

# Gallbladder Disease in Cardiac Transplant Patients

## A Survey Study

Michael J. Englesbe, MD; Derek A. Dubay, MD; Audrey H. Wu, MD, MPH; Shawn J. Pelletier, MD; Jeffery D. Punch, MD; Michael G. Franz, MD

**Hypothesis:** Preemptive cholecystectomy in cardiac transplant patients with radiographic biliary pathology reduces the morbidity and mortality of biliary tract disease following heart transplantation compared with expectant management.

**Design and Setting:** Institutional survey at the University of Washington, Seattle.

**Patients:** Cardiac transplant recipients between January 1, 1992, and January 1, 2001.

**Main Outcome Measure:** Clinical course of patients who were diagnosed as having biliary tract disease following heart transplantation and were managed expectantly (observed) compared with the course of patients whose conditions were diagnosed and who underwent an operation.

**Results:** Sixty (35.7%) of 168 cardiac transplant patients were evaluated for biliary tract pathologic condition. Of the 71.7% (43 of 60 patients) who had an abnormal radiographic evaluation, 46.5% (20 patients) had surgery on their

biliary tract while the other patients were observed. Nine of the 23 patients who were followed up expectantly had cholelithiasis, 7 patients had gallbladder wall thickening, 5 patients had sludge in their gallbladder, and 2 had biliary dilatation. These patients were followed up for a mean±SD of 3.7±1.3 years; none developed biliary tract symptoms during this period. Cholecystectomies were completed for both emergent (7) and elective (14) indications. The mean±SD length of stay for patients who had emergent operations was 24.3±11.2 days, compared with 3.2±2.8 days for the patients who had elective operations. Seven (33%) of the 21 patients who had an operation had a significant complication and 1 patient died.

**Conclusions:** These data suggest that the morbidity of an elective cholecystectomy in cardiac transplant patients is significant and equivalent to the morbidity associated with emergent procedures. Expectant management of patients with radiographic evidence of biliary tract pathology discovered after transplantation was safe in this series.

*Arch Surg.* 2005;140:399-403

### Author Affiliations:

Department of Surgery, Section of General Surgery (Drs Englesbe, Dubay, Pelletier, Punch, and Franz), and the Department of Internal Medicine, Section of Cardiology (Heart Failure–Transplant) (Dr Wu), University of Michigan Health System, Ann Arbor.

**H**EART TRANSPLANTATION IS associated with an increased risk for the development of cholelithiasis.<sup>1</sup> Population-based studies suggest that the incidence of pancreaticobiliary disease is up to 17 times greater in patients receiving heart transplantation compared with the general population.<sup>2</sup> Several series report that 30% to 55% of patients screened after transplantation will develop cholelithiasis.<sup>3-7</sup> However, these studies likely overestimate the true incidence of posttransplant cholelithiasis owing to screening bias introduced by low incidence of posttransplantation biliary tract surveillance. Significant controversy exists regarding the need for comprehensive biliary tract screening after transplantation in asymptomatic patients. Unfortunately, there are limited and conflicting data in the surgi-

cal literature regarding optimal management of cardiac transplant patients with asymptomatic cholelithiasis. Treatment recommendations range from cholecystectomy only for symptomatic patients, to screening of all cardiac transplant patients for biliary tract pathology with preemptive cholecystectomy for those patients with cholelithiasis.<sup>3-5,8-10</sup>

## See Invited Critique at end of article

The argument for comprehensive screening of all cardiac transplant patients for biliary tract pathology and immediate cholecystectomy for those patients with cholelithiasis is based on the following 3 observations: there is a high prevalence of biliary tract disease in the heart transplant population; many pa-

