Hepatopancreaticobiliary Values after Thoracoabdominal Aneurysm Repair

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Abstract

Background: After thoracoabdominal aortic aneurysm (TAAA) repair, blood tests assessing hepatopancreaticobiliary (HPB) organs commonly have abnormal results. The clinical significance of such abnormalities is difficult to determine because the expected postoperative levels have not been characterized. Therefore, we sought to establish expected trends in HPB laboratory values after TAAA repair. *Methods*: This 5-year study comprised 155 patients undergoing elective Crawford extent II TAAA repair. In accordance with a prospective study protocol, all repairs involved left-sided heart bypass, selective visceral perfusion, and cold renal perfusion. Blood levels of aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, amylase, and lipase were measured before TAAA repair and for 7 days afterward. Ratios between postoperative and baseline levels were compared for each time point with 95% confidence intervals. *Results*: Temporal patterns for the laboratory values varied greatly. Amylase, lipase, and AST underwent significant early increases before decreasing to preoperative levels. LDH increased immediately and remained significantly elevated, whereas ALT increased more gradually. GGT remained near baseline through postoperative day 4, and then increased to more than twice baseline. Total bilirubin never differed significantly from baseline. After adjusted analysis, the ischemic time predicted the maximum AST, lipase, GGT, and LDH values. *Conclusions*: Although most HPB laboratory values increase significantly after elective TAAA repair, the temporal trends for different values vary substantially. The ischemic time predicts the maximum AST, lipase, GGT, and LDH levels. These trends should be considered when laboratory values are assessed after TAAA repair. Copyright © 2014 Science International Corp.

Key Words

Thoracoabdominal aortic aneurysm · Hepatopancreaticobiliary function · Laboratory values · Alanine transaminase · Aspartate transaminase

Introduction

Repair of thoracoabdominal aortic aneurysms (TAAAs) is a highly complex process that involves interruption of blood flow to vital organs. Despite adjunctive measures, organ ischemia is unavoidable. Consequently, elevation of hepatopancreaticobiliary (HPB) laboratory values is common after TAAA repair. It is not clear whether a certain degree of elevation should trigger further clinical investigation or could provide information about the degree of ischemic insult. To clarify the clinical significance of these changes, we elucidated the expected trends in HPB laboratory values after extensive TAAA repairs.

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Table 1. Preoperative Exclusion Criteria

Planned Crawford extent I or IV TAAA repair
Planned repair without left heart bypass
Hypothermic circulatory arrest
Previous TAAA repair
Pseudoaneurysm
Free aortic aneurysm rupture
Inability to monitor left kidney temperature
Impaired renal function (renal failure requiring dialysis, or
    serum creatinine ≥3 mg/dL)
Impaired left ventricular function (ejection fraction <20%)
Liver disease (conjugated bilirubin >0.3 mg/dL)
Age younger than 18 years
Inability to obtain consent

TAAA, thoracoabdominal aortic aneurysm.

Table 2. Preoperative Patient Characteristics

Age (years)	62.1 ± 13.1
Male gender (n; %)	99 (64)
Hypertension (n; %)	135 (87)
Diabetes mellitus (n; %)	14 (9)
Smoking history (n; %)	123 (79)
Peptic ulcer disease (n; 5%)	13 (8)
Aortic dissection	
Acute (n; %)	2 (1)
Subacute (n; %)	6 (4)
Chronic (n; %)	70 (45)
Acute and chronic dissection (n; %)	2 (1)
AST (IU/L)	23.5 ± 13.9
ALT (IU/L)	21.3 ± 17.7
GGT (IU/L)	43.9 ± 58.8
LDH (IU/L)	252.3 ± 136.5
Total bilirubin (mg/dL)	1.3 ± 4.8
Amylase (U/L)	59.5 ± 6.9
Lipase (U/L)	55.7 ± 92.7

Values are mean ± standard deviation. AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase.

Table 3. Intraoperative Variables

Total ischemic time (min)	72.2 ± 22.9
Total celiac artery ischemic time (min)	63.1 ± 13.9
Total SMA ischemic time (min)	62.9 ± 13.8
Unprotected celiac artery ischemic time (min)	41.4 ± 11.3
Unprotected SMA ischemic time (min)	41.2 ± 11.2

Values are mean ± standard deviation. SMA, superior mesenteric artery.

