

Reversal of Left Ventricular Diastolic Dysfunction After Kidney-Pancreas Transplantation in Type 1 Diabetic Uremic Patients

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OBJECTIVE — Diastolic function is frequently impaired in diabetic patients. Our aim was to evaluate the effects of glycometabolic control achieved by pancreas transplantation on left ventricular function in uremic type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — Left ventricular systolic and diastolic functions were evaluated using radionuclide ventriculography in 42 kidney-pancreas transplant patients and 26 kidney-alone recipients who had similar clinical characteristics before transplantation. Patients were grouped according to 6, 24, and 48 months of follow-up. Control subjects consisted of 20 type 1 diabetic patients.

RESULTS — The left ventricular ejection fraction was normal in all of the patients. However, kidney-pancreas transplant patients with 4 years of graft function had a higher ejection fraction ($75.7 \pm 1.8\%$) than kidney-alone patients with 4 years of graft function ($65.3 \pm 2.8\%$, $P = 0.02$) and type 1 diabetic patients ($61.3 \pm 3.7\%$, $P = 0.004$). In patients with 4 years of graft function, normal diastolic parameters were evident in kidney-pancreas but not in kidney-alone or in type 1 diabetic patients (peak filling rate: 4.46 ± 0.15 end diastolic volume (EDV)/s in kidney-pancreas patients vs. 2.73 ± 0.24 EDV/s [$P < 0.01$] and 3.39 ± 0.30 EDV/s [$P < 0.01$] in kidney-alone and type 1 diabetic patients, respectively; time-to-peak filling rate: 141.9 ± 7.8 ms in kidney-alone patients vs. 209.4 ± 13.5 ms in kidney-alone patients [$P < 0.01$]; peak filling rate/peak ejection rate ratio: 1.10 ± 0.04 in kidney-pancreas patients vs. 0.81 ± 0.08 in kidney-alone patients [$P < 0.01$]). A significant reduction in diastolic dysfunction rate was observed only in kidney-pancreas patients.

CONCLUSIONS — Kidney-pancreas transplantation results in complete insulin independence, a better glycometabolic pattern and blood pressure control, an improvement of left ventricular function, and a reversal of diastolic dysfunction.

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Abbreviations: ECG, electrocardiogram; EDV, end diastolic volume.

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

Epidemiological studies have clearly demonstrated that diabetic patients are at an increased risk for cardiovascular morbidity and mortality (1). Diabetic cardiomyopathy was first recognized in the 1970s, when four diabetic patients with congestive heart failure and no evidence of valvular, hypertensive, or coronary atherosclerotic disease were described (2). A systolic dysfunction in normotensive diabetic patients was not clearly shown, although a decrease in fractional shortening and an increase of left ventricular mass were reported (3). Abnormality in diastolic dysfunction has been more uniformly observed in asymptomatic diabetic patients with an altered diastolic filling, as shown by impaired values of peak filling rate and time-to-peak filling rate (4). The relationship between diastolic dysfunction and metabolic control in type 1 diabetic patients is still a matter of debate (4). Studies involving the reversal of diabetic cardiomyopathy after tight glycemic control in type 1 diabetes are lacking. In type 2 diabetes, previous authors showed that improvement in glycemic control was not associated with changes in diastolic function over 6 or 12 months of follow-up (5). Different conclusions were reached in other studies performed in animals revealing the biochemical changes related to abnormal contraction and relaxation observed in diabetic animals (6). The diminished calcium transport by sarcoplasmic reticulum reversed after adequate insulin therapy (6).

Pancreas transplantation permits complete insulin independence; creates normal glycometabolic control (7); slows or reverses diabetic nephropathy (8), retinopathy (9), and neuropathy (10); and improves the quality of life (7,11). Furthermore, the tight metabolic control achieved with kidney-pancreas transplantation does not expose patients to severe hypoglycemic episodes (7). Kidney-pancreas transplantation appeared to have a positive influence on arterial blood pressure (12), cardiorespiratory reflex (13), systolic function (14), and patient survival (15). The purpose of our

Table 1—Characteristics before transplant of kidney-pancreas and kidney-alone groups according to years of follow-up

