Secondary sclerosing cholangitis in cardiac surgical patients: A complication with a dismal prognosis

Ina Schade, MD,[a] Dejan Radakovic, MD,[a] Jörg Hoffmann, MD,[a] Sebastian-Patrick Sommer, MD, PhD,[a] Ullrich Stefenelli, MPH,[b] Christoph Schimmer, MD, PhD,[a] Rainer G. Leyh, MD, PhD,[a] and Ivan Aleksic, MD, PhD[a]

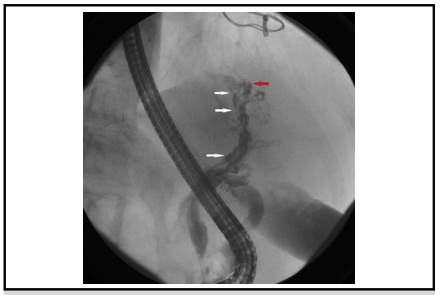
ABSTRACT

Objectives: Secondary sclerosing cholangitis in critically ill patients is a rapidly progressing disease leading to biliary fibrosis and cirrhosis. We describe the course of sclerosing cholangitis in critically ill patients after cardiac surgery and compare this with matched patients.

Methods: A retrospective search for ''secondary sclerosing cholangitis'' and ''liver and/or hepatic failure'' in all adult patients (aged 18-93 years) who underwent cardiac surgery from April 2007 to March 2016 identified 192 of 8625 patients. Of those, 12 were diagnosed with sclerosing cholangitis in critically ill patients (incidence, 0.14%). A 3:1 matching was performed. Laboratory values, pharmacologic requirements, ventilation times, mechanical circulatory support, and endoscopic retrograde cholangiopancreatography studies were extracted from the hospital database.

Results: A total of 9 men and 3 women were affected (age 71 years; range, 59.8-75.5 years). Critically ill patients with sclerosing cholangitis required vasoconstrictors and inotropes longer than control patients (norepinephrine 356.5 hours [264.5-621] vs 68 hours [15-132.5], $P = .003$; enoximone 177 hours [124.3-249.5] vs 48.5 hours [12-81 hours], $P < .001$, respectively). Critically ill patients with sclerosing cholangitis had longer intubation time (628.5 hours [377.3-883] vs 25 hours [9.8-117.5]; $P < .001$) and more surgical revisions (3 [2.5-6] vs 1 [0-2], $P = .003$) than the matching group. Bilirubin (23.3 mg/dL [14.4-32.9] vs 1 mg/dL [0.6-2.7]; $P < .001$), gamma-glutamyltransferase (1082.3 U/L [259.5-2265.7] vs 53.8 U/L [35.1-146]; $P < .001$), and alkaline phosphatase (751.5 U/L [372-1722.3] vs 80.5 U/L [53.3-122]; $P < .001$) were higher in critically ill patients with sclerosing cholangitis. One critically ill patient with sclerosing cholangitis underwent successful liver transplantation. A total of 11 patients sclerosing cholangitis died (92%) versus 12 patients (33%, $P < .001$) in the control group.

Conclusions: Sclerosing cholangitis in critically ill patients is a fatal complication in patients undergoing cardiac surgery who have a complicated postoperative course with prolonged vasoconstrictor, inotropic, and respiratory therapy, or who require frequent surgical revisions. Liver transplantation remains the only curative option but is often precluded by the age and critical state of patients undergoing cardiac surgery. (J Thorac Cardiovasc Surg 2017;154:906-12)



Multifocal strictures and dilatations of intrahepatic bile ducts on endoscopy.

Central Message

Sclerosing cholangitis in critically ill patients is a severe complication after cardiac surgery. Liver transplantation remains the only curative option but is rarely feasible.

Perspective

Sclerosing cholangitis in critically ill patients is an underestimated complication in cardiac surgery. Cardiac surgeons need to become familiar with it because of the exceptionally grim prognosis. Early ERCP is the only palliative life-prolonging intervention for most patients. Few patients will be able to undergo curative liver transplantation.

See Editorial Commentary page 913.

The French surgeon Delbet was the first to describe sclerosing cholangitis as a fibrosing inflammatory state of the

From the [a]Department of Thoracic and Cardiovascular Surgery, and [b]Faculty of Medicine, Julius-Maximilians-University, Würzburg, Germany.

I.S. and D.R. contributed equally to this work.

Received for publication Feb 14, 2016; revisions received April 4, 2017; accepted for publication April 13, 2017; available ahead of print May 26, 2017.

Address for reprints: Ivan Aleksic, MD, PhD, Klinik für Thorax-, Herz- und Thorakale Gefäßchirurgie, Universitätsklinikum Würzburg, Oberdürrbacher Strasse 6, Würzburg 97080, Germany (E-mail: Aleksic_I@UKW.de).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2017.04.041

Scanning this QR code will take you to the article title page.

