Hyperamylasemia and Post-Pump Pancreatitis Following Cardiopulmonary Bypass: A Prospective Study

KARDİYOPULMONER BYPASS SONRASI HİPERAMİLAZEMİ VE PANKREATİT: PROSPEKTİF ÇALIŞMA

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Summary

Although the incidence of hyperamylasemia following cardiopulmonary bypass (CPB) is high, pancreatic complications which have high mortality rates are rare. In this prospective study, we investigated the incidence and risk factors of hyperamylasemia and pancreatitis following CPB.

Thirty seven patients (21 male, 16 female) with a mean age of 41.8 years (ranging between 15-64) undergoing cardiac operation with CPB were included for the study. Ten patients (27,0%) developed hyperamylasemia and only one of these 10 patients developed pancreatitis and this patient was lost due to multiorgan failure (2.7%).

Extended duration of cardiopulmonary bypass and cross clamp times were identified as risk factors for hyperamylasemia. Hyperamylasemia and pancreatitis prolongs the duration of intensive care unit and hospital stay.

Key Words: Hyperamylasemia, Pancreatitis, Cardiopulmonary bypass

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Özet

Kardiyopulmoner bypass (CPB) sonrası hiperamilazemi insidansının yüksek olmasına rağmen, yüksek mortaliteye sahip pankreatit komplikasyonu oldukça nadir izlenir. Bu prospektif çalışmada, CPB sonrası hiperamilazemi ve pankreatit insidansı ve risk faktörlerini inceledik.

Kardiyopulmoner bypass altında kalp operasyonu geçiren yaş ortalaması 41.8 olan 37 hasta (21 erkek, 16 kadın) çalışmaya dahil edildi. 10 hastada (%27) hiperamilazemi gözlenirken, bu 10 hastanın yalnızca birinde pankreatit gelişti ve bu hasta multiorgan yetmezliğine bağlı olarak kaybedildi (%2.7).

Kardiyopulmoner bypass ve kros klempin uzaması hiperamilazemi için risk faktörü olduğu belirlendi. Hiperamilazemi ve pankreatit yoğun bakımda ve hastanede kalış süresini uzatmaktadır.

Anahtar Kelimeler: Hiperamilazemi, Pankreatit, Kardiyopulmoner bypass

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As the number of open heart surgery cases increases, the number of patients with gastrointestinal complications will also increase (1). Advances in cardiac surgery and CPB techniques reduced the operative morbidity and mortality (2-4). However noncardiac complications although rarely seen, carry high peroperative morbidity and mortality (5).

Subclinic splanchnic organ injury generally depends on ischemia caused by perioperative low cardiac output, hypotension, hypoperfusion. Post-pump pancreatitis (PPP) is defined as pancreatitis occuring following cardiac surgery with cardiopulmonary bypass. PPP, although rarely seen, is a well defined complication in cardiac surgery, and can be seen after all kinds of cardiac operations including transplantation and congenital procedures (6-11). PPP is diagnosed by abdominal pain accompanied with elevated serum amylase levels reaching above 1000 IU/L and oedematous pancreas on ultrasonography (8).

Administration of drugs such as phenylephrin, norepinefrin, narcotics, steroids, and calciumchloride are held responsible for PPP (10-12), which is observed in less than 1% of patients undergoing cardiac surgery CPB, but its diagnosis

and treatment is difficult and even when properly diagnosed its mortality is much higher than other types of pancreatitis (9).

This study was designed to investigate the frequency and importence of hyperamylasemia and PPP and risk factors relating to these conditions.

Materials and Methods

Twenty one female, 16 male, in total 37 patients who underwent open heart surgery using CPB were included into this study. Age, sex, body weight, serum calcium, serum amylase and lipase levels, blood urea, creatinin, trigliseride, hematocrite (hct) levels, cardiac output, cardiac index, arterial blood pressure, cardiac and extra cardiac pathologies were recorded preoperatively. None of the patients had preoperative gastrointestinal symptom or disease. Serum amylase, lipase, hepatic and renal function tests were all normal.

