion (0.8 mg/kg body weight for four minutes) as the patient performed a symptom-limited ergometer bicycle exercise test using standard protocol with permanent monitoring by a 12-lead ECG. At near-maximal exercise, 92 MBq of thallium-201 was injected intravenously. The initial images (stress) were obtained five minutes after the injection. The myocardial uptake of thallium was assessed in 32 projections with a 180-degree tomographic acquisition gamma camera. Late redistribution imaging four hours after stress test was obtained at rest after another injection of thallium-201, 37 MBq, through the same technique. For the images, background noise was automatically subtracted, and they were filtered in back position without attenuation correction. Sagittal, coronal, and transverse sections were obtained after reconstruction, and were reoriented to the three standard cardiac planes for visual interpretation. Each left ventricle segment was classified visually as normal or abnormal (transient or persistent defect). The two physicians involved in the interpretation were unaware of any clinical information regarding the patients. Differences in interpretation between observers were resolved by consensus. Patients were assigned to three groups: (*1*) normal images; (*2*) transient defects, that is patients with partial or total normalization (redistribution) in all initially abnormal myocardial segments; and (*3*) persistent defects, that is, patients with no redistribution in any initially abnormal myocardial segments.

Dobutamine stress echocardiography (DSE)

DSE was performed in a standard fashion. A complete echocardiographic examination was first performed, and left ventricular wall motion was analyzed. Dobutamine infusion was begun after the baseline study at 5 μg/kg/min, and then at 10, 20, 30, and up to 40 μg/kg/min, using three-minute increments. Blood pressure and ECG tracing were monitored during dobutamine infusion. A dobutamine test was considered positive if a new wall motion abnormality was detected during dobutamine infusion. Short-acting beta-blocker (Esmolol) was used at the end of the test.

Coronary angiography

Opacification was performed with standard 5F Judkins (Cordis, Issy-les-Roulineaux, France) diagnostic catheter and injection of standard nonionic contrast media. Nitroglycerine (400 μg) was injected in the coronary before the series of contrast injections. Images in multiple views were recorded at a rate of 25 frames/second. Four incidences or more were obtained for the left coronary artery, and two or more for the right. Computerized algorithms were used to quantify the diameter of the lesion (QCA; Philips, Best, The Netherlands). A stenosis was considered significant if the diameter of the lumen was reduced ≥50% in one incidence on QCA analysis. In RTR with abnormal scintigram, the coronary artery that fed the area of the perfusion defect was identified on the basis of anatomic distribution of the vessels. Each angiogram was analyzed by two independent operators (J.L.B., G.H.).

Studied parameters and definitions

For each RTR, the following parameters were recorded: age, sex, weight, body mass index (BMI), primary renal disease, previous graft, time on dialysis and on transplantation, serum creatinine, hypertension, diabetes, current or past smoking (more than 10 cigarettes/day for at least 10 years), hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and family history of CVD. Hypertension was defined (*1*) as blood pressure >140/90 mm Hg measured at least three times after a resting period of 10 minutes in a lying position (Joint National Committee VII criteria), or (*2*) as a need for antihypertensive drugs. Diabetes was defined as a fasting glycemia >7 mmol/L. Hypercholesterolemia was defined as total cholesterol when fasting >6 mmol/L or low-density lipoprotein (LDL) cholesterol >4.9 mmol/L (or as a need for cholesterol-lowering drugs), and hypertriglyceridemia was defined as triglycerides when fasting >2 mmol/L. Overweight was defined as a BMI >25 kg/m^2. Hyperuricemia was defined as uric acid when fasting >550 μmol/L (or as a need for uric acid-lowering drugs).

Previous CVD was recorded: coronary artery disease, left ventricular hypertrophy (LVH), aortic aneurysm and atheroma, ischemic stroke, and lower limb vascular disease. LVH was echocardiographically defined as a ventricular mass greater than 163 g/m^2 in men and 121 g/m^2 in women. The main treatments were also considered: angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium antagonist, diuretics, statins, and insulin.

During the follow-up, major adverse cardiac events (MACE) were defined as the occurrence of sudden death, myocardial infarction, need for coronary revascularization, or angioplasty. Other vascular events, mainly ischemic strokes, were also recorded.

