Effects of Ischemia on the Human Pancreas

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Background & Aims: **Patients undergoing cardiac surgery frequently have pancreatic damage; several factors, including tissue hypoperfusion, have been implicated. The aim of this study is to better understand the effects of decreased blood supply on human pancreas.** ***Methods:*** **Twenty-one consecutive patients undergoing surgery for thoracic or thoracoabdominal aortic aneurysm were studied. During surgery, the descending thoracic aorta was cross-clamped for a mean of 44 minutes (range, 15–85 minutes). Effects of the resultant pancreatic ischemia were assessed by examining the patients daily for evidence of acute pancreatitis for at least 20 days after surgery and by determining serum concentrations of amylase, pancreatic isoamylase, and lipase before clamping the aorta and at varying intervals after its release (1, 2, and 6 hours during the first day and once daily for the following 6 days).** ***Results:*** **One patient died of acute necrotizing pancreatitis. None of the others had symptoms of pancreatitis postoperatively, but all showed a significant increase in serum pancreatic enzyme concentrations soon after declamping; this peaked about 24 hours later and persisted for all 7 days of the study. A significant relationship was found between the increase in pancreatic enzyme concentrations and the aortic clamping time.** ***Conclusions:*** **Acinar cell injury is a constant, rapidly appearing consequence of severe pancreatic ischemia, even that of brief duration; acinar cell injury is usually subclinical but may also present as severe acute pancreatitis.**

Pancreatic lesions ranging from subclinical hyperamylasemia to lethal necrotizing pancreatitis have been described in a significant number of patients undergoing cardiac surgery.[1–9] These lesions have been associated with multiple factors; the most important is hypotension and consequent hypoperfusion of the pancreas. In a recent study, of 300 consecutive patients undergoing cardiac surgery with cardiopulmonary bypass,[10] evidence of acinar cell injury, as indicated by hyperamylasemia of pancreatic origin, was detected in 80 (27%), 3 of whom developed severe acute pancreatitis. In this study,[10] several factors were found to be associated with the development of acinar cell injury, including preoperative renal insufficiency, valve surgery, and arterial hypotension. However, the single most important risk factor for pancreatic injury was the perioperative administration of calcium chloride. To better understand the effects of ischemia on the human pancreas, we studied the prevalence, characteristics, and possible risk factors for pancreatic injury after complete ischemia of the gland in a series of patients undergoing surgery for thoracic or thoracoabdominal aortic aneurysm. During the procedures, the descending thoracic aorta is cross-clamped, which leads to periods of complete, or almost complete,[11] visceral ischemia.

Patients and Methods

Twenty-one consecutive patients (16 men and 5 women; mean age, 63.8 years; range, 48–75 years) undergoing surgery for thoracic (n = 7) or thoracoabdominal (n = 14) aortic aneurysm at the Department of Vascular Surgery (Director, Professor M D'Addato) of the University of Bologna (Bologna, Italy) from November 1991 to December 1994 were studied after informed consent had been given. None was a heavy drinker or had a history of pancreatic disease. Two had chronic renal insufficiency, which was moderate in one but required dialysis in the other. All underwent standard preoperative medical assessment.[12] During surgery, data regarding several variables was recorded, including aortic cross-clamping time, drug administration, and pertinent hemodynamic parameters.[12] The descending thoracic aorta was cross-clamped below the origin of the left subclavian artery (mean duration of clamping, 44.8 minutes; range, 15–85 minutes). None of the patients underwent temporary atriofemoral shunting. The drugs that were administered during surgery were dopamine, dobutamine, calcium gluconate, prostaglandin E_1, furosemide, methylprednisolone, mannitol, sodium bicarbonate, trometha-mine, and ephedrine.

The effects of ischemia on the pancreas were assessed clinically (examination of the patients two or three times daily for at least 20 days for symptoms or signs suggestive of acute pancreatitis) and biochemically (determining the serum concentrations of amylase, pancreatic isoamylase, and lipase in basal conditions before

Abbreviation used in this paper: PAP, pancreatitis-associated protein.