Details of cardiac surgical procedures, drugs used during operation (morphine, hydromorphine, corticosteroid, fentanyl, dopamine, dobutrex) total perfusion time, cross clamp time, mean perfusion pressure, hypothermia, central venous pressure (CVP), amount of blood transfusion, total calcium chloride administered, hct and ionized serum calcium levels were all recorded intraoperatively.

Postoperatively, duration of mechanical ventilation, length of intensive care unit stay, total postoperative hospitalization time, gastrointestinal symptoms (abdominal pain, nausea, vomiting etc..) amylase, lipase, htc and ionized Ca^{++} levels at first and 72nd hours, reports of abdominal ultrasonography (USG) (all abdominal USGs are performed by the same sonographer), development of low cardiac output, postoperative positive inotropic infusion and intraaortic balloon pump support needs and durations, complications (bleeding, tamponade, revisions) were all recorded. Levels of serum amylase were measured by enzymatic colormatic method and values greater than 220 IU/l were accepted as hyperamylasemia. Patients were examined daily and all the gastrointestinal symptoms and signs (abdominal pain, nausea, vomiting, distention, rebound, ileus, etc.) were recorded.

Surgical technique

10mg diazepam was administered intramuscularly for premedication. Anesthetic induction was accomplished by 30 microgram/kg fentanyl, 0.5 microgram/kg diazepam and 0,1 mgr/kg pancuronium. If myocardial performance was poor, reduced doses were used. Maintenance of anesthesia was provided with fentanyl and pavulon administrations.

Surgical approach is performed through median sternotomy. Standard aorto caval cannulation and cardiopulmonary bypass was used for operations. Hollow fiber membrane oxygenator was used for cardiopulmonary bypass with nonpulsatile flow and moderate hypothermia. Hematocrite, perfusion pressure, and perfusion flow, were kept between 20-25%, 50-70 mmHg, and 2.2- 2.5 L/min/m2 respectively. PaCO2 was 40 mmHg and PaO2 was 250 mmHg during CPB. Alpha-stat pH strategy was used for acid base management. Myocardial protection was achieved with antegrade and retrograde administration of cold blood cardioplegia prepared with St. Thomas II solution at 20 minute intervals and topical cooling with cold saline. Before releasing aortic cross clamp retrograde warm blood cardioplegia was administered.

Patients were extubated at 10-14th hours if there were no hemodynamic, pulmonary or neurologic problems. Oral nutrition was began 3 or 4 hours after extubation with clear liquids and normal feeding was began within 24 hours. Second generation cephalosporins were used for infection prophylaxis and continued until all intravenous lines were removed.

Statistical evaluation

The results were evaluated by Fisher's Exact test and one way of analysis of variance test. P values less than or equal to 0.05 are considered statistically significant.

Results

First postoperative hour serum amylase and lipase levels were normal in 27 patients (Group A) and significantly increased in 10 patients (Group

Table 1. Postoperative amylase and lipase levels

	Group A	Group B	p values
Postoperative first hour			
Serum amylase levels	113,92±70	383±131,69	P<0,0001
Serum lipase levels	92,00±115,44	244,42±74,00	P<0,0001
Postoperative third day			
Serum amylase levels	134,95±67,44	149,66±52,44	NS
Serum lipase levels	66,33±60,11	110,33±83,74	NS

Table 2. Preoperative parameters

	Group A (n=27)	Group B (n=10)	P values
Age	40,55±15,41	43,25±16	NS
Sex(F/M)	12/15	4/6	NS
Body weight(kg)	60,8±3	67,0±9,3	NS
Cardiac pathology			
Coronary artery disease	5	3	NS
Valvular heart disease	14	5	NS
Congenital heart disease	8	2	NS
Redo	4	1	NS
Concomitant disease	6	2	NS
Carotid artery disease	1	-	
Diabetes mellitus	1	-	
Hypertension	1	2	
Cholecystectomy	2	-	
Peptic ulcer	1	-	
Cardiac output	5,32±0,71	5,6±0,5	NS
Cardiac index	3,35±0,39	3,28±0,48	NS
Hematocrite	43,5±5,7	42,38±7,0	NS
Serum amylase levels	176,77±74,77	226,28±86,10	NS
Serum lipase levels	119,14±79,85	217,57±216,98	NS

B) as described in Table 1. Statistical evaluation of preoperative parameters of group A and B did not present any significant difference (Table 2).

