Systemic Venous Drainage of Pancreas Allografts as Independent Cause of Hyperinsulinemia in Type I Diabetic Recipients

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To evaluate the metabolic consequences of pancreas transplantation with systemic venous drainage on β-cell function, we examined insulin and C-peptide responses to glucose and arginine in type I (insulin-dependent) diabetic pancreas recipients (n = 30), nondiabetic kidney recipients (n = 8), and nondiabetic control subjects (n = 28). Basal insulin levels were 66 ± 5 pM in control subjects, 204 ± 18 pM in pancreas recipients ($P < 0.0001$ vs. control), and 77 ± 17 pM in kidney recipients. Acute insulin responses to glucose were 416 ± 44 pM in control subjects, 763 ± 91 pM in pancreas recipients ($P < 0.01$ vs. control), and 589 ± 113 pM in kidney recipients (NS vs. control). Basal and stimulated insulin levels in two pancreas recipients with portal venous drainage were normal. Integrated acute C-peptide responses were not statistically different (25.3 ± 4.3 nM/min in pancreas recipients, 34.2 ± 5.5 nM/min in kidney recipients, and 23.7 ± 2.1 nM/min in control subjects). Similar insulin and C-peptide results were obtained with arginine stimulation, and both basal and glucose-stimulated insulin–C-peptide ratios in pancreas recipients were significantly greater than in control subjects. We conclude that recipients of pancreas allografts with systemic venous drainage have elevated basal and stimulated insulin levels and that these alterations are primarily due to alterations of first-pass hepatic insulin clearance, although insulin resistance secondary to immunosuppressive therapy (including prednisone) probably plays a contributing role. To avoid hyperinsulinemia and its possible long-term adverse consequences, transplantation of pancreas allografts into sites with portal rather than systemic venous drainage should be considered. *Diabetes* 39:534–40, 1990

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Modern strategies of insulin therapy, including those with continuous subcutaneous insulin-infusion pumps and multiple daily insulin injections, attain normoglycemia in only a few diabetic patients, usually with the risk of hypoglycemia (1,2). In contrast, when technically successful, pancreas transplantation reproducibly normalizes blood glucose levels. Most type I (insulin-dependent) diabetic recipients of whole-organ or segmental pancreas allografts do not require exogenous insulin or oral-agent therapy and achieve self-regulating insulin secretion resulting in normoglycemia, normal intravenous glucose disappearance rates, and normal glycosylated hemoglobin (HbA_1) levels (3–8). However, pancreas transplantation typically results in a heterotopically located pancreas with no innervation and systemic rather than portal venous drainage and requires immunosuppressive treatment, including corticosteroids. Only limited data have been reported that describe islet β-cell function under these nonphysiological circumstances, and these studies were compromised by small numbers of subjects and/or lack of appropriate control subjects for concurrent drug therapy for immunosuppression (3,7–11).

Because hyperinsulinemia has been identified as a potential independent risk factor (12–15) and is associated with other well-known risk factors (16) for macrovascular disease, and because diabetic patients are at increased risk for macrovascular disease, full resolution of whether pancreas transplantation in type I diabetic recipients causes hyperinsulinemia and how it can be avoided is important. Our study was performed to ascertain whether pancreas transplantation with systemic venous drainage independent of immunosuppressive therapy contributes to hyperinsulinemia and, if so, to determine whether steps may be taken to avoid this potentially adverse metabolic consequence. We determined basal levels of insulin and C-peptide and their responses to intravenous glucose and arginine in pancreas recipients with and without systemic venous drainage of the

TABLE 1
Characteristics of insulin-dependent diabetic recipients of pancreas allografts, nondiabetic recipients of kidney transplants, and nondiabetic control subjects

