# Effects of Hemipancreatectomy on Pancreatic Alpha and Beta Cell Function in Healthy Human Donors

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## Abstract

To assess the metabolic consequences of hemipancreatectomy in humans, we determined pancreatic beta and alpha cell function in healthy donors. Donors examined cross-sectionally were found to have significantly decreased glucose-induced phasic insulin secretion and arginine-induced insulin and glucagon secretion as compared to age, sex, and body index-matched controls. However, their fasting glucose and insulin values were not different from controls. Similar observations were found in the prospective evaluation of eight donors before and 15±2 mo after hemipancreatectomy. Beta cell reserve, as measured by glucose potentiation of arginine-induced insulin secretion, was significantly decreased in donors (maximal acute insulin response  $[AIR_{max}]$ : donors = 666±84 pM vs controls =  $1,772\pm234$  pM) while the PG<sub>50</sub> (the glucose value at which the half-maximal response was observed) was the same in the two groups. Donors and controls responded to 60-min continuous intravenous infusions of glucose by reaching identical serum glucose values, despite significantly lower insulin secretory responses in donors. We conclude that hemipancreatectomy in human donors is associated with decreased pancreatic alpha and beta cell function. Since donors generally maintain normoglycemia after hemipancreatectomy despite diminished insulin secretion, our data suggest that healthy humans may compensate for hemipancreatectomy by increasing glucose disposal. (J. Clin. Invest. 1992. 89:1761-1766.) Key words: insulin • glucagon • pancreas transplantation • diabetes mellitus • glucose homeostasis

## Introduction

The use of living related donors in human transplantation has become a treatment of choice for individuals in kidney failure, but controversy remains about their use in patients with failing pancreata, livers, or lungs. Consequently, hemipancreatectomy for the purpose of organ donation to a diabetic family member remains an active part of only a few pancreas transplantation programs around the world. Although the serum

Address correspondence to Elizabeth R. Seaquist, M. D., University of Minnesota, Diabetes Center and Division of Endocrinology and Metabolism, UMHC Box 101, Minneapolis, MN 55455. glucose values after hemipancreatectomy in humans have been found to be elevated as compared to values obtained before surgery (1, 2), and while as many as 25% of human donors develop abnormal glucose tolerance after surgery (2), the effects of this operation on beta cell function have been only superficially examined (2) while no information about alpha cell function has been reported.

Preoperatively, human pancreas donors, like other healthy individuals, maintain normoglycemia through a precise balance between insulin secretion and insulin action. At the time of surgery, donors experience a sudden and dramatic reduction in their beta and alpha cell mass. Such a reduction may result in significantly decreased hormone secretion, as has been documented in dogs (3) and rats (4), and may require alterations in hormone action for the maintenance of euglycemia. Therefore, understanding how hemipancreatectomized human donors regulate glucose homeostasis in the face of an abrupt loss of pancreatic islet tissue may provide insights into the pathogenesis of type II diabetes mellitus, a disorder characterized both by defects in insulin secretion and insulin action. Consequently, we have performed a detailed evaluation of pancreatic endocrine function in healthy human donors after hemipancreatectomy at the University of Minnesota and compared them to controls with and without a history of type I diabetes in a first degree relative. The specific aims of our investigation were: (a) to determine the effect of hemipancreatectomy on insulin secretion after intravenous pulses of glucose and arginine; (b) to ascertain the adequacy of beta cell reserve after hemipancreatectomy using the technique of glucose potentiation of arginine-induced insulin secretion to determine both the maximal insulin secretory response and the glucose value at which the half-maximal response is observed  $(PG_{50})$ ;<sup>1</sup> (c) to determine the effect of partial pancreatectomy on glucoregulation during intravenously administered glucose given as both a pulse and a continuous infusion; and (d) to assess the effects of partial pancreatectomy on alpha cell function as determined by the glucagon secretory response to arginine injection at basal glucose and during experimentally produced hyperglycemia.

