L-Arginine-Induced Vasodilation of the Renal Vasculature Is Preserved in Uremic Type 1 Diabetic Patients After Kidney and Pancreas but not After Kidney-Alone Transplantation

OBJECTIVE — In uremic type 1 diabetic patients, kidney and pancreas transplantation (KP) and kidney-alone transplantation (KD) provide full restoration of normal renal function; however, only KP, i.e., curing diabetes, is expected to prevent endothelial damages. Our aim was to study L-arginine-induced vasodilation of the renal vasculature in uremic type 1 diabetic patients after KP or KD using magnetic resonance (MR).

RESEARCH DESIGN AND METHODS — MR quantitative flow measurements were performed in 15 KP patients (mean age 39.0 ± 1.7 years, 10 men and 5 women), in 11 KD patients (mean age 47.3 ± 1.9 years, 7 men and 4 women), and in 8 nondiabetic kidney transplant patients (mean age 44.0 ± 4.8 years, 7 men and 1 woman), who were used as control subjects, to measure renal blood flow and velocity and renal vascular resistance before and immediately after infusion of L-arginine.

RESULTS — Renal blood flow and velocity were not different at baseline in KP, KD, and control subjects. In contrast, during L-arginine administration renal blood flow increased significantly in KP subjects (basal 8.4 ± 0.6 vs post 9.6 ± 0.8 ml/s, \( \Delta 14.3 \pm 4.4\%\), \( P < 0.05 \)) and in control subjects (basal 9.3 ± 0.8 vs post 9.1 ± 0.8 ml/s, \( \Delta 17.3 \pm 6.2\%\), \( P < 0.01 \)), while it remained unchanged in KD subjects (basal 10.0 ± 0.8 vs post 11.6 ± 0.9 ml/s, \( \Delta -1.36 \pm 6.9\%\), NS). Parallel results have been achieved for renal blood velocity (KP subjects: 20.1 ± 4.9%, \( P < 0.01 \); control subjects: 23.0 ± 7.90%, \( P < 0.01 \); and KD subjects: −0.3 ± 6.5%, NS). A reduction in renal vascular resistance in response to L-arginine was evident in KP and control subjects but not in KD patients.

CONCLUSIONS — L-Arginine vasodilatory response was successfully assessed with MR quantitative flow measurements. KP patients and control subjects, but not those with KD, showed a preserved L-arginine-induced vasodilation of the renal vasculature.

From the 1Department of Radiology, Università Vita e Salute-San Raffaele, San Raffaele Scientific Institute, Milan, Italy; the 2Department of Internal Medicine, Section of Organ Transplantation, Università Vita e Salute-San Raffaele, San Raffaele Scientific Institute, Milan, Italy; the 3Department of Internal Medicine, Section of Nutrition and Metabolism, Università Vita e Salute-San Raffaele, San Raffaele Scientific Institute, Milan, Italy; and the 4Department of General Surgery, Università Vita e Salute-San Raffaele, San Raffaele Scientific Institute, Milan, Italy.

Address correspondence and reprint requests to Francesco De Cobelli, MD, Department of Radiology, or Paolo Fiorina, MD, PhD, Department of Medicine, Università Vita e Salute-San Raffaele, San Raffaele Scientific Institute Via Olgettina, 60, 20132 Milan, Italy. E-mail: francesco.decobelli@hsr.it or paolo.fiorina@hsr.it.

Received for publication 28 August 2003 and accepted in revised form 23 December 2003.

F.D.C. and P.F. contributed equally to the work.

Abbreviations: ECG, electrocardiogram; eNOS, endothelial nitric oxide synthase; KD, kidney-alone transplantation; KP, kidney and pancreas transplantation; MR, magnetic resonance; RBF, renal blood flow; RBV, renal blood velocity; RVR, renal vascular resistance.

© 2004 by the American Diabetes Association.
para-amino-hippurate clearance (14), Doppler ultrasound (15), or angiography (16).

L-Arginine vasodilatory response assessment using magnetic resonance (MR) quantitative flow measurements has never been reported. MR cine phase-contrast flow quantification can provide noninvasive measurements of volume flow and flow velocity (18–20). Phase-contrast MR imaging has been used in visualization of native and transplanted renal arteries (21,22) and in quantification of renal flow, and it has been compared and validated with para-aminohippuric acid clearance and Doppler sonography in both in vitro and in vivo studies (19,20,23–25).