Statistical analysis

The statistical software was SAS version 6.11 (Cary, NC, USA). Statistiscal analysis was performed by analysis of variance (ANOVA) and Student *t* test for continuous data, and the chi-square test or Fisher exact test for frequency analysis. Time-to-event analysis was performed using the Kaplan-Meier method, with comparison between event-free survival curves made by the log-rank test.

A regression logistic model was used to identify correlates of IMI. Factors included in the model were those obtained after comparison between groups of all the variables in univariate analysis with P less than 0.25. The variables tested were age, sex, time on dialysis, acute rejection, hypertension, hyperuricemia, LVH, cholesterolemia, serum creatinine, and calcium antagonist and beta-blocker treatment.

A Cox proportional hazards regression model was created to identify factors associated with the occurrence of cardiovascular events. Factors included in the model were those obtained after comparison between groups of all the variables in univariate analysis with P less than 0.25. The variables tested were age, sex, time on dialysis, time on transplantation, acute rejection, family history of CVD, diabetes, hypertension, cigarette smoking, dyslipidemia, cholesterolemia, BMI, IMI, and calcium antagonist treatment.

The significance threshold was $P < 0.05$.

RESULTS

Population characteristics

The characteristics of the patients are shown in Table 1. Most were men; the mean age of the population was 58 years. Mean time on dialysis and on transplantation was 41 months and 62 months, respectively. Twenty-six patients (27%) experienced at least one acute rejection at the time of the evaluation. Most patients were treated by steroids and anticalcineurin agents.

A majority of patients had cardiovascular risk factors. No patients had symptoms suggestive of angina at the time of the evaluation. Resting ECG did not show marked ST abnormalities.

Table 1. Characteristics of the study population

Characteristics Mean ± SD (min-max) or Number of patients (%)	$N = 97$
Age *years*	58 ± 6 (50–73)
Sex (male/female)	64/33
BMI	25.7 ± 5.5 (20–39)
Initial nephropathy	
Chronic glomerulonephritis	42
Chronic interstitial nephritis	12
Nephroangiosclerosis	18
Diabetes	3
Polycystic kidney disease	20
Other	1
Unknown	1
Time on dialysis *months*	41 ± 44 (1–249)
Time on transplantation *months*	62 ± 40 (1–108)
Acute rejection (number of patient)	26 (27%)
Acute rejection (number by patient)	0.34/patient
Serum creatinine *μmol/L*	134 ± 42 (70–297)
Steroids %	95 (98%)
Anticalcineurin agents %	93 (96%)
Diabetes %	16 (17%)
Hypertension %	91 (94%)
Dyslipidemia %	75 (77%)
Cholesterolemia *mmol/L*	5.8 ± 0.9 (2.4–8.5)
Triglyceridemia *mmol/L*	1.7 ± 0.8 (0.7–4.5)
Hyperuricemia	68 (70%)
Uricemia *μmol/L*	445 ± 94 (235–622)
Family history of cardiovascular disease %	5 (5%)
History of smoking or current smoker %	46 (47%)
BMI >25 kg/m^2 %	43 (44%)
Previous coronary artery disease %	10 (10%)
Left ventricular hypertrophy %	63 (65%)
Previous aortic aneurysm	3 (3%)
Previous ischemic stroke %	6 (6%)
Previous lower limb vascular disease %	13 (13%)
Statin %	72 (74%)
ACE inhibitor %	43 (44%)
Beta-blockers %	43 (44%)
Diuretics %	36 (37%)
Calcium antagonist %	46 (47%)
Insulin	14 (14.5%)

Prevalence of inducible myocardial ischemia

All the patients had an exercise test. Four were positive for ischemia, showing ST-segment depression in three, and ventricular arrythmias in one. All the patients had a SPECT coupled with dipyridamole. SPECT scan was abnormal in 11 patients, showing transient defect of perfusion. Dobutamine stress echocardiography was performed in 79 patients (81%). It was interrupted due to ventricular arrythmias in one patient, and a wall motion abnormality was observed in three cases (Table 2). On the whole, 12 patients (12%) had at least one abnormal test and were considered as having IMI (IMI group).