	Age (yr)	Sex (M/F)	Body mass index (kg/m²)	Duration of diabetes (yr)	Time since pancreas transplant (mo)	Fasting glucose (mM)	HbA_{1c} (%)	K_G (%)	Insulin antibodies (% binding)	Creatinine (μM)	Prednisone (mg/day)
Pancreas recipients	31	F	25.7	26	24	4.8	5.7	1.9	0.61	106	7.5
Whole allograft*	40	F	23.7	23	20	3.9	5.1	2.0	0.56	230	20.0
	40	M	23.3	26	15	5.6	4.9	1.3	0.55	225	15.0
	33	F	25.2	21	12	4.8	4.6	1.9	1.91	168	15.0
	37	M	21.5	30	12	4.6	6.1	2.1	0.94	124	15.0
	33	F	19.5	12	12	4.8	5.2	2.8	0.19	88	15.0
	23	F	28.0	13	12	5.1	5.4	1.4	0.11	186	12.5
	36	F	29.8	24	12	5.2	4.0	1.8	0.40	97	12.5
	34	M	20.8	27	12	4.2	5.6	1.1	1.02	141	17.5
	24	F	30.7	11	3	4.8	6.2	1.1	0.51	97	27.5
	39	F	25.9	15	3	5.2	5.7	ND	0.83	159	15.0
	39	M	20.4	26	3	5.2	5.5	1.3		150	20.0
	37	M	21.9	25	3	5.4	4.1	0.8		133	30.0
	26	F	19.0	18	3	4.5	ND	2.1	0.45	159	22.5
	36	F	21.8	23	3	5.2	4.8	1.5	0.97	150	17.5
	41	F	20.2	28	3	4.1	4.3	1.5	0.71	115	22.5
	39	M	25.9	39	3	5.4	4.6	1.5	0.86	159	32.5
	36	F	23.7	30	3	4.7	4.5	1.3	1.09	115	15.0
	26	M	19.2	15	3	5.6	4.4	1.4	0.74	88	17.5
	42	M	19.0	37	3	4.0	4.8	1.8	0.41	141	17.5
Segmental allograft†	35	M	22.3	23	60	4.1	5.3	1.2	2.32	109	10.0
	33	M	33.4	19	60	4.2	5.3		1.22	261	10.0
	42	F	21.9	22	42	4.9	5.3	1.5	0.50	124	12.5
	37	M	20.8	16	13	4.9	5.7	2.4	0.13	159	7.5
	36	F	21.6	21	12	5.5	5.0	1.6	1.31	71	0.0
	26	F	23.8	17	12	4.2	5.3	1.5	1.05	150	15.0
	35	F	21.2	27	12	5.1	4.6	1.1	1.13	137	10.0
	27	M	31.0	12	5	5.2	6.1	1.3	0.67	106	25.0
Portal allograft‡	33	F	20.8	24	24	4.2	5.9	1.4	0.90	171	15.0
	29	M	18.8	25	24	4.3	5.4	1.0	1.02	150	12.5
Total	34 ± 5	13/17	23.4 ± 3.9	22 ± 6	14 ± 15	4.8 ± 0.5	5.1 ± 0.6	1.6 ± 0.5	0.83 ± 0.49	142 ± 43	16.2 ± 6.9
Control subjects											
Total	34 ± 14	11/17	23.0 ± 3.0			4.8 ± 0.4	5.1 ± 0.4	1.7 ± 0.6		76 ± 12	
Kidney recipients											
Total	36 ± 7	3/5	23.8 ± 2.5			4.8 ± 0.2	5.2 ± 0.3	2.0 ± 0.8		110 ± 31	14.4 ± 6.2

Values are means ± SD. K_G, intravenous glucose disappearance rate; ND, not determined.
*Whole-organ pancreatic allograft with systemic venous drainage.
†Segmental pancreatic allograft with systemic venous drainage.
‡Segmental pancreatic allograft with portal venous drainage.

pancreas allograft and compared them with data from similarly immunosuppressed nondiabetic kidney recipients and nondiabetic control subjects of comparable age, sex, and leanness (body mass index [BMI]).