When end-stage renal disease has been reached, kidney and pancreas transplantation (KP) is the only treatment able to reverse both uremia and diabetes and to reverse the progression of diabetes complications and preserve endothelial function (26,27). The preservation of renal endothelial-dependent dilation is a functional (26,27). The preservation of renal endothelial-dependent dilation is a functional marker that might influence graft survival.

Our hypothesis is that type 1 diabetic patients with end-stage renal disease undergoing kidney-alone transplantation (KD) have a blunted vasodilatory response to L-arginine, whereas similar patients undergoing KP will have a normal vasodilatory response when compared with a nondiabetic, transplanted control group. We used an MR quantitative flow to assess transplant renal artery flow in this study.

**RESEARCH DESIGN AND METHODS**—Thirty-four consecutive transplanted patients admitted to our hospital for regular follow-up control were prospectively enrolled in the study between January 2002 and March 2003. Twenty-six were uremic type 1 diabetic patients: 15 patients received KP and 11 patients, who either lost their pancreatic graft early in the postoperative period (5 of 11) or who received only a renal transplant due to macroscopic damage of the pancreas at harvesting (6 of 11), constituted the KD group. Eight uremic nondiabetic subjects who received kidney transplantation served as the control group. Patients were submitted to our protocol at 3.1 ± 0.5 years in the KP group, 4.2 ± 1.2 years in the KD group, and 5.8 ± 1.0 years in the control group (P = NS) after transplantation. General characteristics of the three groups are summarized in Table 1. By splitting the KP group according to age over or under the median value, we could obtain a subpopulation of “old” KP patients.

Exclusion criteria for transplantation were previous strokes, major amputations, severe dilated cardiomyopathy, and coronary artery disease. Before transplantation, none of the patients had a pathological ejection fraction or heart failure. Furthermore, all of the patients who entered the transplantation program in our institute were carefully evaluated for known cardiovascular risk factors. No differences were evident with regard to electrocardiogram (ECG), perfusion myocardial scintigraphy, echocardiography, and carotid and lower limb arterial status, as evaluated by Doppler ultrasonography. In regard to immunosuppression, after induction with ATG (Thymoglobulin, Imtix, and Sangstat), immunosuppression was based on cyclosporine (circulating blood levels between 100 and 250 ng/ml), mycophenolate mofetil (500–2,000 mg/day), and methylprednisone (10 mg/day). Steroids were withdrawn within 3–6 months after transplantation. Episodes of renal rejection were treated with pulses of 500 mg of methylprednisolone. Cases of steroid-resistant rejection were treated with OKT3 or a course of ATG. All KP patients were non–insulin dependent, whereas KD patients were on intensive intermittent subcutaneous insulin injection therapy. Only two patients in the KD group were treated with statins. Organs for transplantation were obtained from cadaver donors through Nord Italia Transplant.

Exclusion criteria from this study were clear signs of systemic infection, lymphoproliferative disease, urinary infection, enhanced erythrocyte sedimentation velocity, or elevated C-reactive protein (acceptable levels were <10 mg/l). All of the patients provided informed consent, and the protocol was approved by the institutional review board at our institution and by the Italian Minister of Health.

**MR imaging and analysis**

MR imaging was obtained with a 1.5-T superconducting magnet (Gyrosan Intera Master; Philips Medical Systems, Best, the Netherlands) using an enhanced gradient system with a maximum gradi-
ent strength of 30 mT/m and a maximum gradient slew rate of 150 T · m⁻¹ · s⁻¹. The Cardiac Research software patch (operating system 8) was used. In all cases, the examination was performed with a phased-array multicoil (Synergy Body Coil, four-channel system; Philips Medical Systems).

First, in all patients axial and coronal breath-hold, T1-weighted, fast field-echo sequences were acquired to localize kidneys and to evaluate the volume and morphology of the kidneys. Image acquisition time was 20 s for each plan.

After localizing images, MR angiography was performed with an ECG-gated, 3-D phase-contrast technique. The image acquisition time was between 3 and 5 min, depending on cardiac frequency. The 3-D phase-contrast images were reconstructed using maximum intensity projection techniques to visualize the number, anatomy, and course of the transplanted renal arteries and to exclude the presence of transplanted renal artery stenosis.