Materials and Methods

Study Enrollment

The population consisted of 155 patients who underwent Crawford extent II TAAA repair over a 5-year period and were enrolled in a randomized trial comparing cold crystalloid and cold blood renal perfusion for renal protection [1]. The Institutional Review Board at Baylor College of Medicine approved the randomized trial and also this retrospective analysis. In accordance with the study protocol, left heart bypass (LHB), selective visceral perfusion, and cold renal perfusion were used during all repairs. Patients with preoperative liver dysfunction (conjugated bilirubin level > 0.3 mg/dL) and preoperative left ventricular dysfunction (ejection fraction < 20%) were excluded. Table 1 lists additional exclusion criteria for the trial. Baseline laboratory values for aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, amylase, and lipase were measured preoperatively and for 7 days postoperatively. Table 2 shows the patients' preoperative characteristics.

Surgical Technique

The surgical technique used for TAAA repairs in our practice has been described in detail elsewhere [1]. A standard protocol for selective visceral perfusion was used in all cases. While the thoracoabdominal aorta was exposed, the patient's body temperature was allowed to drift to 32-34℃. Left heart bypass was initiated at a flow of 500 mL/min. After the proximal and mid-thoracic aortic cross-clamps were placed, LHB flow was increased to 2000 mL/min. The proximal anastomosis was then completed. Left heart bypass was discontinued, the mid-thoracic aortic clamp was removed, and the ostia of the visceral arteries were exposed. The celiac and superior mesenteric arteries were perfused via 2 9F Pruitt balloon perfusion catheters (Ideas for Medicine, St Petersburg, Florida), with isothermic blood from the LHB circuit at a total average flow rate of 400 mL/min. The intercostal arteries and then the visceral arteries were reattached to openings in the graft. In 54 patients

(35%), a single patch containing the origins of all 4 visceral vessels was reattached to an opening in the side of the graft. Table 3 shows the intraoperative variables.

Statistical Analysis

We compared the mean ratios between the postoperative and baseline levels for each time point with 95% confidence intervals. The maximum postoperative laboratory value was determined for each patient for each of the 7 laboratory tests of interest (Table 4 [2]). We defined total ischemic time as the period during which an artery is not receiving blood flow directly from the heart, and unprotected ischemic time as total ischemic time minus left heart bypass time. To determine the effect of total ischemic times on the maximum laboratory value, multiple linear regression models were constructed for each laboratory test. For each model, the age, sex, and preoperative baseline laboratory value were always included for covariate adjustment. In addition, smoking status, hypertension, diabetes mellitus, and packed red blood cell (PRBC) transfusion were tested for potential confounding effects. The total ischemic times were then tested for a unique effect on the maximum laboratory value, adjusted for the baseline levels

Table 4. Postoperative Hepatopancreaticobiliary Values

	Median ± SD	Normal values [2]
AST (IU/L)	86.5 ± 105	12–38
ALT (IU/L)	52 ± 94.5	7–41
GGT (IU/L)	72 ± 104.5	9–58
LDH (IU/L)	543 ± 634.7	115–221
Total bilirubin (mg/dL)	1.8 ± 1.51	0.3–1.3
Amylase (U/L)	169.5 ± 361.4	20–96
Lipase (U/L)	85 ± 591.2	3–43

AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase.

Figure 1. Overall summary of changes in hepatopancreaticobiliary values after thoracoabdominal aortic aneurysm repair. AST, aspartate transaminase; LDH, lactate dehydrogenase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase.

(age, sex, preoperative laboratory value, smoking status, hypertension, diabetes, PRBC). All of the maximum laboratory test values were extremely skewed, violating the assumption of normality of residuals for linear regression. A log transformation was conducted for each of the maximum laboratory tests; this measure showed improved normality and was the variable modeled. All analyses were conducted with Statistical Analysis Software, Version 9.3 (SAS, Cary, NC). In multiple regression models testing for potential factors, backward selection was used with a threshold of $P = 0.20$ to enter the model and $P = 0.10$ to stay in the model.

Results

The temporal patterns of the laboratory values were highly variable (Fig. 1). The AST levels showed significant early increases, then decreased toward baseline (Fig. 2). The ALT levels continued to increase during the postoperative period (Fig. 2). The GGT levels remained near baseline through postoperative day 4, and then increased significantly to more than 2 times baseline (Fig. 2). Similarly, the LDH levels also increased immediately and remained significantly elevated throughout the week before trending downward (Fig. 2). The amylase levels increased initially but then trended downward toward baseline (Fig. 3). The lipase levels increased initially, returned to near baseline levels, and then slowly increased again (Fig. 3). The total bilirubin levels were highly variable and showed no definite trend.

