Successful Islet Autotransplantation in Humans

Functional Insulin Secretory Reserve as an Estimate of Surviving Islet Cell Mass

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Islet autotransplantation for treatment of chronic painful pancreatitis in nondiabetic patients reliably establishes normoglycemia and phasic insulin secretion and can achieve prolonged insulin independence. Whether functional transplanted β-cell reserve is normal after intrahepatic islet transplantation is not known, nor is it known whether conventional measures of insulin secretion accurately reflect the functional β-cell mass. To determine insulin secretory reserve after islet transplant, we performed studies of glucose potentiation of arginine-induced insulin secretion (GPAIS) in eight recipients of intrahepatic islet autotransplants. All eight subjects (and matched, healthy controls) were studied cross-sectionally 49 ± 12 months posttransplant, and four subjects were studied pre- and posttransplant. Subjects had received a mean ± SE of 479,000 ± 79,000 islets, and all were insulin independent and normoglycemic at the time of study. Acute insulin responses to arginine, glucose, and GPAIS were significantly reduced after islet transplantation in both study groups. Importantly, the magnitudes of these three responses were highly correlated to the mass of islets transplanted (response to glucose: $r = 0.84$, $P < 0.01$; response to arginine: $r = 0.69$, $P < 0.05$; response to GPAIS = 0.81, $P < 0.01$). Data from hemipancreatectomized and normal control subjects generally agreed with the regression lines. These findings demonstrate that despite normoglycemia and insulin independence, recipients of intrahepatic islet transplantation have significantly reduced functional β-secretory reserve and that after islet transplantation, functional β-cell mass can be estimated by measurements of glucose and arginine-induced insulin responses. Thus, these measurements can be used to estimate the mass and functional capacity of islets surviving intrahepatic transplantation in humans. *Diabetes* 47:324–330, 1998

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AIR, acute insulin response; AST, arginine stimulation test; GPAIS, glucose potentiation of arginine-induced insulin secretion; IVGTT, intravenous glucose tolerance test.

Transplantation of isolated pancreatic islet tissue continues to be intensely investigated as a potential treatment for type 1 diabetes. Despite more than 25 years of experience with islet transplantation, however, less than 10% of humans with type 1 diabetes undergoing this procedure achieve insulin independence for 1 to 12 weeks (1). The success rate of this procedure is even more dismal if insulin independence greater than 3 months after transplant is used as the criterion. In contrast to the lack of success of islet *allo*transplantation, islet *auto*transplantation has been a reliable procedure to prevent postsurgical diabetes in patients with chronic pancreatitis who undergo total pancreatectomy for relief of chronic pain. Intrahepatic islet autotransplantation establishes normoglycemia and sustained insulin independence in up to 70% of subjects if ≥250,000 islets are transplanted (2–4). Advantage can be taken of these successful procedures in nondiabetic patients to gain insights into transplanted islet function in humans in anticipation of eventual success of allo-islet transplantation in diabetic patients. For example, recipients of intrahepatic islet autotransplant grafts have been shown to have preserved phasic insulin responses to glucose and to the non-glucose secretagogues secretin and arginine (2).

The absolute mass of transplanted islets has been identified as a critical determinant of success in islet transplantation. However, it is not possible to determine the actual number of islets that implant in the liver and survive the transplantation process. Consequently, posttransplantation metabolic studies have not been able to provide critically needed information that relates the degree of metabolic success (regulation of glycemia) with the number of islets surviving transplantation. This unsatisfactory state of affairs led us to question whether measurement of insulin secretory reserve might provide a valid measure of surviving islets. Insulin secretory reserve is measured by the technique of glucose potentiation of arginine-induced insulin secretion (GPAIS). It is a sensitive indicator of subclinical abnormalities in β-cell function (5–7) and reflects the maximal insulin secretory capacity or reserve from a given mass of islet tissue. Studies of GPAIS after islet transplant have not been reported previously. Consequently, we performed studies of GPAIS in human recipients of successful intrahepatic islet autotransplantation to determine whether functional β-cell secretory reserve is normal or diminished and to ascertain whether measures of β-cell function correlate with transplanted islet mass.