RESEARCH DESIGN AND METHODS

Thirty type I diabetic recipients of pancreas allografts who had undergone transplantation between 3 and 60 mo previously were studied (Table 1). In 28 of these subjects, the pancreas allograft vascular anastomoses used iliac vessels, thereby providing systemic venous drainage of the graft (17). Exocrine drainage was diverted into the bladder in 22 patients and enterally in 8 patients (18). Two segmental pancreas allografts were portally drained by vascular anastomoses to the inferior mesenteric vein. Sixteen pancreas recipients had also received kidney transplants (although not necessarily simultaneously). All recipients were normoglycemic and had normal HbA_{1c} levels, and none was receiving exogenous insulin or other medication for diabetes. Immunosuppression was achieved with azathioprine, cyclosporin, and prednisone (3). Twenty-eight nondiabetic volunteers comparable in age, sex, and BMI and 8 nondiabetic recipients of kidney transplants treated with the same immunosuppressive drugs were tested to obtain control data. All subjects were admitted to the University of Minnesota Clinical Research Center, and tests were started at 0800 with the subjects at bed rest after fasting overnight. The protocol was approved by our institutional review board, and all subjects gave written informed consent. All tests were not performed in all subjects.

Twenty-nine type I diabetic recipients of pancreas allografts, 8 nondiabetic recipients of kidney transplants, and 19 nondiabetic control subjects underwent intravenous glucose tolerance tests (IVGTTs). Intravenous lines were placed in both antecubital veins; one was used for injecting glucose and the other for drawing samples for glucose, insulin, and C-peptide. Three baseline samples were drawn before the glucose pulse (20 g dextrose as 50% solution) was given. After the glucose pulse, samples were drawn at 3, 4, 5, 7, 10, 15, 20, 25, and 30 min.

To assess non–glucose-induced insulin secretion, responses to an arginine bolus (5 g/50 ml water i.v.) were studied in 19 type I diabetic recipients of pancreas allografts and 21 nondiabetic control subjects. Three baseline samples

and additional samples 2, 3, 4, 5, 7, and 10 min after injection were drawn for determination of insulin and C-peptide levels.

Twenty-four-hour urine C-peptide was measured on two separate days in 12 recipients and 13 control subjects. During the sampling period, all individuals were on a standardized weight-maintaining diet with 45–50% of total calories in the form of carbohydrates.

Serum glucose was measured with a glucose oxidase method. Serum insulin was assayed with a commercial insulin radioimmunoassay kit (Cambridge Medical, Billerica, MA). To exclude possible interference of insulin antibodies with insulin measurements, insulin antibodies were determined after Skom and Talmage (19) with dextran-coated charcoal for precipitation. Insulin binding was above mean ± SD (0.66 ± 0.50% insulin binding) of nondiabetic control subjects in only four pancreas recipients. Basal insulin levels in these four patients were not elevated compared with other pancreas recipients. C-peptide was determined according to Heding (20) with antiserum M1221 (Novo, Copenhagen). Urine C-peptide levels were determined with the same method but via antiserum M1230.

Basal levels of glucose, insulin, and C-peptide were calculated by averaging the values of the preinjection samples. Acute insulin responses (AIR) were calculated as the average of the three peak values between 3 and 5 min after injection of glucose and between 2 and 5 min after injection of arginine, from which the basal insulin level was subtracted. Integrated responses were calculated as the area under the curve (AUC) over 30 min with baseline subtracted. Integrated insulin and C-peptide responses were used to determine insulin–C-peptide ratios. Intravenous glucose disappearance rates (K_G) were calculated based on the best linear fit of the natural log of glucose values as a function of time from 10 to 30 min with least-squares linear regression: $K_G = (\Delta \text{ ln plasma glucose}/\Delta_{min}) \times 100$. Data are means ± SE unless otherwise stated. Statistics for intergroup comparisons were performed by analysis of variance followed by Fisher's protected least-significant difference or where applicable by Student's unpaired *t* test. Least-squares linear regression was used to assess bivariate interdependency. Two-tailed *P* values <0.05 were considered statistically significant.

