The Glucose Intolerance of Acute Pancreatitis

Hormonal Response to Arginine

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SUMMARY

Patients with acute pancreatitis were studied by arginine infusion at 48–72 h, 7–10 days, and 18–21 days after onset of their illness. Plasma glucose, insulin, and glucagon values were determined. Acute pancreatitis was characterized by fasting hyperglycemia and hyperglucagonemia, associated with relative hypoinsulinemia. Arginine stimulation early in the disease (48–72 h) demonstrated hyperglycemia and hyperglucagonemia, which normalized by 18–21 days. Both phases of the normal biphasic insulin response to arginine were decreased during the initial arginine infusion. By 18–21 days, although the first phase was completely normal, the second phase of insulin secretion remained depressed.

Acute pancreatitis is associated with damage to both the endocrine and exocrine pancreas. Glucose intolerance seen with this disease appears to be the result of hyperglucagonemia and relative hypoinsulinemia. Although the healing process at 3 wk is associated with return of plasma glucose and glucagon concentrations to normal, the impaired second phase insulin secretion persists. DIABETES 29:22–26, January 1980.

Clinicians have long observed the presence of transient hyperglycemia in patients with acute pancreatitis[1–3] and the development of diabetes mellitus in patients with chronic pancreatitis.[1,3–5] In chronic pancreatitis the carbohydrate intolerance is most frequently attributed to hormonal deficiency, with absolute decreases in both insulin and glucagon secretion as the pancreatic insufficiency progresses.[2,4–6] In contrast, the pathogenesis and progression (or resolution) of the hyperglycemia associated with acute pancreatitis and the nature of the alterations in insulin and glucagon secretion are less clear.[2] In the initial phase of acute pancreatitis (first 24 h), hyperglycemia is almost invariably present and is accompanied by hyperglucagonemia.[2,7] The increase in glucagon levels is much greater than that caused by stress alone.[7] Insulin levels have also been reported to be elevated during the first 24 h of acute pancreatitis,[2,8] but, in another study, insulin levels were considered low relative to the blood glucose.[7]

Because the changing patterns of pancreatic endocrine function have not been adequately described past the first 24 h of acute pancreatitis, we examined basal and stimulated insulin and glucagon secretion in a group of patients with acute pancreatitis. Following are the results of this study, in which repeated arginine infusions were given for 21 days after the acute episode.

MATERIALS AND METHODS

Patients. Twelve patients who had a diagnosis of acute pancreatitis received arginine infusions to study the effects of the disease on pancreatic endocrine function. The diagnosis was established by finding consistent clinical features—elevated serum and urine amylase and/or lipase and an appropriate history. Nine patients had no prior history, two had a history of one episode, and one had had two previous episodes of acute pancreatitis. No evidence of chronic pancreatitis[1,3,9] was present by clinical, laboratory, or x-ray findings. No patient had previously been diagnosed to have diabetes mellitus or glucose intolerance. The patients ranged in age from 24 to 61 yr, were all within 15% of their ideal body weight, and were male veterans (Tables 1 and 2). The population studied was compared with an age-, weight-, sex-, and race-matched population without pancreatitis, hospitalized for unrelated problems, who had the same degree of ambulation as the pancreatitis population. All patients were taking or had just discontinued intravenous therapy and were receiving only narcotics for pain. All drugs were discontinued during the study. Arginine infusions were given at three times after admission: 48–72 h

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TABLE 1
Clinical findings in 12 patients with acute pancreatitis

Subject	Age (yr)	Height	Weight (lb)	History of alcoholism	Previous attack of pancreatitis	Evidence of chronic pancreatitis, gallstones, x-ray, malabsorption	Other diseases and medication
L.C.	44	5'11"	163	+	1	–	0
W.J.	40	6'	170	+	0	–	Diet controlled AODM; Maalox PRN
C.A.	28	5'6"	142	+	0	–	0
J.C.	38	6'	153	+	0	–	0
M.L.	28	6'3"	180	+	0	–	Maalox for ? ulcer
W.C.	55	5'9"	165	+	2	–	0
P.F.	57	5'7"	152	+	0	–	0
F.M.	50	5'11"	141	+	0	–	0
M.C.	61	5'9"	166	–	0	–	Thorazine (schizophrenia); motrin (arthritis)
W.B.	24	6'	200	–	0	–	0
R.S.	47	5'11"	158	+	0	–	0
T.R.	50	6'1"	150	–	1	–	Maalox, Valium, Tylenol
Ave $\bar{X}$	43.5	5'9"	162	+			

(ARG-I), 7–10 days (ARG-II), and 18–21 days (ARG-III). Twenty-two individual patient studies in 12 subjects were conducted. Six patients from ARG-I were restudied in ARG-II. Four patients in ARG-II were restudied in ARG-III. Additional fasting plasma samples for determination of glucose, insulin, and glucagon were obtained from other patients recovering from an episode of acute pancreatitis. A total of 53 fasting samples was obtained from 26 patients at varying times after admission for acute pancreatitis.