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the induction of anesthesia and again just before aortic cross-clamping and at varying intervals after release of the clamp). After declamping, enzymes were determined 1, 2, and 6 hours during the first day and once daily for the following 6 days. The enzymes were also measured 20 days later.

In the last 8 patients studied, the serum concentration of pancreatitis-associated protein (PAP) was also determined. PAP is a secretory protein that is overexpressed by the pancreas during acute pancreatitis and has been shown to be a sensitive marker of the severity of this disease.[13]

As controls, 10 patients (10 men; mean age, 65 years; range, 59–73 years) undergoing surgery for abdominal aortic aneurysm during the same period were also studied; in this procedure the abdominal aorta is cross-clamped below the origin of the renal arteries.

Amylase activity was determined using a chromogenic method (alfa-Amylase EPS; Boehringer, Mannheim, Germany), pancreatic isoamylase was determined by an inhibitor method (Pancreatic alfa-Amylase EPS; Boehringer), and lipase was determined by a turbidimetric method (Lipase; Boehringer). Serum PAP concentration was determined using an immunoenzymatic assay (PANCREPAP; Dynabio, La Gaude, France).

Statistical analysis was performed using the Wilcoxon's test for paired data and the Spearman correlation test.

Results

Clinical Findings

None of the 21 patients who underwent surgery for thoracic or thoracoabdominal aortic aneurysm developed symptoms or signs of acute pancreatitis in the postoperative period. However, one woman developed irreversible shock about 4 hours after surgery and died 24 hours later; no precipitating factors had been apparent, and severe hemorrhagic necrotizing pancreatitis was found at autopsy. The aortic cross-clamping time in the patient was 43 minutes. Another died about 12 hours after surgery because of severe hemorrhagic shock; an autopsy was not performed. Among the remaining 19 patients, none developed significant hemodynamic or other complications postoperatively, except for one with preexisting, moderate renal insufficiency in whom there was a significant worsening of renal function. Three patients died of cardiopulmonary complications about 1 month after surgery. At the time these complications developed they had no clinical or imaging evidence of pancreatitis.

The 10 patients who underwent abdominal aneurysm repair had no symptoms or signs of pancreatitis or other complications after surgery.

Serum Pancreatic Enzymes

The 2 patients who died (one of acute pancreatitis and the other of hemorrhagic shock) had basal serum levels of pancreatic enzymes that were within normal limits; those measured 1, 2, and 6 hours after release of the clamp (the only measurements taken) were slightly lower.

Basal enzyme levels were slightly elevated in the patient with chronic renal failure who had been undergoing dialysis, and these values did not change significantly after aortic cross-clamping. In the one in whom renal insufficiency worsened after surgery, while basal enzyme concentrations were within normal limits, they increased markedly after surgery. Because chronic renal insufficiency may cause an abnormal increase in serum pancreatic enzyme concentrations and structural changes of the pancreas,[14,15] the results obtained from these 2 patients were excluded from calculations.

For the remaining 17 patients, the pattern of the various enzymes studied is summarized in Figure 1. Basal concentrations were in the normal range for all 17. After the release of the aortic clamp, a significant increase was already evident in the initial (1 and 2 hour) determinations and reached a peak about 24 hours after the clamp was removed; subsequently, the enzyme concentrations tended to decrease but remained significantly elevated for all 7 days of the study.

The increase in serum pancreatic enzyme concentration was also statistically significant ($P < 0.05$) in 8 of these 17 patients for whom the aortic cross-clamping time was very brief (mean, 27 minutes; range, 15–35 minutes).

In all 17 patients the increase in amylase concentration was attributable to an increase in both pancreatic and salivary isoamylases.

Spearman correlation analysis was performed to ascertain whether there was an association between the percent increase in serum pancreatic enzyme concentration and the following variables: aortic cross-clamping time, the drugs and quantities administered (during and for 24 hours after surgery), units of blood transfused, and urine output. A significant relationship was found only with the duration of aortic clamping (Figure 2); none was found for any of the drugs, including calcium gluconate, which had been administered in dosages ranging from 1.0 to 8.0 g.