RESULTS

Responses to intravenous glucose. Fasting plasma glucose levels in pancreas recipients, nondiabetic kidney recipients, and control subjects were not significantly different from one another (Table 1). Similarly, during IVGTT, plasma glucose curves in pancreas recipients and control subjects were superimposable, and K_G values in pancreas recipients were normal (1.6 ± 0.1 vs. 1.7 ± 0.1% in control subjects and 2.2 ± 0.3% in nondiabetic kidney recipients). However, mean fasting insulin levels in pancreas recipients with systemic venous drainage of the graft (204 ± 18 pM, $n = 28$) were 3.1-fold increased compared with nondiabetic control subjects (66 ± 5 pM, $n = 19$, $P < 0.0001$; Table 2) and 2.6-fold increased compared with nondiabetic kidney recipients (77 ± 17 pM, $n = 8$, $P < 0.0001$). AIR were significantly increased ($P < 0.01$) in pancreas recipients (763 ± 91 pM, $n = 27$) compared with control subjects (416 ± 44 pM, $n = 19$), whereas no significant difference was found between nondiabetic kidney recipients (589 ± 113 pM, $n = 8$) and control subjects (Fig. 1). Insulin responses to intravenous glucose did not differ significantly between pancreas recipients who received a whole-organ pancreas allograft and those who received a segmental pancreas allograft (Fig. 2), although insulin levels in the latter were arithmetically somewhat lower. In contrast to the findings in pancreas recipients with systemic venous drainage of the graft, basal insulin levels (99 ± 29 pM) and AIR (440 ± 117 pM) in two recipients with portal venous drainage were within the mean ± SD of control subjects (Fig. 3).

Similar to basal insulin levels, basal C-peptide levels in pancreas recipients with systemic venous drainage of the graft (1.59 ± 0.17 nM, $n = 19$) were elevated compared with control subjects (0.66 ± 0.05 nM, $n = 15$, $P < 0.0001$; Table 2). Basal C-peptide levels in nondiabetic kidney recipients were intermediate (1.12 ± 0.41 nm, $n = 8$), and differences from the other two groups did not reach significance. Basal C-peptide correlated with serum creatinine in pancreas recipients ($r = 0.45$, $P < 0.05$) and in the three groups combined ($r = 0.65$, $P < 0.001$). Basal insulin–C-peptide ratios in pancreas recipients (158 ± 13) were significantly greater ($P < 0.02$) than in control subjects (107 ± 9) and kidney recipients (65 ± 9). C-peptide responses to intravenous glucose expressed as AUC over the first 30 min after stimulation with baseline subtracted did not differ significantly among the three groups (27.60 ± 4.63 nM/min in pancreas recipients, $n = 19$; 34.23 ± 5.47 nM/min in nondiabetic kidney recipients, $n = 8$; and 23.73 ± 2.06 nM/min in control subjects, $n = 15$; NS; Fig. 1). However, integrated insulin–C-peptide ratios were significantly higher

TABLE 2
Basal insulin levels, peak insulin levels, and acute insulin responses (AIR) during intravenous glucose tolerance tests

	Pancreas-allograft recipients		Control subjects		Kidney-allograft recipients	
	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*
Basal insulin (pM)	230 ± 22*	28	66 ± 5	19	77 ± 17	8
Basal C-peptide (nM)	1.59 ± 0.17	19	0.66 ± 0.05	15	1.12 ± 0.14	8
Insulin–C-peptide basal ratio	158 ± 13†	19	107 ± 9	15	65 ± 9	8
AIR (pM)	763 ± 9†	27	416 ± 44	19	589 ± 113	8
Integrated C-peptide (nM/min)	27.60 ± 4.63	19	23.73 ± 2.06	15	34.23 ± 5.47	8
Insulin–C-peptide stimulated ratio	0.54 ± 0.07‡	19	0.28 ± 0.02	15	0.23 ± 0.03	8

*$P < 0.0001$, †$P < 0.01$, ‡$P < 0.001$, vs. control subjects.

