Islet Transplantation Is Associated With an Improvement of Cardiovascular Function in Type 1 Diabetic Kidney Transplant Patients

PAOLO FIORINA, MD[1]
CHIARA GREMIZZI, MD[1]
PAOLA MAFFI, MD[1]
ROSSANA CALDARA, MD[1]
DAVIDE TAVANO, MD[1]
LUCILLA MONTI, MD[1]
CARLO SOCCI, MD[2]
FRANCO FOLLI, MD[1]
FERRUCCIO FAZIO, MD[3]
ETTORE ASTORRI, MD[4]
ALESSANDRO DEL MASCHIO, MD[5,6]
ANTONIO SECCHI, MD[1,6]

OBJECTIVE — Cardiovascular mortality and morbidity are major problems in type 1 diabetic patients with end-stage renal disease (ESRD). The aim of this study was to determine whether islet transplantation can improve cardiovascular function in these patients.

RESEARCH DESIGN AND METHODS — We assessed various markers of cardiac function at baseline and 3 years later in a population of 42 type 1 diabetic patients with ESRD who received a kidney transplant. Seventeen patients then received an islet transplant that had persistent function as defined by long-term C-peptide secretion (kidney-islet group). Twenty-five patients did not receive a functioning islet transplant (kidney-only group).

RESULTS — GHb levels were similar in the two groups, whereas the exogenous insulin requirement was lower in the kidney-islet group with persistent C-peptide secretion. Overall, cardiovascular parameters improved in the kidney-islet group, but not in the kidney-only group, with an improvement of ejection fraction (from 68.2 ± 3.5% at baseline to 74.9 ± 2.1% at 3 years posttransplantation, $P < 0.05$) and peak filling rate in end-diastolic volume (EDV) per second (from 3.87 ± 0.25 to 4.20 ± 0.37 EDV/s, $P < 0.05$). Time to peak filling rate remained stable in the kidney-islet group but worsened in the kidney-only group ($P < 0.05$). The kidney-islet group also showed a reduction of both QT dispersion (53.5 ± 4.9 to 44.6 ± 2.9 ms, $P < 0.05$) and corrected QT (QTc) dispersion (67.3 ± 8.3 to 57.2 ± 4.6 ms, $P < 0.05$) with higher erythrocytes Na^+-K^+-ATPase activity. In the kidney-islet group only, both atrial natriuretic peptide and brain natriuretic peptide levels decreased during the follow-up, with a stabilization of intima-media thickness.

CONCLUSIONS — Our study showed that type 1 diabetic ESRD patients receiving a kidney transplant and a functioning islet transplant showed an improvement of cardiovascular function for up to 3 years of follow-up compared with the kidney-only group, who experienced an early failure of the islet graft or did not receive an islet graft.

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From the [1]Department of Medicine, San Raffaele Scientific Institute, Milan, Italy; the [2]Department of Surgery, San Raffaele Scientific Institute, Milan, Italy; the [3]Department of Nuclear Medicine, San Raffaele Scientific Institute, Milan, Italy; the [4]Department of Cardiology, University of Parma, Parma, Italy; the [5]Department of Radiology, San Raffaele Scientific Institute, Milan, Italy; and [6]Universita' Vita e Salute, San Raffaele Scientific Institute, Milan, Italy.

Address correspondence and reprint requests to Antonio Secchi, MD, Medicina, San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milano, Italy. E-mail: secchi.antonio@hsr.it.

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Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; ESRD, end-stage renal disease; IMT, intima-media thickness; QTc, corrected QT.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Most cardiac disease and events in type 1 diabetic patients are due to *1*) diabetic cardiomyopathy, with progressive deterioration of left ventricular function; *2*) diabetic coronary angiopathy, with progression of coronary atherosclerosis; or *3*) diabetic sudden death resulting from myocyte electrical failure (1–3).

With diabetic cardiomyopathy, systolic dysfunction in normotensive diabetic patients has not been clearly shown (3). Abnormality in diastolic dysfunction has been uniformly observed in asymptomatic diabetic patients, but its relationship with metabolic control in type 1 diabetic patients is still a matter of debate (4–6).

With diabetic coronary angiopathy, progressive worsening of coronary artery atherosclerosis and macroangiopathy is evident in patients with diabetes, but pancreas and islet transplants reduce this risk (7–11). A noninvasive marker of atherosclerosis and coronary events is intima-media thickness (IMT) (12), which is stabilized with pancreas transplantation (9).

In diabetic sudden death, diabetic hearts showed a variety of electrical abnormalities (13). An increase in QT dispersion, a marker of heart electrical properties, was evident in diabetic patients and is positively associated with the risk for serious ventricular arrhythmias (14–24). Pancreas transplantation has been shown to exert positive effects on diabetic cardiomyopathy (25–27).