Evaluation of intraoperative parameters of group A and B showed statistically significant difference for total perfusion and aortic cross clamp times. and ionized serum calcium levels. There were differences among groups for ionized serum calcium levels, the amount of cardioplegia delivered, units of transfused packed blood, and the amount of calcium administered but these differences did not reach to statistical significance. Again there were no statistical difference between group A and B for the arterial and venous perfusion pressure, degree of hypothermia, and hematocrite levels during CPB (Table 3).

Evaluation of postoperative parameters of group A and B did not show any difference for the duration of mechanical ventilation, development of abdominal symptoms, the need for inotropic and intraaortic balloon pump support, and the duration of intensive care unit stay. Hospitalization time however was longer for group B patients (Table 4).

On third postoperative day except one, all patients 72nd hour serum amylase levels returned to normal (Table 1).

Of the 10 (27,0%) patients having hyperamilasemia recorded at first hour blood sample only one (2,7 %) developed PPP and this patient was lost due to multiorgan failure on postoperative day 63.

Discussion

Although gastrointestinal complications are rare following cardiac operations under CPB (%0.4-2.1) mortality rates of these complications are high (%13-67) (1-4,13-15). GIS complications following CPB are usually silent which cause difficulty and delay in diagnosis and eventually leading to high mortality (1,3,16). Autopsy series and prospective studies demonstrate higher GIS complications following CPB when compared with retrospective studies(8).

Hanks et al reported that of the 5080 CPB cases 43 developed GIS complications, of these 7 were pancreatitis and only 3 have survived (13).

Feiner reported 34 pancreatitis in 182 autopsy series following cardiac surgery (17). Warshaw and Ohara reported 11 (11%) major pancreatitis findings in 101 autopsy series following CPB (11). The rate of pancreatitis is higher in autopsy series than in clinical series. This is because many patients die before the diagnosis of pancreatitis can be esthablished (13,18).

Although pancreatitis is rarely seen (0.1-5.2%) following CPB, hyperamylasemia however may be observed in 30-50% of the cases (5,6,8,10,19,20). This may be caused by pancreas or other organs as salivary glands, lungs, etc. (18,21). Carlos et al studied 300 cases prospectively and measured pancreatic isoamylase and lipase activity and found

Table 3. Intraoperative parameters

	Group A (n=27)	Group B (n=10)	P values
Mean blood pressure	68,44±9,64	63,75±6,9	NS
Central venous pressure	3,2±2,6	3,9±1,78	NS
Total perfusion period(min)	71,51±38,11	105,75±34,73	0,02
Cross clamp period(min)	44,8±28,9	67,8±26,6	0,05
Cardioplegia	1901±650	2700±927	0,07
Blood transfusion	0,689±0,76	1,37±1,59	0,09
Hypothermia(degree)	30±1,4	29±1,3	NS
Calcium chloride	1,06±0,25	1,37±0,74	0,06
Ionized serum calcium	0,86±0,44	1,07±9,44	0,05
Hematocrite	29,7±3,0	30±3,0	NS
Adjuvant treatment			
Hydrmorphine (HM)	25	8	NS
Dobutrex-dopamine(DD)	9	6	NS
Fentanyl	17	4	NS
Norepinephrine	3	2	NS
Corticosteroids	3	2	NS

Table 4. Postoperative parameters

	Group A	Group B	P values
Intensive care unit stay(day)	2,2±1,6	3,1±2,6	NS
Postoperative hospitalization(day)	7,6±3,9	16,5±19,1	0,02
Mechanical ventilation period(hours)	13,46±2,46	15,0±4,0	NS
Mean hematocrite	29±5	30±5	NS
Abdominal symptoms(case)			
Nausea	12	5	NS
Vomiting	7	3	NS
Abdominal pain	7	4	NS
Constipation	5	1	NS
Diarrhea	1	1	NS
Distention	1	1	NS
Inotropic support			
Dopamine	3	2	NS
Dobutrex	3	2	NS
IABP	-	1	NS

that in 27% of cases hyperamylasemia following CPB is pancreas related (5).

