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Cardiac evaluation of candidates for kidney transplantation: value of exercise radionuclide angiocardiography

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In view of the high incidence and mortality of coronary artery disease (CAD) in patients with kidney transplantation, a systematic cardiac evaluation was prospectively performed in 103 uraemic patients eligible for transplantation. After clinical examination, 28 patients with symptoms of CAD or diabetes mellitus were referred directly for coronary angiography, whereas the remaining 75 patients had rest and exercise radionuclide angiocardiography for evaluation of possible asymptomatic CAD. Among them, left ventricular ejection fraction was below 40% at rest or fell during exercise by at least 5 EF% in 12 patients; coronary angiography in nine showed CAD in four and hypertensive heart disease in five. In the remaining 63 (of 75) patients without severe resting left ventricular dysfunction or exercise ischaemia, the follow-up of 28 ± 7 months revealed no clinical manifestation of CAD. Overall incidence of CAD in symptomatic and asymptomatic patients during a follow-up of 27 months after cardiac evaluation was 20 and 25% in non-diabetic and diabetic candidates for kidney transplantation, respectively (P = n.s.). Thus, clinical examination combined with exercise radionuclide angiocardiography in patients without signs or symptoms of heart disease had a high predictive accuracy for presence or absence of late manifestations of CAD. Exercise radionuclide angiocardiography is therefore a useful method for screening kidney transplantation candidates for asymptomatic CAD.

Introduction

Cardiovascular disease is common in patients with chronic renal failure[1–3]. Of 59 patients who died after kidney transplantation in Basel between 1967 and 1985, and in whom autopsy was performed, 21 (36%) showed significant coronary artery disease and in nine (15%) acute myocardial infarction was the cause of death. The EDTA Registry has reported a similar proportion of fatal coronary events after kidney transplantation[4].

Therefore, it is important to identify patients with significant coronary artery disease (CAD) before kidney transplantation. This is routine practice in patients with symptoms of cardiac disease, but non-invasive examination should allow detection of clinically occult CAD at an early state and thus institution of vigorous medical and/or surgical therapy. In addition, patients with severe heart disease and poor prognosis could be identified who might be denied kidney transplantation based on objective cardiac investigations.

Based on such considerations, a protocol for systematic cardiac evaluation was set up and followed prospectively between 1984 and 1987. Symptomatic cardiac patients underwent coronary angiography; patients without cardiac symptoms were screened by exercise radionuclide angiocardiography (RNA) which was followed by left heart catheterization if the examination suggested CAD. Patients with renal failure due to juvenile diabetes mellitus underwent coronary angiography irrespective of cardiac symptoms. The following report presents the results of a systematic assessment and follow-up of this strategy in order to define a 'best' future cardiac evaluation of patients with chronic renal failure before kidney transplantation.

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Patients

From January 1984 to October 1985 113 uraemic patients were evaluated as candidates for kidney

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Table 1 Baseline characteristics of 103 candidates for kidney transplantation

	Group 1	Group 2	Group 3
Number of patients (n)	75	19	9
Women (%)	63	47	87
Age (years)	51·6 ± 9·3	56·3 ± 5·4	46·2 ± 9·9
Cause of renal failure (%):			
toxic interstitial nephritis	36	42	0
glomerulonephritis	26	5	0
polycystic kidney disease	14	11	0
pyelonephritis, postrenal obstruction	12	5	0
nephrosclerosis	1	11	0
tuberculosis	0	5	0
diabetes mellitus	0	0	100
cause unkown	10	21	0
Arterial hypertension (%)	66	46	89
Patients on haemodialysis (%)	96	95	44
duration (months)	11·9 ± 12·8	17·3 ± 18·2	5 5 ± 3·8

Group 1: no clinical evidence of cardiac disease; Group 2: with clinical evidence of cardiac disease; Group 3: diabetes mellitus type 1.

transplantation in Basel. Patients were eligible if they developed irreversible renal failure below the age of 66 years. Of these 113 patients, 98 received a renal transplant between 1984 and 1987 (95 cadaveric grafts and three kidneys from living relative donors). All were treated after transplantation with cyclosporine and low dose prednisone. Among these 98 patients, only 10 received a kidney graft without undergoing cardiac evaluation. In three cases a matched graft was available before cardiac examination, and in six the nephrologist in charge decided not to do the exercise RNA in view of the patients' young age (mean age of all 10 patients: 33 ± 9 years). One patient refused cardiac investigations.