**Table 1. Base Characteristics of 60 Cardiac Transplant Patients Who Had an Evaluation of Their Biliary Tract\***

Characteristic	Radiographic Study Result	
	Negative (n = 17)	Positive (n = 43)
Male	13 (76.5)	31 (72.1)
Age at transplant (mean ± SD), y	52.8 ± 11.8	45.4 ± 24.1
Diagnosis leading to cardiac failure		
Ischemic	8 (47.1)	28 (65.1)
Idiopathic	5 (29.4)	12 (27.9)
Other	3 (17.6)	3 (7.0)
Diabetes mellitus	5 (29.4)	14 (33.3)
Hypertension	14 (82.3)	38 (90.5)
Chronic obstructive pulmonary disease	3 (17.6)	6 (14.6)
Cause of death	1 (5.8)	6 (14.0)
Sepsis	0	2 (33.3)
Graft failure	0	1 (16.7)
Liver failure	0	1 (16.7)
Stroke	0	1 (16.7)
Renal cell cancer	0	1 (16.7)
Asystolic arrest	1 (100)	0

\*There were no significant differences between the group with a positive result and the group with an abnormal result for baseline characteristics. Data are given as the number (percentage) of patients unless otherwise indicated.

**Table 2. Clinical Presentation of 60 Cardiac Transplant Patients Who Were Evaluated for Biliary Pathology\***

Characteristic	Radiographic Study Result	
	Negative (n = 17)	Positive (n = 43)
Posttransplant presentation		
Abdominal pain	7 (41.2)	27 (62.8)
Nausea	2 (11.8)	15 (34.9)
Elevated serum bilirubin level	10 (58.8)	11 (25.6)†
Fever/abscess	1 (5.8)	3 (7.0)
Febrile	1 (5.8)	3 (7.0)
Atypical symptoms	2 (11.6)	7 (16.3)
Cirrhosis	0	3 (7.0)
Ascites	0	2 (4.7)
Serum creatinine level, mean ± SD, mg/dL		
Maximum	2.0 ± 0.9	2.1 ± 1.3
Mean	1.7 ± 0.6	1.8 ± 1.3
White blood cell count, mean ± SD, ×10 <sup>3</sup> /μL	7.5 ± 3.7	7.6 ± 4.9
Albumin level, mean ± SD, ng/mL	3.7 ± 1.0	3.8 ± 0.5
Underwent surgery	1 (5.8)	20 (46.5)†

SI Conversion: To convert serum creatinine values to micromoles per liter, multiply by 88.4.

\*Data are given as the number (percentage) of patients unless otherwise indicated.

†*P* < .05 vs negative study group.

tients develop symptomatic biliary tract disease shortly after transplantation; and there is substantial morbidity and mortality associated with urgent biliary tract operations in this population. Using the framework of these 3 observations, the aim of this study was to specifically address whether preemptive cholecystectomy in the asymptomatic cardiac transplant patients reduces the morbidity

and mortality of biliary tract disease following heart transplantation compared with expectant management.

## METHODS

Approval for this study was obtained through the University of Washington Institutional Human Subjects Committee, Seattle. Data were collected retrospectively and entered in “de-identified” research records. The medical records of all adults cardiac transplant recipients treated at the University of Washington Medical Center between January 1, 1992, and January 1, 2001, were reviewed to identify patients who were evaluated for biliary tract pathology. Data obtained included demographic information (gender and age at transplantation), baseline clinical information (type of disease leading to end-stage heart failure, medical comorbidities, ejection fraction, renal function, and liver function), data on general clinical course (immunosuppressive regimen, length of stay, and cause of death), and information specific to the biliary tract disease (method of diagnosis, age at time of diagnosis, imaging results, pathology reports, and operative reports). A positive imaging study was defined as cholelithiasis, choledocholithiasis, gallbladder wall thickening determined to be “significant” by an attending radiologist, sludge in the gallbladder, or biliary tract dilatation. Perioperative morbidity and mortality were limited to 30 days following a biliary operation. An emergent operation was defined as surgery within 24 hours of diagnosis or admission to the hospital. Atypical symptoms are defined as no abdominal pain, nausea, or vomiting.

Baseline characteristics were compared using the Fisher exact test for dichotomous variables and the Wilcoxon rank sum test for continuous variables. Statistical analysis was performed using SAS version 8.0 (SAS Institute, Cary, NC).