All studies were conducted under the auspices of the Human Studies Committee of the VA Hospital and the University of Tennessee Center for the Health Sciences. Informed consent was obtained from all patients and from volunteer control subjects.

Studies. All studies were conducted in the morning after an overnight fast. Fasting blood samples (N = 53) were taken for 21 days from the time of admission and the plasma was analyzed for glucose, insulin, and glucagon.

The patients chosen for investigation received an arginine infusion, amounting to 11.7 mg/kg body wt/min, i.v., in normal saline, for 40 min. Blood samples were taken at 0, 2, 5, 10, 20, 30, 40, 50, 60, 75, and 90 min and again analyzed for glucose, insulin, and glucagon. Arginine infusions were done three times, at 48 h, 7–10 days, and 18–21 days.

Laboratory methods. Plasma glucose was determined by the glucose oxidase method.[10] Plasma insulin and glucagon were determined by previously described radioimmunoassay procedures, employing 30K glucagon antiserum for glucagon determinations.[11–13] Statistical analyses were done by standard Student's *t* test.[14]

RESULTS

Data shown in Table 1 establish a clinical profile of patients studied who had the diagnosis of acute pancreatitis. Data shown in Table 2 establish baseline laboratory findings in these patients. These patients have decreased serum proteins, elevated serum and urinary amylase, and elevated alkaline phosphatase, SGOT, LDH, and CPK. With the history

TABLE 2
Laboratory findings in 12 patients with acute pancreatitis*

Subject	Ca (mg/dl)	P (mg/dl)	Proteins (g/dl)	Amylase (U/dl)	Urinary amylase (U/dl)	Alk PO_4 (mU/ml)	Direct bilirubin (mg/dl)	SGOT (IU/ml)	LDH (IU/L)	CPK (IU/L)	CHOL (mg/dl)	TG (mg/dl)
L.C.	9.2	2.3		960	1296	73	0.7	22	279	109	261	77
W.J.	9.9	2.9	6.0	264	1535	123	0.8	14	294	67	189	191
C.A.	9.2	3.6	6.3	690	1540	60	0.7	43	437	608	177	51
J.C.	10.4	0.8		240	2720	189	—	91	381	226	198	112
M.L.	9.7	3.0	6.7	91	270	—	—	13	255	280	—	—
W.C.	9.2	2.3		88	375	85	1.0	96	334	38	190	156
P.F.	—	—		400	—	—	—	—	—	—	—	—
F.M.	8.8	2.1		336	2240	123	0.8	89	240	—	133	72
M.C.	11.2	2.1		371	1720	107	0.4	15	130	74	154	86
W.B.	8.4	3.4		320	1200	84	1.1	30	—	—	146	100
R.S.	10.1	4.3		272	4336	114	—	48	235	178	234	72
T.R.	8.7	—		272	112	—	—	—	—	—	116	65
N	11	10	3	12	11	9	7	10	9	8	10	10
$\bar{X}$	9.5	2.7	6.3	358	1577	106	0.8	46	287	207	180	98
Normal	8.4–10.7	2.5–4.5	6.4–7.9	80–150	90–560	30–110	0.2–1.0	0–20	130–290	0–50	310	160

* Unless indicated otherwise, values are for serum.

and clinical findings, these laboratory data are diagnostic of acute pancreatitis.

Fasting plasma glucose, insulin, and glucagon values were obtained from a group of pancreatitis patients at various times after an acute attack (data not shown). Patients studied shortly after the acute episode have fasting hyperglycemia, hyperglucagonemia, and relative hypoinsulinemia. With time, the glucose and glucagon values gradually decreased, returning to normal by about 2 wk.

In order to evaluate the ability of the pancreas to respond to a stimulus, arginine infusions were performed at 48–72 h, 7–10 days, and 18–21 days after admission for acute pancreatitis. Plasma glucose, insulin, and glucagon levels were measured during each of these infusions. Figure 1 shows the glucose values. Acute pancreatitis results in hyperglycemia. All glucose values obtained during the first arginine infusion were significantly greater than control. In contrast to control subjects, the average glucose values of the pancreatitis patients did not increase in response to arginine, but this apparent lack of response was caused by the more erratic pattern seen in pancreatitis patients. If the maximal change from basal glucose (fasting) to peak glucose is determined for each patient regardless of time of occurrence, then the response for pancreatitis patients and controls is similar (Table 3).