Our aim was to evaluate cardiovascular function at 3 years of follow-up in type 1 diabetic patients with end-stage renal disease (ESRD) who received a kidney transplant with or without a functioning islet transplant.

RESEARCH DESIGN AND METHODS

— This is a retrospective study evaluating a pool of type 1 diabetic patients with ESRD, all of whom received

Table 1—*Pre- and posttransplant characteristics of ESRD type 1 diabetic kidney transplant patients with or without a functioning islet transplant*

	Kidney-islet group	Kidney-only group	*P* value
n	17	25	
Age (years)	47.7 ± 1.3	49.2 ± 2.2	NS
Sex (male/female)	7/10	16/9	NS
C-peptide levels before islet transplant (ng/ml)	0.14 ± 0.02	0.15 ± 0.03	NS
C-peptide levels at year 3 (ng/ml)	1.7 ± 0.2	0.3 ± 0.1*	<0.01
Duration of diabetes (years)	31.9 ± 2.3	30.4 ± 1.7	NS
Duration of dialysis (years)	3.8 ± 0.5	2.8 ± 0.3	NS
Cardiovascular events (*n*)	8 of 17	5 of 25	NS
GHb (%)	7.7 ± 0.3	8.6 ± 0.6	NS
Body weight (kg)	59.7 ± 2.0	59.3 ± 3.1	NS
BMI before islet transplant (kg/m^2)	22.2 ± 0.8	23.4 ± 0.9	NS
BMI at year 3 (kg/m^2)	23.1 ± 0.9	24.2 ± 1.0	NS
Time to graft function (h)	30.0 ± 22.7	24.8 ± 17.5	NS

Data are means ± SE.

a kidney transplant from a cadaveric donor. Seventeen patients subsequently received a functioning islet transplant (kidney-islet group) and 25 did not (kidney-only group) based on ABO matching. They were admitted yearly to San Raffaele Hospital in Milan, Italy, and received regular check-ups each 6 months even if they had functioning islets or no difference in medical appointments and diabetes management, and they were followed for 3 years. Patients who developed a myocardial infarction during the follow-up period were excluded from the analysis (two in the kidney-islet and one in the kidney-only group), so that impairment of ventricular function did not influence any other beneficial/detrimental effects of islet transplant. All subjects provided informed consent before enrollment in the transplant program. There was no difference in time from the kidney transplant until the cardiovascular assessment (kidney-islet group = 2.55 ± 0.75 years, kidney-only group = 1.90 ± 0.90 years; NS).

Patients underwent radionuclide ventriculography and ultrasound evaluation of carotid IMT yearly. The QT dispersion and corrected QT (QTc) dispersion values from the follow-up electrocardiograms were compared with values from pretransplant electrocardiograms. Furthermore, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels were evaluated at baseline and after 3 years.

Exclusion criteria for islet transplant were as follows: *1*) severe hepatic dysfunction, *2*) major stroke with neurological inability, *3*) major amputation, *4*) severe dilated cardiomyopathy, or *5*) severe coronary artery disease. Patients were carefully screened for known cardiovascular risk factors and underwent perfusional myocardial scintigraphy, echocardiography, and carotid and lower-limb Doppler ultrasonography. Patients who had a perfusion defect (nonreversible at rest) on scintigraphy were excluded from receiving an islet transplant until they underwent a coronarography. Some of the patients in both groups reported cardiovascular events before kidney transplantation (i.e., episodes of heart failure and angina) with no differences between the two groups (Table 1).

The use of antihypertensive and cardiovascular medications (β-blockers, calcium antagonists, digoxin, amiodarone, and ACE inhibitors) was recorded before and after the islet transplant and compared.

Islet transplantation

Islet transplantation was based on ABO matching. Islets were isolated from the pancreases obtained from multiorgan donors, according to Ricordi (28,29). Islets were injected under local anesthesia into the portal vein via a percutaneous approach under ultrasonographic and fluoroscopic guidance.

Immunosuppression and postoperative management

Immunosuppression was induced with ATG (thymoglobulin; IMTIX, SANGSTAT) and maintained with cyclosporine, mycophenolate mofetil, and prednisone. The two groups received the same triple-standard immunosuppression protocol, with a progressive withdrawal of steroids during the follow-up period (Table 2). All patients received 100 mg aspirin daily as maintenance antiplatelet treatment.

Radionuclide left ventriculography

Patients underwent radionuclide left ventriculography after a 15-min rest in the recumbent position. All the patients were in sinus rhythm. The following parameters were calculated: left ventricle ejection fraction, peak ejection rate, peak filling rate, and time to peak filling rate. Diastolic dysfunction was defined as previously described (30).