Characteristics	6 months		2 years		4 years	
	KP	KA	KP	KA	KP	KA
n	14	9	13	8	15	9
Age (years)	39 ± 1	45 ± 1	39 ± 2	43 ± 3	42 ± 2	46 ± 2
Type 1 diabetes duration (years)	24 ± 1	26 ± 1	24 ± 1	26 ± 1	28 ± 1	25 ± 1
Duration dialysis (months)	31 ± 3	39 ± 6	29 ± 7	34 ± 6	33 ± 5	40 ± 5
Hypertensive patients (%)	100	100	100	100	100	100
Cholesterol (mg/dl)	204 ± 21	209 ± 13	247 ± 2	225 ± 14	211 ± 16	193 ± 13
Triglycerides (mg/dl)	171 ± 2	187 ± 13	183 ± 16	218 ± 43	179 ± 17	209 ± 37
C-peptide (ng/ml)	0.18 ± 0.02	0.20 ± 0.04	0.19 ± 0.04	0.17 ± 0.03	0.20 ± 0.04	0.16 ± 0.02
Ejection fraction (%)	64 ± 1	64 ± 3	65 ± 2	63 ± 3	65 ± 1	66 ± 2
Diastolic dysfunction (%)	100	88	84	75	73	88

Data are means ± SEM. KA, kidney-alone transplant group; KP, kidney-pancreas transplant group.

study was to evaluate the effects of duration/quality of metabolic control after a pancreas transplantation in type 1 diabetic patients using a cross-sectional study.

RESEARCH DESIGN AND METHODS

Patients and study groups

Between January 1993 and January 1997, 668 type 1 diabetic uremic patients were submitted to kidney transplantation. Of these 68 patients, 42 received a simultaneous bladder-drained pancreas transplantation, according to Sollinger et al. (16), whereas 26 received only the kidney transplantation, because of macroscopic damage of the pancreas at harvesting.

Patients were grouped according to years of follow-up at the moment of investigation: 6 months (14 kidney-pancreas and 9 kidney-alone patients), 2 years (13 kidney-pancreas and 8 kidney-alone patients), and 4 years (15 kidney-pancreas

and 9 kidney-alone patients). Kidney-pancreas recipients were insulin-independent, whereas kidney-alone recipients were on intensive subcutaneous insulin therapy. Before the transplantation, patients were comparable for metabolic parameters and clinical characteristics (Table 1). Left ventricular systolic and diastolic function were evaluated before the transplant with Doppler echocardiography. The presence of coronary artery disease was assessed before the transplantation with a resting electrocardiogram (ECG) and a myocardial scintigraphy. All of the patients underwent a myocardial perfusion scan with 201-thallium. Patients who presented a perfusion defect that was nonreversible at rest after an ECG test with a cicloergometer and after a reinjection with 201-thallium were excluded from the study. The analysis of scintigraphic images was performed by two physicians who were not aware of the clinical conditions. Blood pressure was recorded at each outpatient control session

(approximately every 3–6 months), and the presence of hypertension was defined according to previous authors (12).

All of the transplantation patients received the following immunosuppressive treatment: antithymoglobulins (thymoglobulin [IMTIX] for 10 days), cyclosporin (6 mg · kg⁻¹ · day⁻¹), azathioprine (1 mg · kg⁻¹ · day⁻¹), and prednisone (10 mg/day). Control subjects consisted of 20 type 1 diabetic patients comparable in age (40.3 ± 1.9 years), BMI (24.5 ± 0.8 kg/m²), duration of diabetes (15.9 ± 0.6 years), HbA_{1c} (9.5 ± 0.5%), systolic blood pressure (135 ± 2 mmHg), diastolic blood pressure (81 ± 1 mmHg), and the other clinical characteristics.

Study design

All of the patients underwent radionuclide left ventriculography through a cross-sectional study. The following parameters were collected before transplantation and when patients were stud-

Table 2—Comparison between hypertension rate and metabolic parameters in kidney-pancreas and kidney-alone groups