Flow mapping was performed with an ECG-gated, quantitative flow measurement, 2-D, phase-contrast, fast field-echo sequence positioned perpendicular to the transplanted renal artery; fast field-echo MR flow mapping was performed during free breathing and took ~3–5 min, depending on the heart rate. This sequence was retrospectively ECG gated, with a temporal resolution of 25 phases per cardiac cycle. Imaging parameters included the following: repetition time (in milliseconds)/echo time (in milliseconds)/flip angle, 8–11/5.2–6.4 ms, 15° flip angle, 6-mm section thickness, data matrix of 128 × 256, 30 cm 50% rectangular field of view, and three-signal acquired. Velocity-encoding gradients were applied in the slice-selective direction with a velocity of 100 cm/s.

Both magnitude and phase MR images of the transplanted renal artery were displayed on an image-processing workstation (EasyVision; Philips Medical Systems) by using the flow analytic software package (release 5x). The luminal area was traced manually on the magnitude images and automatically transferred to the velocity phase images by an experienced operator. The position and the size of each contour were adjusted according to the cardiac phase. The mean velocity and mean flow (in milliliters per second) within each region of interest and the area of region of interest (in squared centimeters) were determined for each cardiac frame and, subsequently, curves of velocity and flow rate versus time were automatically reconstructed. Renal vascular resistance (RVR) was evaluated according to a previous study (28) by dividing mean blood pressure by mean RBF.

1-Arginine infusion
After quantification of transplanted renal artery blood flow at baseline with MR flow analysis, an intravenous 1-arginine infusion was started (30 g 1-arginine HCl in 100 ml distilled H₂O solution was injected during a period of 30 min). Blood pressure monitoring was performed at baseline and during 1-arginine infusion in all patients at 15, 30, 45, 60, 75, and 90 min. Blood pressure was measured with a sphygmomanometer with subjects in the sitting position, and the average of the last two measurements was recorded. Hyperension was considered present if any of the following conditions were met: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or reported use of a medication for hypertension. The categories of medication assessed in this study were ACE inhibitors, vasodilatory agents, β-blockers, and calcium-channel antagonists (24). In KD patients, hyperglycemia was partially corrected during the whole test period by means of a continuous subcutaneous insulin injection associated with glycemic monitoring to avoid the effects mediated by acute hyperglycemia on endothelial function.

Metabolic studies
During the test, sequential blood samples were drawn to evaluate insulin and C-peptide levels, glycemia, and NO levels. Serum C-peptide levels were assayed by radioimmunoassay using commercial kits (Medical System, Genoa, Italy). NO levels were assayed by measurement of the end products of their metabolism (i.e., nitrite and nitrate levels [NO₃⁻/NO₂⁻]) using an enzymatic catalysis coupled with Griess reaction. Specifically, NO₂⁻ was reduced to NO₃⁻ by 0.1 unit nitrate reductase, 5 × 10⁻⁶ mol/l flavin adenine dinucleotide, and 250 × 10⁻⁶ mol/l nicotinamide adenine dinucleotide phosphate (reduced form). Samples were incubated at 37°C for 3 h, 8.8 units lactate dehydrogenase and 10⁻² mol/l pyruvate were added to each well, and the sample was incubated for 90 min at 37°C. Finally, Griess reactives were added to each well, and the sample was read at 540 nm. The other parameters were assessed with a common laboratory assay kit.

Statistical analysis
All data were expressed as means ± SE. Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with Levene’s test. Two-sided paired Student’s t test (for parametric data) and Kruskal-Wallis (for nonparametric data) were used to compare baseline parameters versus post-1-arginine infusion. When the three groups were cross-sectionally compared, ANOVA (for parametric data) or Kruskal-Wallis (for nonparametric data) was used according to distribution. When ANOVA was used, multiple post hoc comparison analysis was performed with Tukey’s test. Correlations were assessed with a Spearman rank correlation coefficient. A P value <0.05 (by two-tailed testing) was considered an indicator of statistical significance. Analysis of data was done using SPSS statistical package for Windows (SPSS, Chicago, IL).

RESULTS

General characteristics
No differences in kidney rejection, HLA matching, panel reactive antibodies, cold ischemia time, and donor age were evident between the KP and KD groups. In the KD group, a nonstatistically significant higher donor and recipient age were evident (Table 1). The three groups were similar in regard to kidney function (Table 1). The hypertension rate was similar in the three groups (for normotensive and hypertensive subjects: KP, 7 and 8; KD, 5 and 6; and control subjects, 3 and 5, respectively; NS). No significant differences in regard to therapy with ACE inhibitors, vasodilatory agents, β-channel blockers, or calcium antagonists were shown in the three groups.