Of the remaining 103 patients with cardiac evaluation, 75 had no signs or symptoms of cardiac disease (group 1), 19 had a history suggestive of cardiac disease (group 2) and nine suffered from diabetes mellitus type 1 (group 3). Table 1 shows the baseline characteristics of the patients in these three groups. Diabetic patients were younger than group 2 patients. Toxic interstitial nephritis was the leading cause of renal failure in both group 1 and 2. Almost all patients in group 1 and 2 were on haemodialysis, whereas five of nine diabetics were not on haemodialysis.

Methods

CARDIAC INVESTIGATION

All patients underwent a thorough clinical assessment that included history, physical examination, chest X-ray and a 12-lead electrocardiogram (ECG). The Minnesota criteria for CAD were applied in the interpretation of the resting ECG[5]. Patients without clinical evidence of cardiac disease (group 1) were studied by exercise RNA. If left ventricular ejection fraction (LVEF) at rest was below 40% and/or LVEF decreased $\geqslant 5\%$ from rest to symptom-limited exercise and regional left ventricular wall motion abnormalities were observed, coronary angiography was performed.

Patients with a history of heart disease, signs of heart failure or valvular disease at physical examination, signs of ischaemic heart disease in the resting ECG or an important enlargement of the cardiac silhouette on chest X-ray were studied by angiography prior to kidney transplantation (group 2). All patients with insulin-dependent diabetes mellitus (group 3) were investigated by coronary angiography only.

EXERCISE RADIONUCLIDE ANGIOCARDIOGRAPHY

Radionuclide data were accumulated at rest and continuously during exercise for LVEF determination, as previously described[6]. Multiple gated equilibrium radionuclide angiograms were performed by in vivo labelling of red blood cells with 20 mCi technetium-99m after cold pyrophosphate had been injected 20–30 min earlier. Imaging was then recorded with a single crystal scintillation camera of the Anger-type equipped with a high sensitivity collimator in a 40°–50° left anterior oblique and 5°–10° caudal tilt projection which best allowed

separation of the left ventricle from other heart chambers. Data acquisition was accomplished with a commercially available nuclear medicine computer system (Medtronic/MDS-A^2 system). The cardiac cycles of a 2 min acquisition period at rest or peak exercise were assembled at corresponding times to generate composite images throughout the heart cycle and to calculate LVEF. Ejection fraction was determined as previously reported; values calculated by this technique have been shown to correlate well with those determined from biplane cineangiography[7]. Regional wall motion was visually assessed in five sectors of the left ventricle.

All patients underwent supine bicycle exercise on an electronically braked Elema-Schönander ergometer (type EM 350). The initial workload was 25 W. The load was increased in steps of 25 W until appearance of symptoms: marked dyspnoea and/or pain and fatigue in the legs and/or angina pectoris. ECG and blood pressure were monitored during the exercise test. The ECG was visually analysed and the criteria for myocardial ischaemia were applied as described by Fortuin and Weiss[8]. Leads with ST abnormalities at rest were not analysed. On the day of exercise RNA, the patients were on their usual medication including, in some, β-blockers and calcium-antagonists. No effort was made to observe the same delay between the exercise RNA and the last haemodialysis in all patients.

LEFT HEART CATHETERIZATION

Coronary angiography was performed using standard Judkins technique (femoral artery puncture). Right and left coronary artery were filmed in three to four projections and visually assessed. Obstruction in lumen diameter of $>50\%$ was considered significant for CAD. Biplane contrast ventriculography was done routinely and left ventricular end-systolic volume, left ventricular end-diastolic volume and LVEF were calculated on a Philips semi-automatic Grafomed computer system[9].

FOLLOW-UP

Follow-up was based on medical records of the nephrology out-patient service and on autopsy reports. CAD was diagnosed if autopsy revealed CAD as the cause of death or if two of the three following criteria for myocardial infarction were present: ECG changes typical for myocardial infarction; ischaemic pain lasting >30 min; transient elevation of creatine phosphokinase. Angina pectoris and dyspnoea were not included as end-points into follow-up.

STATISTICS

Data are given as mean $\pm$ 1 standard deviation. Comparisons between groups were performed using Student's t-test for unpaired comparisons and chi-square tests where appropriate. P values of $<0{\cdot}05$ were considered significant.