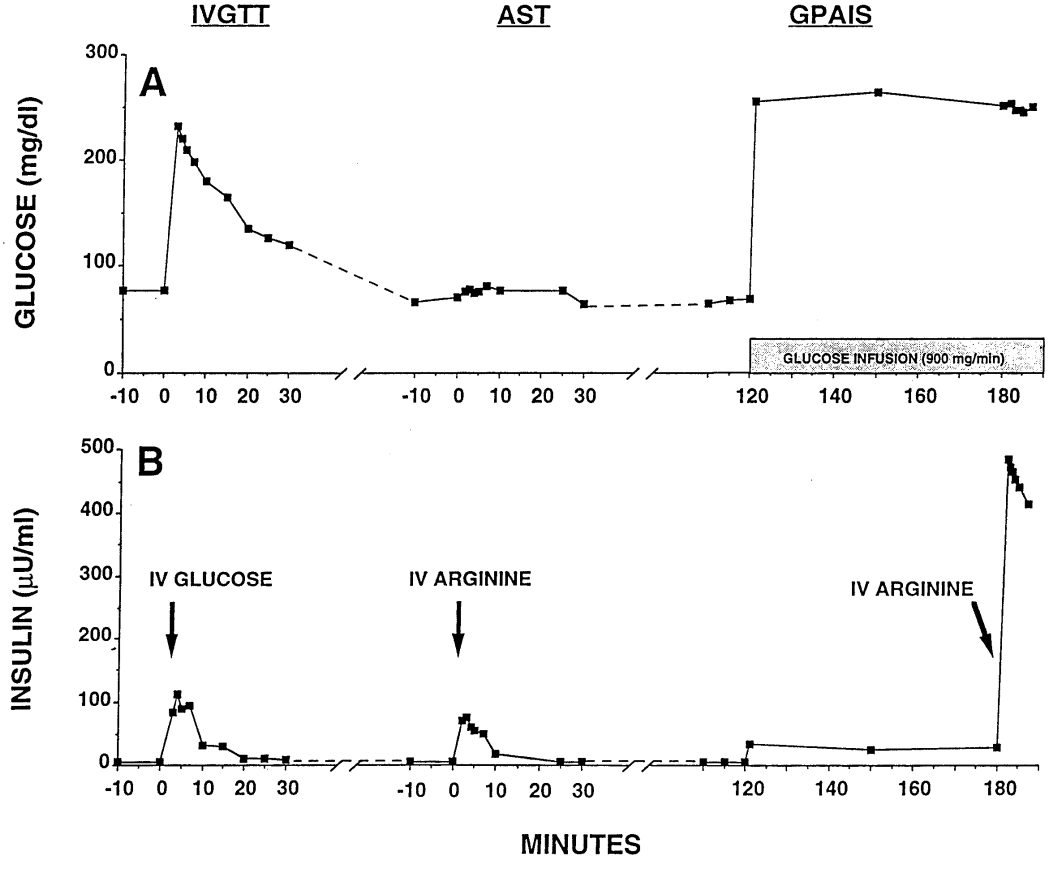

FIG. 1. Representative example of glucose (*A*) and insulin (*B*) levels during IVGTT, AST, and glucose potentiation study in a healthy control subject. IVGTT was performed by intravenous administration of 20 g glucose. Arginine stimulation was achieved by administration of 5 g intravenously. Potentiation was performed during a 70-min glucose infusion at a rate of 900 mg/min. At 60 min, a second bolus of arginine (5 g) was administered with the resultant potentiation of the AIR to arginine.

RESEARCH DESIGN AND METHODS

Study subjects. Eight patients who had undergone 100% pancreatectomy with Whipple procedure and successful intrahepatic islet autotransplantation were recruited for study (Table 1). Three patients participated in a previously reported study (2), but all of the data reported in this article are new. The details of the surgical procedures of autotransplantation (3,4) have been previously reported. Briefly, all patients were referred to the University of Minnesota for consideration of total pancreatectomy for purposes of treatment of chronic, painful pancreatitis. Each patient underwent pylorus-sparing total pancreaticoduodenectomy, with isolation of islets from the pancreas graft by collagenase digestion. Unpurified preparations of dispersed islet tissue were infused via the portal vein to achieve implantation within the hepatic parenchyma. At the time of study, no subject was using exogenous insulin, and all had fasting glucose levels <110 mg/dl. Healthy subjects matched for age, sex, and BMI with the islet recipients served as control subjects. To control for the effect of preexisting pancreatitis on islet function and measures of insulin secretion, four islet transplant recipients were studied both before and after the procedure. Each of these individuals underwent identical studies of insulin secretory response before and between 7 and 18 months after total pancreatectomy and intrahepatic islet autotransplantation. No immunosuppression was required for maintenance of the autotransplanted grafts. No patients or control subjects were taking medication that would be expected to interfere with insulin secretion or glucose tolerance; the few patients who were taking pain medications abstained for at least 12 h prior to study.