Abbreviations and Acronyms

ALP = alkaline phosphatase
AVR = aortic valve replacement
CABG = coronary artery bypass grafting
ECMO = extracorporeal membrane oxygenation
ERCP = endoscopic retrograde cholangiopancreatography
GE = gastroenterology
GGT = gamma glutamyl transpeptidase
IABP = intra-aortic balloon pump

biliary tract leading to obstruction. The causes of secondary sclerosing cholangitis normally can be identified and include massive surgical trauma, chemical intoxication, obstructive, infectious, immunologic, and ischemic conditions.[1]

Two types of secondary sclerosing cholangitis portend a particularly poor outcome: acquired immune deficiency syndrome cholangiopathy and sclerosing cholangitis in critically ill patients. The causative cascade of sclerosing cholangitis in critically ill patients is believed to be ischemia to the biliary tree with consecutive bacterial colonization leading to destructive biliary changes.[2] However, various other causes have been described (Table 1). Most of these severely ill patients died before a diagnosis was established, and perhaps the development of intensive care medicine per se is responsible for the increasing observation of sclerosing cholangitis in critically ill patients.

The incidence and outcome of this disease in patients undergoing cardiac surgery have not been addressed so far. Few reports have included critically ill patients with sclerosing cholangitis after cardiac surgery,[2-5] but they did not study these patients exclusively.

The aim of this retrospective analysis was to describe the key features of the clinical course of sclerosing cholangitis in critically ill patients undergoing cardiac surgery, compare them with matched controls, highlight important management aspects, and alert cardiac surgeons to this underdiagnosed disease in complicated cases with long-term intensive care unit therapy after cardiac surgical intervention.

MATERIALS AND METHODS

The study was approved by the local ethics committee. Individual patient consent was waived.

A retrospective search for the diagnosis "secondary sclerosing cholangitis" and "liver and/or hepatic failure" in all adults (aged 18-93 years) who underwent cardiac surgery with the use of extracorporeal circulation from April 2007 to March 2016 was conducted. A typical laboratory value pattern of elevated bilirubin, gamma glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP) levels combined with only moderately elevated aspartate and alanine aminotransferases led to a gastroenterology (GE) consult. The suspected diagnosis was confirmed by endoscopic retrograde cholangiopancreatography (ERCP) or autopsy. In addition, data on amylase and lipase were collected. Patients with postoperative ischemic hepatitis as indicated by high transaminase levels and later increment of cholestatic parameters and lack of ERCP were excluded from analysis.

TABLE 1. Possible causes of secondary sclerosing cholangitis

Etiology	Cause	Pathogenesis
Chronic obstruction[6]	Biliary strictures	Recurrent cholangitis
	Neoplasms	
	Choledocholithiasis	
Immunologic	Autoimmune pancreatitis[7]	Inflammation
	Mast cell cholangiopathy[6]	
Infection	Cytomegalovirus[8]	Inflammation
	Cryptosporidiosis in patients with AIDS[8]	
Ischemia	Hepatic artery thrombosis[8]	
	Hepatic artery chemotherapy infusion[9]	
	Embolization therapy[10]	
	Systemic vasculitis[11]	
Ischemic-like cholangiopathy	Patients with ARDS[2]	Unknown
Toxic	Alcohol or formaldehyde instillation in bile ducts[11]	Epithelial injury

AIDS, Acquired immunodeficiency syndrome; *ARDS*, adult respiratory distress syndrome.

A group of 36 patients were identified for comparison to perform a 3:1 matching. These patients were matched for age, preoperative American Society of Anesthesiology class, body mass index, use of any mechanical circulatory support, need for postoperative dialysis, baseline bilirubin, ALP and GGT, and preoperative European System for Cardiac Operative Risk Evaluation (Table 2). Ultrasound excluded gallstones and confirmed normal caliber of the common bile duct in all critically ill patients with sclerosing cholangitis, and an additional computed tomography was performed in 2 patients. Stenosis of the hepatic artery and obstruction of the hepatic veins or the portal vein were excluded by duplex sonography.

All parameters were extracted from the hospital database, including indication for surgery, preoperative medical data, comorbidities, potential confounding factors for the development of sclerosing cholangitis in critically ill patients (Table 2), length of intensive care unit stay, total length of stay and time until death, laboratory values, intraoperative parameters, inotropic requirements, ventilation times, renal replacement therapy, any mechanical circulatory support, microbiology results, and ultrasound and ERCP studies.

Endoscopic therapy consisted of sphincterotomy with removal of any occlusive material from the common bile duct using a balloon or basket and dilation of any gross stenosis (Figure 1). All patients with evidence of bacterial cholangitis by cultures from biliary fluids and no signs of sclerosing cholangitis receiving ERCP were treated with broad-spectrum antibiotics.

Statistical Analysis

Data are presented as median ± interquartile range. For matching purposes, the standardized difference (Cohen's D) with 95% upper and lower confidence intervals was calculated. The Mann–Whitney *U* test was used for direct comparison between the critically ill patients with sclerosing cholangitis and the matching group and the Fisher test when appropriate (Table 3). The statistical package R was used for all calculations.

RESULTS

Between April 2007 and March 2016, 8625 patients underwent operation using the heart-lung machine. By using