## RESULTS

One hundred eighty-three patients underwent heart transplantation between January 1, 1992, and January 1, 2001. Fifteen patients had a cholecystectomy prior to heart transplantation and are excluded from all analyses. An imaging study of the biliary tract was done in 60 (35.7%) of the 168 posttransplantation patients. Forty-nine of these patients were referred for imaging owing to suspicion of biliary tract disease, while 11 had an imaging study for other indications and biliary tract findings were noted incidentally. An abnormal radiographic study was found in 43 (71.6%) of 60 posttransplantation patients who underwent imaging. Twenty-one (35%) of the 60 patients who underwent imaging had a biliary tract operation following transplantation.

The baseline characteristics of the 60 patients who had an evaluation of their biliary tract following their cardiac transplantation are listed in **Table 1**. There were no significant differences in the baseline characteristics between the groups with an abnormal and normal radiographic study.

The mean ± SD age at the time of diagnosis of biliary tract disease was 48.7 ± 21.1 years. The mean ± SD interval between transplantation and the first abnormal study was 619.1 ± 799.2 days. Nine of 43 posttransplantation patients had an initial ultrasonogram that was negative for cholelithiasis, but the patients later developed cholelithiasis. The mean ± SD interval between the normal and ab-

**Table 3. Of the Patients Who Had an Abnormal Radiographic Biliary Tract Study, Comparisons Between Those Who Had Surgery vs Those Who Did Not Have Surgery on Their Biliary Tract\***

Characteristic	Patients With Positive Radiographic Result	
	Who Were Observed (n = 23)	Who Underwent Surgery (n = 20)
Male	15 (65.2)	16 (80.0)
Age at transplantation, mean ± SD, y	47.3 ± 20.8	43.3 ± 27.9
Diabetes mellitus	7 (30.4)	7 (35.0)
Hypertension	19 (82.6)	19 (95.0)
Chronic obstructive pulmonary disease	6 (26.1)	0*
Cause of death	4 (17.4)	2 (10.0)
Sepsis	2 (50.0)	0
Graft failure	1 (25.0)	0
Liver failure	0	1 (50.0)
Stroke	0	1 (50.0)
Renal cell cancer	1 (25.0)	0
Posttransplantation presentation		
Abdominal pain	10 (43.5)	17 (85.0)†
Nausea	6 (26.1)	9 (45.0)
Elevated serum bilirubin level	4 (21.1)	7 (35.0)
Febrile	2 (8.7)	1 (7.1)
Fever/abscess workup	3 (13.0)	0
Atypical symptoms	5 (21.7)	2 (10.0)
White blood cell count, mean ± SD, ×10 <sup>3</sup> /μL	7.9 ± 4.9	7.3 ± 5.2

\*Data are given as the number (percentage) of patients unless otherwise indicated.

†*P* < .05.

normal study was 903 ± 800.7 days. The clinical characteristics of the 60 patients who had an evaluation of their biliary tract are listed in **Table 2**. Patients with a negative study were more likely to have an elevated serum bilirubin level (58.8% vs 26.8%, *P* = .01). As expected, patients with an abnormal result were more likely to undergo an operation (46.5% vs 5.8%, *P* = .004). Immunosuppressive medications used included cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine sodium, and corticosteroids. Immunosuppressive regimen was not associated with either a positive radiographic study or need for an operation.

Of the 43 patients who had an abnormal radiographic evaluation, 20 patients (46.5%) had surgery on their biliary tract while the other 23 were observed. The characteristics of patients who had surgery were compared with patients who did not have an intervention (**Table 3**). As expected, patients with abdominal pain were more likely to have an operation (43.5% vs 85.0%, *P* = .01). Nine of the 23 patients who were followed up expectantly had cholelithiasis, 7 patients had gallbladder wall thickening, 5 patients had sludge in their gallbladder, and 2 had biliary dilatation. These patients were followed up for a mean of 3.7 ± 1.3 years and none developed biliary tract symptoms during this period. Four of these 23 patients who were clinically followed up died. The causes of death include graft failure, renal cell cancer, fungal sepsis (pulmonary), and sepsis from a liver abscess. The patient with the liver abscess had diffuse gall-