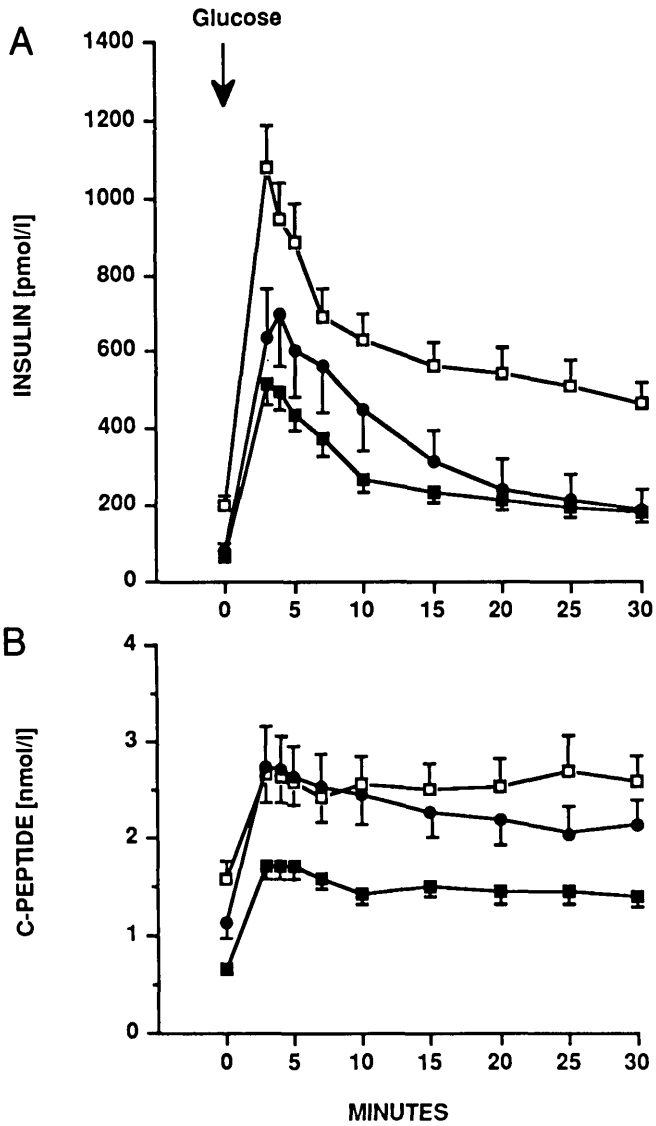

FIG. 1. *A*: Increased basal insulin levels and insulin responses during 20-g glucose intravenous glucose tolerance test (IVGTT) in 27 type I (insulin-dependent) diabetic recipients of pancreas allografts with systemic venous drainage (□) vs. 19 nondiabetic control subjects (■) and 8 nondiabetic recipients of kidney transplants (●). *B*: increased basal C-peptide levels but not C-peptide responses during IVGTT in 17 type I diabetic recipients of pancreas allografts with systemic venous drainage compared with 17 nondiabetic control subjects and 8 nondiabetic recipients of kidney transplants.

($P < 0.001$) in pancreas recipients (0.54 ± 0.07) than in nondiabetic control subjects (0.28 ± 0.02) and kidney recipients (0.23 ± 0.03).

Responses to intravenous arginine. Responses to arginine were determined in 19 pancreas recipients and 21 nondiabetic control subjects (Fig. 4). Basal insulin levels were more than threefold elevated in pancreas recipients with systemic venous drainage of the graft (195 ± 22 vs. 51 ± 7 pM in nondiabetic control subjects, $P < 0.0001$; Table 3). AIR (650 ± 78 pM in pancreas recipients, $n = 19$; 267 ± 61 pM in nondiabetic control subjects, $n = 21$; $P < 0.001$) were clearly exaggerated in pancreas recipients. Whereas basal C-peptide levels were significantly higher in pancreas recipients compared with nondiabetic control subjects (1.61 ± 0.18 [$n = 14$] vs. 0.61 ± 0.04 nM [$n = 11$]; $P <$ 0.001), C-peptide responses expressed as AUC over the first 10 min after stimulation did not differ significantly between pancreas recipients and nondiabetic control subjects (7.18 ± 1.11 [$n = 14$] vs. 4.96 ± 0.98 nM/min [$n = 11$]; NS).

Urine C-peptide. Twenty-four-hour urine C-peptide excretion was determined in 12 pancreas recipients and 13 nondiabetic control subjects while on a standardized weight-maintaining diet. The average of two 24-h urine determinations of C-peptide in recipients (28.8 ± 11.8 pM/24 h) and nondiabetic control subjects (26.6 ± 5.0 pM/24 h) was not significantly different.