RBF and renal blood velocity
RBF and renal blood velocity (RBV) mean values were not statistically different among groups at baseline (P = NS), and no transplanted renal artery stenosis was found.

The transplanted renal artery blood flow response to the intravenous infusion of 1-arginine was different in KD, KP, and...
control groups (Fig. 1A). After l-arginine administration, RBF increased significantly in the KP group (Δ 14.3 ± 4.4%, P < 0.05) (Table 2) and in the control group (Δ 17.3 ± 6.2%, P < 0.01), but not in the KD group (Δ −1.36 ± 6.9%, NS) (Table 2 and Fig. 1A). By splitting the KD group (11 patients) into two subgroups constituting patients who received only the kidney due to macroscopic damage of the pancreas at harvesting (KD1, n = 5) and patients with early failure of the pancreas (KD2, n = 6), the two subgroups showed a similar behavior in regard to l-arginine response (RBF increase: KD1 versus KD2, 0.47 ± 15.8 vs. −2.88 ± 3.4%, respectively, P = NS), confirming the absence of the risk of bias in the grouping of the KD patients.

RBV confirmed the tendency observed by flow data. Its increase was highly significant in the KP (Δ 20.1 ± 4.9%, P < 0.01) and control groups (Δ 23.0 ± 7.99%, P < 0.01) (Table 2 and Fig. 1B). In the KD group, the variation in RBV was absent (Δ −0.3 ± 6.5%, NS) (Table 2 and Fig. 1B).

To evaluate the role of chronic exposure in the diabetic milieu, the changes in RBF were evaluated accordingly to years of follow-up in the KD, KP, and control groups, separately. Interestingly, although a progressive decline in RBF was evident during the follow-up in the KD group (change in RBF at 2 years, 9.5 ± 11.8; at 4 years, −3.2 ± 5.0; and at 8 years, −17.6 ± 12.8), this was not evident for the KP and control groups (change in RBF at 2 years, 9.8 ± 5.0; at 4 years, 22.2 ± 6.5; and at 8 years, 14.0 ± 6.8).

To better address the point of whether different glycemic control could have a role in the alteration of l-arginine–induced vasodilation of the renal vasculature, the KD group was split according to high (9.6 ± 0.3%) or low (7.4 ± 0.4%) HbA1c levels. The low-HbA1c group showed better, though not statistically significant, RBF changes (change in RBF, 1.3 ± 1.2%) than the high-HbA1c group (changes in RBF, −3.5 ± 13.2%).

**Arterial blood pressure and RVR**

In regard to the systemic effects of l-arginine infusion, a reduction in arterial blood pressure was evident in the KP and control groups, but not in the KD group. In the KP group, systolic (P < 0.01), diastolic (P < 0.05), and mean arterial blood pressures (P < 0.01) (Table 2) blood pressures lowered during l-arginine infusion. In the control group, only diastolic (P < 0.01) and mean arterial blood pressures (P < 0.05) (Table 2) lowered during l-arginine infusion. In the KD group, there were no significant changes in systolic, diastolic, and mean arterial blood pressures during l-arginine infusion (Table 2). Consequently, a reduction in RVR in response to l-arginine was evident in KP (P < 0.05) and control patients (P = 0.06), but not in KD patients (P = NS) (Table 2 and Fig. 1C).

**Insulin, C-peptide, and NO levels**

Higher glucose levels were evident during testing in the KD group than in the KP and control groups (Fig. 2A, B, and G). Due to continuous subcutaneous insulin infusion, insulin levels were higher in the KD group than in the KP and control groups (KP group: 0 min, 12.6 ± 2.1 μU/ml; 30 min, 46.6 ± 19.0; 60 min, 15.7 ± 2.8; and 90 min, 12.4 ± 2.6; control: 0 min, 12.1 ± 4.3 μU/ml; 30 min, 67.0 ± 28.2; 60 min, 22.0 ± 9.8; and 90 min, 8.8 ± 3.6; and KD group: 0 min, 14.4 ± 3.3 μU/ml; 30 min, 76.7 ± 38.9; 60 min, 82.2 ± 36.7; and 90 min, 73.6 ± 50.9) (Fig. 2B, E, and H).