Figure 3 shows the behavior of serum amylase, pancreatic isoamylase, and lipase in the 10 patients, who underwent surgery for an abdominal aneurysm, in whom the aorta was cross-clamped below the origin of the renal vessels. No statistically significant changes in enzyme concentrations were observed, although an increase in pancreatic enzyme concentration was seen 1, 2, and 6 hours after release of the aortic clamp in 2 of these patients.

Figure 4 shows the serum concentrations of PAP in (*A*) 8 patients undergoing surgery for thoracic or thora-

coabdominal aortic aneurysm and (*B*) 4 who underwent surgery for abdominal aneurysm; in the former, there was a slight increase in this protein, which was statistically significant starting from the day after surgery, and in the latter, no significant changes were seen.

Discussion

One of 21 patients who had the thoracic aorta clamped during surgery died of acute necrotizing pancreatitis. In this patient, the close temporal relationship with aortic clamping and the absence of other known risk factors for acute pancreatitis suggest that pancreatic ischemia played a primary role in its development. As it has been previously reported in patients who have died of acute pancreatitis after cardiac surgery,[2,6,7,9,10] ours was asymptomatic until the sudden development of shock without apparent cause (about 4 hours after surgery); early serum pancreatic enzyme determinations (1, 2, and 6 hours after release of the aortic clamp in our study) were in the normal range. In these cases, the lack of an increase in enzyme levels is probably because of the early development of massive pancreatic necrosis. These findings suggest that in patients undergoing such procedures determination of serum pancreatic enzymes is an unreliable means of confirming acute pancreatitis; however, the sudden development of severe shock without apparent cause should raise the suspicion of a severe necrotizing pancreatitis.