In the adjusted analysis, the total ischemic times were not predictive of maximum laboratory values for amylase, ALT, or total bilirubin. Ischemic times were predictive of maximum AST, lipase, GGT, and LDH values. After adjusting for age, sex, and preoperative baseline AST levels, we found that smoking [$\beta = 0.347$; standard error (SE) = 0.109; $P = 0.0019$], PRBC
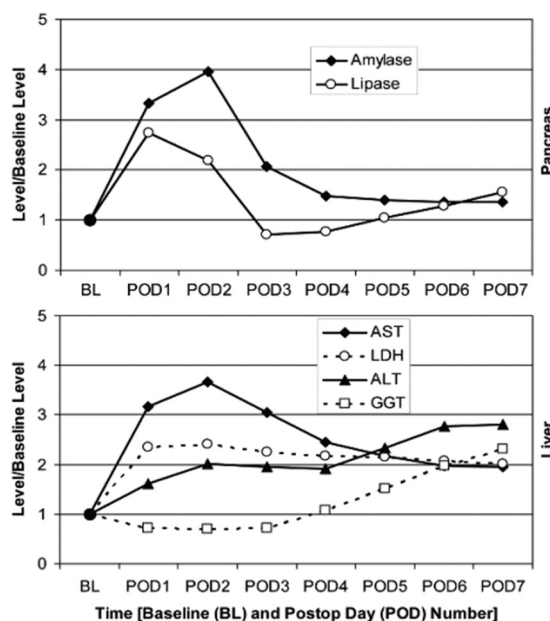
($\beta = 0.035$; SE = 0.013; $P = 0.0064$), and the total ischemic time ($\beta = 0.005$; SE = 0.002; $P = 0.0133$) were significantly associated with the maximum AST value. Therefore, an increase of 1 min in the total ischemic time was associated with an approximate increase of 0.005 unit in the log of the maximum AST value (10 min would raise the log of the maximum AST by 0.05, 100 min would raise the log of the maximum AST value by 0.5).

After adjusting for age, sex, and the preoperative baseline lipase level, we found that the total celiac artery ischemic time ($\beta = 0.027$; SE = 0.008; $P = 0.0011$) was significantly associated with the maximum lipase value. None of the other potential confounders were significant.

After adjusting for age, sex, and the preoperative baseline GGT level, we found that the total ischemic time ($\beta = 0.005$; SE = 0.0027; $P = 0.0612$) was significantly associated with the maximum GGT value. None of the other potential confounders were significant.