## Methods

Patient selection. Hemipancreatectomized individuals were recruited from patients who have served as pancreas organ donors at the University of Minnesota. As of June 1, 1991, 75 first degree relatives of patients with type I diabetes mellitus have participated as donors in the pancreas transplant program. Details of their preoperative evaluation and the surgical procedure are included in an earlier publication (2). Donors receiving medical therapy for clinical diabetes were excluded

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<sup>1.</sup> *Abbreviations used in this paper:* AIR, acute secretory response of insulin; ANOVA, analysis of variance; Kg, glucose disappearance rate; PG<sub>50</sub>, glucose value at which acute insulin response is half-maximal.

from participation. Healthy controls were selected to match the donors with respect to age, sex, and body mass index. In control group 1, no member had a family history of diabetes in a first degree relative. In control group 2, members were all first degree relatives of someone with type I diabetes mellitus. Our protocol was approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota, and all participants provided written consent.

Metabolic evaluation. All testing was performed in the General Clinical Research Center at the University of Minnesota after the subjects had fasted for at least 10 h. Beginning at 8 a.m. patients underwent an intravenous arginine stimulation test followed 30 min later by either an intravenous glucose tolerance test or the glucose potentiation study detailed below. The insulin secretory response to an intravenous injection of glucose and the glucose disappearance rate (Kg) were assessed on a separate morning in some patients. The intravenous glucose tolerance test was performed by the administration of 20 g of glucose (given as dextrose 50 gm per 100 ml water) over 30 s, with time zero set at half-way through the injection volume. Samples for glucose and insulin were obtained at -10, -5, 0, 2, 3, 4, 5, 7, 10, 15, 20, 25, and 30 min. The arginine stimulation tests were performed by the intravenous administration of 5 g of arginine (given as 10% arginine HCI; Kabi Vitrum, Inc., Clayton, NC) over 30 s, with time zero set at the time at which one-half of the injection volume was given. Samples for glucose, insulin, and glucagon were obtained at -10, -5, 0, 2, 3, 4, 5, 7, and 10 min.

The glucose potentiation study was modified from that previously described (5, 6) to determine more precisely the glucose value at which the insulin secretory response was half-maximal (PG<sub>50</sub>) in our donor population. In our modification, five arginine stimulation tests were done at different levels of serum glucose. The serum glucose values at which the arginine stimulation tests were performed were baseline, those levels achieved by continuous infusion of glucose (as dextrose 10 gm per 100 ml water) for 1 h at rates of 300 mg/min, 600 mg/min, 900 mg/min, and a final infusion of dextrose 20 gm per 100 ml water at a variable rate calculated to bring to serum glucose to 27.8 mM, as described by Ward and colleagues (7). The continuous infusion of glucose at rates of 300 mg/min, 600 mg/min, and 900 mg/min allowed us to compare the donors and the controls with respect to their glycemic responses to fixed infusions of glucose. Before beginning the study, intravenous lines were placed in both arms of the subjects. The arm from which blood was sampled was placed in a warming chamber heated to 55°C at least 30 min before the study to assure arterialization of the venous blood (8). A 2-h rest period was allowed between each of the glucose potentiation studies to allow the patient's serum glucose, insulin, and glucagon to return to baseline (6). Subjects studied via this protocol included the 10 donors studied cross-sectionally, the 10 members of the first control group, and 6 members of the second control group. No donors were followed prospectively using the glucose potentiation protocol.

#### Table I. Subject Characteristics

Determination of serum glucose, insulin, and glucagon values. Serum glucose values were determined by the glucose oxidase method using an autoanalyzer (Beckman Instruments, Inc., Fullerton, CA). Serum insulin values were measured by radioimmunoassay as previously described (9). Samples for glucagon determinations were collected into prechilled tubes containing 2.5 mg EDTA and 500 U Trasylol (Miles, Inc., FBA Pharmaceuticals, West Haven, CT) per milliliter blood, put on ice, and centrifuged immediately. Glucagon was measured by radioimmunoassay (10) with antibody 04A obtained from Dr. R. H. Unger (University of Texas, Dallas).