Hyperamylasemia generally is an indicator of pancreatic cellular injury and subclinical pancreatitis but it does not allways signifies the development of clinical pancreatitis. Svenson et al reported the incidence of hyperamylasemia following CPB as 36 % but clinical pancreatitis developed in 4,2% of these patients (8). Although hyperamylasemia is common, this situation by itself does not lead to high mortality and morbidity. Abdominal symptoms and abdominal ultrasonograophy findings must support the diagnosis in order to name hyperamylasemia as PPP (18,21).

In our study, although incidence of early postoperative hyperamylasemia was 27,0% clinical pancreatitis, developed in only one case (2,7%). The reasons for increase of serum amylase levels following CPB and its effects on prognosis of pancreatitis was investigated by several studies. Jacops et al reported that serum amylase level is not a prognostic factor in acute pancreatitis (22) Traveso et al confirmed that amylase to creatinin clearance ratio (ACCR) is increased excessively in early postoperative period following CPB and this returns to normal before the development of acute pancreatitis findings, usually on second postoperative day (12). Murray et al however reported that, significant increase in ACCR following nonpulsatile CPB is an important indicator of acute pancreatic dysfunction and this may predict ischemia (23).

Common causes of GIS complications following CPB are splanchic ischemia and hypoperfusion. Experimental and clinical studies showed that especially nonpulsatile CPB decrease the splanchic flow leading to hypoperfusion and ischemia of GIS (2-5,23-25). During hypotermic CPB, 46% decrease in gastric mucosal flow and 20 % decrease in hepatic blood flow are measured by laser Doppler flowmeter measurements (26,27). Ohri et al reported that hypothermia further increases the splanchic vasoconstriction caused by CPB (2,4,26). CPB also activates complement system which may cause granulocyte aggregations and these aggregates may result in occlusion arterioles which eventually lead to ischemic organ dysfunction (25).

Also there are reports about the prolonged CPB increasing the rate of GIS complications (4,25,28). In this study prolonged CPB and cross clamp times were found to be related with hyperamilasemia.

Experimental studies in canines showed that hypotension causes severe pancreatic hypoperfusion resulting in edema, injury in acinar

cells, lysosomal swelling, vacuolization, increased serum amylase level, increased levels of proteolytic enzymes, and release of myocardial depressing factor (MDF) (8,9,24,29)

It is reported by many studies that fluid sequestration over 2 L/day and lasting more than 2 days is an important risk factor for development of acute pancreatitis following CPB (30).

Another important risk factor in development of acute pancreatic cell damage following CPB is the usage of calcium chloride perioperatively. Castillo et al reported that calcium chloride (CaCl) more than 800 mg/m^2/day is an independent risk factor in pancreatic cell damage (5). Calcium is used in many centers to increase the myocardial performance (31). Calcium provides temporary and minimal improvement in myocardial performance but at the same time it causes vasoconstriction which leads to ischemia and hypoperfusion at splanchic area. In this study, the difference of intraoperative serum ionized calcium levels between the two groups were significant. Cautious and limited use of CaCl during perioperative period is therefore advised and medications other than CaCl should be selected to support myocardial performance (32).

Furthermore, in this study, it was observed that the amount of cardioplegia and the amount of blood transfusion were more for hyperamylasemia group. As the aortic cross clamp time legthens the amount of cardioplegia increases and the amount of calcium in cardioplegia preparation (even in very low concentration) may play an important role in development of hyperamylasemia. In addition, for each unit of blood transfused, 1/3 ampul of Ca gluconate (225 mg) is added. At the end of CPB for neutralization of heparin, protamin sulfate is used with 1 amp calcium gluconate, all these may add up to a significant amount and may become a factor for development of hyperamylasemia, and acute pancreatitis following CPB.

Intraoperative risk factors leading to PPP should be eliminated when possible. CPB and aortic cross clamp times should be as short as possible. Unnecessary blood transfusions and calcium administrations must be avoided. GIS symptoms, hyperamylasemia and supporting abdominal USG findings are guidelines for early diagnosis of PPP which will reduce the mortality, morbidity, and hospitalization period.

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