Furthermore, after adjusting for age, sex, and the preoperative baseline LDH level, we found that smoking ($\beta = 0.225$; SE = 0.100; $P = 0.0264$) and the total ischemic time ($\beta = 0.0055$; SE = 0.0016; $P = 0.0011$) were significantly associated with the maximum LDH value.
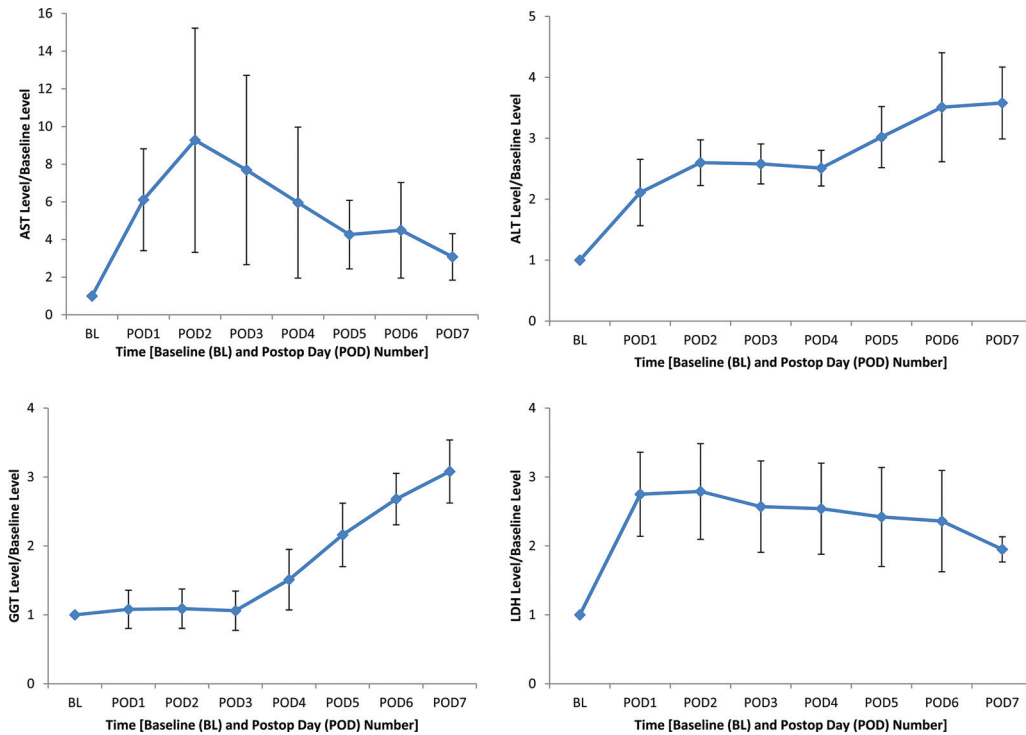
Figure 2. Changes in aspartate transaminase (AST) values, alanine transaminase (ALT) values, γ-glutamyl transpeptidase (GGT) values, and lactate dehydrogenase (LDH) values after thoracoabdominal aortic aneurysm repair.
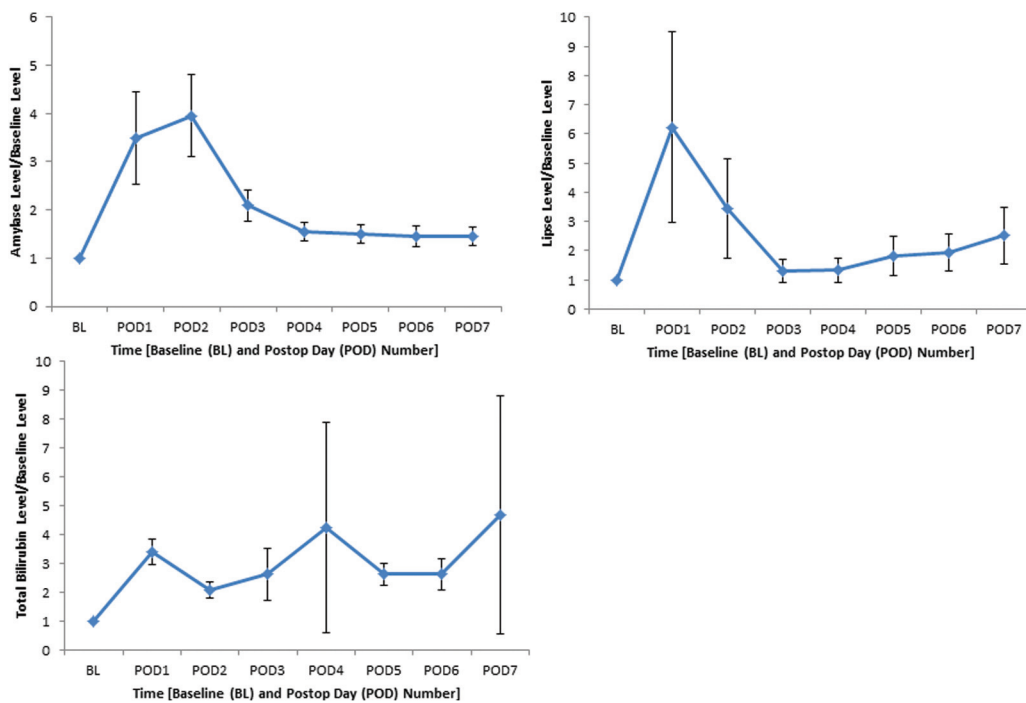

Figure 3. Changes in amylase values, lipase values, and total bilirubin values after thoracoabdominal aortic aneurysm repair.

Eight patients (5.2%) died within the first 30 days. Five patients (3.2%) developed paraplegia or paraparesis. No patients developed clinically significant hepatic, pancreatic, or gastrointestinal complications.