Furthermore, in the KP and control groups C-peptide levels rose during the l-arginine infusion as a result of the secretory ability of l-arginine (KP group: 0 min, 1.4 ± 0.2 ng/ml; 30 min, 2.1 ± 0.3; 60 min, 1.9 ± 0.3; and 90 min, 1.7 ± 0.3; and control group: 0 min, 4.2 ± 1.1 ng/ml; 30 min, 9.2 ± 2.4; 60 min, 6.0 ± 2.1; and 90 min, 4.4 ± 2.2) (P < 0.05 vs. baseline) (Fig. 2C and F). In the KD group, C-peptide levels were low during the test (0 min, 0.4 ± 0.1 ng/ml; 30 min, 0.4 ± 0.1; 60 min, 0.5 ± 0.2; and 90 min, 0.5 ± 0.2) (Fig. 2F).

In particular, no differences were evident between the three groups during the test for NO levels (baseline [for KP, KD, and control groups]: 22.3 ± 2.08, 25.6 ± 6.1, and 22.7 ± 3.18, respectively, NS; and 30 min post-l-arginine infusion: 21.8 ± 2.1, 23.5 ± 4.6, and 21.5 ± 4.22 μmol/l, respectively, NS) (Fig. 2D). The change in RBF before and after l-arginine infusion correlates negatively with HbA1c (r = −0.46, P < 0.05), but not with age, years of follow-up, total cholesterol, and triglycerides.
Subanalysis for age
By splitting the KP group according to ages that were higher or lower than the median value, we obtained a subpopulation of “old” KP patients (KP$_{old}$, n = 7). They were similar to KD patients for age (KP$_{old}$ vs. KD, 44.8 ± 1.5 vs. 47.3 ± 1.9 years, respectively, NS), dialysis (KP$_{old}$ vs. KD, 39.8 ± 11.5 vs. 36.1 ± 8.1 months, respectively, NS), and diabetes duration (KP$_{old}$ vs. KD, 27.7 ± 1.9 vs. 31.7 ± 2.9 years, respectively, NS). After l-arginine administration, RBF also increased significantly in the KP$_{old}$ group (13.3 ± 7.6%, $P < 0.05$), but not in the KD group, as has already been shown. A similar behavior was confirmed for RBV, its increase was highly significant in the KP group (23.0 ± 7.4%, $P < 0.01$), whereas in the KD group, the variation in renal blood velocity was absent, as has already been shown.

CONCLUSIONS — Our results demonstrate that simultaneous KP has a protective role on arginine-induced, transplanted renal artery vasodilation in uremic diabetic patients when compared with recipients of KD. An increased flow was found in the transplanted renal artery of KP and control patients but not in KD patients after administration of l-arginine. This suggests a preserved vasodilatory reserve in KP patients that is related to more appropriate glycemic control.

The novel method of this study is the combined use of MR quantitative flow with the infusion of l-arginine to evaluate the renal vasodilatory response. To the best of our knowledge, this is the first study that addresses the use of MR flow analysis in assessing the renal vasodilatory reserve in transplanted renal arteries after l-arginine infusion. Bello et al. (14) found a greater renal vasodilatory response to l-arginine infusion in normal subjects and in hypertensive patients without complications than in hypertensive patients with more severe disease. In a previous study (29), the increase in renal flow was similar to the variation we found in our work in the control group and in KP patients, although we used a different method to calculate renal flow.

Several lines of evidence support the hypothesis that changes in endothelial function of the renal vasculature are associated with the development of diabetic nephropathy (30). Notably, in our study, only KP was able to prevent the development of a blunted kidney vasodilatory reserve, which confers adjunctive beneficial effects in the protection of the kidney.

Similar to what happens in the periphery, changes in renal endothelium-dependent dilation could precede structural changes (31,32).

It is possible that NO pathway alterations and/or renin-angiotensin system activation could blunt endothelial function in the renal artery of the transplanted kidney. It is interesting to observe that nonstatistically higher basal RBF and NO levels were evident in KD patients. There are reports (12,33) of increased NO synthesis in the renal vasculature in early diabetes, which accounts for the glomerular hyperfiltration found in the state of early diabetic nephropathy. These higher NO and RBV levels in the KD group compared with the KP group could suggest a sort of hyperfiltration. Therefore, an abnormal l-arginine–induced increase of RBF in the KD group could be due to chronic stimulation of NO pathways in these patients. It is interesting to observe that a previous study (34) showed that pancreas transplantation was able to prevent the progression of diabetic nephropathy in the kidney after 10 years from transplantation. In our study, it took <5 years (the mean follow-up of our casuistry) to observe a beneficial effect on renal vascular function.