Prevalence of coronary stenosis

The 12 patients with IMI had coronary angiography (Table 2). Nine presented abnormalities on angiogram, but a ≥50% stenosis was observed in only five cases (42%). Thus, IMI was not related to a significant lesion in seven cases. None of the 12 patients referred to coronary angiography underwent coronary revascularization.

Correlates of IMI

The results of the multivariate analysis are shown in Table 3. Acute rejection, LVH, and calcium antagonists were the only correlates of IMI (calcium antagonists being protective against IMI).

Predictive factors for major cardiovascular events

All the patients had been followed-up for four years. During the observation time, three patients died from noncardiac cause (one of gastric neoplasia, one of lung neoplasia, one of pneumonia), and two lost their graft because of chronic rejection. Kaplan-Meier event-free survival curves showed a significant increase in major cardiovascular events in the IMI group ($P = 0.0001$, Fig. 2). The IMI group had higher four-year incidence of MACE

Table 2. Results of the tests for detecting IMI and of coronary angiography

Patient	Sex	Age	Exercise test	SPECT scan	Stress echocardiography	Coronary angiography
1	M	51	Nondiagnostic	Positive inferior	Not performed	Occlusion right coronary artery
2	M	54	Normal	Positive inferior-apical	Normal	Diffuse narrowing Nonsignificant stenosis of right coronary artery
3	M	63	Normal	Positive inferior-septal	Nondiagnostic	Diffuse narrowing
4	M	51	Positive ventricular arrythmias	Positive inferior	Nondiagnostic ventricular arrythmias	Normal
5	M	65	Nondiagnostic	Positive inferior	Not performed	Stenosis right coronary artery
6	M	63	Positive	Positive inferior, lateral, apical	Normal	Stenosis left anterior descending and right coronary artery
7	M	56	Positive	Normal	Positive apical	Normal
8	M	63	Nondiagnostic	Positive inferior	Positive all segments	Normal
9	F	59	Positive	Positive lateral	Normal	Diffuse narrowing
10	M	65	Nondiagnostic	Positive inferior-septal	Normal	Diffuse narrowing
11	F	62	Normal	Positive anterior	Normal	Occlusion diagonale branch
12	M	54	Normal	Positive inferior defect	Positive inferior-apical	Stenosis right coronary artery

Table 3. Multivariate analysis of correlates of IMI

Variables	Odds ratio	95% CI	*P* value
Acute rejection	11.4	1.4–95.5	0.025
Left ventricular hypertrophy	17.6	1.4–223.1	0.027
Calcium antagonist treatment	0.09	0.01–0.7	0.022

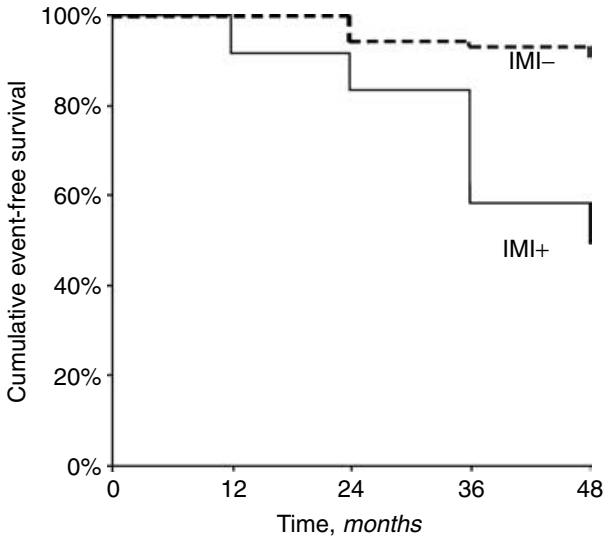

Fig. 2. Survival free of major cardiovascular events in the IMI+ and in the IMI− populations.

(42% vs. 8%), sudden death (25% vs. 1.2%), and nonfatal myocardial infarction or coronary revascularization (17% vs. 7%) and ischemic stroke (8% vs. 1.2%) (Table 4). In this group, a MACE was observed in four of the five patients with coronary stenosis, and in one patient with normal angiography. The Cox proportional hazards regression model revealed that only diabetes mellitus and IMI had an independent significant effect on major cardiovascular events (Table 5).