QT analysis

QT intervals from 12-lead electrocardiograms were analyzed. On a surface 12-lead electrocardiogram (25 mm/s), the QT interval was taken from the onset of the QRS to the end of the T wave (return to the T/P baseline). If U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves (14,17,18). QT intervals were corrected with Bazett's formula (QTc = QT/RR) (14,17,18). QTc dispersion, defined as the difference between maximum and minimum QTc, was calculated.

Na^+-K^+-ATPase activity

Na^+-K^+-ATPase activity of erythrocytes was assessed cross-sectionally at 3.9 ± 0.5 years posttransplant as previously described (31).

IMT

Patients underwent ultrasonographic analysis of IMT of the carotid artery as previously reported. The operators measuring IMT, as well as people who read all cardiovascular tests, were blinded on patients' conditions (9). Briefly, ultrasonographic analysis of the carotid artery was done with a high-resolution ultrasound scanner (Acuson 128 Xp/10) equipped with a linear array 3.5- to 5-MHz transducer. A single trained technician recorded all the images for IMT. All IMTs were analyzed in the same session by a single blinded and trained physician. IMT

Table 2—*Metabolic parameters in ESRD type 1 diabetic kidney transplant patients with or without a functioning islet transplant*

	Kidney-islet group		Kidney-only group	
	Baseline	Year 3	Baseline	Year 3
Creatinine (mg/dl)	1.4 ± 0.1	1.6 ± 0.2	1.6 ± 0.3	1.7 ± 0.3
GHb (%)	7.7 ± 0.3	7.7 ± 0.2	8.6 ± 0.6	8.1 ± 0.5
Exogenous insulin requirement (U/day)	25.2 ± 4.3*†	17.3 ± 3.4*†	32.1 ± 7.0*	35.1 ± 4.4*
Fasting glucose (mg/dl)	216.5 ± 28.8	192.8 ± 24.4	195.1 ± 29.3	231.1 ± 41.4
Systolic blood pressure (mmHg)	139.6 ± 4.0	143.0 ± 5.2	146.0 ± 4.9	150.1 ± 4.6
Diastolic blood pressure (mmHg)	81.8 ± 2.6	85.3 ± 1.8	86.1 ± 2.8	88.5 ± 1.4
Cholesterol (mg/dl)	214.6 ± 11.1	202.3 ± 12.8	196.8 ± 20.02	199.8 ± 11.5
Triglycerides (mg/dl)	121.4 ± 14.2	130.8 ± 15.9	110.0 ± 18.5	112.5 ± 16.0
Cyclosporin (ng/ml)	174.5 ± 16.5	155.9 ± 9.6	150.6 ± 8.7	163.8 ± 26.0
HDL (mg/ml)	65.7 ± 6.8	65.4 ± 3.9	57.1 ± 6.1	55.8 ± 5.0
LDL (mg/ml)	114.8 ± 12.7	117.0 ± 8.4	125.3 ± 15.1	112.0 ± 8.6
Prednisone (mg/day)	7.3 ± 1.2	3.5 ± 0.8	7.5 ± 0.9	4.6 ± 0.8
Verapamil	6	1	8	3
β-Blockers	4	1	4	1
Digoxin-amiodarone	1	1	3	3
ACE	7	5	10	8
Statin	1	2	1	2

Data are means ± SE or *n*. Exogenous insulin requirement is lower in the kidney islet group. *Kidney-islet versus kidney-only both at baseline and year 3, $P < 0.05$. †Kidney-islet showed a statistical reduction of insulin requirements, $P < 0.05$.

was defined as the distance from the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall. The mean of the right and the left longitudinal common carotid artery IMT measurements was used in the analysis. Intraobserver variability was 0.02 ± 0.02 mm in our group as previously reported (9).

Clinical follow-up and laboratory measurement

All patients underwent annual clinical and laboratory assessments, particularly for GHb. GHb analysis was performed by high purified liquid chromatography (Variant II-BioRad) with intrassay variations of 2.6%. The normal range for GHb with our assay is between 3.5 and 6.0%. Blood pressure was recorded at each outpatient visit as the mean of three standard measurements, and the presence of hypertension was determined as described (9). ANP and BNP levels were assayed with an ELISA kit (Peninsula Laboratories) with a minimum detectable dose of 0.04–0.06 ng/ml. Technicians who assayed GHb, C-peptide levels, and ELISAs were blinded to patients' conditions. All laboratory tests were done with the same assay pre- and posttransplant.