Discussion

Hepatosplanchnic hypoperfusion and ischemia are rare, but severe, complications after cardiac surgery, and even transient hepatosplanchnic hypoperfusion can lead to severe postoperative complications [3]. In TAAA repair, hepatosplanchnic ischemia is unavoidable, and patients undergoing repair of extent II TAAAs can have unprotected ischemic times of greater than 40 min. In the postoperative period, an alarming elevation of HPB enzymes is common, but the clinical significance of this elevation is not clear. We found that, in the absence of significant heart and liver dysfunction, patients undergoing elective repair of extent II TAAAs had substantial variations in their HPB laboratory values.

Hepatic dysfunction is difficult to measure in the postoperative period because commonly performed laboratory measurements reflect only gross functional abnormalities and are more indicative of cell damage than of dysfunction [4,5]. This is particularly evident in the liver, which has regional variations in the number of hepatocytes and in the ability of different hepatic cell types to withstand hypoxia. We know from metabolic studies of visceral organs protected by adjunctive measures that the resulting flow is not physiologic [6]. Although normal liver blood flow may resume as early as 4-6 h after surgery, the change in hepatocyte metabolism resulting from diminished flow may persist for longer periods [1]. Increases in liver enzyme levels can indicate only hepatocyte damage, not regional perfusion or functional defects. Nevertheless, we chose to use the results of commonly performed liver function tests as markers for liver injury and not liver dysfunction.

Because cytoplasmic enzymes are present in liver parenchymal cells, AST and ALT are indicators of parenchymal injury; however, cardiac, skeletal muscle, and hematologic disorders can also cause elevation of these enzymes. In our series, we found that, despite a continued increase in ALT values throughout the 7-day postoperative period, maximal ALT values were not associated with the total ischemic time, even after adjusted analysis. In contrast, after adjusting for age, sex, and preoperative baseline values, we found that maximal AST values were associated with a history of tobacco use, PRBC transfusion, and the total ischemic time. Because ALT is more sensitive than AST as an indicator of liver damage, elevations of AST may reflect systemic damage resulting from ischemia rather than ischemic damage to the liver. For instance, smoking is known to increase oxidative stress in the body, and differences between ALT and AST after adjusted analysis may relate to differences in the susceptibility of multiple organs to ischemic damage [7]. Elevation of ALT and AST levels has also been correlated with changes in the iron concentration after transfusion [8]. Transfusion of blood products leading to changes in the chelatable iron pool may exceed the hepatocellular iron-chelating capacity and lead to a greater increase in AST than in ALT levels. Because we did not measure the preoperative and postoperative iron levels, we cannot comment further about this association.

GGT and LDH are also widely distributed in the liver and other tissues. In this study, we found that both enzymes became increasingly elevated with time and also were associated with the total ischemic time. However, elevations of these enzymes can be caused by other disorders in the absence of liver disease or dysfunction and are not specific indicators of liver ischemia or injury. Similarly, elevations of the total bilirubin level can be caused by factors other than liver injury. Cholestasis secondary to impaired bile flow may be due to intrahepatic causes (hepatocellular dysfunction resulting from ischemia) or extrahepatic causes, such as biliary obstruction. In this series, we did not find any pattern for changes in the total bilirubin level.

Although the synthetic function of the liver is best assessed by analyzing coagulation factors, we did not do this because (1) there was little variation in these laboratory values, (2) patients often received blood products in the immediate postoperative period to correct coagulopathy, and (3) because of the blood's interaction with the Dacron graft, patients were often in a mild state of disseminated intravascular coagulation after surgery. Moreover, albumin levels depend on a number of factors, including nutritional status and renal dysfunction, and because of its long half-life, albumin is not a marker of acute hepatic dysfunction. Therefore, the interpretation of abnormal laboratory values depends on the type of abnormality that predominates: hepatocellular damage, abnormal synthetic function, or cholestasis. In this instance, patients with underlying liver dysfunction (e.g., hepatitis C), as

diagnosed by preoperative liver function tests, were excluded from our study.

Elevations in amylase and lipase levels in the postoperative period are indicative of pancreatic ischemia. However, in this study, we found that only a postoperative increase in lipase was associated with the total ischemic time. This insult was manifested by the immediate elevation of pancreatic enzymes on postoperative day 1, followed by a later increase in lipase levels during the ensuing postoperative period. However, depending on the extent of dissection and bowel manipulation, it is common practice to resume enteral nutrition after the return of bowel function, usually around postoperative day 4. The resulting increase in lipase levels may reflect an exacerbation of pancreatic damage induced by the surgery. All patients in our series with elevation of amylase or lipase levels tolerated feeding without abdominal pain or other sequelae, indicating that, despite evidence of ischemic pancreatitis, total metabolic function might not have changed.

