Hyperamylasemia After Cardiac Surgery

Incidence, Significance, and Management

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The significance of hyperamylasemia and its relationship to pancreatitis after cardiac surgery is controversial. Three hundred consecutive patients undergoing cardiopulmonary bypass were prospectively studied to determine the incidence and significance of postoperative hyperamylasemia. Ninety-six of three hundred patients (32%) developed hyperamylasemia. Fifty-six patients (19%) were classified as having isolated hyperamylasemia because they were asymptomatic and had normal serum lipase. Thirty-two patients (10.7%) had subclinical pancreatitis defined as elevation of serum amylase and lipase or pancreatic isoamylase. Many of these patients had mild gastrointestinal symptoms that were self-limited. Eight patients (2.7%) had overt pancreatitis documented by clinical findings, biochemical abnormalities, and computed tomography (CT) scan or autopsy. Isoamylase analysis demonstrated that isolated hyperamylasemia usually originated from nonpancreatic sources. However, hyperamylasemia occurring in conjunction with abdominal signs and symptoms or elevated serum lipase was almost always pancreatic in origin. Patients with hyperamylasemia had a significantly higher mortality rate (seven of 96 patients, 7.5%) than those with normal serum amylase(two of 204 patients, 0.9%) ($p < 0.01$) even when the amylase was nonpancreatic in origin (five of 56 patients, 9%). The reason that nonpancreatic hyperamylasemia is associated with increased postoperative mortality is not established but may represent a variety of metabolic aberrations or tissue injuries. It is concluded that 1) hyperamylasemia after cardiopulmonary bypass is a marker of potential clinical importance, and 2) pancreatitis in this setting is more common than previously recognized and is a potentially lethal complication. Successful treatment depends on early diagnosis and aggressive treatment.

CORONARY ARTERY BYPASS GRAFTING (CABG) is the most commonly performed operation in the United States. As techniques have improved, the morbidity and mortality rates for this procedure have become remarkably low. Acute pancreatitis is a reported but poorly understood complication of cardiopulmonary bypass.[1] Although hyperamylasemia has been noted in a large proportion of patients after bypass, many authors have felt the amylase elevation did not reflect pancreatic injury and thus was of no clinical concern.[2-4] Several studies have documented that the amylase-creatinine clearance ratio, which is said to indicate the likelihood of pancreatitis,[5] is elevated after bypass in the absence of any discernible pancreatic lesion.[3,4,6] It has therefore been tempting to attribute hyperamylasemia to altered renal function rather than to pancreatic injury.

The diagnosis of pancreatitis after cardiac surgery can be difficult. Epigastric pain, back pain, and vomiting that characterize other types of pancreatitis are unusual in this form of the disease.[7] Rather, it tends to have subtle findings and a bland early clinical course until a complication such as infection or necrosis develops (Fig. 1). Consequently, many of the previously published studies rely heavily on information obtained at autopsy.[1,7,8] Our recent experience in treating three patients within a 6-month period who presented with pancreatic abscesses several months after CABG prompted us to initiate a prospective study of the incidence and significance of hyperamylasemia after cardiopulmonary bypass. Our aims were to evaluate 1) the incidence of hyperamylasemia, 2) whether hyperamylasemia was due to pancreatic or nonpancreatic sources, 3) the relationship of hyperamylasemia to perioperative alterations in renal function, 4) the incidence of genuine pancreatitis, and 5) guidelines for management of postbypass hyperamylasemia and pancreatitis.