Statistical analyses

Data are expressed as means ± SE. A two-sided paired Student's *t* test (for parametric data) and Wilcoxon test (for nonparametric data) were used to compare baseline parameters versus follow-up data. A χ^2 test for categorical variables was used when necessary. When the two groups were compared cross-sectionally, a two-sided unpaired Student's *t* test (for parametric data) or Mann-Whitney test (for nonparametric data) was used according to distribution. $P < 0.05$ (by two-tailed testing) was considered an indicator of statistical significance. Analyses of data were done using an SPSS statistical package for Windows (SPSS, Chicago, IL).

RESULTS — Forty-two type 1 diabetic patients with ESRD were enrolled in the study. Of these, 17 patients had received a functioning islet transplant in addition to the kidney transplant (kidney-islet group) defined on the basis of sustained C-peptide secretion (fasting C-peptide serum concentration >1.0 ng/ml for >1 year). The remaining 25 kidney transplant recipients (kidney-only group) were on a waiting list for an islet transplant ($n = 15$) or had experienced early failure (within 6 months) of the islet transplant ($n = 10$).

Table 1 summarizes patient characteristics pretransplant. At the time of recruitment for kidney transplantation, the two groups were comparable regarding the most important clinical characteristics (Table 1). All patients were C-peptide negative (<0.5 ng/ml) at that time.

During the follow-up period, persistent C-peptide secretion was evident in the kidney-islet group, statistically higher than that in the kidney-only group ($P < 0.01$ throughout follow-up) with a lower exogenous insulin requirement ($P < 0.05$ throughout follow-up) (Tables 1 and 2). However, the two groups showed no significant differences in GHb levels (Table 2). Twelve patients from the kidney-islet group maintained insulin independence for >3 months (mean duration, 21.5 ± 4.2 months).

Patients in both groups showed a trend toward increased creatinine levels during the follow-up period with no significant differences in mean creatinine levels being evident between the two groups. As shown in Table 2, ambulatory systolic blood pressure, diastolic arterial blood pressure, triglyceride levels, and cholesterol levels were similar in both groups of patients during the follow-up. Finally, there was no difference in BMIs between the two groups at baseline, after 3 years of follow-up, and between the time to kidney graft function (Table 1).

Cardiovascular medications and cardiovascular risk factors

There was a nonstatistical reduction in the mean number of cardiovascular drugs assumed in both the kidney-islet group