By 7–10 days after admission (ARG-II), glucose values had decreased but fasting levels remained significantly elevated over controls, as did values at the early times of the arginine infusion (Figure 1). By 18–21 days, all values were within the normal range. Table 4 shows the total area under the glucose curve for the three arginine infusions, demonstrating the progressive decrease in plasma glucose response to arginine with time.

In response to an arginine infusion, insulin is secreted in a biphasic manner in normal subjects (Figure 2). In pancreatitis patients 48–72 h after admission, first phase insulin secretion was significantly decreased and very little second phase secretion could be identified. All insulin values during the arginine infusion (ARG-I) were significantly less than control (Figure 2). If the maximal change for each patient is calculated, the average increase during the first 5 min of the arginine infusion (peak 1) was 34 ± 5 μU/ml for control and 15 ± 3 μU/ml for pancreatitis patients ($P < 0.005$) (Table 3). For peak 2 (highest value after 5 min) the control value was 59 ± 7 μU/ml and for pancreatitis patients, 11 ± 3 μU/ml ($P < 0.001$).

By 7–10 days, the first phase insulin secretion was completely restored, but the second phase remained impaired (Figure 2 and Table 3). Even at 18–21 days after the acute episode, second phase insulin secretion remained significantly decreased compared with control.

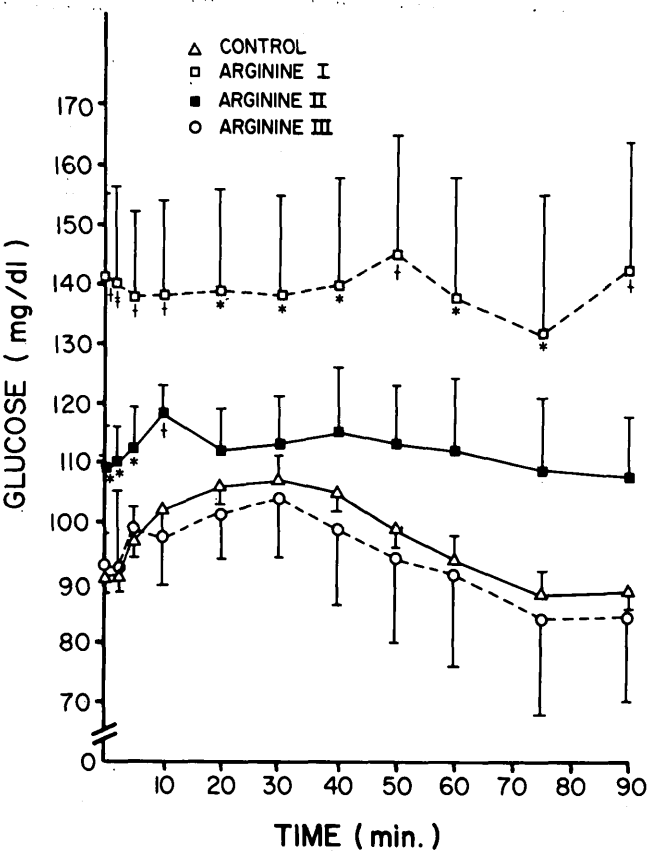


FIGURE 1. Studies of three arginine infusions in 12 patients with acute pancreatitis. Control values are shown (N = 9). Arginine (ARG) infusions were performed at 48–72 h (ARG-I, N = 7), at 7–10 days (ARG-II, N = 11), and at 18–21 days (ARG-III, N = 4). Plasma samples were analyzed for glucose (mg/dl). Values are shown as average ± SEM. Statistical significance for each point compared with control: *P < 0.05; †P < 0.01; and ‡P < 0.001.

Glucagon levels were strikingly elevated in patients with acute pancreatitis. During the first arginine infusion, all glucagon levels were significantly increased in patients with acute pancreatitis (Figure 3). The net change (basal to peak), however, although greater in patients with pancreatitis than in controls, was not statistically significant because of a wide variation in individual responses (Table 3).