Patients and Methods

Three hundred consecutive patients undergoing cardiac surgical procedures requiring cardiopulmonary bypass were studied. Blood samples were obtained on the first,

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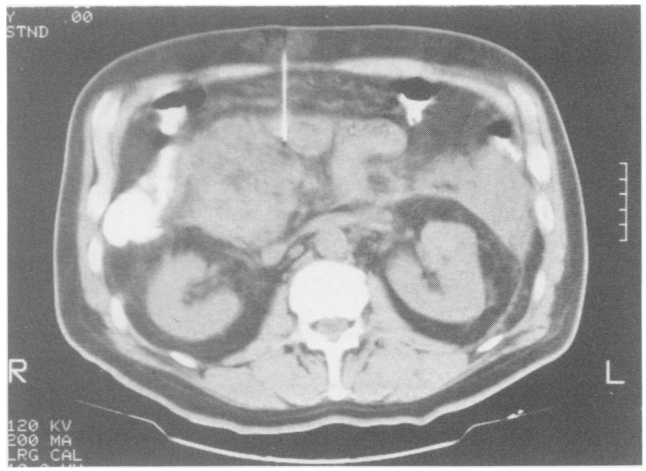

FIG. 1. CT scan demonstrating infected necrosis in the head of the pancreas (marked by percutaneous needle). This patient developed fever and ileus 8 days after an uncomplicated CABG. He had no abdominal tenderness and did not complain of abdominal or back pain. He recovered slowly after surgical debridement.

second, and third mornings after the operation. Serum amylase levels were determined by the Beckman-Astra system. Serum lipase was determined by the turbidimetric method described by Vogel and Zieve.[9] Patients with persistent elevation of serum amylase, elevated serum lipase, or clinical signs and symptoms of pancreatitis had serum collected for isoamylase determination. Isoenzymes of amylase (isoamylase) were separated and quantified by polyacrylamide gel electrophoresis and saccharogenic assay as described by Warshaw and Lee.[10] The results were interpreted by an observer who was unaware of the patients' clinical status.

Radiologic investigations and patient management were guided by the cardiac surgical team. In general, computed tomography (CT) scans were obtained in patients with persistent hyperamylasemia or in patients with abdominal complaints and hyperamylasemia. Patients were examined daily by the cardiac surgical team and any abdominal complaints and findings recorded in the chart were noted.

TABLE 1. *Cardiac Surgical Procedures in 300 Consecutive Patients*

Operation	No. of Cases (Re-do Operations)
CABG	221 (22)
AVR or MVR	31 (8)
AVR or MVR + CABG	28
AVR and MVR	9 (4)
Postinfarct VSD	2
ASD	2
Others	7

AVR = aortic valve replacement.
MVR = mitral valve replacement.
VSD = ventricular septal defect.
ASD = atrial septal defect.

TABLE 2. *Classification of Patients With Hyperamylasemia*

Classification	No. of Patients	Percentage of Total
No hyperamylasemia	204	68.0
Isolated hyperamylasemia	56	18.7
Subclinical pancreatitis	32	10.7
Overt pancreatitis	8	2.7

Autopsies were performed on four patients, and the findings are included in this study.

Statistics were analyzed by two-way analysis of variance and the chi-square test; p values less than 0.05 were regarded as significant. Data is expressed as mean ± standard deviation.

Results

The mean age of the patients in this study was 65 years (range of 27–84 years). There were 230 men and 70 women. Three hundred cardiac surgical procedures requiring cardiopulmonary bypass included 221 CABG, 31 mitral or aortic valve replacement, 28 valve replacement + CABG, nine double valve replacements, two postinfarct ventricular septal defect repairs, two atrial septal defect repairs, and seven others (Table 1). Thirty-four of the cases were reoperations (11.3%). Fifteen per cent were either urgent or emergency operations in unstable patients. There were nine deaths in this series, accounting for an overall mortality rate of 3%.

Hyperamylasemia was defined as any elevation of the serum amylase > 123 U/l. There were 96 patients with at least one elevated serum amylase after operation. Thus the overall incidence of hyperamylasemia was 32%. The average serum amylase level in patients without hyperamylasemia was 73 ± 23.