To assess the degree of ischemic insult, we compared the ratios between postoperative values and baseline laboratory results for each postoperative day. We did not perform a frequency analysis to further stratify risk factors associated with specific organ dysfunction. Analyzing these risk factors would have been inconsequential because patients with preoperative liver or renal dysfunction were excluded, few patients had diabetes (9%), and most patients smoked (79%). Instead, we used a multiple linear regression model with generalized estimating equations, which allowed us to adjust for the correlated nature of the laboratory values measured. Because the study's main goal was to establish generalized trends in the postoperative period, we did not perform a statistical analysis examining all the different variables that correlated with extreme postoperative laboratory values.

The primary determinant of whether a patient will develop postoperative multiple organ dysfunction (MOD) is visceral ischemia lasting for longer than 40 min [9,10]. In our series, the mean total ischemic time was 72.2 min, with a mean unprotected celiac artery ischemic time of 41.4 min and mean superior mesenteric artery ischemic time of 41.2 min. However, none of our patients developed MOD. Use of adjunctive measures such as LHB significantly reduces the duration of visceral ischemia. Although our patients had a mean ischemic time of >40 min, selective visceral perfusion may have offered a protective effect against

MOD, even in the presence of elevated postoperative HPB laboratory values.

Despite improved surgical techniques, spinal cord ischemia and renal failure remain the most devastating complications associated with repair of TAAA. The rate of paraplegia in our series was 3.2%. There was no correlation between significant elevations in HPB laboratory values and the development of either paraplegia or renal failure. However, in paraplegia patients, this may have been due to a small sample size. Most importantly, none of the patients in our series developed clinically significant postoperative HPB dysfunction. This may have been due to the fact that patients had relatively normal preoperative liver function and moderate-to-good left ventricular function, and most often underwent elective TAAA repair. Safi et al. [11] have shown that a history of hepatitis, extent II aortic aneurysm, ruptured aortic aneurysm, and emergency presentation are significant predictors of elevated postoperative liver function values. Therefore, patients with borderline liver function or prolonged ischemic times may be pushed into liver failure and perhaps even multisystem organ failure.

Limitations

This study has a number of limitations. First, although data were collected prospectively in accordance with a randomized clinical trial protocol, the secondary analysis of HPB enzyme levels was retrospective and, thus, consequently can provide only a descriptive picture of the metabolic changes that occur in patients who undergo elective repair of extent II TAAAs. Second, use of a longitudinal analysis model over a 7-day period limits the amount of information that can be gained. Third, we acknowledge that providing 400 mL/min through balloon-perfusion catheters may not provide optimal visceral flow. The 9F catheters have been used in our practice in part to facilitate safe catheter placement in vessels that often have small ostia and atherosclerotic plaques and to avoid vessel injury and dislodgement of atherosclerotic debris. Although we have been satisfied with the clinical results achieved when using these catheters (an extremely low incidence of overt hepatic, pancreatic, and gastrointestinal ischemic complications), the current study suggests that substantial subclinical organ injury occurs and that use of larger catheters warrants consideration. The study leaves several significant questions unanswered, such as (1) whether there is a relationship between the duration of visceral ischemia and

injury to the liver or other organs, (2) whether any of the abovementioned preoperative HPB laboratory values are more or less specific in predicting organ dysfunction postoperatively, (3) whether there is a relationship between HPB injury and dysfunction of other organs (as indicated by elevated laboratory values) or development of multisystem organ failure, and (4) whether adjunctive measures are significantly protective in patients who have preoperative hepatic dysfunction or cirrhosis to allow safe repair of TAAAs. Moreover, in some instances proximal aortic clamping is not possible; the trends revealed by this study can not be applied to patients in whom circulatory arrest is used.

Conclusion

In patients undergoing TAAA repair, HPB enzyme levels are expected to be elevated postoperatively in the absence of liver dysfunction or multisystem organ dysfunction. In this study, we established the normal expected patterns for HPB laboratory values in the postoperative period after TAAA repair. In some cases, the degree of elevation correlated with the duration of ischemia. We hope that our findings may be useful for evaluating laboratory results in similar cases and for interpreting the results of future studies related to visceral protection.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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EDITOR'S COMMENT

We are indebted to Dr. LeMaire and colleagues for documenting this important information. We always wondered, but never knew, how to interpret these LFT abnormalities.