Metabolic studies. Subjects were admitted to the University of Minnesota Clinical Research Center on one or more days for completion of the studies. The metabolic studies were performed at 0800 after an overnight fast of at least 10 h. Intravenous catheters were placed in both arms of each study subject. The arm from which the samples were obtained was warmed to 55°C in a heated chamber to assure arterialization of venous samples. Insulin secretion was evaluated in response to intravenous glucose (by intravenous glucose tolerance test [IVGTT]) and intravenous arginine in the fasting state (arginine stimulation test [AST]) and during GPAIS. IVGTT was performed 30 min after the completion of arginine infusion by administration of 20 g glucose (given as $D_{50}W$). Samples for glucose and insulin were obtained at baseline and 3, 4, 5, 7, 10, 15, 20, 25, and 30 min after injection of the glucose solution. Acute insulin response to glucose was defined as the mean of the 3-, 4-, and 5-min insulin values following the glucose injection with the basal value subtracted. Glucose disposal rate (Kg) after intravenous glucose was calculated as the slope of the natural log of glucose values between 10 and 30 min after injection. Arginine stimulation and glucose potentiation studies were performed as outlined in Fig. 1. ASTs used an intravenous injection of 5 g of arginine (given as 10% arginine HCl; KabiVitrum, Clayton, NC) administered over 30 s with time 0 set halfway through the arginine injection. Samples for glucose and insulin were collected from the contralateral arm at baseline and 2, 3, 4, 5, 7, and 10 min after the arginine injection. Acute insulin response (AIR) to arginine was defined as the mean of the peak three insulin values between 2 and 5 min following the arginine injection with the basal value subtracted. GPAIS was performed as described in the studies of Seaquist and Robertson (5) and Teuscher et al. (6). Prior glucose infusion was initiated, and basal samples for glucose and insulin were again obtained. Thereafter, glucose (as $D_{20}W$) was infused at a rate of 900 mg/min by intravenous pump. We have previously demonstrated that this rate of glucose infusion results in maximal potentiation of arginine-induced insulin secretion (5,6). Glucose infusion was maintained for a total of 70 min. At minute 60, and while the glucose infusion was continued, 5 g of arginine (10% arginine HCl) was administered intravenously over 30 s. GPAIS samples (for glucose and insulin) were obtained at 2, 3, 4, 5, 7, and 10 min after arginine injection. AIR-900 was calculated as the mean of the peak three insulin values between 2 and 5 min following the arginine injection with the basal value subtracted.

Statistical methods. Plasma glucose was determined by automated glucose analyzer. Serum insulin was measured by standard double antibody radioimmunoassay (8). Hemoglobin A_{1c} measurement was performed by high-performance liquid chromatography.

Data are expressed as mean ± SE. Statistical evaluation was performed with the InStat statistical software package (GraphPad Software, Malvern, PA). Comparisons in the cross-sectional evaluation of islet autograft recipients and matched control

TABLE 1
Clinical profile of eight recipients of islet autotransplantation and age-, sex-, and BMI-matched control subjects

	Islet Tx	Control
Sex (F/M)	7/1	7/1
Age (years)	39 ± 3	37 ± 3
Months of follow-up	34 ± 13	—
BMI (kg/m^2)	22.4 ± 1.1	22.9 ± 1.0
Islet mass ($\times 10^3$)	479 ± 79	—
Fasting glucose (mg/dl)	99 ± 3*	83 ± 3
HbA_{1c} (%)	5.5 ± 0.2*	5.1 ± 0.1
Glucose disposal (kg)	1.07 ± 0.10*	1.50 ± 0.16

Data are means ± SE. *P < 0.05 vs. control subjects.

subjects were performed utilizing two-tailed, unpaired Student's t tests. Nonparametric data were analyzed by the Mann-Whitney U test. One-tailed, paired t testing was used for comparisons of the four subjects studied prospectively. Correlation coefficients were calculated using the Pearson parametric linear correlation. Data for the cross-sectional and prospective portions of the study are presented separately. Values of P < 0.05 were considered statistically significant.

RESULTS

Cross-sectional study

Patient characteristics. Characteristics of the eight islet autograft recipients and matched control subjects are listed in Table 1. Islet autograft recipients were studied a mean of 34 ± 13 months after total pancreatectomy and intrahepatic islet autotransplantation (range 11–104 months). All islet transplant recipients were insulin independent after receiving a mean of 479,000 ± 79,000 islets (as estimated by dithiozone staining). All islet recipients and control subjects were matched for age, sex, and BMI (Table 1).

Fasting glucose and HbA_{1c}. Mean fasting glucose levels (mg/dl) and HbA_{1c} (%) values for the study subjects are also listed in Table 1. Mean HbA_{1c} was normal in both groups of subjects but was significantly higher in the islet recipients than in the healthy control subjects (P < 0.05). Fasting glucose levels (mg/dl) were less than 110 mg/dl in the islet transplant subjects at the time of study, but the fasting glucose levels were significantly higher in the islet transplant recipients than in matched control subjects (P < 0.01).