Characteristics	6 months			2 years			4 years		
	KP	KA	P	KP	KA	P	KP	KA	P
n	14	9	—	13	8	—	15	9	—
Hypertension rate (%)	57	66	NS	69	62	NS	33	77	NS
HbA _{1c} (%)	6.0 ± 0.1	8.3 ± 0.2	<0.01	6.6 ± 0.2	8.7 ± 0.6	<0.01	6.1 ± 0.1	10.3 ± 0.6	<0.01
Serum-free insulin (μU/ml)	15.7 ± 1.0	26.5 ± 2.9	<0.01	21.2 ± 2.7	25.3 ± 3.2	NS	17.1 ± 1.5	27.3 ± 3.0	<0.01
C-peptide (ng/ml)	3.78 ± 0.81	0.20 ± 0.04	<0.01	4.26 ± 0.48	0.17 ± 0.03	<0.01	3.01 ± 0.33	0.16 ± 0.02	<0.01
Triglycerides (mg/dl)	150 ± 17*	149 ± 26†‡	NS	137 ± 14*	143 ± 17†§	NS	85 ± 6*‡	261 ± 80†‡	<0.01
Cholesterol (mg/dl)	193 ± 12	208 ± 15	NS	222 ± 18	237 ± 19	NS	226 ± 10	256 ± 24	NS
Creatinine (mg/dl)	1.3 ± 0.1	1.5 ± 0.2	NS	1.5 ± 0.1	1.8 ± 0.2	NS	1.4 ± 0.1	1.8 ± 0.2	NS
Cyclosporine (ng/dl)	169 ± 10	173 ± 14	NS	163 ± 14	175 ± 15	NS	173 ± 13	189 ± 20	NS

Data are means ± SEM. *4 years significant vs. 6 months and 2 years; †4 years significant vs. 6 months and pretransplantation; ‡significant vs. pretransplantation; §2 years and 6 months significant vs. pretransplantation. KA, kidney-alone transplant group; KP, kidney-pancreas transplant group.

ied: HbA_{1c}, blood glucose, plasma creatinine, total plasma cholesterol, total plasma triglycerides, whole-blood cyclosporin, and serum C-peptide/insulin. The rate of patients on antihypertensive therapy was considered.

Radionuclide left ventriculography

During the test, all patients underwent radionuclide left ventriculography after a 15-min rest in a recumbent position. All of the patients were in sinus rhythm and had similar mean arterial blood pressure values, without any differences among all of the groups considered. Erythrocytes were labeled in vivo by intravenous administration of stannous pyrophosphate followed by the intravenous administration, after 20 min of 20–30 mCi of ^{99m}Tc-Na-pertechnetate. Images were acquired with a gamma camera (Prism 3000 XP or a Prism 2000 XP; Picker International, Cleveland, OH). The images were taken by a gated acquisition, synchronized with the R wave of the ECG, in the left anterior-oblique projection between 30 and 45°, and with craniocaudal tilting of the gamma camera at 10°. At least 16 image frames using 64 × 64 matrices and zoom 2 were acquired for each ECG cycle, and the end point was established at 5,000 K counts. Of the R-R interval variation, 20% was assumed as the arrhythmia rejection window. Images were analyzed after filtering, background correction, and semiautomated detection of ventricle borders. The following parameters were calculated: left ventricle ejection fraction, peak ejection rate, peak filling rate, and time-to-peak filling rate.

Diastolic dysfunction

Diastolic dysfunction was defined as previously reported (17). After transplantation, diastolic dysfunction was calculated when both abnormal peak filling rate and time-to-peak filling rates were present (17). Radionuclide ventriculography was not available when patients underwent transplantation. Before transplantation, diastolic dysfunction was calculated based on an altered ratio between the early and late peaks of the diastolic flow velocity (E:A ratio <1) at echocardiography examination, as an index of ventricular filling properties. Patients demonstrating an increased resistance to diastolic filling, mechanical and external to the ventricular myocardium (e.g., constrictive pericarditis and mitral stenosis), were excluded from