Results

PATIENTS WITHOUT A HISTORY OF CAD

Seventy-five patients with renal failure but no clinical symptoms or signs of cardiac disease were examined by exercise RNA (group 1). In 63 (84%) LVEF at rest was $\geqslant 40\%$ and did not fall more than 5% during exercise; no regional wall motion abnormalities were found (group 1a, see Table 2). In this group, maximally tolerated workload on supine exercise was 53 ± 12 W at a heart rate of 111 ± 18 beats min^{-1}. Average LVEF at rest was $62 \pm 10\%$, and at maximal exercise $66 \pm 10\%$. Four patients showed a significant ST-depression on ECG with no definite signs of ischaemia on RNA.

Sixty of 63 patients from group 1a received a kidney transplant 10 ± 7 months after the exercise radionuclide study. These 60 patients were followed-up for a period of 28 ± 7 months after cardiac evaluation and of 19 ± 9 months after transplantation (Table 3). No patient in this group developed signs or symptoms of CAD on clinical grounds. One woman aged 60 years at the time of the exercise test later presented with new Q waves in V1–V3 on the ECG. Her radionuclide study had shown general hypokinesia of the right ventricle. Echocardiographic evidence for regional akinesia was not found. The ECG changes in this patient reflected cor pulmonale due to chronic obstructive lung disease. In 49 patients the function of the kidney graft was well preserved. Nine were back on dialysis again and two patients had died (one from septicaemia of unknown origin, one from pneumonia).

In 12 of 75 patients (16%) the radionuclide angiogram showed LVEF at rest $<40\%$ and/or a fall in LVEF during exercise of $\geqslant 5\%$ with or without regional wall motion abnormalities (group 1b, see Table 2). In comparison with group 1a, maximal workload, exercise heart rate and LVEF at rest as well as age did not differ. But this group of patients showed, instead of an increase, a significant fall in LVEF during exercise ($-5 \pm 5\%$ vs $+4 \pm 6\%$

Table 2 Exercise RNA in 75 candidates for kidney transplantation without clinical evidence of cardiac disease

	Group 1a	Group 1b
Number of patients (n)	63	12
Women (%)	59	83
Age (years)	52±10	56±10
Maximal workload (W)	53±12	51±9
Exercise heart rate (beats min^{-1})	111±18	112±19
ECG: ST-depression > 1 mm (n)	4	2
LVEF at rest (%)	62±10	58±10*
LVEF during exercise (%)	66±10	53±9**
Change in LVEF from rest to exercise (%)	+4±6	−5±5**
Coronary angiograms performed (n)		9
one- or two-vessel CAD		4
hypertensive heart disease		5

* = not significant, paired two-tailed *t*-test, group 1a vs 1b; ** = $P<0.01$, paired two-tailed *t*-test, group 1a vs 1b.
Abbreviations RNA = radionuclide angiocardiography; CAD = coronary artery disease; LVEF = left ventricular ejection fraction.
Group 1a: no signs of CAD; Group 1b: signs of CAD present (LVEF <40%, decrease of LVEF during exercise of ≥5% and regional wall motion abnormalities).

Table 3 Follow-up in 88 patients after kidney transplantation

	Group			
	1a	1b	2	3
Number of patients (n)	60	10	13	5
Follow-up after				
cardiac evaluation (months)	28±7	28±9	26±10	27±6
kidney transplantation (months)	19±9	15±9	17±9	21±9
Graft function well preserved (n)	49	8	8	5
On haemodialysis at follow-up (n)	9	1	1	0
Death from cardiac disease (n)	0	0	3	0
Death from other cause (n)	2	1	1	0

LVEF; $P<0.01$, Table 2). Only two patients presented with significant ST-depression during exercise in this group. Coronary angiography was performed in nine of the 12 patients: one- or two-vessel CAD was found in four patients (7% of the total group 1). The risk of myocardial infarction was considered low in these four subjects and coronary artery bypass grafting or percutaneous transluminal coronary angioplasty not recommended. Five patients showed hypertensive heart disease defined as LVEF <40% at rest and/or a fall in LVEF of more than 5% during exercise without regional wall motion abnormalities but with left ventricular hypertrophy without CAD at contrast angiography and with a history of high blood pressure treated with more than one antihypertensive drug for more than 1 year. Angiography was not performed in three patients: one received a kidney transplant before the planned angiographic procedure, one patient died of myocardial infarction before angiography at the age of 65 years, and another was later denied kidney transplantation for

other reasons. Ten out of 12 patients received a kidney transplant; 15±9 months after transplantation the grafts were functioning well in 8 subjects, one patient was on dialysis again (Table 3). None developed myocardial infarction. A 44-year-old man died from cytomegalovirus infection after kidney transplantation.