TABLE 3
Plasma glucose, insulin, and glucagon after three arginine (ARG) infusions

		Glucose (mg/dl)			Insulin (μU/ml)					Glucagon (pg/ml)		
	N	B	P	P − B	B	P_1	P_2	P_1 − B	P_2 − B	B	P	P − B
Control	9	91 ± 3	107 ± 4	17 ± 2	12 ± 1	46 ± 6	71 ± 7	34 ± 5	59 ± 7	171 ± 26	588 ± 117	410 ± 115
ARG-I	7	141 ± 14	154 ± 19	13 ± 8	15 ± 1	30 ± 2	25 ± 3	15 ± 3	11 ± 3	648 ± 177	1394 ± 325	710 ± 333
		0.001	0.001	NS	NS	0.01	0.001	0.005	0.001	0.001	0.01	NS
ARG-II	11	110 ± 7	126 ± 9	16 ± 5	17 ± 3	50 ± 7	44 ± 7	34 ± 5	28 ± 7	301 ± 39	678 ± 89	378 ± 74
		0.025	0.05	NS	NS	NS	0.005	NS	0.001	0.01	NS	NS
ARG-III	4	93 ± 7	107 ± 9	14 ± 5	16 ± 1	48 ± 13	43 ± 12	32 ± 14	26 ± 13	196 ± 44	610 ± 126	414 ± 106
		NS	NS	NS	0.025	NS	0.025	NS	0.01	NS	NS	NS

B = basal; P = peak; P_1 = first peak, 0–5 min; P_2 = second peak, after 5 min; and (P − B) = net difference. Values shown are average ± SEM. N = number of patients studied. P values are shown against controls in each case.

TABLE 4
Integrated area under curve for glucose, insulin, and glucagon after three arginine infusions

	Control (N = 9)	ARG-I (N = 7)		ARG-II (N = 11)		ARG-III (N = 4)	
Glucose	8,713 ±301	12,456 ±1,674	0.01	9,763 ±1,262	NS	8,438 ±1,017	NS
Insulin	3,481 ±379	1,655 ±201	0.001	2,578 ±322	NS	2,781 ±450	NS
Glucagon	34,684 ±4,180	94,498 ±14,293	0.001	41,510 ±3,740	NS	42,229 ±9,478	NS

Values shown are average ± SEM. N = number of patients studied. P values are shown against controls in each case. Integrated areas for glucose, mg/dl/90 min; insulin, μU/ml/90 min; and glucagon, pg/ml/90 min.

By 7–10 days, although fasting plasma glucagon levels remained significantly elevated, most of the stimulated values were within the normal range (Figure 3 and Table 3), and the total area under the curve was not significantly different from that of control (Table 4). By 21 days, all values had returned to normal.

DISCUSSION

These data demonstrate that patients with acute pancreatitis, examined within 48–72 h after onset of their illness, have fasting hyperglycemia, hyperglucagonemia, and relative hypoinsulinemia. With recovery from the acute episode, these changes gradually reverse, reaching normal by about 15 days. In other studies, hyperglycemia and hyperglucagonemia have been demonstrated during the acute phase (first 24 h) of pancreatitis,[2,7] but the time required for restoration of normal fasting levels has not previously been well defined.

We have also examined the response of the endocrine pancreas to stimulation at various times after an episode of acute pancreatitis. Elevated glucagon levels are characteristic of acute pancreatitis, and all glucagon values obtained during an arginine infusion 72 h after the acute episode were significantly greater than control values. The change in glucagon levels (basal to peak) in response to arginine was greater in patients with pancreatitis, but, because of marked variability in individual responses, this did not achieve statistical significance. In any case, certainly, the ability of the pancreas to respond to the glucagon secretagogue was not decreased. This is consistent with earlier reports.[2,7,8] With time, glucagon levels and responses gradually returned to normal, and, by 21 days, all aspects of glucagon secretion were normal.

The mechanism for the marked hyperglucagonemia in acute pancreatitis remains unclear. The prolonged duration of the elevation, the normal or excessive response to a stimulus, and the lack of comparable insulin increases would all suggest that the hyperglucagonemia does not result merely from release of stored hormone from damaged or destroyed

FIGURE 2. Studies of three arginine infusions in 12 patients with acute pancreatitis. Control values and arginine (ARG) infusions were performed as indicated in the legend to Figure 1. Plasma samples were analyzed for insulin (μU/ml). Values are shown as average ± SEM.