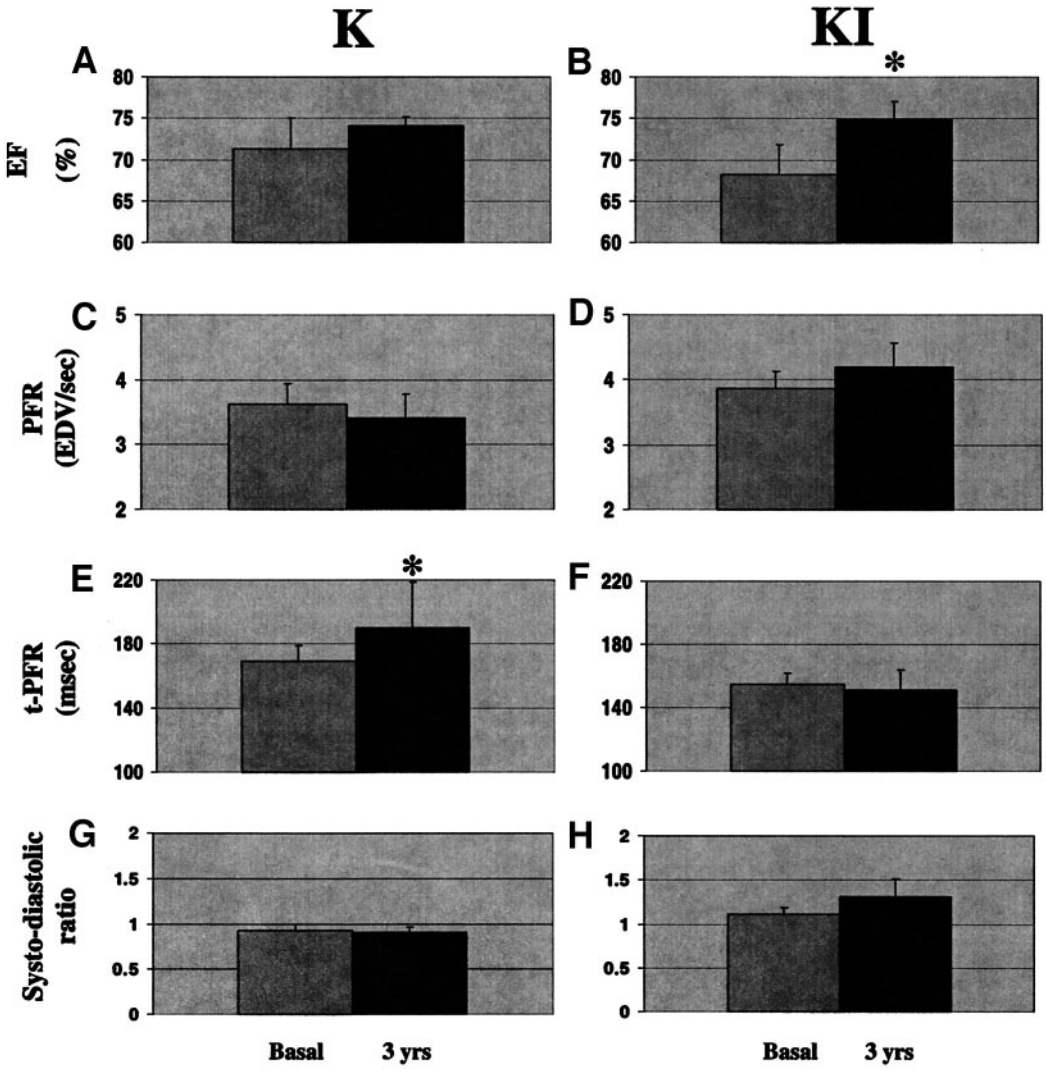

Figure 1—*Parameters of systolic and diastolic function in ESRD type 1 diabetic kidney transplant patients with a functioning islet transplant (KI) or a nonfunctioning islet transplant (K).* A *and* B*: An improvement of ejection fraction (EF) was observed in the KI but not in the K (NS).* C *and* D*: Peak filling rate (PFR) improved in KI, whereas it declined in K.* E *and* F*: Time to peak filling rate (t-PFR) worsened in K, whereas in KI it remains stable (NS).* G *and* H*: Systodiastolic ratio (PFR/peak ejection rate) improved in KI but not in K (NS).* *P < *0.05.*

(from 1.35 ± 0.27 drugs/day to 0.88 ± 0.14 drugs/day) and the kidney-only group (1.48 ± 0.16 to 1.12 ± 0.16). In particular, no changes were observed for digoxin, amiodarone, or ACE inhibitors, whereas a reduction in verapamil and β-blocker intake was evident. For other cardiovascular risk factors, no differences were evident in smoking status (three smokers in the kidney-islet group and four in the kidney-only group). One patient in each group was receiving treatment with a hydroxymethylglutaryl-CoA reductase inhibitor before the enrollment and another one was added in each group at 3 years (Table 2). No differences between the two groups were evident for ACE inhibitors and adrenergic receptor binder blockade, nor was a statistical reduction evident in either group during the follow-up (Table 2). Regarding steroids, no differences in the mean dosage between the two groups at baseline and at 3 years were found (Table 2).

Left ventricular systolic function and heart rate

Mean ejection fraction increased significantly from baseline in the kidney-islet group ($P < 0.05$) but remained stable in the kidney-only group (Fig. 1*A* and *B*). Neither group showed a significant change from baseline in mean peak ejection rates after 3 years (data not shown).

The two groups differed significantly in mean heart rate at 3 years follow-up, although within each group there was no significant change from baseline after 3 years. At 3 years follow-up, patients in the kidney-islet group showed a slight decrease from baseline in mean value heart rate (from 75.4 ± 2.8 to 69.6 ± 2.9 bpm, NS) and patients in the kidney-only group showed a slight increase from baseline in mean heart rate at 3 years follow-up (from 78.8 ± 5.0 to 81.9 ± 4.4, NS).

Left ventricular diastolic function

Mean peak filling rate improved in the kidney-islet group after 3 years ($P < 0.05$) but remained stable in the kidney-only group (Fig. 1*C* and *D*). Mean time to peak filling rate showed a slight improvement from baseline in the kidney-islet group and slight worsening in the kidney-only group ($P < 0.05$) (Fig. 1*E* and *F*). Finally, diastolic ratio, an index of global left ventricular function, increased nonstatistically in patients in the kidney-islet group and remained stable in patients in the kidney-only group (Fig. 1*G* and *H*).