PATIENTS WITH CLINICAL SIGNS OF CAD

Nineteen patients with signs or symptoms of cardiac disease were included in group 2 (Table 1). Coronary angiography was performed in 18 and showed one- to three-vessel disease in 14, hypertensive heart disease in three and valvular heart disease in one patient. Two patients underwent coronary artery bypass surgery prior to transplantation. In two patients coronary surgery and kidney transplantation was not recommended due to extensive CAD during the observation period. Thirteen of the 19 patients received a kidney graft; three of them died after transplantation from CAD, one despite coronary artery bypass surgery. At follow-up after 17±9 months the kidney grafts were functioning well in eight subjects; one patient had to undergo nephrectomy and was on dialysis again.

PATIENTS WITH JUVENILE DIABETES

Nine patients with juvenile diabetes mellitus were in group 3 (Table 1). Coronary angiography was performed in eight and CAD documented in two patients. Coronary artery bypass surgery was not recommended as the coronary disease was not severe. Five of the nine patients including those two with CAD have since received a kidney transplant which showed satisfactory function at a follow-up of 21±9 months. Three patients died before kidney transplantation (none from CAD) and one was refused as a candidate for transplantation due to general illness.

The overall incidence of CAD in candidates for kidney transplantation examined either by RNA or coronary angiography was therefore 20% (20/101). The incidence did not differ between non-diabetic and diabetic patients (20% vs 25%).

Discussion

We report the results of a systematic prospective cardiac evaluation of 103 candidates for kidney transplantation by exercise RNA and/or coronary angiography and their follow-up over 19 months after kidney transplantation. CAD is a major cause of death in patients treated with kidney transplantation[4]. Our primary interest was to study those candidates for kidney transplantation who showed no clinical signs or symptoms of heart disease. We assumed that detection of clinically occult CAD would allow us to institute medical and/or surgical therapy at an early stage of the disease and thereby lower the incidence of myocardial infarction and cardiac death.

DETECTION OF CAD IN PATIENTS WITH RENAL FAILURE

Coronary angiography would most accurately identify patients at risk of CAD, but this expensive examination, which is not without hazard, should not be used in a population with relatively low disease prevalence. On the other hand, the exercise ECG alone is not very helpful in this patient group, as confirmed by our findings: only 2 of 12 patients without clinical evidence of CAD but radionuclide signs of exercise-induced ischaemia showed clear-cut ST-segment depression during exercise. This low diagnostic accuracy of the exercise ECG is partly due to the limited physical work capacity of uraemic subjects. In addition, the exercise ECG is difficult to interpret in patients with ST-T wave changes already at rest as in patients with hypertensive heart disease. Therefore, only horizontal or downsloping ST-depression of >1 mm in leads with a normal ST-segment at rest was accepted as diagnostic for myocardial ischaemia in this study. Furthermore, thallium-201 stress testing has been found to be no more predictive of future coronary events than history and exercise ECG in uraemic diabetics[10]. Exercise RNA has a sensitivity of at least 90% and a specificity of around 80% in patients with chest pain and normal kidney function, when compared with coronary angiography[6,7], but the high prevalence of arterial hypertension and hypertensive heart disease in patients with end-stage renal disease results in lower specificity if the usual criteria for normal exercise RNA are applied (resting LVEF $>50\%$, increase from resting to exercise LVEF $\geq 5\%$ and absence of regional left ventricular wall motion abnormalities). Wassermann *et al.* showed that the increase in LVEF from rest to exercise was below 5% in most hypertensive patients with chest pain in whom CAD could be excluded by angiography[11]. Therefore, we diagnosed significant myocardial ischaemia in patients with renal failure only if a decrease in LVEF from rest to exercise of at least 5% in the presence of regional wall motion abnormalities was found. Further invasive investigation

was also considered mandatory if resting LVEF was <40%. This would not only identify patients with CAD but also, hopefully, all those with significant heart disease of other causes justifying invasive examination.