DISCUSSION

Various studies have shown that between 40 and 85% of pancreatic insulin output is rapidly extracted by the liver during first passage (21–23). Our study was performed to ascertain whether pancreas transplantation with systemic venous drainage independent of drug therapy for immunosuppression contributes to hyperinsulinemia. Twenty-eight recipients received a graft that was heterotopically implanted in the pelvis and drained by an iliac vein. In contrast, two recipients had a vascular anastomosis to the inferior mesenteric vein to provide portal venous drainage. None of the patients received exogenous insulin or other drugs for treatment of hyperglycemia, and all were taking combined azathioprine, cyclosporin, and prednisone for immunosuppression. All patients were normoglycemic with normal fasting glucose levels and had normal HbA_{1c} levels. In addition, timing of insulin and C-peptide responses to various secretagogues and glucose disappearance rates after intravenous glucose were normal. However, patients with systemic venous drainage of the transplanted pancreas had threefold elevated basal insulin levels compared with both nondiabetic control subjects and nondiabetic kidney recipients who were treated with similar doses of prednisone. Insulin responses to intravenous glucose and arginine were elevated roughly twofold in pancreas recipients with systemic venous drain-

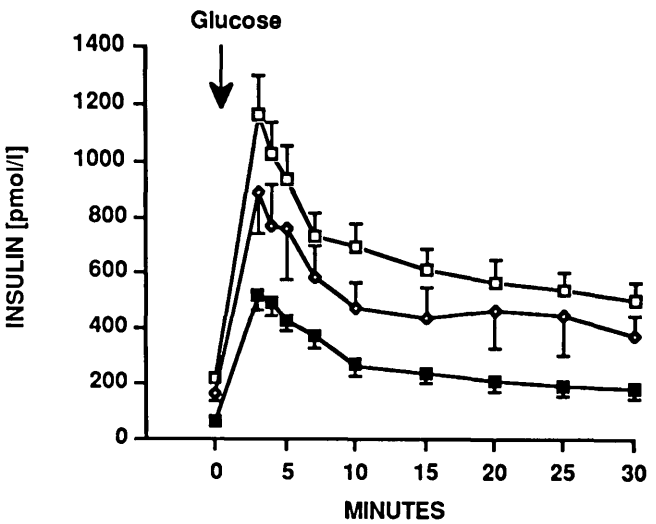

FIG. 2. Serum insulin levels during 20-g glucose intravenous glucose tolerance test in 19 pancreas recipients of whole-organ grafts (□) compared with 8 pancreas recipients of segmental grafts (◇) and nondiabetic control subjects (■). No differences were observed between recipients of whole-organ and segmental grafts.

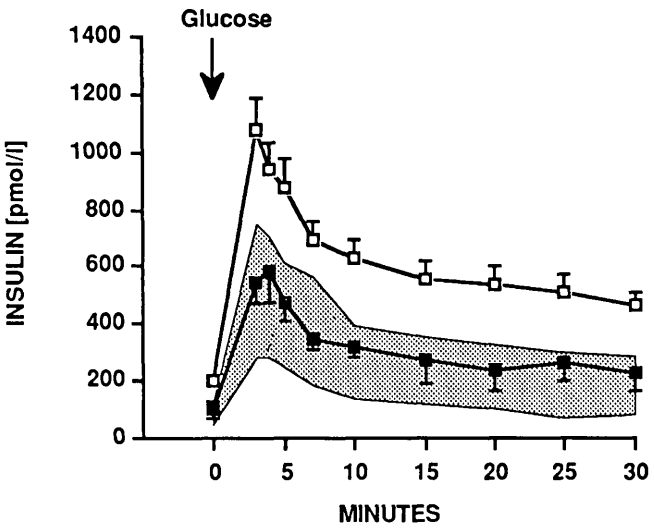

FIG. 3. Serum insulin levels during 20-g glucose intravenous glucose tolerance test in 2 recipients of pancreas allografts with portal venous drainage (■) compared with 27 recipients of pancreas allografts with systemic venous drainage (□). *Stippled area* depicts means ± SD of nondiabetic control subjects.