Intravenous glucose tolerance testing. Results of IVGTTs performed in the eight islet autotransplant recipients and control subjects are shown in Fig. 2. Islet transplant recipients had significantly higher peak glucose levels during the IVGTT (270 ± 13 vs. 237 ± 7 mg/dl, P < 0.05; Fig. 2*A*). The glucose disposal rate (Kg) following injection of glucose was significantly lower in the autotransplant patients than in the control subjects (1.07 ± 0.10 vs. 1.50 ± 0.16%, P < 0.05; Fig. 2*A*). Although fasting insulin levels during IVGTT were not different between the two groups, the magnitude of the AIR to glucose was significantly lower in islet autotransplant recipients than in the matched control subjects (AIR-glucose = 42 ± 10 in islet recipients vs. 111 ± 30 μU/ml in control subjects, P < 0.05; Fig. 2*B*).

AST and GPAIS. Glucose and insulin values during arginine stimulation and glucose potentiation studies in these study subjects are shown in Fig. 3. During the AST, glucose values were significantly higher in transplant recipients (mean glucose during AST = 103 ± 4 in islet recipients vs. 96 ± 3 mg/dl in control subjects, P = 0.03; Fig. 3*A*). Fasting insulin levels

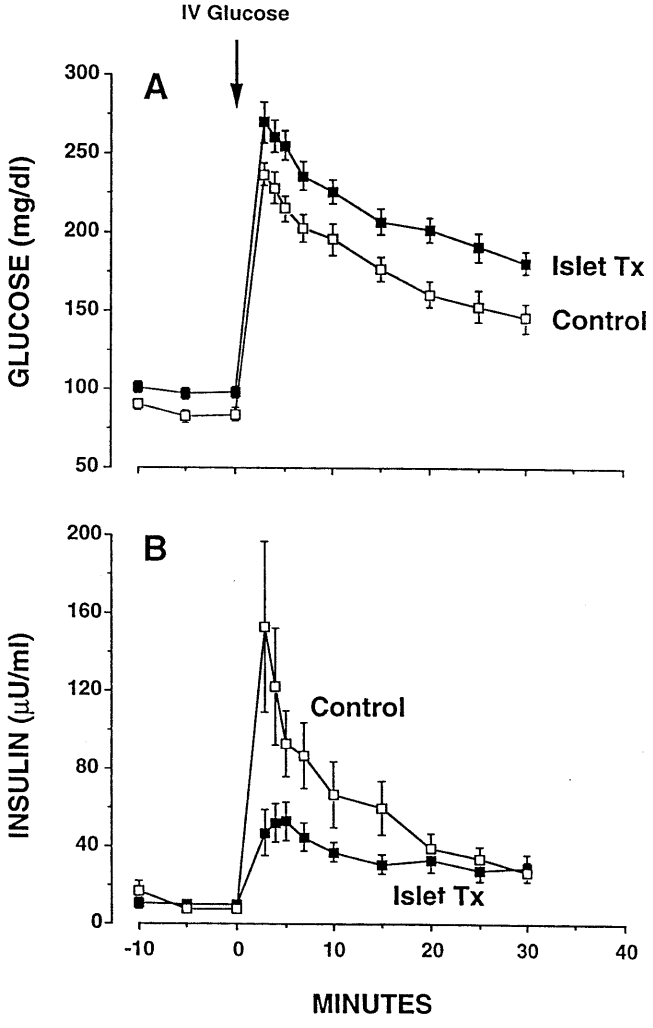

FIG. 2. Serum glucose (*A*) and insulin (*B*) levels during IVGTT in recipients of successful islet autotransplantation (Islet Tx, n = 8) and matched control subjects (n = 8). Islet Tx patients had significantly higher fasting and stimulated glucose levels and had a lower rate of glucose disposal during IVGTT (*A*). Despite similar levels of fasting insulin, Islet Tx recipients had a significant reduction in the acute insulin response to glucose (*B*).

were not different between the two groups. However, the AIR during the AST was significantly less in islet autotransplant recipients than in the matched control subjects (Fig. 3*B*). AIR-arginine was 32 ± 8 in islet recipients and 73 ± 15 in control subjects (P < 0.04). During GPAIS, the continuous glucose infusion resulted in a greater increase in serum glucose in the islet recipients compared with the healthy control subjects (mean glucose 310 ± 13 in islet recipients vs. 261 ± 16 in control subjects, P < 0.04; Fig. 3*A*). The glucose infusion resulted in significant potentiation of the arginine-induced insulin response in both groups (P < 0.05 vs. arginine alone; Fig. 3*B*). However, AIR potentiation was significantly lower in islet recipients when compared with control subjects (160 ± 33 vs. 477 ± 100, P < 0.01).