SENSITIVITY AND SPECIFICITY OF EXERCISE RNA IN URAEMIC PATIENTS WITHOUT SYMPTOMS OF HEART DISEASE

Since the majority of the 75 subjects without manifest heart disease (group 1) of our trial were not studied by angiography, the sensitivity of exercise RNA for CAD in patients with end-stage kidney disease cannot be determined. It is of note, however, that over a follow-up period of 28 ± 7 months after the radionuclide study or 19 months after kidney transplantation, none of the 60 patients without ischaemia during exercise RNA developed CAD based on clinical information. Therefore, significant CAD is very unlikely to develop over the following 2–3 years in uraemic patients with a negative radionuclide exercise text. Exercise RNA, therefore, successfully identified patients at low risk of cardiac complications.

On the other hand, 16% of uraemic patients without signs or symptoms of heart disease showed severe resting or exercise-induced left ventricular dysfunction in the radionuclide study as defined above. In half of them one- or two-vessel CAD was detected, in the other half left ventricular dysfunction could be explained by hypertensive heart disease. Blood pressure during exercise was of no value in differentiating these two subgroups. Thus, the sensitivity of exercise RNA for CAD was only 50%; the sensitivity for CAD *or* severe hypertensive heart disease, however, was excellent.

PATIENTS WITH RENAL FAILURE AND DOCUMENTED CAD

In contrast to expectations, this protocol did not identify patients with clinically occult high-grade coronary stenoses, who would undoubtedly benefit from coronary artery bypass surgery or angioplasty. We based the selection of uraemic patients for surgery or angioplasty on the usual criteria derived from the CASS study and the European Trial on Coronary Surgery[12,13]. However, the number of patients was too small to allow definite conclusions. Over a follow-up of 15 ± 7 months after kidney transplantation, the four patients with a one- or two-vessel CAD developed no clinical signs of CAD after transplantation. Repeated RNA in these patients will hopefully allow early detection of an increase in coronary stenoses and prevention of myocardial infarction by surgery or angioplasty.

Eighteen patients with clinically apparent cardiac disease were studied by coronary angiography. The angiographic findings were useful for the identification of patients with severe CAD and a limited prognosis who had to be excluded from kidney transplantation for this reason. On the other hand, the high mortality rate from CAD after kidney grafting in this group (3/13, 23%) raises the question of the management of patients after kidney transplantation with known CAD. As reported by several authors, surgery is feasible in uraemic patients but at an increased risk[14] and symptomatic CAD can also successfully be treated with balloon angioplasty in these patients[15–18]. However, we still lack a larger controlled trial to answer the question whether interventions such as angioplasty or coronary surgery should be performed more aggressively in patients with known of CAD after kidney transplantation[19,20].

CAD IN RENAL FAILURE DUE TO JUVENILE DIABETES

Eight patients with diabetic kidney failure without clinically apparent heart disease were studied by coronary angiography. CAD was found only in two patients, comparable to the incidence of CAD in non-diabetic patients with renal failure (20%). This is in accordance with a report of Braun *et al.*, who observed a prevalence of 21% of CAD in 100 diabetic patients with chronic renal failure[21].

Conclusions and implications

This study confirms the high incidence of CAD of 20% to 25% in patients with chronic renal failure who are candidates for kidney transplantation. According to the reported observation, this incidence was similar for diabetic and non-diabetic patients. In asymptomatic patients, scintigraphic cardiac evaluation using rest and exercise radionuclide angiocardiography had a high prognostic accuracy to exclude CAD: no patient developed clinical signs or symptoms of CAD during a mean follow-up of 28 months. On the other hand, patients with an abnormal scintigraphic result as defined for this study all had either CAD or hypertensive left ventricular dysfunction.

Thus, in patients with renal failure and no signs or symptoms of heart disease, clinical examination combined with exercise RNA had a high diagnostic accuracy to predict absence of late manifestations

of CAD. However, patients with non-invasively detected asymptomatic CAD had no cardiac events during the observation period of this study; it remains to be shown by future studies, therefore, whether the treatment of silent ischaemia will improve long-term prognosis. If it can be demonstrated prospectively that medical or interventional treatment of early, clinically silent CAD is beneficial as suggested in a retrospective analysis[22], then a screening strategy as proposed in this study will provide important information.

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