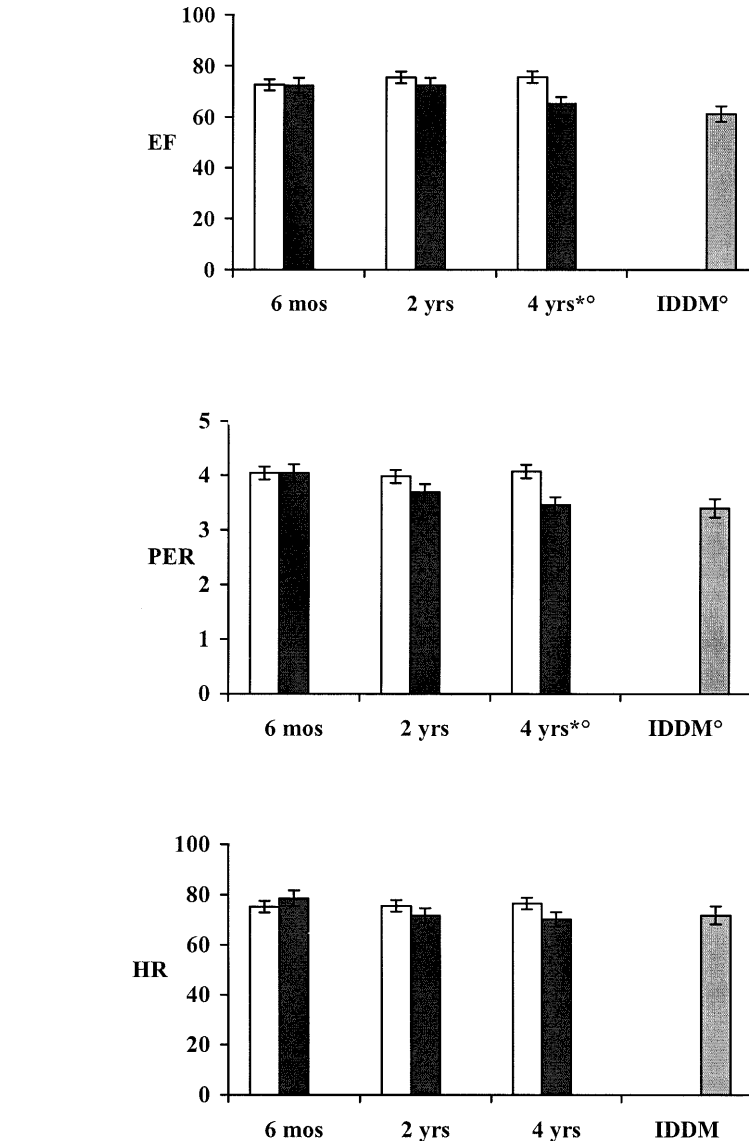


Figure 1—Ejection fraction (EF) (%), peak ejection rate (PER) (EDV/s), and heart rate (HR) (bpm) in kidney-pancreas (□) and kidney-alone (■) transplant patients at 6 months, 2 years, and 4 years and in type 1 diabetic patients (IDDM, ▒). *P < 0.05, kidney-pancreas vs. kidney alone; °P < 0.05, kidney-pancreas vs. type 1 diabetes.

the study. E:A ratio was evaluated independently by two cardiologists. In particular, a good correlation was present between the descent of the Doppler early-diastolic flow velocity peak, and the peak filling rate measured with radionuclide angiography (17). Moreover, one previous report showed that quantitative indexes of left ventricular diastolic function, obtained with the two techniques, could distinguish normal from abnormal diastolic performance in the vast majority of patients. The two techniques also showed complete agreement in identifying normal diastolic function (17).

Statistical analysis

Data were expressed as mean ± SEM. Data were compared by means of Student's *t* test for unpaired data, and the χ^2 test was used for categorical variables. The Mann-Whitney *U* test was used when necessary. Correlations were assessed using Spearman's rank correlation test.

RESULTS

Left ventricular systolic function

The mean arterial blood pressure was similar in the different groups of patients (Table 2). The ejection fraction was normal in all