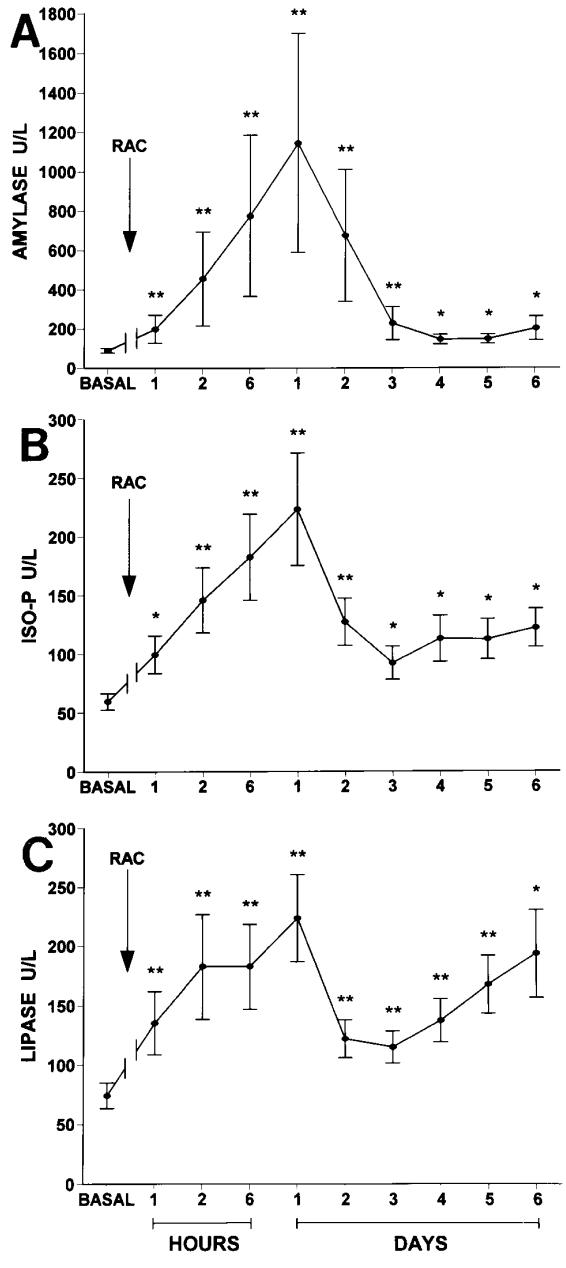

Figure 1. Serum concentrations of (*A*) amylase, (*B*) pancreatic isoamylase (ISO-P), and (*C*) lipase in 17 patients undergoing surgery for thoracic or thoracoabdominal aortic aneurysm. Results are expressed as means ± SEM. $*P < 0.01$; $**P < 0.001$. BASAL, mean of the values obtained before the induction of anesthesia and before the descending thoracic aorta cross-clamp; RAC, release of the aortic clamp.

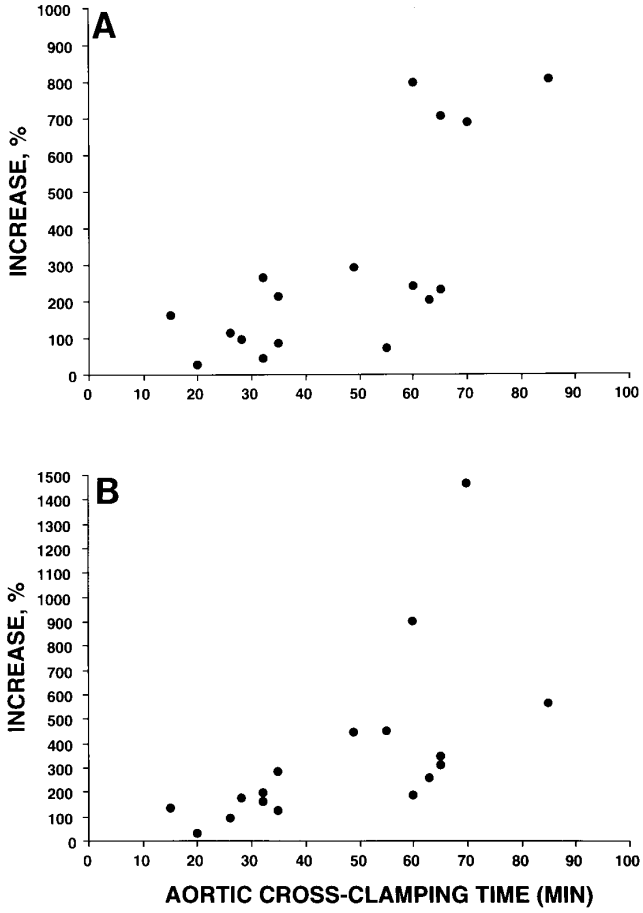

Figure 2. Relationship between the percent increase in (*A*) pancreatic isoamylase (r, 0.691; $P < 0.002$) and (*B*) lipase (r, 0.800; $P < 0.001$) (maximal value observed during the first 24 hours after exposition of the pancreas to ischemia) and aortic cross-clamping time (Spearman correlation test).

Among the remaining 20 patients who had the descending thoracic aorta clamped during surgery, none had symptoms or signs of pancreatitis. With two exceptions (one who died of hemorrhagic shock and the other with severe chronic renal failure), all showed a significant increase in serum pancreatic enzyme concentration after exposition of the pancreas to ischemia, even that of brief duration (15–20 minutes), indicating that subclinical pancreatic injury is a constant occurrence among patients undergoing this kind of surgery. Moreover, as would be expected, the percent increase in pancreatic amylase and lipase concentrations over basal values, an indicator of the degree of acinar cell injury, was significantly greater in those with longer clamping time.

Our results are in accordance with those of an experimental model of pancreatic ischemia induced by hemorrhagic hypotension of 30-minute duration in rats in which serum pancreatic isoamylase activity was found to be significantly increased at 1 hour from induction of ischemia (with a further increase 24 hours later), and morphological evidence of pancreatic edema and acinar necrosis was also present at 24 hours.[16]

Our findings also agree with those from Broe et al.,[17] who used an isolated perfused canine pancreas to show that ischemia caused a significant increase in amylase concentration. However, in this study the amylase increase became evident only after 2 hours of complete suppression of blood flow, indicating that the dog pancreas is less sensitive to ischemia than are human or rat glands.