QT interval

Mean RR remained stable in both the kidney-islet and kidney-only groups (from

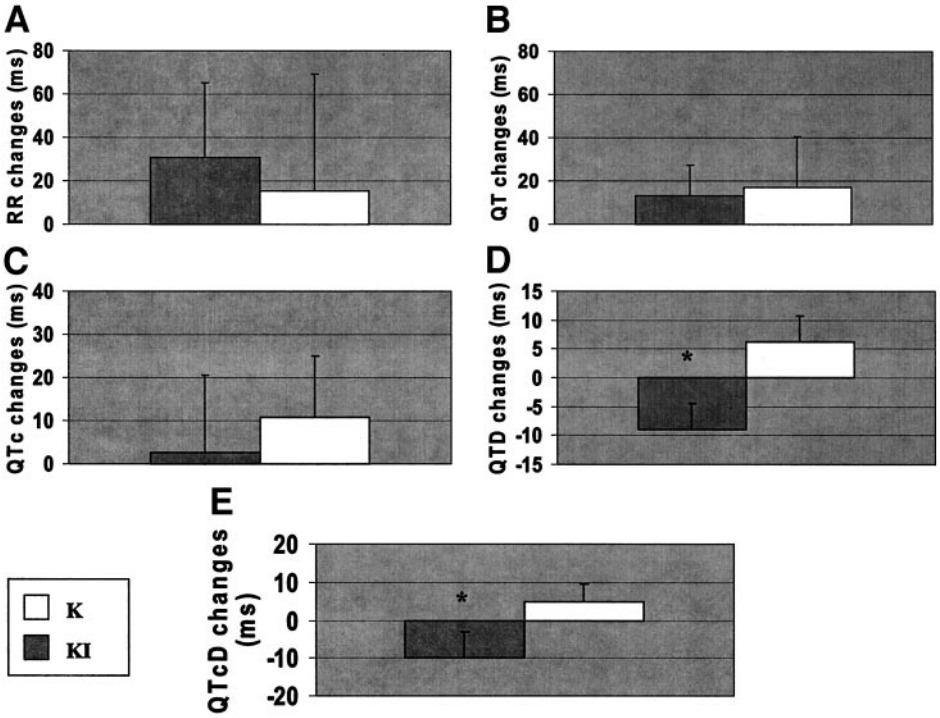

Figure 2—*Parameters of electrical function in ESRD type 1 diabetic kidney transplant patients with a functioning islet transplant (KI) or a nonfunctioning islet transplant (K).* A*: RR increased in both KI and K (NS).* B*: QT increased in KI and K (NS).* C*: QTc increased in KI and K (NS).* D *and* E*: KI but not K showed a reduction of both QTc dispersion and QT dispersion.* *P $<$ *0.05.*

768.8 ± 26.4 to 799.5 ± 37.1 ms and from 846.0 ± 51.5 to 861.3 ± 70.3 ms, respectively) (Fig. 2*A*). Mean QT and QTc remained stable in both groups (Fig. 2*B* and *C*). Patients in the kidney-islet group but not in the kidney-only group showed a reduction of both mean QTc dispersion (kidney-islet: from 67.3 ± 8.3 to 57.2 ± 4.6 ms, $P < 0.05$ vs. kidney-only: from 62.0 ± 10.7 to 67.7 ± 10.1, NS) and mean QT dispersion (kidney-islet: 53.2 ± 6.6 to 45.7 ± 3.9, $P < 0.05$ vs. kidney-only: 48.8 ± 6.4 to 53.0 ± 7.0, NS) (Fig. 2*D* and *E*).

Na^+-K^+-ATPase activity

Na^+-K^+-ATPase activity in erythrocytes appeared higher in patients in the kidney-islet group compared with patients in the kidney-only group (4.05 ± 0.29 vs. 3.08 ± 0.30 mmol · Na^{-1} · l^{-1} cell/h, respectively; $P < 0.05$).

BNPs and ANP

Patients in the kidney-islet group experienced a decrease from baseline in both BNP ($P = 0.01$) and ANP ($P = 0.07$) (Fig. 3*A* and *B*). In the kidney-only group, mean BNP and ANP remained stable (Fig. 3*A* and *B*).

IMT

For patients in the kidney-islet group, IMT remained stable at the 3-year follow-up. By contrast, patients in the kidney-only group showed significant worsening of mean IMT after 3 years ($P < 0.05$) (Fig. 3*C*).

For the kidney-only group, we separately analyzed patients who received an islet transplant and experienced an early lost of function and those who did not receive the transplant. The parameters of cardiovascular function showed a similar behavior as when they were pooled together, without a statistically significant difference between them (data not shown).

CONCLUSIONS — In this report, we describe for the first time the course of cardiovascular function over a 3-year follow-up period in kidney transplant patients with or without a functioning islet transplant. Islet transplantation is associated with an improvement of cardiac function in our kidney transplant patients, with an amelioration of diastolic function, QT dispersion, and a reduced IMT progression. Furthermore, a reduction in ANP level, a marker of atrial and ventricular function, was evident during the follow-up period.