Correlations of AIR with islet mass and measures of glycemia. A summary of the acute insulin responses for islet transplant recipients and control subjects (who were assumed to have the normal complement of approximately

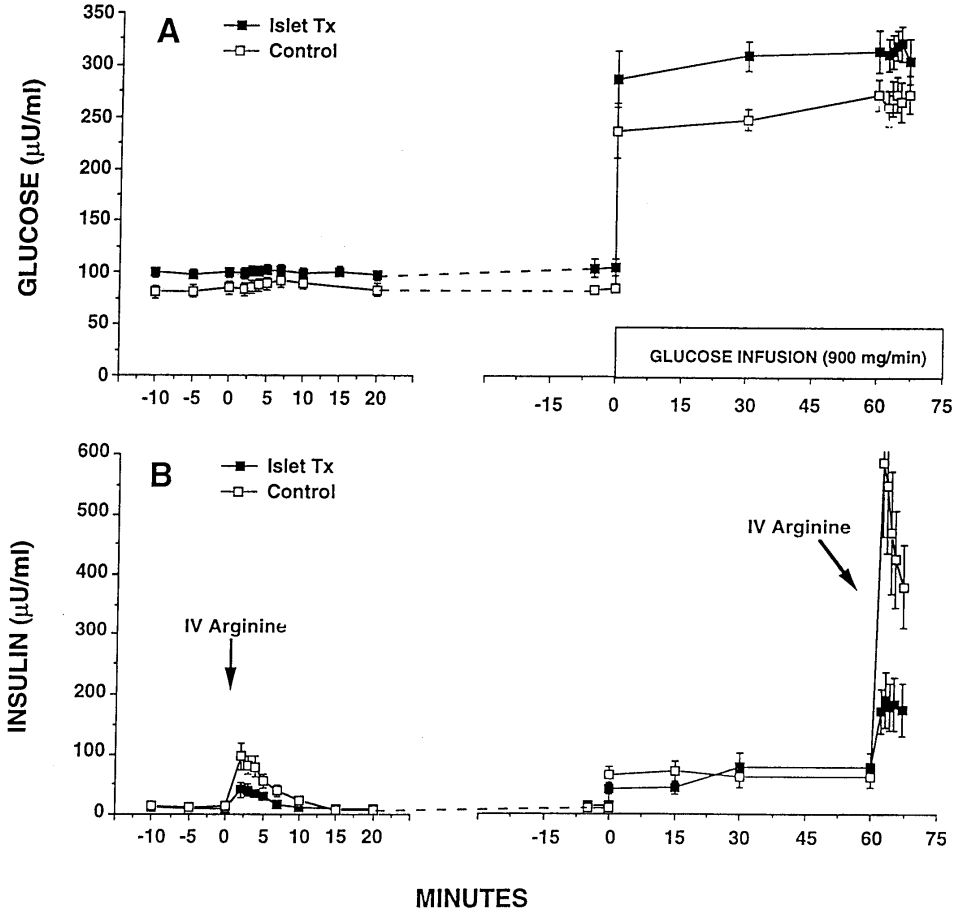

FIG. 3. Mean glucose levels and AIR to intravenous arginine and glucose potentiation tests. Fasting glucose, glucose values during AST, and peak glucose during potentiation were significantly greater in islet transplant recipients (*A*). The acute insulin response to arginine and potentiation was significantly lower in islet Tx recipients than in control subjects (*B*; $P < 0.05$).

1 million islets) for each of the studies performed is shown in Fig. 4. After islet transplantation, AIR was reduced by 60, 65, and 71% to intravenous glucose, intravenous arginine, and glucose potentiation studies, respectively. To determine the degree to which AIR during GPAIS correlated with the mass of islet tissue infused at the time of transplantation, correlation analysis was performed (Fig. 5). Responses to GPAIS significantly correlated with islet mass transplanted ($r = 0.81$, $P < 0.01$; Fig. 5*A*) and responses to AST ($r = 0.97$, $P < 0.001$; Fig. 5*B*). AIR-glucose and AIR-arginine also correlated with islet number (AIR-glucose $r = 0.84$, $P < 0.01$; AIR-arginine, $r = 0.69$, $P < 0.05$; Fig. 5*C–D*). Previously published data (5) from hemipancreatectomized donors and their control subjects fell close to the regression lines generated.