Patients with hyperamylasemia were divided into three groups according to their clinical status. Patients who were totally asymptomatic and who had no abdominal tenderness or unexplained fever were classified as having isolated hyperamylasemia. There were 56 such patients, and this was by far the largest group. There were 32 patients who were thought to have subclinical pancreatitis because of mild ileus, nausea, or anorexia that occurred in conjunction with an elevated serum lipase. Patients with hyperamylasemia, hyperlipasemia, abdominal pain or tenderness, ileus, and evidence of pancreatitis by CT scan or autopsy were classified as having overt pancreatitis. There were eight such patients. Thus the incidence of clinically obvious pancreatitis was 2.7% (Table 2). Interestingly, the degree of hyperamylasemia correlated with the patients' clinical course. Patients with overt pancreatitis had a significantly higher amylase than those with either subclinical pancreatitis or isolated hyperamylasemia (Fig. 2).

Isoamylase determinations were made of forty patients.

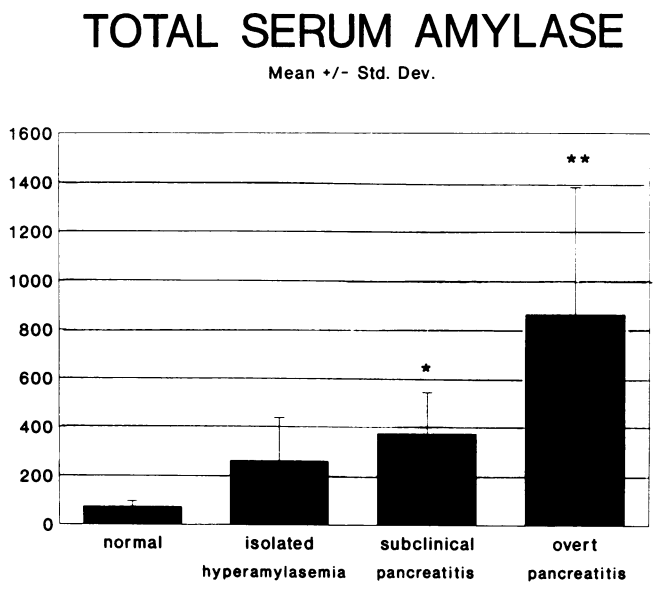

FIG. 2. Serum amylase value and clinical classification. All hyperamylasemic groups differ significantly from normal by definition.
*Isolated hyperamylasemia and subclinical pancreatitis are not significantly different.
** $p < 0.01$ *versus* normal; $p < 0.05$ *versus* isolated hyperamylasemia and subclinical pancreatitis.

All forty patients had elevated total serum amylases. In twelve patients, hyperamylasemia was due to nonpancreatic amylase, whereas in 28 patients, pancreatic isoamylase accounted for hyperamylasemia. Because isoamylase analysis is not routinely available in most institutions, we compared the sensitivity of serum lipase to isoamylase. Thirty-three per cent of the patients with nonpancreatic hyperamylasemia had minimal elevations of serum lipase, whereas 83% of those with elevated pancreatic isoamylase had significant elevations of their serum lipase. The presence of pancreatic isoamylase correlated closely with the patients' clinical status. Among those tested, all patients (six of six) with overt pancreatitis and nearly all with subclinical pancreatitis (21 of 22 patients) had elevated pancreatic isoamylase. By contrast, only one of twelve patients with isolated hyperamylasemia had elevated pancreatic isoamylase. This difference was highly significant ($p < 0.01$).

The relationship between renal function and hyperamylasemia was also examined. Serum BUN and creatinine were not significantly different among patients with or without hyperamylasemia. However, patients with overt pancreatitis had a statistically significant rise in BUN and creatinine during the postoperative period when compared with normoamylasemic patients ($p < 0.05$). Smaller rises in BUN and creatinine occurred in patients with subclinical pancreatitis and patients with isolated hyperamylasemia, but these were not significantly different than controls (Table 3).