The natural history of β-cell replacement through an islet transplant showed that after a variable a period of normoglycemia with insulin independence (up to 4 years in some patients) (32), β-cell function underwent a progressive deterioration. In our populations, at least 12 patients maintained insulin independence for at least 3 months. After that, β-cells started to lose their function, but residual C-peptide and insulin secretions were evident, leading to a period of better glycometabolic control with lower postprandial glucose levels and an important impact on lifestyle and diabetes complications.

Survival in uremic type 1 diabetic patients undergoing hemodialysis is extremely poor, and kidney transplantation does not completely improve this situation (8,26). Different studies have shown that patients with type 1 diabetes with nephropathy have increased left ventricular hypertrophy and diastolic dysfunction, whereas systolic function is still normal (33,34). In our group of kidney transplant patients with a functioning islet, an improvement of diastolic function was particularly evident after a functioning islet transplant.

ANP and BNP are peptide hormones with a variety of biological effects, including relaxation of vascular smooth muscle and augmentation of urinary volume and urinary sodium excretion, and are markers of heart failure (35–37). A slight elevation of BNP level, as in our patients, may reflect early pathologic processes occurring before the development of apparent cardiac manifestations (35). An

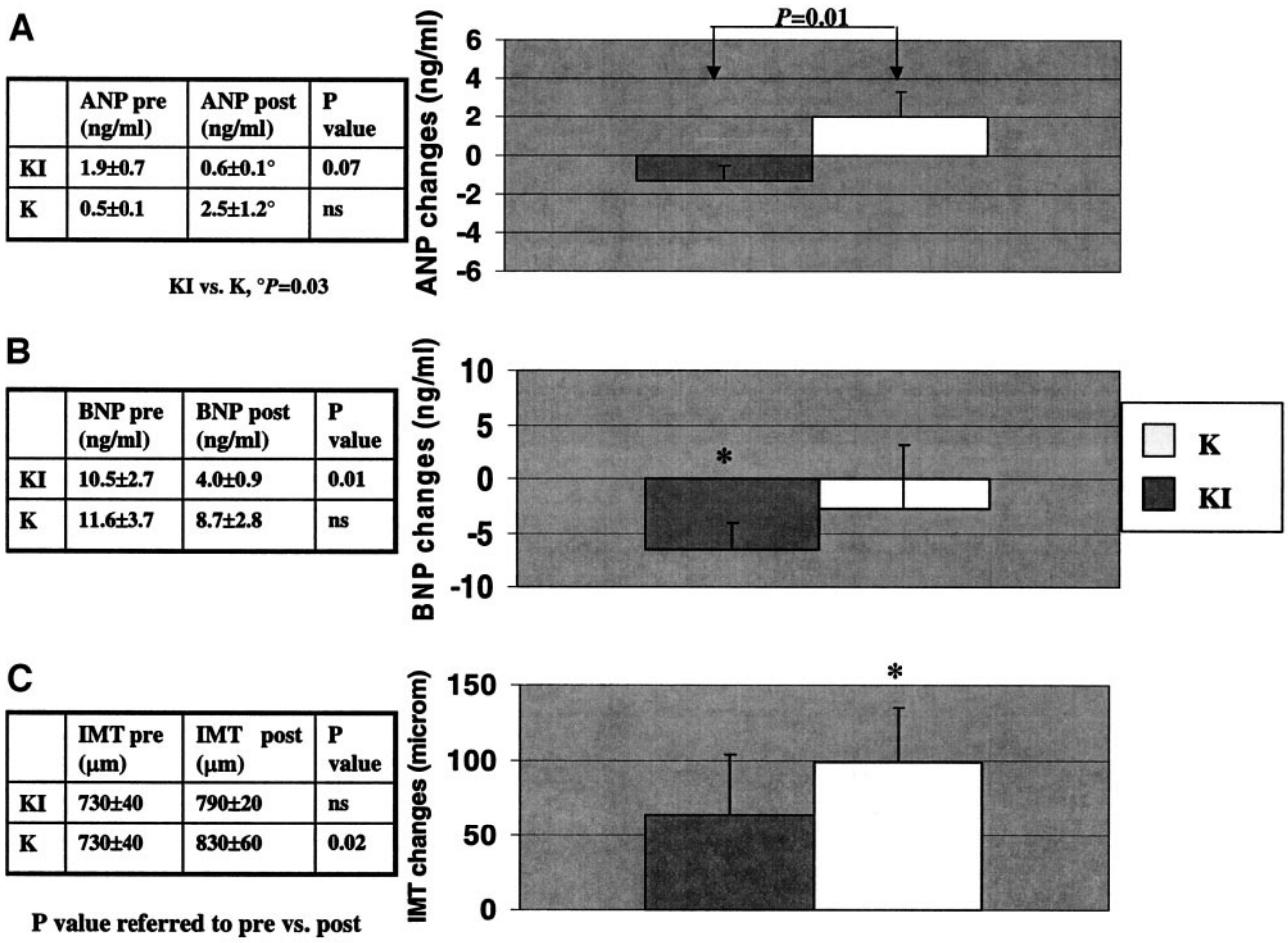

Figure 3—*Parameters of cardiovascular function in ESRD type 1 diabetic kidney transplant patients with a functioning islet transplant (KI) or a nonfunctioning islet transplant (K). A and B: BNP and ANP both decreased in KI (P = 0.01 for BNP) but not in the K group. C: KI showed a stabilization of IMT (NS), whereas IMT worsened in K. *P < 0.05.*

alternative explanation is that increased levels of BNP may reflect early diastolic dysfunction (36). As previous studies demonstrated (37,38), reduced levels of both these hormones in the kidney-islet group suggests an improvement in loading conditions and may indicate a reduced likelihood of heart failure or diastolic dysfunction in the kidney-islet group. The kidney-islet group had higher baseline ANP levels (possibly suggesting worse cardiovascular conditions in this group), which might even strengthen the role of islet transplantation in improving cardiovascular outcomes.

During the follow-up period, patients in the kidney-islet group attained HbA_{1c} values similar to those found to prevent diabetic microvascular complications in the Diabetes Control and Complications Trial (39,40). The beneficial effects of functioning islets could be the consequence of improved metabolic control and of the restoration of islet endocrine function in the kidney-islet group. Increased levels of C-peptide secreted by functioning islets may lead to improvement of microvascular dysfunction. In fact, previous studies have shown that C-peptide administration in diabetic rats could improve neural and vascular function (28,41). Infusion of C-peptide in type 1 diabetic patients leads to a redistribution of microvascular blood flow levels (42), which could induce an improvement of diastolic filling. An observation in support of this hypothesis is that the kidney transplant patients in our study without functioning islets experienced increased IMT, which correlates with coronary atherosclerosis. The nonsignificant difference observed by sex between the kidney-islet and kidney-only groups will not affect IMT progression.