**Table 4. Characteristics of the 21 Cardiac Transplant Patients Who Had Biliary Surgical Procedures Performed\***

Laparoscopic cholecystectomy	19 (90.4)
Exploratory/open cholecystectomy	1 (4.8)
Exploratory laparotomy	1 (4.8)
Emergent	7 (33.3)
Complications	7 (33.3)
Length of stay, median (intraquartile range)	3.0 (1.0-6.0)
Indications for intervention	
Symptomatic cholelithiasis	14 (66.6)
Acute cholecystitis	3 (14.3)
Acute cholecystitis, cholangitis	1 (4.8)
Biliary pancreatitis	3 (14.3)
Symptomatic choledocholithiasis	1 (4.8)
Pathology available (n = 18)	
Chronic cholecystitis	9 (50.0)
Acute cholecystitis	1 (5.6)
Stones	15 (83.3)

\*Data are given as the number (percentage) of patients unless otherwise indicated.

bladder wall thickening along with heart failure and a patent biliary system by nuclear scan. The abscess contained *Fusobacterium* and was not thought to be associated with biliary tract pathology at autopsy.

Nineteen laparoscopic cholecystectomies were completed for both emergent (7/7) and elective (12/14) indications (**Table 4**). Two open cholecystectomies were also done. None of the 108 patients who did not have imaging of their biliary system required an operation. The mean length of stay for patients who had emergent operations was 24.3 ± 11.2 days compared with 3.2 ± 2.8 for the patients who had elective operations. Most of the patients who required emergent operations were admitted for other significant medical problems (ie, line sepsis, renal failure, or adult respiratory distress syndrome). The mean ± SD white blood cell count was significantly higher in patients who had an emergent operation (11.2 ± 6.9 vs 5.4 ± 2.4, *P* = .05). Emergent operations were not associated with more complications. Complications included biliary fistula, rupture of pancreatic pseudocyst, recurrent choledocholithiasis, bleeding (requiring transfusion), cerebrovascular accident, and acute renal failure. The biliary fistula and the bleeding occurred in 2 patients who had an open repair. The patient with the biliary fistula was cirrhotic and died from liver failure in the postoperative period.

Diabetic patients were significantly more likely to undergo an emergent procedure (71.4% [5/7]) rather than an elective operation (14.3% [2/14], *P* = .02). In addition, diabetic patients were more likely to present with abdominal pain (78.9% [15/19]) compared with nondiabetic patients (46.3% [19/41], *P* = .047).

#### COMMENT

This study confirms that cardiac transplant patients have a high prevalence of biliary tract disease. Radiographic evidence of biliary tract pathology (gallbladder wall thickening excluded) was found in 35 (20.8%) of 168 cardiac transplant patients. This is approximately twice the ex-

pected prevalence compared with North American groups of the same age, gender, and race.<sup>7</sup> Posttransplant cholelithiasis developed relatively early in the postoperative period. The mean time from heart transplant to diagnosis of cholelithiasis was  $1.69 \pm 2.19$  years. Several potential explanations for the increased prevalence of biliary tract disease in these patients include vagotomy with associated biliary stasis following transplantation, rapid weight loss following transplantation, obesity, atherosclerosis, and hemolysis.<sup>1</sup> There also are reports that cyclosporine therapy increases bile lithogenicity.<sup>11</sup> Our study did not establish any correlation between cholelithiasis and any specific immunosuppressant medication or regimen, although the small cohort of patients studied may limit the ability to detect any significant correlations.

Despite the high incidence of biliary tract pathology, there is no uniform consensus regarding the optimal management of cholelithiasis in cardiac transplant patients. Studies reported in the surgical literature seem to favor prophylactic cholecystectomy for patients identified with cholelithiasis preoperatively. Patients with asymptomatic cholelithiasis before transplantation commonly develop symptoms and often complications after transplantation. Two studies noted that biliary-associated symptoms developed within 2 years following heart transplantation in 58% and 45% of patients with documented asymptomatic gallstones before transplantation.<sup>10,12</sup> There also are several reports of patients developing complicated biliary tract pathologic conditions in the immediate postoperative period associated with a high mortality rate.<sup>3</sup> The other main argument favoring preoperative elective cholecystectomy is a significantly decreased perioperative morbidity compared with posttransplant elective or emergent cholecystectomy, despite the obvious impaired preoperative cardiac function.<sup>5</sup>