TABLE 3. *Relationship of Renal Function and Hyperamylasemia*

	Preoperative		Postoperative Change	
Group	BUN	Creatinine	BUN	Creatinine
Normal	19 ± 10	1.2 ± 0.4	−1.4 ± 6	0.08 ± 0.5
Isolated Hyperamylasemia	22 ± 11	1.2 ± 0.4	1.8 ± 5	0.25 ± 0.7
Subclinical Pancreatitis	24 ± 10	1.3 ± 0.5	3.4 ± 9	0.24 ± 0.5
Overt Pancreatitis	15 ± 4	1.0 ± 0.3	5.6 ± 8*	0.85 ± 1.1*

* $p < 0.05$ compared with normal amylase patients.

There were seven deaths among 96 patients with hyperamylasemia (7.5%), whereas only two of 204 patients without hyperamylasemia died (1%). This difference was highly significant ($p < 0.01$) (Table 4). Of the seven patients who died with hyperamylasemia, one had hemorrhagic pancreatitis, one had subclinical pancreatitis, and five had isolated hyperamylasemia. Isoamylase determination in the patient with subclinical pancreatitis showed pancreatic amylase. Isoamylase determinations for the other patients were not available. Autopsies were performed on four of the seven patients with hyperamylasemia. Hemorrhagic pancreatitis was confirmed at postmortem examination in the patient with overt pancreatitis. In three patients with isolated hyperamylasemia, the pancreas appeared normal. An autopsy was not performed on the patient with subclinical pancreatitis.

Discussion

There is an increasing awareness of the gastrointestinal (G.I.) complications that may follow cardiac surgery.[11,12] Although some authors have minimized the incidence and significance of pancreatitis after cardiopulmonary bypass,[2,3] those reports contained small numbers of patients. Others have found significant acute pancreatitis and its sequelae in 20–25% of patients dying after cardiac surgery.[1,7,8]

It is important to distinguish between postperfusion hyperamylasemia and postperfusion pancreatitis. The former is common, whereas the latter is not. The incidence of postperfusion hyperamylasemia in this series (32%) is similar to that of other reports.[2,13] The incidence of clinically significant pancreatitis in this series is 2.7%, which is higher than that of other reported series.[2-4,7,13,14] All cases were documented by a combination of anatomic

TABLE 4. *Mortality and Hyperamylasemia*

Serum Amylase	No. of Patients	Deaths	Mortality Rate
Elevated	96	7	7.5%*
Normal	204	2	0.9%

* $p < 0.01$.

(CT scan or autopsy), biochemical (amylase, isoamylase, and lipase), and clinical parameters (ileus or other abdominal complaints). Asymptomatic or minimally symptomatic patients were not classified as having overt pancreatitis, regardless of their serum biochemical values.

Hyperamylasemia occurring in the absence of abdominal complaints or elevated serum lipase was unlikely to be of pancreatic origin, as demonstrated by isoamylase analysis. Over half the cases in this series (54 of 96 patients) were due to isolated elevation of nonpancreatic amylase. These patients had no evidence of subclinical pancreatic injury and had no morbidity related to the pancreas.

A surprising finding in this series is the association of nonpancreatic amylase elevation with postoperative mortality. Patients with isolated hyperamylasemia had a mortality rate of 9% (five of 54 patients), which was significantly greater than the 1% mortality rate (two of 204 patients) in patients without hyperamylasemia ($p < 0.01$). The source of amylase, as well as the mechanism responsible for hyperamylasemia in these patients, is unclear. Amylase-creatinine clearance ratios were not calculated, although others have shown this to be elevated after cardiopulmonary bypass.[3,4,6,8] Although altered renal clearance of serum amylase may account for isolated hyperamylasemia, the postoperative changes in BUN and creatinine in this series were not significantly different from controls (Table 4). Perhaps there is a metabolic derangement in these patients, as seen in diabetic ketoacidosis,[15] head trauma,[16] and other postoperative states[17] that causes serum amylase activity to rise. Regardless of the precise source and pathogenetic mechanism, isolated hyperamylasemia is probably an epiphenomenon that requires no specific therapy.