In this study, the increase of serum pancreatic enzyme concentration was significantly correlated only with the aortic clamping time. In their study of pancreatic cellular injury after cardiopulmonary bypass, Fernandez-del Castillo et al.[10] showed that the dose of calcium chloride given during surgery was the single most important risk factor for the development of pancreatic injury. The amount of calcium administered in our work was comparable if not greater than that of Fernandez-Del Castillo et al.[10] The reason for this discrepancy with our results is not apparent, although it could be speculated that the type and conditions of surgery and perhaps more

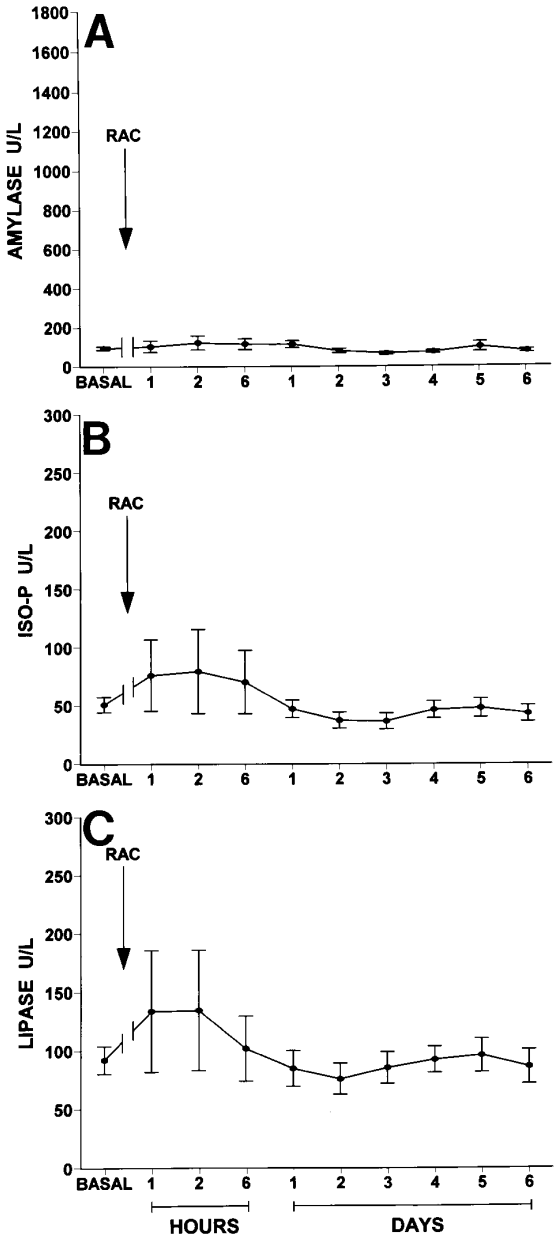

Figure 3. Serum concentrations of (*A*) amylase, (*B*) pancreatic isoamylase (ISO-P), and (*C*) lipase in 10 patients undergoing surgery for abdominal aneurysm. Results are expressed as means ± SEM. BASAL, mean of the values obtained before the induction of anesthesia and before the abdominal aorta cross-clamping; RAC, release of the aortic clamp.