Prospective study

Patient characteristics. Four subjects underwent studies before and after total pancreatectomy and islet transplantation. They completed identical IVGTT, AST, and GPAIS studies before and 10 ± 1 months after surgery. These four individuals had a mean age of 37 ± 5 years and received a mean of 498,000 ± 160,000 islets (range 337,000–868,000). There was no significant change in BMI at the time of follow-up (23.3 ± 1.5 before vs. 21.5 ± 1.4 after, NS). Fasting glucose values increased in all subjects, with a mean increase from 93 ± 2 pretransplant to 101 ± 3 posttransplant ($P < 0.001$; Table

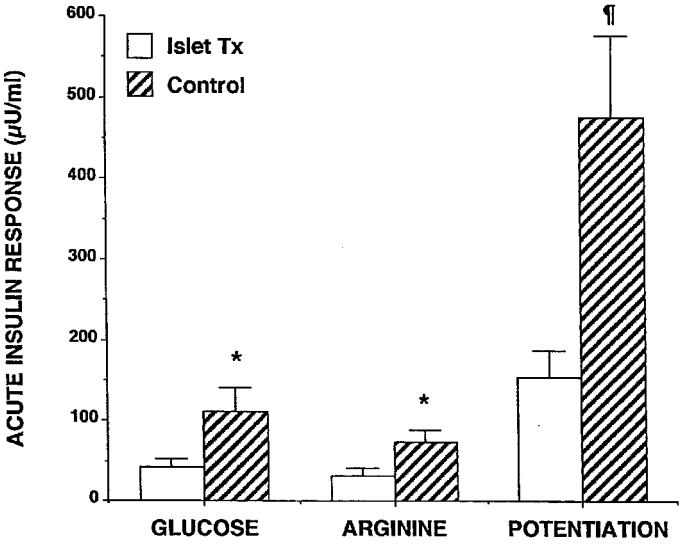

FIG. 4. Control (pretransplant) and posttransplant AIR during IVGTT, AST, and glucose potentiation study in recipients of successful islet autotransplantation (Islet Tx) in four recipients of islet autotransplantation studied in a prospective fashion. Each individual had a significant reduction in AIR following transplantation of between 290,000 and 868,000 islets, with significant reduction in the mean AIR for each comparison ($P < 0.02$).