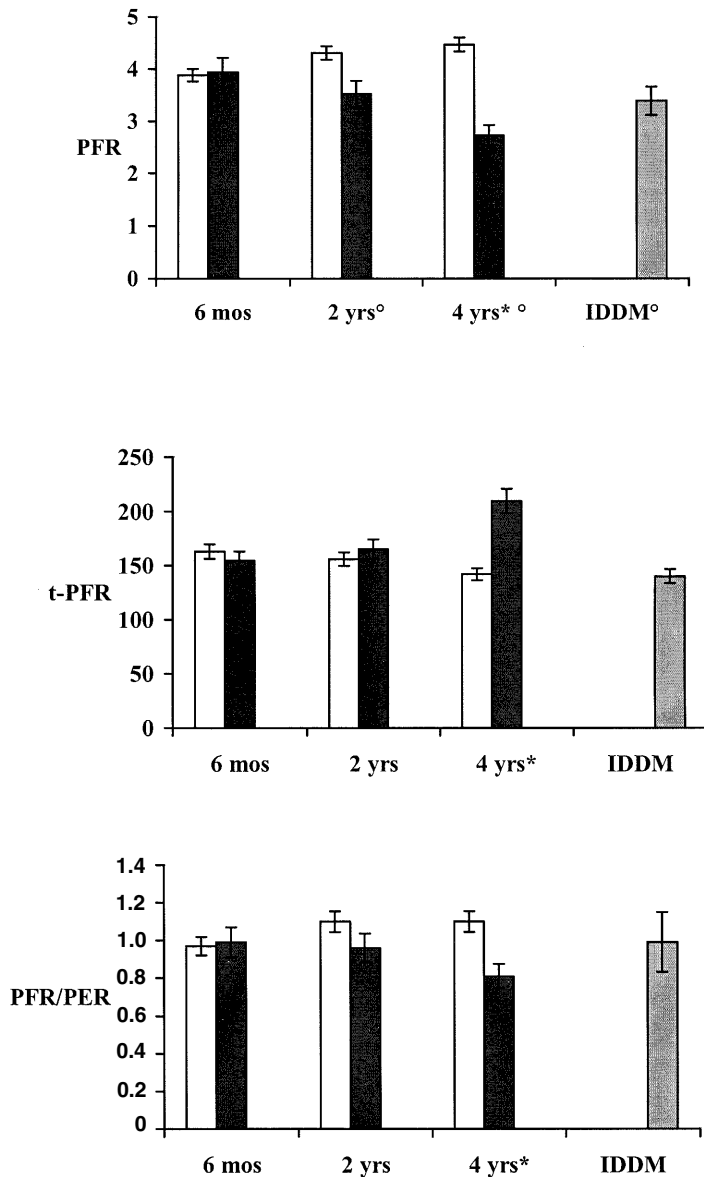


Figure 2—Peak filling rate (PFR) (EDV/s), time-to-peak filling rate (t-PFR) (ms), and peak filling rate/peak ejection rate (PFR/PER) in kidney-pancreas (□) and kidney-alone (■) transplanted patients at 6 months, 2 years, and 4 years and in type 1 diabetic patients (IDDM, ▒). * $P < 0.01$, kidney-pancreas vs. kidney-alone; ° $P < 0.05$, kidney-pancreas vs. type 1 diabetes.

of the patients before the transplantation (Table 1); normal values of the ejection fraction (Fig. 1) were present in both groups after the transplantation. When analyzing transplantation patients with 4 years of graft function, a significantly higher ejection fraction was present in kidney-pancreas transplantation patients compared with kidney-alone transplantation patients and type 1 diabetic patients (kidney-pancreas vs. kidney-alone, $P = 0.02$; kidney-pancreas vs. type 1 diabetic patients, $P = 0.004$) (Fig. 1). The peak ejec-

tion rate was significantly higher in kidney-pancreas patients with 4 years of follow-up than in kidney-alone patients with 4 years of follow-up and type 1 diabetic patients (kidney-pancreas vs. kidney-alone, $P = 0.02$; kidney-pancreas vs. type 1 diabetic patients, $P = 0.01$) (Fig. 1).

Left ventricular diastolic function

The peak filling rate was similar in the two groups with 6 months of follow-up, whereas it was higher in kidney-pancreas transplantation patients than in kidney-alone trans-

plantation patients at 2 and 4 years, reaching significance only at 4 years ($P < 0.01$, Fig. 2). The peak filling rate was higher in kidney-pancreas patients with 4 years of follow-up than in kidney-pancreas patients with 6 months of follow-up, whereas it was lower in kidney-alone patients with 4 years of follow-up than in kidney-alone patients with 6 months of follow-up ($P < 0.01$, Fig. 2). Kidney-pancreas transplantation patients with 2 and 4 years of follow-up had a higher peak filling rate than type 1 diabetic patients ($P = 0.04$ and $P < 0.01$, respectively). The time-to-peak filling rate was similar in kidney-pancreas patients with 6 months of follow-up; it was lower in kidney-pancreas patients than in kidney-alone patients at 2 and 4 years, reaching significance only at 4 years ($P < 0.01$, Fig. 2). The time-to-peak filling rate was lower in kidney-pancreas patients with 4 years of follow-up than in kidney-pancreas patients with 6 months of follow-up ($P = 0.03$), whereas it was higher in kidney-alone patients with 4 years of follow-up than in kidney-alone patients with 6 months of follow-up ($P < 0.01$, Fig. 2). The peak filling rate/peak ejection rate ratio was similar in the two groups with 6 months of follow-up, whereas it was higher in kidney-pancreas patients than in kidney-alone patients at 2 and 4 years, reaching significance only at 4 years ($P < 0.01$, Fig. 2). The peak filling rate/peak ejection rate ratio was higher in the kidney-pancreas patients with 4 years of follow-up than in kidney-pancreas patients with 6 months of follow-up (NS), whereas it was lower in kidney-alone patients with 4 years of follow-up than in kidney-alone patients with 6 months of follow-up.