Data analysis. Data are reported as means±standard errors of the mean. The acute secretory response of insulin (AIR) and glucagon was calculated as the mean of the three peak values obtained within 5 min of secretagogue injection, with the basal values subtracted. Intravenous Kg were calculated based on the best linear fit of the natural log of glucose values as a function of time from 10 to 30 minutes with leastsquares linear regression: Kg = ( $\Delta$  in ln plasma glucose/ $\Delta$  min)  $\times$  100. Normal Kg values were defined as those > 1.00%/min. The slope of potentiation was calculated as the difference between the acute insulin responses to arginine obtained after the 900 mg/min glucose infusion and at basal glucose divided by the difference between the serum glucoses obtained after 1 h of 900 mg/min of glucose and that obtained at basal glucose (slope =  $[AIR_{900} - AIR_{basal}]/[glucose_{900} - glucose_{basal}])$ . The maximal acute insulin response (AIR<sub>max</sub>) was taken as the secretory response measured at a serum glucose  $\geq 27.8$  mM. The glucose value at which the secretory response was half-maximal (PG<sub>50</sub>) was estimated from graphs of individual glucose potentiation data and then meaned within groups. In all subjects this determination was aided by the use of a computer generated line demonstrating the relationship between AIR and serum glucose concentration. Accuracy of the PG<sub>50</sub> determination was assured by the presence of at least two studies at glucose concentrations at or above that at which glucose maximally potentiated arginine-induced insulin secretion. Differences between groups were assessed using the nonparametric one-tailed Mann Whitney U Test (for single values of glucose, insulin, glucagon, glucose disappearance rates, and acute hormonal secretion) or a two-way analysis of variance (ANOVA) (for data from intravenous glucose tolerance tests, arginine stimulation tests of insulin and glucagon secretion, and glucose potentiation). A P value equal to or less than 0.05 was considered statistically significant.

### Results

Subject characteristics. 10 donors were studied  $69\pm12$  mo (mean $\pm$ SEM) after hemipancreatectomy (Table I). They were matched with respect to sex, age, and body mass index with two groups of 10 healthy controls that differed in their family history of type I diabetes mellitus (listed under Cross-sectional

Group	Male/Female	Age	Body mass index	Fasting glucose	Kg	Months since donation
	(#/#)	(yr)	(kg/m²)	( <i>mM</i> )	(%/min)	
Cross-sectional data						
Control Group 1	3/7	39±4	22.3±0.6	4.8±0.2	1.55±0.23	
Control Group 2	3/7	38±3	24.7±1.6	4.8±0.1	1.67±0.19	
Donors	3/7	39±4	22.9±0.8	5.2±0.2	1.26±0.17	69±12
						(range: 12-146)
Prospective data						
Preoperative	2/5	36±5	24.7±2.0	4.7±0.2	1.63±0.16	
Postoperative	2/5	38±5	25.3±1.9	6.3±0.9	1.21±0.19*	15±2
	·					(range: 11-24)

\* P < 0.05 as compared to preoperative value.



Figure 1. Intravenous glucose tolerance tests in donors and controls. After a 10-h fast, donors ( $\Box$ , n = 10) and matched controls ( $\blacksquare$ , control group 1, n = 10;  $\blacklozenge$ , control group 2, n = 10) were given a 20-g pulse of glucose at time 0. The insulin secretory response is shown in A and the glycemic response is shown in B. Donors had significantly diminished insulin secretion compared to controls (P < 0.001). Individuals in control group 1 were without a history of type I diabetes in a family member. Subjects in control group 2 each had a first degree relative with type I diabetes.

Data in Table I). Subjects in control group 1 were without a family history of type I diabetes, whereas subjects in control group 2 had a first degree relative with type I diabetes. An additional eight donors were studied before and  $15\pm 2$  mo after hemipancreatectomy (listed under Prospective Data in Table I). After hemipancreatectomy, donors had higher fasting glucoses compared to matched controls (cross-sectional data:  $5.2\pm 0.2$  mM in donors vs  $4.8\pm 0.2$  mM in control group 1 and  $4.8\pm 0.1$  mM in control group 2) or to their own preoperative values (prospective data:  $4.7\pm 0.2$  mM vs.  $6.3\pm 0.9$  mM; pre-vs



Figure 2. Prospective evaluation of the effect of hemipancreatectomy on intravenous glucose tolerance tests in donors. Eight donors received an intravenous pulse of 20 g of glucose both before and  $15\pm 2$ mo after hemipancreatectomy. A demonstrates a significant (P< 0.05) decrease in the acute insulin response to glucose after hemipancreatectomy. B demonstrates a significant (P < 0.05) decrease in the glucose disappearance rate (Kg) postoperatively.

postoperative values). However, this difference was statistically significant only when donors were compared to control group 2 (P < 0.02).