Moreover, it seems likely that hyperglycemia per se could only partially account for the differences of endothelial function between KP and KD, particularly after a recent study (35), which showed that recent-onset type 1 diabetic patients without complications did not present with endothelial dysfunction. In fact, it is possible that the full restoration of pancreatic endocrine function (with C-peptide secretion) could improve renal vascular function, given that C-peptide was able to stimulate eNOS in endothelial cells (36). It is likely that glycemic control has a role in inducing impairment of l-arginine vasodilation of the renal vascula-
ture as reinforced by the subanalysis in the KD group. Paradoxical vasoconstriction is evident in the group with high HbA1c levels, suggesting deep alterations of endothelial function. The absence of any statistical differences in NO peripheral levels cannot exclude a role for the NO pathway at local levels of the renal artery, which has a limited contribution to systemic NO levels. Furthermore, it was shown that the longer the exposure to the diabetic milieu, the greater the impairment of L-arginine vasodilation of the renal vasculature.

In addition, L-arginine infusions lowered systemic blood pressure significantly, particularly in the KP and control groups, which is in agreement with findings made by other investigators (37,38). However, a decrease in systemic blood pressure is usually accompanied by a decrease in RBF. In our study, we observed that a decrease in blood pressure was linked to an increase in RBF. This negative correlation argues against any major influence of systemic hemodynamic factors.

Addressing why NO levels were not statistically higher in the KD group compared with the other groups is intriguing. It is possible that the very short life of NO does not allow the direct effect of L-arginine on NO release. Again, the infusion of insulin, a well-known NO releaser, in the KD group during the test could have masked the real effect of L-arginine. Finally, we can hypothesize that reduced vasodilation in the presence of raised NO levels could be related to so-called NO resistance, as has been suggested in the dorsal foot of patients with type 2 diabetes (39,40). Other possibilities are that endothelial responses to NO are not synchronized with elevated NO production or that blood flow responses are not commensurate with NO levels (40). Previous studies suggest that individuals with type 2 diabetes are resistant to the actions of NO (39,40) and that blood flow responses to the direct NO donor sodium nitroprusside are impaired in type 2 diabetes (41). This is further supported by the increased excretion of nitrates and nitrotyrosine levels in insulin-resistant individuals or in those with early type 1 diabetes (42).

The three populations were homogeneous before transplant, as well as in car-

Figure 2—Metabolic parameters in the three groups of patients during L-arginine infusion. KP and control (K) patients showed lower glucose (A and B) and free insulin (D and E) levels than the KD patients (C and F) during the test. KP and control patients showed a statistically significant increase in C-peptide levels during the test compared with the KD patients (G, H, and I) (P < 0.01). The relative increase for each panel has been reported (Δ). *P < 0.05 vs. the other two groups.
diovascular status; however, a limitation of this study was the use of a cross-sectional approach. Another point could be that a part of the effects of L-arginine may be unspecific (unrelated to NO). Again, it is possible that L-arginine infusion might be an unsuitable tool for assessing endothelial-dependent vasodilation of the renal vasculature in transplanted patients. Finally, L-arginine infusion provided an amount of chloride, which can cause changes in renal hemodynamics without any involvement of the endothelium, particularly in patients with disturbed tubulo-glomerual feedback (12).

In conclusion, this study demonstrated that L-arginine–induced vasodilation of the renal vasculature is blunted in type 1 diabetic patients receiving KD and is preserved in those receiving combined KP. It is noteworthy that these results were achieved during a relatively short follow-up period, confirming the rapid beneficial impact of pancreas transplantation on vascular function in the recipients. Therefore, in our opinion, this test could be used to detect early markers of diabetic nephropathy in the transplanted kidney and could define a high-risk population of transplanted patients suitable for a specific therapeutic approach aimed at reducing vascular damages.

Acknowledgments — This work was partially supported by the Italian Minister of Health (Ricerca Finalizzata, 2001) and the Italian Minister of University (Murst Co-fin, 2000).

We are grateful to Tamara Canu for performing MR examinations and to Chiara Gremizzi for database collection.

References


De Cobelli, Fiorina, and Associates