age of the graft. Nondiabetic kidney recipients had slightly but not significantly higher acute insulin responses after stimulation with glucose than nondiabetic control subjects. Because both integrated C-peptide responses to stimulation with glucose and arginine in pancreas recipients and 24-h urine C-peptide excretion in pancreas recipients were normal, and because two recipients with portal venous drainage of their graft had normal insulin responses, our data strongly suggest that the elevation of basal and stimulated insulin levels are mainly due to the systemic insulin delivery with alterations in first-pass hepatic clearance. However, an important component of the elevation of basal insulin and C-peptide levels in pancreas recipients may be a physiological response by the allograft to increased glucose output from the liver, which would have been present initially due to less than normal portal vein insulin concentrations after organ transplantation with systemic venous drainage.

Basal C-peptide levels in pancreas recipients were significantly greater than in control subjects, but this was not the case in nondiabetic kidney recipients. Because basal C-peptide levels correlated with creatinine levels in both pancreas recipients and the three groups overall, these differences may be due to a combination of insulin resistance caused by prednisone and alterations in C-peptide clearance secondary to impaired kidney function. Because C-peptide is not degraded by the liver, the magnitude of C-peptide levels in the systemic circulation after stimulated C-peptide responses should be independent of the type of pancreatic venous drainage. C-peptide levels, even when measured in a peripheral vein, are therefore better suited than peripherally measured insulin levels to compare insulin secretion in pancreas recipients with systemic venous drainage of the graft with data from control subjects. In contrast to basal C-peptide levels, integrated C-peptide responses to intravenous glucose were not significantly different between the three groups, which strongly suggests that actual insulin secretion rates are also not different. In addition, the ratio of both basal and integrated insulin–C-peptide responses after intravenous glucose stimulation was significantly higher in pancreas recipients than in kidney recipients and in nondiabetic control subjects. These data again indicate that alterations in insulin clearance rather than increased insulin secretion rates are responsible for the elevated insulin levels observed in pancreas-transplant recipients.

