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For further information about this article or if you need reprints, please contact:

Masih Shafa
Department of Cardiac Surgery
Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Tel: 09131710124

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Cholecystitis and its Risk Factors among Patients Undergoing Coronary Artery Bypass Grafting

[1]Daryoush Javidi and [2]Masih Shafa

The aim of this study was to assess the incidence of cholecystitis and its risk factors in patients undergoing Coronary Artery Bypass Grafting (CABG). In a cohort study, 574 patients undergoing CABG in Dr. Shariati Hospital from March 2003 to March 2004 were enrolled. In patients with cholecystitis signs and symptoms, ultrasonography and Liver Function Tests (LFTs) were performed. All the patients were followed for six months following the surgery. In 6 patients (1.06%) cholecystitis occurred, all during hospitalization. There were no significant differences in mean of age, BMI, CPB and cross clamp time, both sexes and patients with three vessels involvement and low cardiac output frequencies between patients with or without cholecystitis. In bivariate analysis, Frequency of patients with diabetes (83.33 vs. 12.16% with OR 36.10; 95% CI 4.16-313.67), hyperlipidemia (83.33 vs. 29.87% with OR 11.74; 95% CI 1.36-101.23) and postoperative biliary colic (83.33 vs. 3.58% with OR 70.54; 95% CI 8.03-619.53) were significantly higher in patients with cholecystitis than others. Also elevation of LFTs, Inotropic and IABP usage were significantly higher in patients with cholecystitis (All p = 0.01). When all variables were modeled using multivariable logistic regression analysis, a significant association was revealed between diabetes mellitus and post CABG cholecystitis (p = 0.01). All the patients with cholecystitis were treated by medical strategies including IV fluids, GI resting and broad spectrum antibiotics and no patients need surgical interventions. The presence of preoperative diabetes, hyperlipidemia, postoperative biliary colic, inotropic usage, elevation of LFTs and IABP could be significantly more frequent in patients with postoperative cholecystitis, although in multivariable analysis, diabetes mellitus was only detected as a significant risk factor of post CABG cholecystitis. Medical treatments for management of post-CABG cholecystitis carry acceptable results, advocating more studies.

Key words: Cholecystitis, CABG, medical treatment, prognosis

[1]Department of Cardiac Surgery, Dr. Shariati Hospital Complex, Tehran University of Medical Sciences, Tehran 14197, Iran
[2]Department of Cardiac Surgery, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

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INTRODUCTION

Gastrointestinal problems are infrequent but serious complications of cardiac surgery, with high rates of morbidity and mortality. Predictors of these complications are not well developed and the role of fundamental variables remains controversial (Zacharias *et al*., 2000).

The growing prevalence of cardiac surgeries has led to increase the frequency of surgical complications and mortalities. The most common GI complications are upper GI bleeding (due to gastritis or ulcer), pancreatitis, cholecystitis, perforation, ischemia of intestines and mesentery and paralytic ileus (Egleston *et al*., 1993; Huddy *et al*., 1991) Acute cholecystitis is the second most common (after GI bleeding) complication following cardiac surgeries. Its prevalence has been reported from 0.2 to 0.5%. (Egleston *et al*., 1993; Huddy *et al*., 1991).

In spite of the vast studies performed to evaluate GI complications of cardiac surgeries, acute cholecystitis has not been studied alone in this entity. The purpose of this study was to investigate the incidence of cholecystitis and its risk factors in patients undergoing Coronary Artery Bypass Grafting (CABG).

MATERIALS AND METHODS

After approval of medical ethics committee of Tehran University of Medical Sciences, 574 patients who underwent CABG in Shariati Hospital from March 2003 to March 2004 were enrolled in a cohort study.

The patients with a history of cholecystectomy and the patients who underwent any other simultaneous surgeries such as valve replacement, etc. were excluded from the study.