An equally controversial topic is the management of patients identified with asymptomatic cholelithiasis after heart transplantation. The main argument supporting prophylactic cholecystectomy is that there is substantial morbidity and mortality associated with emergent biliary operations in transplant patients. Graham et al<sup>4</sup> reported morbidity in 14% and mortality in 7% of renal and pancreas transplant patients who required emergent biliary tract interventions as well as a 20% graft loss. The Mayo Clinic experience documented a mortality rate of 29% in heart and lung transplant patients who required emergent biliary tract surgery in the posttransplantation period.<sup>5</sup> An older series reported 4 major complications and 3 eventual mortalities in 7 patients who had emergent cholecystectomies after cardiac transplantation.<sup>13</sup> Conversely, 17 patients had elective cholecystectomies (open) with no reported morbidity or mortality. The significant disparity between elective and emergent and morbidity and mortality outcomes have provided the rationale for preemptive cholecystectomy for patients with asymptomatic cholelithiasis after transplantation. However, most studies reporting high morbidity and mortality rates have a biliary tract screening of only 10% to 30%; thus, there is a selection bias or there is a significant cohort of transplant patients with asymptomatic cholelithiasis who do not go on to develop complications. There is a relative scarcity of data available re-

garding the natural history of asymptomatic cholelithiasis in postcardiac transplant patients.

This study identified 43 patients (25.6% of the transplantation population) with radiographic evidence of biliary tract pathology after cardiac transplantation. Most studies were performed for suspicion of biliary tract disease. Roughly half of the patients (21/43) were treated with cholecystectomy, while the remaining patients were followed up expectantly (22/43). Over a mean follow-up period of 3.7 years, none (n=9) of the patients with asymptomatic cholelithiasis managed conservatively developed biliary tract symptoms or needed an operative intervention on their biliary tree, suggesting that expectant management may be safe and appropriate for this patient population. Furthermore, this series confirms significant morbidity associated with all operative interventions on the biliary tree. Thirty-three percent of patients undergoing cholecystectomy developed significant complications. In contrast to other series, there was no significant increase in postoperative morbidity following emergent procedures compared with elective operations in our series.<sup>3,5,14</sup> Major complications incurred following elective cholecystectomy include rupture of pseudocyst on postoperative day 3, recurrent choledocholithiasis, cerebrovascular accident, and acute renal failure requiring hemodialysis. The only major outcomes difference between emergent and elective cholecystectomy was a significant increase in length of stay in the hospital.

Patients with an elevated serum bilirubin level were more likely to have a negative imaging study. Many of these patients were in the intensive care unit. They had biliary tract imaging for an increased serum bilirubin level, which was likely from cholestasis related to perioperative low blood flow to the liver. Venous congestion of the liver is also common in these patients and may be related to the significant numbers of ultrasonograms that were positive for gallbladder wall thickening. We consider gallbladder wall thickening a nonspecific finding in cardiac transplant patients, especially if they have poor graft function or if they are in the immediate postoperative period. In general, biliary tract pathology necessitating an operation did not occur in the immediate posttransplantation hospital course.

Diabetic patients may be an exception to expectant management of asymptomatic cholelithiasis after cardiac transplantation. Diabetic patients have a particularly aggressive course of biliary tract pathology. This series suggests that diabetic patients were more likely to present acutely with abdominal pain and require an emergent operation. Epidemiologic data and experimental series generally support the concept that diabetic persons in the general population have an increased risk of cholelithiasis.<sup>15-17</sup> In the past, prophylactic cholecystectomy was common in diabetic patients with asymptomatic gallstones. More recent literature has noted that many diabetic patients in the general population also remain asymptomatic and prophylactic cholecystectomies are no longer standard practice.<sup>14,18</sup> Diabetes mellitus and a heart transplantation are both significant risk factors that may synergistically increase morbidity and mortality following emergent cholecystectomy, suggesting that these patients may benefit from preemptive cholecystectomy.<sup>14,19</sup>

In summary, this series confirms that the development of postcardiac transplantation biliary tract pathology is common (20.8%), although the absolute risk of requiring an emergent operation is low (4.2%). These data suggest that the morbidity of an elective cholecystectomy in cardiac transplant patients is significant and equivalent to the morbidity associated with emergent procedures. Expectant management of nonacutely ill patients with cholelithiasis discovered after transplantation was safe in this series. Diabetic patients may benefit from preemptive cholecystectomy after cardiac transplant.