Hyperglycemia may induce QT changes by increasing the cytosolic calcium content, by stimulating sympathetic activity, or both (19–21). Acute hyperglycemia in normal subjects produces significant increases of QTc and QTc dispersion (20). QTc dispersion could be due to patchy myocardial fibrosis, ischemia, left ventricular dilatation, or neurohormonal activation leading to electrical inhomogeneity (15–18). In the kidney-islet group, the reduction of insulin resistance or C-peptide per se could be the key for the improvement of QT dispersion. The exogenous insulin requirement in the kidney-islet group was half that of the kidney-only group, and higher circulating insulin levels could have been present in the latter group. Finally, our study suggests that C-peptide has a direct effect on Na^+-K^+-ATPase activity in myocytes, al-

though we assessed Na^+-K^+-ATPase only in the erythrocytes.

Cardiovascular medications could partially affect our results, given that a nonsignificant decrease in the number of drugs assumed was evident in both groups. Among the other medications, it is interesting to observe that cyclosporine values did not differ at either the beginning or the end, although they were going in different directions from the outset in the two groups, which could contribute to differences in interval renal function, blood pressure, lipid metabolism, and ultimately cardiovascular outcomes.

This study has several possible limitations. Other factors could influence cardiac function and diastolic properties, but this study was not designed to evaluate these effects. Moreover, coronary artery disease could be an important factor influencing the progression of diastolic dysfunction. We assessed coronary artery disease using noninvasive methods to avoid the risks of contrast medium–induced nephropathy on the transplanted kidneys. The techniques we used, such as an at-rest electrocardiogram or myocardial scintigraphy with ^{201}Tl, cannot always detect coronary microvascular disease, which could be a limitation of our study. Finally, the cohort of patients is relatively small; only a multicenter approach would allow recruitment of an adequate population size. It is important to note that the kidney-only group showed higher exogenous insulin requirements at baseline with a higher degree of insulin resistance. It was not a purpose of our study to address the question of insulin resistance before and after islet transplant. However, insulin resistance can be an unstudied cardiovascular risk factor (44,45), partially influencing our results.

It is possible that the small sample size may not allow identification of significant differences between the two groups. Finally, it is possible that some new pre- or peritransplant cardiovascular risk factors not evaluated by our study (45,46) could partially bias our data.

In conclusion, our study showed that type 1 diabetic patients with ESRD who received a kidney transplant and a functioning islet transplant showed improvement in mechanical, electrical, and vascular aspects of cardiac function after up to 3 years of follow-up compared with the group receiving only a kidney transplant.

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