One third of the patients with hyperamylasemia probably had a subclinical pancreatic injury (32 of 96 patients). In these cases, a pancreatic source of amylase was corroborated by isoamylase analysis or elevated serum lipase. Most patients appeared clinically well. A few patients had a mild ileus. All CT scans on these patients were normal, although some patients had elevations of serum lipase and amylase that persisted for 3–4 weeks. In the current series, none of these patients developed overt pancreatitis, but outside of this study group we have seen several comparable cases of subclinical pancreatitis that became complicated by necrosis or abscesses 2 weeks to 3 months after cardiac surgery. However, because this appears to be an uncommon occurrence, it does not seem justifiable to fast all patients with elevations of pancreatic isoamylase or lipase for prolonged periods if the patient has no symptoms of pancreatitis. Even if small areas of necrosis are seen on the CT scan, there is little evidence to suggest that prolonged bowel rest and hyperalimentation will improve the outcome. We conclude that patients with subclinical pancreatitis should receive standard postoperative care, but if they develop abdominal pain, ileus, unexplained fever or other G.I. symptoms, a CT scan of the abdomen should be obtained in order to find complications such as pancreatic necrosis or abscess.

Acute pancreatitis occurring in the setting of recent cardiac surgery is a potentially lethal disease. Mortality rates of 35–80% have been reported for postperfusion pancreatitis.[7,13,14] Although experience at this institution in dealing with complicated cases of pancreatitis has led to markedly improved survival,[18] the mortality rate is still high, and in this series was 12.5% (one of eight patients). These patients had prolonged hospitalizations, frequently requiring surgical debridement of pancreatic necrosis or percutaneous drainage of intra-abdominal collections. Of note is that two patients in whom postperfusion pancreatitis developed had a previous history of pancreatitis, perhaps rendering them more susceptible to a further ischemic insult.

Experimental and autopsy studies have suggested that the pancreas is susceptible to ischemic injury.[7,8,19,20] This study provides additional data that implicate ischemia as the pathogenetic mechanism responsible for postperfusion pancreatitis. Patients with overt pancreatitis had significant changes in renal function after operation, presumably because of hypoperfusion-induced tubular injury. As the age of the cardiac surgical patient population increases, mesenteric vascular lesions are likely to be more common. Because hypoperfusion is believed to be a major element in the pathogenesis of postperfusion pancreatitis, this may contribute to the apparently increasing incidence of pancreatitis. It is tempting to speculate that the prophylactic use of agents that maintain splanchnic perfusion (dopamine) or prevent venous sludging (dextran) may be beneficial in patients undergoing cardiac surgery. We are not aware of any clinical studies addressing this issue.

The management of patients with postperfusion pancreatitis requires special consideration of the cardiac surgical procedures that they have recently undergone. Patients with acute pancreatitis are likely to require a prolonged period of fasting. Central total parenteral nutrition should be started promptly so that nutritional requirements for recovering from cardiac surgery are provided. Patients undergoing valve replacement frequently require anticoagulation. Pancreatitis *per se* is not a contraindication to carefully controlled anticoagulation, but stress gastritis is common in these patients, and therefore antacid regimens or H_2 antagonists are helpful in preventing G.I. bleeding. Hemorrhagic pancreatitis or G.I. bleeding both require cessation of anticoagulants. Because infection is a common complication of severe pancreatitis, patients with prosthetic heart valves are at risk of developing endocarditis if bacteremia occurs. Although we do not use antibiotics in the absence of sepsis, we aggressively search for intra-abdominal infection so that it can be treated

promptly when diagnosed. Serial CT scans should be obtained every 7–10 days to assess changes in the retroperitoneal anatomy. Large collections, particularly in sick patients, should be sampled percutaneously under CT guidance to search for infection that would require early surgical intervention.[21] If extensive necrosis is present, it may be wise to proceed with surgical debridement before the collection becomes secondarily infected. After successful corrective heart surgery, most patients are reasonable candidates for further surgery if it becomes necessary. We believe that the low mortality in this series (12.5%) compared with that of previous reports (35–80%)[13,14] reflects an aggressive approach to these patients.

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