Beta cell function. Beta cell function was assessed by the insulin secretory response to glucose and to arginine (Figs. 1, 2, 3, and 4). No differences were found between the fasting insulin values in donors and controls (30±6 pM in donors vs 42±6 pM in both groups 1 and 2) or between the values obtained at the two time points in donors studied prospectively (66±6 pM preoperatively vs 60±12 pM postoperatively). Donors displayed significantly less insulin secretion in response to glucose whether compared to matched controls (AIR: donors =  $174\pm30$  pM [n = 10]; control group 1 =  $372\pm66$  pM [n = 10]; control group  $2 = 690 \pm 150$  pM [n = 10]; Fig. 1, donors vs controls P < 0.001 by ANOVA) or to their preoperative values (Fig. 2, P < 0.05). The Kg for donors and the controls in control groups 1 and 2 were not statistically different (Table I). However, the postoperative Kg values of donors followed prospectively were significantly less than the preoperative values (Table I, Fig. 2).

The insulin secretory response to arginine was also significantly decreased in the donors when compared to the matched controls (AIR: donors =  $168\pm30$  pM [n = 10]; control group 1 =  $258\pm36$  pM [n = 10]; control group 2 =  $264\pm36$  pM [n = 10]; Fig. 3, donors vs controls P < 0.001 by ANOVA). Decreases in the acute insulin response to arginine were seen in six of eight



Figure 3. Arginine-induced insulin secretion in donors and controls. After a 10-h fast, donors  $(\Box, n = 10)$  and matched controls  $(\blacksquare, \text{ control}$  group 1, n = 10;  $\blacklozenge$ , control group 2, n = 10) were given an intravenous pulse of 5 g of arginine at time 0. The insulin secretory response was significantly less in the donors than in the controls (P < 0.001).



Figure 4. Prospective evaluation of arginine-induced insulin secretion in donors. Arginine-induced insulin secretion was studied in eight donors before and  $15\pm 2$  mo after hemipancreatectomy. No significant difference was found between the acute insulin responses to arginine measured at these time points.

donors studied prospectively (Fig. 4) but the mean responses were not significantly different.

Beta cell reserve was assessed by examining glucose potentiation of arginine-induced insulin secretion. Donors demonstrated significantly less beta cell reserve than did their matched controls (Fig. 5, P < 0.001). The maximal acute insulin response (AIR<sub>max</sub>) was lower in donors than in matched controls (666±84 pM in donors vs 1,680±312 pM in control group 1 or 1,776±390 pM in control group 2; P < 0.01) although the PG<sub>50</sub> was not significantly different for these two groups (8.1±0.4 mM in donors vs 9.8±1.0 mM, in control group 1 or 8.1±0.3 in control group 2, P > 0.1). Donors had a significantly lower slope of potentiation than did their controls (0.43±0.05 in donors vs 1.02±0.19 in control group 1 and 1.12±0.36 in control group 2, P < 0.02).

During the glucose potentiation study, donors and controls achieved identical values of serum glucose in response to each rate of continuous glucose infusion over 60 min (Fig. 6). Despite this, the insulin values obtained simultaneously were significantly lower in the donor group than in the control group (Fig. 6, P < 0.001).



Figure 5. Glucose potentiation of arginine-induced insulin secretion in donors and controls. Arginine-induced insulin secretion was studied at five different levels of glycemia. Donors  $(\Box, n = 10)$  demonstrated significantly less arginine-induced insulin secretion at each level of glycemia as compared to controls ( $\Box$ , control group 1, n = 10;  $\blacklozenge$ , control group 2, n = 6; P < 0.001).