### LIMITATIONS

This study is limited by its small numbers and retrospective nature. To our knowledge, there are no prospective or randomized prospective trials addressing prophylactic cholecystectomy. The debate will continue until randomized, prospective trials are completed.

**Accepted for Publication:** September 30, 2004.

**Correspondence:** Michael J. Englesbe, MD, University of Michigan Health System, 2926 Taubman Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0331 (englesbe@med.umich.edu).

### REFERENCES

1. Steck TB, Costanzo-Nordin MR, Keshavarzian A. Prevalence and management of cholelithiasis in heart transplant patients. *J Heart Lung Transplant.* 1991;10:1029-1032.
2. Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreaticobiliary disease. *Ann Intern Med.* 1996;124:980-983.
3. Richardson WS, Surowiec WJ, Carter KM, Howell TP, Mehra MR, Bowen JC. Gallstone disease in heart transplant recipients. *Ann Surg.* 2003;237:273-276.
4. Graham SM, Flowers JL, Schweitzer E, Bartlett ST, Imbembo AL. The utility of prophylactic laparoscopic cholecystectomy in transplant candidates. *Am J Surg.* 1995;169:44-49.
5. Gupta D, Sakorafas GH, McGregor CG, Harmsen WS, Farnell MB. Management of biliary tract disease in heart and lung transplant patients. *Surgery.* 2000;128:641-649.
6. Girardet RE, Rosenbloom P, DeWeese BM, et al. Significance of asymptomatic biliary tract disease in heart transplant recipients. *J Heart Transplant.* 1989;8:391-399.
7. Diehl AK. Epidemiology and natural history of gallstone disease. *Gastroenterol Clin North Am.* 1991;20:1-19.
8. Lord RV, Ho S, Coleman MJ, Spratt PM. Cholecystectomy in cardiothoracic organ transplant recipients. *Arch Surg.* 1998;133:73-79.
9. Mueller XM, Tevæarai HT, Stumpe F, et al. Gastrointestinal disease following heart transplantation. *World J Surg.* 1999;23:650-656.
10. Peterseim DS, Pappas TN, Meyers CH, Shaeffer GS, Meyers WC, Van Trigt P. Management of biliary complications after heart transplantation. *J Heart Lung Transplant.* 1995;14:623-631.
11. Stone BG, Udani M, Sanghvi A, et al. Cyclosporin A-induced cholestasis: the mechanism in a rat model. *Gastroenterology.* 1987;93:344-351.
12. Milas M, Ricketts RR, Amerson JR, Kanter K. Management of biliary tract stones in heart transplant patients. *Ann Surg.* 1996;223:747-764.
13. Sekela ME, Hutchins DA, Young JB, Noon GP. Biliary surgery after cardiac transplantation. *Arch Surg.* 1991;126:571-573.
14. Aucott JN, Cooper GS, Bloom AD, Aron DC. Management of gallstones in diabetic patients. *Arch Intern Med.* 1993;153:1053-1058.
15. Chapman BA, Wilson IR, Frampton CM, et al. Prevalence of gallbladder disease in diabetes mellitus. *Dig Dis Sci.* 1996;41:2222-2228.
16. Jorgensen T. Gall stones in a Danish population: relation to weight, physical activity, smoking, coffee consumption, and diabetes mellitus. *Gut.* 1989;30:528-534.
17. De Santis A, Attili AF, Ginanni Corradini S, et al. Gallstones and diabetes: a case-control study in a free-living population sample. *Hepatology.* 1997;25:787-790.
18. Schwesinger WH, Diehl AK. Changing indications for laparoscopic cholecystectomy: stones without symptoms and symptoms without stones. *Surg Clin North Am.* 1996;76:493-504.
19. Begos DG, Franco KL, Baldwin JC, Lee FA, Revkin JH, Modlin IM. Optimal timing and indications for cholecystectomy in cardiac transplant patients. *World J Surg.* 1995;19:661-667.