Diastolic dysfunction

The patients' diastolic dysfunction rate, calculated in each group before and after the transplant, showed a reduction (pretransplantation versus posttransplantation) in kidney-pancreas groups with 6 months, and 2 and 4 years of follow-up ($P < 0.05$) and in kidney-alone groups with 6 months of follow-up (Fig. 3). No reduction was observed in kidney-alone groups with 2 and 4 years of follow-up (Fig. 3).

Hypertension and clinical parameters

Hypertension was present in all patients before the transplantation. A reduction of hypertensive patients was observed in all of the groups after the transplantation (even if not significant). HbA_{1c} was statistically lower in the kidney-pancreas patients than in the

kidney-alone patients (Table 2). Triglyceride levels were lower in kidney-pancreas patients than in kidney-alone patients with 4 years of follow-up. Blood total cholesterol, plasma creatinine, and blood cyclosporin levels were similar in all of the groups (Table 2). Serum insulin levels were higher than those of normal subjects in both groups of transplantation patients, but kidney-alone patients presented higher levels than kidney-pancreas patients (26.0 ± 3.5 vs. 18.1 ± 1.5 μ U/ml in kidney-alone vs. kidney-pancreas transplantation patients, respectively; $P = 0.02$) due to intensive subcutaneous insulin therapy (Table 2). When these parameters were compared with pretransplantation values in each group, a statistical difference was observed only for triglycerides in the two groups of patients with 4 years of follow-up (kidney-pancreas group: pretransplantation 179.5 ± 16.9 mg/dl, posttransplantation 85.3 ± 6.3 mg/dl, $P < 0.01$; kidney-alone group: pretransplantation 209.3 ± 37.2 mg/dl, posttransplantation 261.0 ± 80.6 mg/dl, $P < 0.01$).

The data of the transplanted patients pooled together showed that glycated hemoglobin and triglycerides were negatively correlated with the peak filling rate ($r = -0.38$, $P = 0.001$, and $r = -0.31$, $P = 0.007$, respectively) and the peak filling rate/peak ejection rate ratio ($r = -0.20$, $P = 0.08$, and $r = -0.35$, $P = 0.005$, respectively) and positively correlated with time-to-peak filling rate ($r = 0.33$, $P = 0.005$, and $r = 0.24$, $P = 0.04$, respectively) (Fig. 4). Serum C-peptide was present in all kidney-pancreas groups, whereas it was not present in kidney-alone groups.

CONCLUSIONS — Our data show that kidney-pancreas and kidney-alone groups had a normal systolic function, even if kidney-pancreas patients experiencing 4 years of graft function have a higher ejection fraction than kidney-alone patients with the same amount of follow-up. A lower diastolic dysfunction rate was observed in kidney-pancreas patients with 2 and 4 years of function than in kidney-alone patients. The rate of diastolic dysfunction was reduced after the transplant in all patients receiving kidney-pancreas and in kidney-alone patients with 6 months of follow-up, whereas it remained impaired in kidney-alone patients with the longest duration of follow-up. Moreover, in kidney-pancreas recipients, an amelioration of left ventricular diastolic function appeared to be positively associated with glycometa-

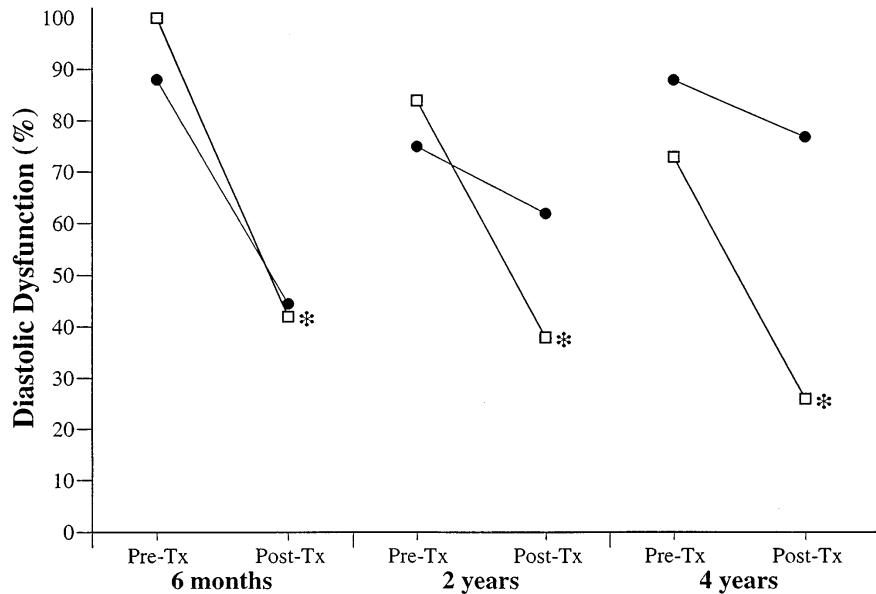


Figure 3—Rate of diastolic dysfunction pretransplantation (Pre-Tx) and posttransplantation (Post-Tx) in type 1 diabetic patients submitted to kidney-pancreas (□) and kidney-alone (■) transplantation. * $P < 0.05$, posttransplantation vs. pretransplantation.