1764 E. R. Seaguist and R. P. Robertson

Alpha cell function. Alpha cell function was assessed by measuring the glucagon secretory response to the intravenous administration of arginine. No differences were observed when comparing basal glucagon values in the donors (84±9 ng/liter, n = 10), control group 1 (105±13 ng/liter, n = 10), and control group 2 (72 $\pm$ 27 ng/liter, n = 7). The acute glucagon response to arginine at basal glucose levels was significantly decreased in donors compared to their matched controls (90±8 ng/liter in donors vs  $256\pm42$  ng/liter in control group 1 [n = 10, P] < 0.001] and 181±30 ng/liter in control group 2 [n = 7, P < 0.05], P = 0.001, Fig. 7). Hyperglycemia during the glucose potentiation studies significantly inhibited arginine-induced glucagon secretion in both donors and controls (P < 0.001, Fig. 8). At a serum glucose exceeding 27.8 mM, donors secreted significantly less glucagon in response to arginine than did controls in group 1 (40±5 ng/liter vs 123±21 ng/liter; donors vs controls; P = 0.001). No statistical difference was found between arginine-induced glucagon secretion at a serum glucose exceeding 27.8 mM in donors and controls in group 2 (40 $\pm$ 5 ng/liter [n = 10] vs 74±19 ng/liter [n = 6]; donors vs controls).

In donors studied prospectively, the acute glucagon response to arginine was decreased after hemipancreatectomy in each of the four patients studied. However, the mean response measured preoperatively was not significantly different from that measured postoperatively ( $169\pm39$  ng/liter vs  $99\pm15$  ng/ liter; pre- vs postoperatively).

#### Discussion

These data uniquely document the fact that after hemipancreatectomy, healthy human donors experience deterioration in both pancreatic alpha and beta cell function. Donors have significantly decreased arginine-induced glucagon secretion and glucose- and arginine-induced insulin secretion when compared to matched controls. In donors followed prospectively, statistically significant differences were found between the Kg values measured before and after hemipancreatectomy but no differences in Kg values were noted between the donors studied cross-sectionally and their controls. Donors and controls were also both observed to achieve identical glucose values in response to four increasing rates of continuous intravenous infusion of glucose. Importantly, this response occurs despite the significant decrease found in donor beta cell reserve. Both the maximal acute insulin response to arginine during hyperglycemia and the slope of potentiation were found to be significantly lower in donors than in controls. However, the glucose value at which the acute insulin value was half-maximal was the same in both subject groups. We believe these observations suggest that healthy hemipancreatectomized human donors may compensate for postoperative decrements in insulin secretion by increasing glucose disposal. If our hypothesis is correct, the appearance of hyperglycemia after partial pancreatectomy for organ donation may represent failure to compensate for diminished hormone secretion by altering glucose utilization.

This investigation is the first to compare the effect of partial pancreatectomy on phasic hormone secretion from both alpha and beta cells in human donors to that in matched controls with or without a history of type I diabetes in a first degree relative and to reinforce cross-sectional observations with a prospective evaluation of patients pre- and postdonation. Previously, Kendall et al. have reported that glucose intolerance or frank diabetes occurs in up to 25% of human pancreatic donors followed for prospectively for one year (2) with serial oral glu-



cose tolerance tests and that this is associated with diminished insulin responses to oral glucose. Earlier, Bolinder and colleagues observed decreased glucose-induced insulin secretion and rates of glucose disappearance in two subjects 12 mo after hemipancreatectomy (1). In our investigation, we have determined glucose-induced insulin responses to intravenous glucose to be significantly decreased in 10 donors studied a mean of 69±12 mo after organ donation as compared to matched controls, and have confirmed the validity of these observations by comparing them to data obtained from studies of eight subjects examined before and 15±2 mo after hemipancreatectomy. Moreover, we have assessed in vivo measures of beta cell reserve in donors using the technique of glucose potentiation of arginine-induced insulin secretion. Our observations in humans confirms the experimental evidence in animals (3, 11) that partial pancreatectomy leads to a decrease in the functional reserve of the beta cell.

Our studies demonstrate that the beta cell dysfunction found after hemipancreatectomy is a global rather than a secretagogue-specific phenomenon since both glucose and arginineinduced insulin secretion were significantly decreased in donors compared to their matched controls. These data confirm those from dogs reported by Ward and colleagues (3) after a two-thirds pancreatectomy, but are in conflict with data from

Figure 6. Response of donors and controls to continuous intravenous glucose infusions. Arginine stimulation tests were performed at basal glucose, after 60-min continuous infusions of glucose at rates of 300 mg/min, 600 mg/min, and 900 mg/min, and after a variable infusion of glucose calculated to bring serum glucose to  $\geq 27.8$ mM. In response to these infusions, donors  $(\Box, n = 10)$  and matched controls ( $\blacksquare$ , control group 1, n = 10;  $\blacklozenge$ , control group 2, n =6) achieved the same glucose values (A). The insulin values achieved after the glucose infusions were significantly lower in the donors than in the controls (P < 0.001, **B**).