Although systemic venous drainage of pancreatic grafts

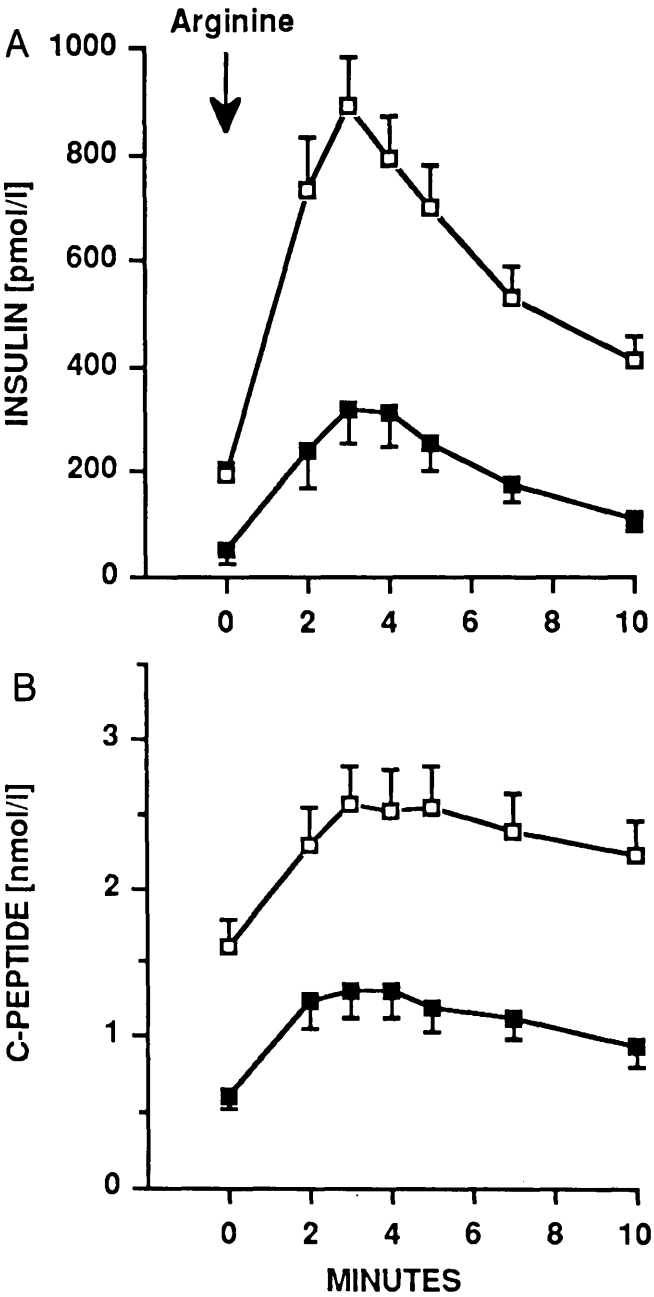

FIG. 4. *A*: increased basal insulin levels and insulin responses during 5-g i.v. arginine stimulation in 19 type I (insulin-dependent) diabetic recipients of pancreas allografts with systemic venous drainage (□) compared with 21 nondiabetic control subjects (■). *B*: increased basal C-peptide levels but not C-peptide responses during 5-g i.v. arginine stimulation in 15 type I diabetic recipients of pancreas allografts with systemic venous drainage compared with 11 nondiabetic control subjects.

TABLE 3
Basal insulin levels, peak insulin levels, and acute insulin responses (AIR) during arginine stimulation

	Pancreas-allograft recipients		Control subjects	
	Mean ± SD	*n*	Mean ± SD	*n*
Basal insulin (pM)	195 ± 22*	19	51 ± 7	21
Basal C-peptide (nM)	1.61 ± 0.18*	14	0.61 ± 0.04	11
AIR (pM)	650 ± 78†	19	267 ± 61	21
Integrated C-peptide (nM/min)	7.18 ± 1.11	14	4.96 ± 0.98	11

*$P < 0.0001$, †$P < 0.001$, vs. control subjects.

is associated with higher insulin levels than portal venous drainage in dogs (24–26), pigs (27), and primates (28), insulin levels seem to be similar with both techniques in rats (29). Few data of this nature are available from studies performed in humans who have undergone pancreas transplantation, and all previous studies were compromised by comparatively small groups of patients and/or lack of control subjects for drug therapy with immunosuppression. In an early study, Pozza et al. (9) studied insulin release induced by various secretagogues and did not report hyperinsulinemia. In a second report, the same group mentioned elevated insulin levels during 24-h insulin profiles at baseline, between meals, and at night (8). These studies included only 4 and 10 pancreas recipients, respectively, and they all had undergone a segmental pancreas graft with duct obstruction, which has been shown to exhibit lower insulin levels at baseline and after glucose challenge (30). In addition, some of these patients were studied during the immediate postoperative period. Hence, some of these patients may not have been truly normoglycemic, because fasting blood glucose levels and circadian mean blood glucose levels were significantly higher in these patients than in control subjects, and not all patients had normal K_G values. Secchi et al. (10) studied 9 patients who had received segmental pancreas grafts with duct obstruction and did not find hyperinsulinemia at baseline or after stimulation with arginine. Östman et al. (11) recently reported hyperinsulinemia in a study of 5 pancreas recipients with systemic venous drainage of their graft compared with kidney recipients on the same immunosuppressive regimen. Perhaps most important, none of these cited studies provided a detailed analysis of C-peptide responses, which is important in assessing possible mechanisms of hyperinsulinemia.

We conclude that normoglycemic recipients of heterotopic transplantation of pancreas allografts with systemic venous drainage have elevated basal insulin and C-peptide levels but only elevated insulin responses to glucose and arginine stimulation. We believe this is mainly due to changes in hepatic insulin clearance secondary to systemic venous drainage. To avoid hyperinsulinemia, which has been reported to be a potential risk factor for hypertension and macrovascular disease in both diabetic and nondiabetic subjects (12–16), transplantation of pancreas allografts in sites with portal rather than systemic venous drainage should be considered.

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