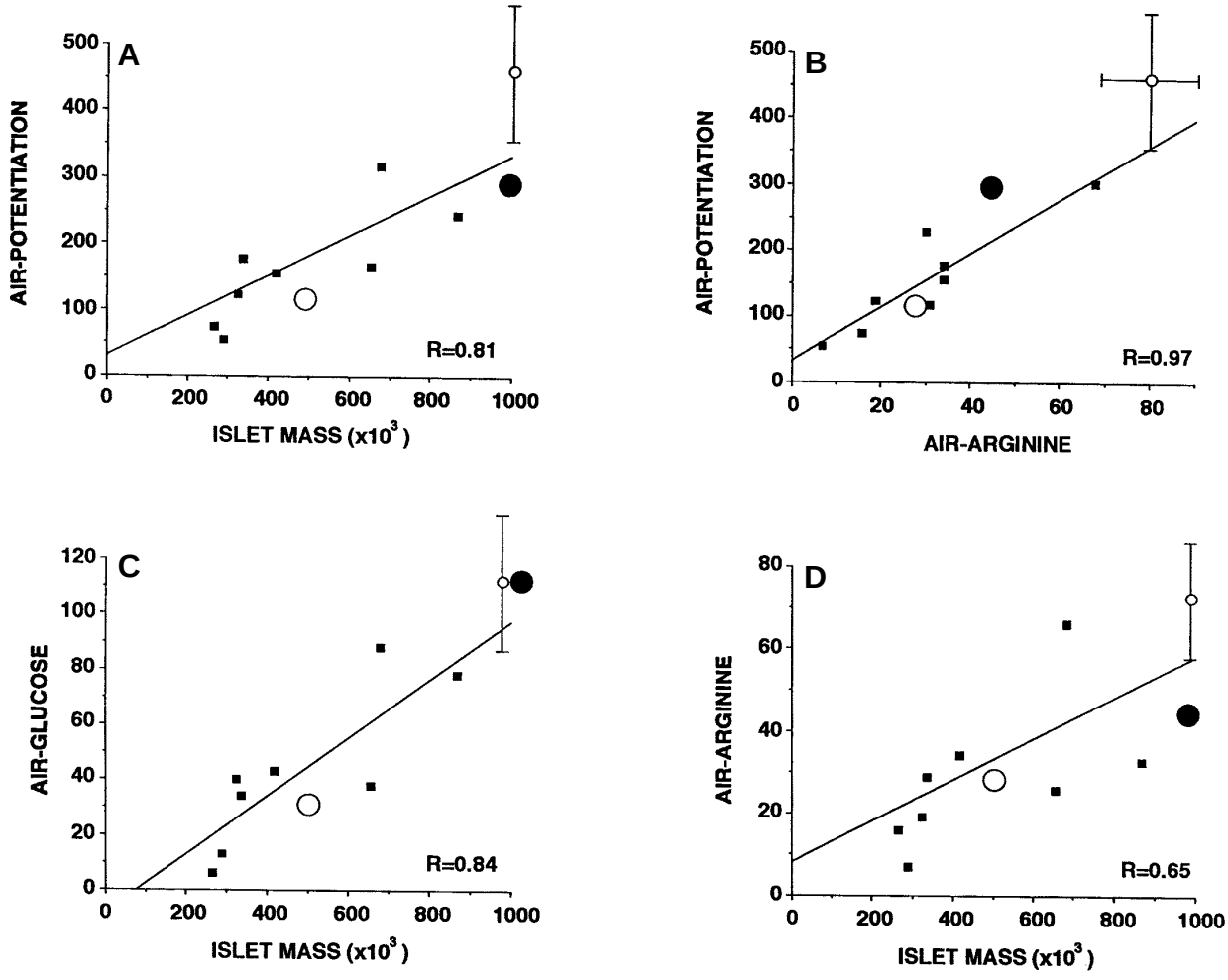

FIG. 5. Correlation of AIR during glucose potentiation (*A*), intravenous glucose (*C*), and intravenous arginine (*D*) to estimated mass of transplanted islet tissue in insulin-independent, normoglycemic recipients of islet autotransplantation. Correlation of AIR-potentiation and AIR-arginine is also shown (*B*). Each measure of insulin release correlated significantly with the islet transplant mass infused ($P < 0.03$ for all correlations using data from transplanted patients only). Correlation coefficients (R) for each measure are listed. AIRs for healthy control subjects in this study are shown (○) at estimated islet mass of 10^6 islets. AIR for hemipancreatectomized healthy donors and their controls from a previous publication (5) are shown by the larger open and filled circles, respectively.

2), but mean HbA_{1c} levels were not significantly different before and after transplantation (5.20 ± 0.11 vs. 5.24 ± 0.21%). Mean glucose disposal rates decreased from 1.36 ± 0.19 pretransplant to 1.09 ± 0.20 posttransplant (NS). Maximal glucose levels achieved during the glucose infusion of the GPAIS study were higher after islet autotransplantation (286 ± 16 before vs. 323 ± 14 after), but this difference was not statistically significant. Following islet autotransplantation, each individual had a decrease in insulin to all stimuli (Table 3). The mean AIR declined from 70 ± 14 to 32 ± 16 for AIR-arginine, from 97 ± 18 to 53 ± 18 for AIR-glucose, and from 554 ± 139 to 259 ± 85 for GPAIS, respectively ($P < 0.03$ pre- vs. posttransplant for all comparisons). Among these four patients, measures of β-cell function, expressed as percent of pretransplant results, decreased in proportion to the number of islets transplanted (Table 3).

DISCUSSION

These studies demonstrate that nondiabetic successful recipients of intrahepatic pancreatic islet autotransplantation who remain normoglycemic and insulin independent have a marked reduction both in AIR during fasting and in functional insulin secretory reserve. All three measures of insulin secretion correlated highly to the number of islets transplanted and thus can be used as estimates of surviving, functional transplanted islet mass.

Our study is the first to evaluate insulin secretory reserve following islet transplantation in humans. Other investigators have performed studies of GPAIS in animal models of islet transplantation. Tobin et al. (9) investigated AIR to both arginine and glucose to assess islet mass in a rodent transplant model. As we observed in human islet transplant recipients, they found that AIR-glucose was a useful correlate of islet mass. In contrast to our studies, however, they found that AIR-arginine did not correlate with islet mass. The findings of our studies and those of Tobin et al. are in contrast to studies in dogs and baboons reported by Ward et al. (10) and McCulloch et al. (7). These investigators concluded that potentiation of AIR-arginine was a more sensitive indicator of islet mass than was fasting AIR to arginine. In our studies

TABLE 2
Clinical profile before and after total pancreatectomy and islet autotransplant in four subjects

	Before	After
Fasting glucose	91 ± 3	99 ± 3*
HbA_{1c}	5.2 ± 0.1	5.2 ± 0.2
Glucose disposal (kg)	1.36 ± 0.19	1.09 ± 0.20
Glucose-GPAIS	286 ± 16	323 ± 14†

Data are means ± SE. Follow-up studies were performed between 8 and 18 months posttransplantation. *P < 0.001 vs. pretransplant; †P = 0.07 vs. pretransplant.

of human islet transplant recipients, AIR-glucose and AIR-potentiation were reduced to a similar degree, and each correlated well with islet mass. Ward et al. (10) have also published that GPAIS is maximally reduced by 50% pancreatectomy. However, our studies demonstrate that a linear relationship exists between glucose potentiation and islet number when islet mass is 25–75% of that in the normal pancreas. Importantly, our studies uniquely evaluated four subjects pre- and posttransplant. Their results confirm that the reduction in insulin secretion is in great part the consequence of the transplantation procedure and not preexisting pancreatitis. All of the subjects studied prospectively had a decline in insulin secretion, a reduction that was commensurate with the number of islet cells transplanted. Reduced functional insulin secretory reserve has also been reported in humans undergoing hemipancreatectomy (5). These individuals have AIR-potentiation that is ~50% of normal; their data are plotted on Fig. 5 for comparison. The latter individuals were also demonstrated to have an increase in the plasma proinsulin-to-insulin ratio (11), which suggests that in the face of reduced functional insulin secretory reserve, pancreatic islets may compensate by recruiting immature secretory granules.