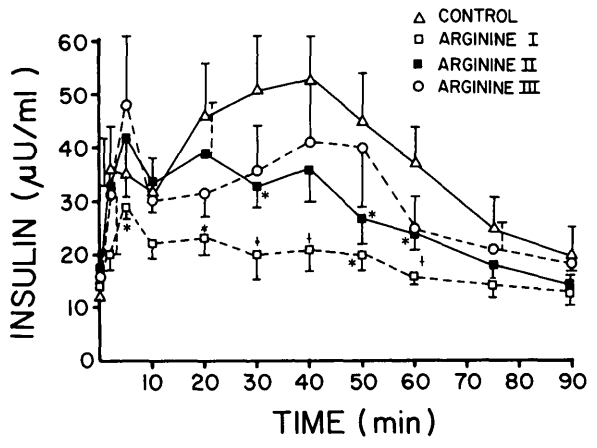
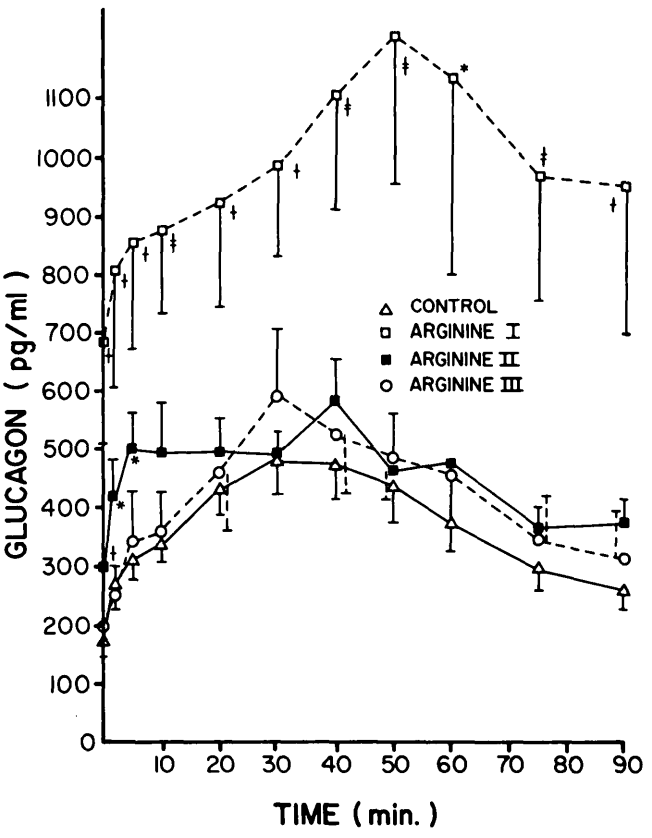


FIGURE 3. Studies of three arginine infusions in 12 patients with acute pancreatitis. Control values and arginine (ARG) infusions were performed as indicated in the legend to Figure 1. Plasma samples were analyzed for glucagon (pg/ml). Values are shown as average ± SEM.



alpha cells. In addition, the nature of the glucagon secreted is not yet clarified, so that abnormal or "big" glucagon, which has a slower clearance rate, remains a real possibility in pancreatitis.

Insulin responses to arginine were clearly abnormal early after the illness and also at subsequent times. At 48–72 h after the patients were admitted for acute pancreatitis, the fasting insulin levels were in the normal range but were low for the level of blood glucose. After arginine stimulation, both first and second phase insulin secretion was decreased. By 7–10 days after the patients were admitted, the first phase was restored to normal but the second phase was significantly decreased; even at 21 days, when all glucose and glucagon responses had returned to normal, second phase insulin secretion remained impaired. Further sequential studies of patients with persistent defects in second phase secretion are needed in order to see if this could prove useful as a test for continuing damage or recovery in pancreatitis.

In an earlier study, Donowitz et al.[2] found hyperinsulinemia and an exaggerated response to alanine in patients with acute pancreatitis examined within 24 h after admission. Differences between the present studies and those of Donowitz et al. may in part be a result of the use of different provocative stimuli, i.e., arginine vs. alanine, or to the timing of the test. It is possible that the insulin stores in the pancreas are sufficient to produce a normal or even excessive response to a stimulus early after the acute insult, but, by 48–72 h, insulin stores are so depleted that the response becomes subnormal.[17] Damage to the beta cells by pancreatitis could result in impairment of the biosynthetic process and decreased insulin production, resulting in inadequate stores of hormone.

Of considerable interest is the persistent defect in second phase insulin secretion after acute pancreatitis. Although the occurrence of a biphasic insulin response to an infusion of glucose or arginine (in the presence of glucose) has been well established, the mechanism(s) responsible for this has not. Although several theories have been advanced, the most widely held one, perhaps, is that insulin is stored in two compartments—a rapidly releasable and a slowly releasable pool.[15] The relative importance of these two pools for the maintenance of glucose tolerance is not known, but the rapidly releasable component is most often found to be abnormal in diabetes.[16] The finding that acute pancreatitis affects the second phase response more than the first phase is of considerable interest, but the explanation for this is not readily apparent. It could be caused by a defect in the release process or to a deficiency of hormone stored in the second phase pool. Thus, the demonstration that patients recovering from acute pancreatitis have a selective abnormality in second phase secretion may facilitate studies of the importance of this aspect of insulin secretion.

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