Table 4. Four-year incidence of major cardiovascular events in the IMI+ and in the IMI− populations

	MACE	Death cardiac origin	Myocardial infarction or coronary revascularization	Ischemic stroke
IMI+ ($N = 12$)	5 (42%)	3 (25%)	2 (17%)	1 (8%)
IMI– ($N = 85$)	7 (8%)	1 (1.2%)	6 (7%)	1 (1.2%)

MACE, major adverse cardiac events.

DISCUSSION

We found a 12.4% prevalence of IMI, silent in all cases, in our population of renal transplant recipients (RTR). IMI was investigated in only two previous studies: in one, the prevalence was 18%, but patients were either hemodialyzed or transplanted [16]. In the second study, performed only among RTR, Derfler et al [25] found a 39% prevalence of IMI. These two studies were small, with only 42 and 23 RTR, respectively. The study of Derfler et al is the only one we can compare our results with; our IMI prevalence was four times lower.

This relatively low prevalence of IMI was unexpected because the patients had numerous risk factors of coronary artery disease. Multiple factors may explain this low prevalence. The first factor is the low incidence of coronary artery disease among our dialysis patients. In fact, only 10% of our RTR had a previous history of coronary artery disease. The second factor is the low number of diabetic patients in our population. At the time of the evaluation, only 17% of the studied population was diabetic. In the United States, post-transplant diabetes mellitus occurred in more than 25% of the transplant population in the first three years after transplantation [26, 27]. The third factor is our policy of very active treatments of all the treatable risk factors for cardiovascular disease. The large use of ACE inhibitors and statins may also play a role because these drugs are known to decrease the incidence of cardiovascular events in high-risk patients [28, 29]. Furthermore, we selected dialyzed patients for

Table 5. Cox model of risk factors of major cardiovascular events

Variables	Hazards ratio	95% CI	*P* value
Diabetes	58.2	1.25–2734	0.04
Inducible myocardial ischemia	31.1	1.4–689	0.03
Acute rejection	18.4	0.9–3946	0.06
Calcium antagonist treatment	0.04	0.01–1.02	0.05

transplantation on the basis of recommended criteria [17]. Only patients older than 65 years of age, type II diabetics with lower limb amputation, and patients with extensive nonrevascularizable cononary artery disease are judged not suitable for transplantation, thus there is no bias in selection. It is also unlikely that we underestimated the prevalence of IMI because most of the patients performed two detection tests, and 81% of them underwent DSE. Finally, as acute rejection was a correlate for IMI, the low prevalence of IMI could have been explained by a low prevalence of acute rejection. This was not the case since we observed a usual rate of acute rejection.

The multivariate analysis evidenced that the only correlates for IMI were acute rejection and LVH. The correlation between acute rejection and IMI is an interesting finding, but this result should be considered preliminary because our study is small and the confidence interval is wide. Two features can explain the increased risk of IMI in patients with acute rejection. First, the high doses of steroids given as treatment for acute rejection aggravate cardiovascular risk factors such as hypertension and diabetes. Second, the inflammatory process triggered by the immunologic reaction is associated with cardiovascular events [5]. This study also strengthens the relationships between LVH and myocardial ischemia [30].

Another result of this study is that IMI had a strong effect on the occurrence of MACE and of ischemic stroke. More than 40% of the patients in the IMI group had a cardiovascular event, and 25% died because of cardiac causes. Furthermore, this result was obtained after a relatively short follow-up.

What are our study limitations? One limitation of the methods for detecting stress-induced myocardial ischemia is the dependence of these methods on flow-limiting coronary stenosis. In this study, five patients had significant coronary stenosis, and four had coronary narrowing. In the latter, IMI might be due to resistance to blood flow resulting from diffuse atherosclerosis and endothelial dysfunction. We studied only RTR ≥50 years of age. We chose this age limit because it was not possible to look for IMI in the whole population of RTR, and age is a major risk factor for cardiovascular events.

CONCLUSION

In RTR aged ≥50 years, acute rejection and LVH were correlates of IMI. IMI and diabetes mellitus were associated with MACE and ischemic stroke. Regular screenings of IMI may be useful to select patients who need intensive reduction of cardiovascular risk factors.

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Reprint requests to Pr. Bertrand Dussol, Service de Néphrologie, Hôpital de la Conception, 147 Bd Baille, 13385 Marseille Cedex 05, France.
E-mail: bdussol@mail.ap-hm.fr

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