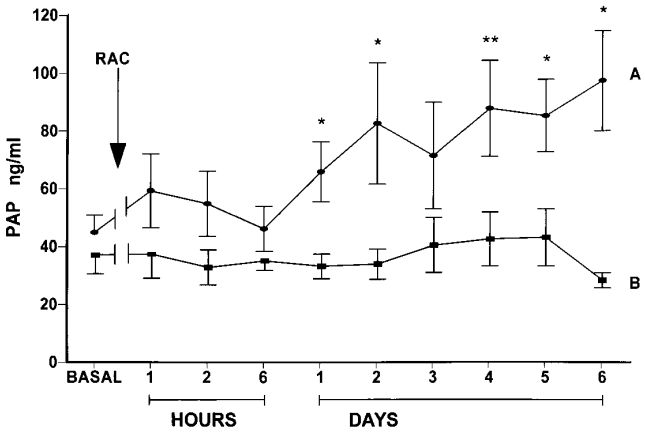

Figure 4. Serum concentrations of PAP in (*A*) 8 patients undergoing surgery for thoracic or thoracoabdominal aortic aneurysm and (*B*) 4 patients undergoing surgery for abdominal aneurysm. Results are expressed as means ± SEM. $*P < 0.05$; $**P < 0.02$. BASAL, mean of the values obtained before the induction of anesthesia and before aortic clamping; RAC, release of the aortic clamp.

importantly the degree of the pancreas' exposure to ischemia were quite different in the two studies. Moreover, it may be noteworthy that these investigators reported a correlation between the doses of calcium administered and pancreatic injury, but they neither provided detailed information about the serum calcium levels reached after such administration nor determined whether a correlation was present between these levels and pancreatic injury.

The same group of investigators has also recently reported that calcium administration significantly aggravates hypotension-induced injury of the pancreas in rats.[18] In these experiments, calcium administration caused a significant hypercalcemia of 3 hours' duration. In our patients, calcium was administered to normalize citrate-induced hypocalcemia resulting from blood transfusions[12]; no incidence of significant hypercalcemia was documented in any of our patients.

The mechanism of pancreatic injury among our patients is not completely clear because in addition to ischemia a role cannot be excluded for reperfusion injury. Recent studies[19,20] have shown significant generation of oxygen free radicals and polymorphonuclear neutrophil activation after aortic cross-clamping.

Among our patients, the persistence of elevated enzyme levels for at least 6 days after the surgery signifies that the damage was significant; the fact that they were normal 20 days later indicates that the changes were reversible.

The increase in serum amylase concentration noted in our patients after aortic cross-clamping was because of an increase in both pancreatic and salivary amylase concentration. The reason for the increase in the salivary isoenzyme concentration is not clear, but this has also been reported in patients undergoing cardiac or other surgery[21–25]; it has been attributed to aspiration of saliva,[25] injury of the salivary glands,[22,24] and a release of salivary-type isoamylase from lung tissues.[23]

Serum concentrations of pancreatic enzymes did not increase with ischemia in the patient who died of hemorrhagic shock or the one under dialysis. This could probably be explained by the fact that severe pancreatic lesions (e.g., diffuse necrosis in hemorrhagic shock[26,27] and marked fibrosis in uremia[15]) may preclude serum enzyme concentration increases.

Recent studies[13] have shown that PAP is a sensitive marker of acute pancreatitis and the extent of its increase is an indicator of the severity of this disease. In our study, this protein slightly increased after pancreatic ischemia in the 8 study patients in whom it was measured, whereas it did not increase in patients undergoing surgery for abdominal aneurysm; this provided further evidence that the patients who had the thoracic aorta clamped during surgery had significant pancreatic injury.

Among the 10 subjects undergoing surgery for an abdominal aneurysm, there were no significant changes in serum pancreatic enzyme concentrations with respect to basal values, indicating that the changes observed in the study group were not likely dependent on factors related to anesthesia or surgery. Two of the 10 patients showed an increase of pancreatic enzyme concentration during the first 24 hours after surgery, a finding consistent with the observations of other investigators[26] who found evidence of pancreatic damage in 12% of their patients undergoing surgery for abdominal aneurysm. Pancreas hypoperfusion is a possible cause.[26]

In conclusion, this is the first study that has examined the effects of total, or near total, suppression of blood flow on the human pancreas. The results indicate that severe ischemia, even of brief duration, produces significant pancreatic injury; the damage occurs rapidly and constantly and it is usually subclinical. Moreover, the results provide direct evidence that pancreatic ischemia can trigger acute pancreatitis. Under the conditions of this study, the only factor significantly associated with the degree of the postischemic serum pancreatic enzyme increase, which is a likely expression of acinar cell injury, was the duration of ischemia.

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