bolic control. All of the groups had the same systolic/diastolic function and cardiovascular risk factors before transplantation.

Cardiovascular complications in type 1 diabetes represent a major problem with severe economic impact (18). Diabetic nephropathy exerts an important role in increasing cardiovascular mortality in type 1 diabetes; the relative mortality from cardiovascular diseases increased 40-fold in type 1 diabetic patients with nephropathy when compared with the general population (18). Increased left ventricular mass could have possibly contributed to the increased cardiovascular risk, because left ventricular hypertrophy is an independent risk factor for sudden death, ventricular dysrhythmia, myocardial ischemia, coronary artery disease, and heart failure (18). Different studies showed that type 1 diabetes with nephropathy has an increased left ventricular hypertrophy and diastolic dysfunction, while systolic function is normal (18). Impaired or abolished autonomic function could be a potential contributor to impaired diastolic function (18). Furthermore, the possible influence of arterial blood pressure on the appearance of diastolic dysfunction in the early stages of diabetic nephropathy was postulated (19). Systolic blood pressure in conjunction with left ventricular mass and mild hypertension could have affected the mechanical properties of the ventricle in the early stage of

nephropathy (19). Diastolic function is abnormal in normotensive diabetic patients without apparent coronary artery disease, raising the possibility of a specific “diabetic cardiomyopathy.” Diastolic dysfunction was found in patients who had diabetes for 8 years, and systolic dysfunction appeared in those who had diabetes for 18 years (20). The prevalence of diastolic dysfunction increases with the duration of disease, reaching 80% in 10–20 years; a greater increase was observed if complicated type 1 diabetes was considered (20). A normal or high ejection fraction was observed in our study. It is interesting to note that other authors showed an increased contractility in young type 1 diabetic patients before the appearance of microvascular complications; this was related to a condition of hyperperfusion and decreased precapillary resistance (21). The increased blood flow in our kidney-pancreas transplant patients could be sustained by relative hyperinsulinemia and by C-peptide secretion, which has been demonstrated to enhance microvascular blood flow (22).

Effects of glycometabolic control and C-peptide secretion

Even if a clear definition of diabetic cardiomyopathy is still a matter of debate (23), it is likely that glucose and insulin availability could modify myocyte metabolism (24). Glycometabolic control and C-pep-