Demographic variables including age, gender, BMI (Body Mass Index), history of diabetes mellitus and hyperlipidemia (total cholesterol of more than 200 mg dL^{-1} or LDL more than 130 mg dL^{-1}) were assessed prior to operation. Cardiac output was determined based on the Ejection Fraction (EF) of the left ventricle measured by angiography. The Ejection fraction of less than 35% was assumed as low cardiac output. The presence of gallstones was evaluated by ultrasonography prior to operation.

Other variables such as cardiopulmonary bypass time (CPB time) and aortic cross clamp time were recorded during operation. Post-operative use of inotropic drugs or Intra-aortic Balloon Pump (IABP) was also recorded.

Presence of the symptoms (e.g., RUQ or epigastric pain with possible radiation to the right upper part of the back or interscapular area, biliary colic, fever, anorexia, nausea, vomiting) and the signs of cholecystitis (e.g., focal RUQ tenderness and/or guarding, RUQ mass, positive Murphy sing) was our indication to perform an ultrasonography and measuring AST, ALT, Alkaline phosphates, WBC and bilirubin. Verifying the diagnosis (verification by signs and symptoms of cholecystitis, ultrasonography (presence of stones, gallbladder wall thickness, pericholecystic fluid, ultrasonographic Murphy sing, cystic duct obstruction, gall bladder enlargement) and mild elevation of alkaline phosphates, transaminases and rise of bilirubin to less than 4 mg dL^{-1} and leukocytosis of 12.000 or more) we initiated the conservative treatment including IV fluid therapy, bowel rest and broad-spectrum antibiotics during the observation the patients. The patients underwent surgery if their pain aggravated or they experienced complications of cholecystitis (e.g., perforation, gangrene, cholangitis) during the observation.

The rest of the patients were followed for the signs and symptoms of cholecystitis at 1, 4, 12, 24 weeks after operation.

Data are expressed as mean±SD or number of patients. Means were compared using Mann-Whitney or independent samples t-test. For categorical data analysis Chi-square test or Fischer's exact test were utilized. In addition, multivariable logistical regression analysis was performed to take account of compounding factors and determine which factors were most likely to independently affect outcome. Statistical calculations were performed utilizing SPSS version 12.0. Differences were considered significant at $p<0.05$.

RESULTS

Nine patients were excluded because of a history of cholecystectomy and the remaining 565 patients were studied.

The mean age of the patients was 57.32±9.71. There were 424 men (75.04%) in our study. Five hundred forty nine patients (97.16%) underwent on-pump CABG while the remaining 16 patients had off-pump operation. Eighteen patients (3.19%) needed IABP after operation. Pre-operation studies indicated the presence of gallstones in 45 patients (7.96%). There were no significant differences in the means of age, BMI, frequency of 3-vessel involvement or more and diabetes mellitus in patients with or without gallstones. However, frequency of male patients, hyperlipidemia and biliary colic was significantly higher in patients with gallstones (Table 1).

Cholecystitis occurred in 6 patients (1.06%) during hospitalization. Five cases of these patients (83.33%) had gallstones. None of these patients were NPO for more than 12 h. There were no significant differences in the

Table 1: The comparison of means and frequencies of different variables in patients with and without gallstones (in the form of mean±standard deviation or number (%)

Variable	Patients with gallstones	Patients without gallstones	p-value	OR (CI 95%)
No.	45	520	-	-
Mean age	56.53±10.32	57.39±9.67	0.59	-
BMI	27.09±4.69	27.39±5.09	0.68	-
Male Gender	42 (93.30%)	382 (73.46%)	0.01	5.06 (1.54-16.58)
3-vessel involvement and more	44 (97.78%)	458 (88.08%)	0.05	-
Diabetes mellitus	8 (17.78%)	65 (12.50%)	0.35	-
Hyperlipidemia	37 (82.22%)	135 (25.96%)	0.01	13.19 (5.99-29.03)
Biliary Colic	39 (86.67%)	3 (0.58%)	0.01	1120.16 (269.78-4651.01)