Bonner-Weir and colleagues (4). Our disagreement with the latter group could be attributed to the species difference in our models (human vs weanling rat).

Arginine-induced glucagon secretion at both basal and elevated glucose values was found to be significantly lower in hemipancreatectomized subjects than controls. Since the majority of pancreatic glucagon is contained in the body and tail of the human pancreas (12), distal pancreatectomy might be expected to diminished glucagon secretion. Our observations confirm the report of Gotoh et al. (13) that glucagon secretion is decreased after resection of the distal half of the pancreas from dogs. The functional significance of diminished glucagon secretion after partial pancreatectomy is uncertain, but the maintenance of a nearly normal insulin to glucagon ratio may facilitate normal glucose regulation.

After hemipancreatectomy, a statistically insignificant rise in the fasting glucose levels of both donor groups was noted. While the clinical significance of this rise is uncertain, it is worth considering that with time, hemipancreatectomized patients may become susceptible to the effects of "glucose toxicity." According to the glucose toxicity hypothesis, which has gained strong experimental support (14–20) and recently been reviewed (21–23), hyperglycemia can be both a cause and an effect of the diminished insulin secretion and the increased



Figure 7. Arginine-induced glucagon secretion in donors and controls. After a 10-h fast, donors  $(\Box, n = 10)$  and matched controls ( $\blacksquare$ , control group 1, n = 10;  $\blacklozenge$ , control group 2, n = 7) were given an intravenous pulse of 5 g of arginine. The glucagon secretory response was significantly decreased in the donors as compared to the controls (P < 0.05).



ACUTE GLUCAGON

insulin resistance seen with diabetes. If the glucose toxicity hypothesis is correct, the relative hyperglycemia seen after partial pancreatectomy may eventually lead to decreased insulin secretion and to decreased glucose disposal. While decreased insulin secretion was observed in our donor group, our investigation cannot determine whether this was due to the surgically induced decrease in beta cell mass or to potentially adverse effects of chronic, relative hyperglycemia. However, our data suggest that hemipancreatectomized humans may increase, rather than decrease, glucose utilization after surgery. Since total glucose disposal is equal to the sum of insulin-dependent and glucose-dependent mechanisms of glucose uptake (24, 25), careful study of human donors after hemipancreatectomy should provide important insights into the relative contributions of beta cell secretion, insulin-mediated glucose uptake, and glucose-mediated glucose uptake to the overall maintenance of normoglycemia. In addition, long-term follow-up of hemipancreatectomized donors, especially of those who develop hyperglycemia, is likely to provide fresh insights into the glucose toxicity hypothesis.

Our observations are clinically relevant for pancreas transplantation programs using living related human donors. Previous investigation has demonstrated that 25% of such donors develop impaired glucose tolerance or frank diabetes within one year of the operation (2). The current report demonstrates that all donors are likely to experience a significant decrease in both alpha and beta cell function. While the long-term consequences of these changes in pancreatic endocrine function are unknown, prudence dictates that cadaver donors be used for pancreas transplantation in all but the most exceptional circumstance, such as when a suitable cadaveric organ cannot be located for a patient with a very pressing need for a new pancreas.

In summary, we have assessed alpha and beta cell function of healthy humans undergoing hemipancreatectomy for the purpose of organ donation. Our observations demonstrate that such donors experience decreases in glucose- and arginine-induced insulin secretion, decreases in arginine-induced glucagon secretion, and diminished beta cell reserve as compared to controls. Despite these alterations, donors have normal basal insulin and glucose values and respond to increasing rates of continuous glucose infusions by maintaining levels of hyperglycemia identical to those found in normal control subjects. Our observations suggest that after hemipancreatectomy, humans may maintain normoglycemia by compensatory increases in glucose disposal. Further investigation of healthy, hemipancreatectomized humans may provide important insights into compensatory mechanisms responsible for maintaining normal glucose homeostasis and the contribution that failure of such mechanisms might make to the pathogenesis of type II diabetes mellitus.

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