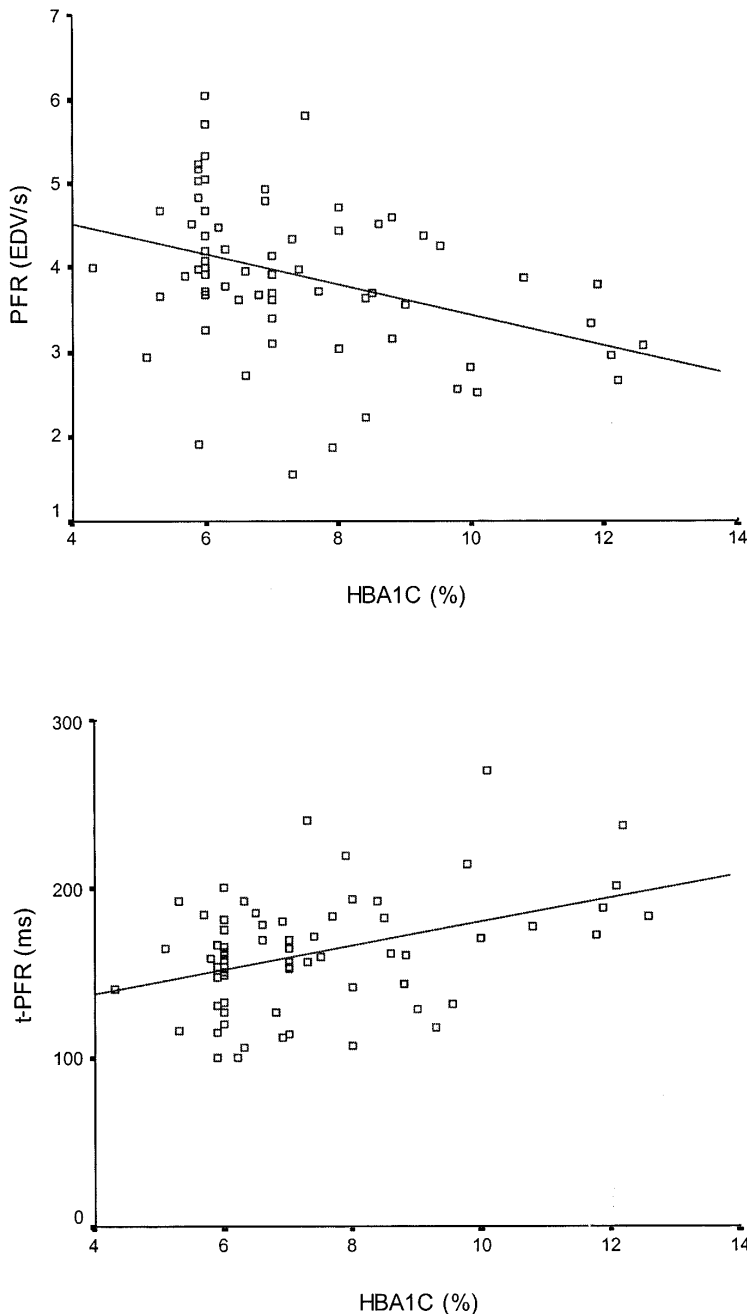


Figure 4—Correlations among glycated hemoglobin and peak filling rate (PFR) ($r = -0.38$, $P = 0.001$) and time-to-peak filling rate (t -PFR) ($r = 0.33$, $P = 0.005$), respectively, in the whole group of transplanted patients.

tide/insulin secretion are the most important differences observed between type 1 diabetic patients receiving a kidney-alone or a kidney-pancreas transplant. Insulin or C-peptide, finely secreted by a transplanted pancreas, could directly affect diastolic function by inducing peripheral vasodilation or by affecting myocyte relaxation properties (24,25). Moreover, C-peptide

seems to induce an overexpression of inducible endothelial nitric oxide synthase, with improvement of endothelial-dependent vasodilation (25). Infusion of C-peptide in type 1 diabetic patients leads to a redistribution of microvascular blood flow levels (22). Although data in literature are not available, a redistribution of coronary blood flow could improve diastolic filling.

It is difficult to establish whether hyperinsulinemia observed in both groups could play a role in diastolic function, although the two groups did not present coronary artery disease when they enrolled. Particularly, it is possible that hyperinsulinemia observed in the kidney-alone group could contribute to worsen coronary artery disease, which may partially explain the observations noted in the kidney-alone group.

Hypertension and metabolic status

It is noteworthy that an amelioration of hypertension is correlated with an improvement of cardiac function and diastolic properties (26). This reduction could partly account for the improvement of ventricular filling. Possible factors concurrent to the impairment of diastolic function in kidney-alone patients are high triglyceride levels and insulin resistance, which were already present in type 1 diabetic patients undergoing kidney-alone transplant (27).

Worsening of coronary artery disease

Coronary artery disease could be an important factor influencing the progression of diastolic dysfunction in uremic type 1 diabetic patients. Therefore, patients suffering from coronary artery disease were not enrolled in the study. Progression of microvascular disease, which is not always detectable at resting ECG or with 201 -thallium myocardial scintigraphy, could also partially explain our results. Interestingly, in this case, the eventual progression of microvascular disease takes place only in kidney-alone patients and not in kidney-pancreas patients. A positive effect of pancreas transplant on microcirculation was already reported (28).

Limitations of the study

Conducting a cross-sectional study rather than a perspective study could be a limitation. Nevertheless, the homogeneity of the groups before transplantation could overwhelm this limit. Moreover, left ventricular filling is influenced by a number of conditions other than diabetes, which could affect interpretation of the data. To reduce the risks of contrast medium-induced nephropathy on transplanted kidneys, coronary artery disease was studied with noninvasive methods (for ethical reasons). Diastolic dysfunction was calculated by two different methods before and after transplantation, although previous studies have demonstrated the reliability of the two methods (17).

In conclusion, kidney-pancreas but not kidney-alone transplant in diabetic patients showed an improvement of diastolic function; this finding was positively associated with the duration of transplantation and the quality of metabolic control.

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