GPAIS has not been assessed after intrahepatic allotransplantation in patients with type 1 diabetes because of the rarity of normoglycemic, insulin-independent diabetic recipients. However, our observation of decreased insulin secretory reserve in nonimmunosuppressed, successful, nondiabetic human recipients of islet transplantation suggests that the limited success of islet allotransplantation using islets from a single organ may be partially a consequence of the reduction in islet-cell secretory reserve. The mass of islet tissue derived from a single organ is generally reduced by 50–70% compared with the intact pancreas. Although mass of islet tissue is clearly a critical determinant of the success of this procedure (12–14), other factors governing the success of islet transplantation include early posttransplant glycemic control, prevention of early, nonspecific immune responses (e.g., by use of anti-macrophage agents), and use of immunosuppressive drugs that do not independently adversely affect islet function.

The issue of adverse effects of immunosuppressive drugs requires further consideration. Reduced functional insulin secretory reserve has been reported to occur after whole-organ pancreas transplantation (6). In these individuals, the immunosuppressive regimen may in part be responsible for the observed reduction in GPAIS, considering that nondiabetic recipients of kidney transplants also had a marked reduction in insulin secretory reserve. Which specific agents are most responsible for this adverse effect is not known. Glucocorticoids, cyclosporine A, and tacrolimus may all adversely affect islet function. Because glucocorticoids induce significant insulin resistance, steroid-based immunosuppressive regimens could result in islet graft failure due to exhaustion of insulin secretory reserve and consequent hyperglycemia. Controversy exists as to the potential for agents such as cyclosporine and tacrolimus to alter islet function in a clinical setting. Cyclosporine A has been reported to adversely affect insulin secretion and insulin gene transcription in islets and islet cell lines (15), although 2 years of treatment with cyclosporine A did not alter insulin secretion in patients with multiple sclerosis (16). Recently, we reported that tacrolimus has significant negative effects on insulin release and insulin gene transcription in the HIT-T15 β-cell line (17), and tacrolimus has been reported to be diabetogenic in patients receiving renal transplantation (18). However, to date no direct clinical evaluation of the effects of tacrolimus on insulin secretion in humans has been reported. Further studies of possible adverse effects of the currently available immunosuppressive drugs on β-cell function are needed in humans to clarify this issue.

TABLE 3
Insulin secretion results from four successful recipients of pancreatic islet autotransplantation and eight normal control subjects

		AIR-glucose			AIR-arginine			AIR-potentiation		
	Islets	Before	After	% decrease	Before	After	% decrease	Before	After	% decrease
Subject										
1	868,000	95	78	82	38	19	50	277	228	82
2	678,000	149	88	59	106	78	74	784	348	44
3	337,000	67	34	51	60	25	42	439	138	31
4	290,000	80	13	16	78	7	9	355	55	16
Mean ± SE		97 ± 18	53 ± 18	—	70 ± 14	32 ± 16	—	554 ± 139	259 ± 85	—
Control mean ± SE (n = 8)		111 ± 30	—	—	73 ± 15	—	—	477 ± 100	—	—

Follow-up studies were performed 8–18 months posttransplantation. Before, pretransplant; after, posttransplant; % decrease expressed as after/before × 100.

Although it is impossible to determine from any human study the number of islets that survive intrahepatic transplantation, our study provides unique methods that allow valid estimations. This contention is defensible because transplanted islet mass correlated significantly with AIR, and because healthy control subjects (with an approximate islet mass of 10^6) had AIRs that generally agreed with the correlation seen in islet transplant patients receiving 265,000–868,000 islets. Furthermore, data from hemipancreatectomized healthy donors and their control subjects from a previous publication (5) also agreed generally with the regression lines generated by the correlation analyses. Although each of the measures of insulin secretion used correlated well with the mass of islet tissue transplanted, GPAIS does not appear to be a significantly better measure of engraftment than either arginine- or glucose-induced AIR in the fasting state. This observation is important because it supports the recommendation that insulin response to either intravenous arginine or glucose bolus can be employed as a posttransplant measure of functional islet-cell mass. Such measurements should provide needed insights into the fate of transplanted islets and how their survival relates to variables such as islet harvesting, pre- and posttransplant drugs used, and control of posttransplant glycemia by exogenous insulin.

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