Table 2: The comparison of the means or frequencies of the variables in patients with and without cholecystitis after CABG (in form of mean±SD or number (%)

			Bivariate		Multivariable*	
Variable	Patients with cholecystitis	Patients without cholecystitis	OR (95% CI)	p-value	OR (95% CI)	p-value
Mean age (year)	58.33±7.42	57.31±9.74	-	0.75	-	-
BMI	26.14±2.37	27.39±5.08	-	0.55	-	-
CPB time (min)	123.33±34.54	124.20±32.90	-	0.95	-	-
Cross clamp time (min)	64.00±19.31	80.21±29.04	-	0.10	-	-
Female Gender	1 (16.67%)	140 (25.04%)	-	0.99	-	-
-3-vessel involvement and more	6 (100.00%)	496 (88.73%)	-	0.99	-	-
Diabetes Mellitus	5 (83.33%)	68 (12.16%)	36.10 (4.16-313.67)	0.01	22.10 (2.02-241.18)	0.01
Hyperlipidemia	5 (83.33%)	167 (29.87%)	11.74 (1.36-101.23)	0.01	-	0.21
Use of inotropic drugs	6 (100.00%)	232 (41.50%)	Immeasurable	0.01	-	0.99
Use of IABP	2 (33.33%)	16 (2.86%)	16.97 (2.89-99.49)	0.01	-	0.08
Biliary colic	5 (83.33%)	37 (6.62%)	70.54 (8.03-619.53)	0.01	-	0.99
Gallstones	5 (83.33%)	40 (7.16%)	64.88 (7.40-568.76)	0.01	-	0.99
Rise of liver enzymes	6 (100.00%)	23 (4.11%)	Immeasurable	0.01	-	0.71
Low cardiac output	1 (16.67%)	47 (8.41%)	-	0.41	-	-

*Multivariable analysis was performed using logistic regression models adjusted for age, sex and other variables with $p<0.05$ in bivariate analysis

means of age, BMI, CPB time, cross clamp time, distribution of both genders, frequency of 3-vessel involvement or more and low cardiac output in patients with or without acute cholecystitis (Table 2). However the presence of diabetes mellitus (83.33 vs. 12.16% with, OR 36.10; 95% CI 4.16-313.67), hyperlipidemia (83.33 vs. 29.87% with, OR 11.74; 95% CI 1.36-101.23) and post-op biliary colic (83.33 vs. 3.58% with, OR 70.54; 95% CI 8.03-619.53) were significantly higher in patients with cholecystitis. Use of inotropic drugs (100 vs. 41.5%) and IABP (100 vs. 4.11%) and rise of liver enzymes (33.33 vs. 2.86%) were also significantly higher in patients with cholecystitis (All $p = 0.01$).

When all variables were modeled using multivariable logistic regression analysis, a significant association was revealed between diabetes mellitus and post CABG cholecystitis (OR 22.10, 95% CI 2.02-241.18, $p = 0.01$). The multivariable logistic regression model adjustments were made for age, sex and all variables with $p<0.05$ in their bivariate analysis including: diabetes mellitus, hyperlipidemia, use of inotropic drugs and IABP, biliary colic, gallstones and rise of liver enzymes.

All patients with cholecystitis were managed conservatively and none of them needed surgery. Cholecystitis did not occur in any patients after the hospital discharge and during the follow-up period. Ten patients died in the one year period of our study (5 men and 5 women) due to non-GI reasons.

DISCUSSION

Cholecystitis happened in 6 patients (1.06%) which yielded a higher result than similar studies that had reported the prevalence of cholecystitis after cardiac surgery as 0.2-0.5%. (Egleston *et al*., 1993; Huddy *et al*., 1991). Simic *et al.* (1999) showed that GI complications happen in 1.4% of the patients after cardiac surgery.

Our study indicated that the prevalence of gallstones in patients above 60 who undergo cardiac surgery was about 15% which was similar to the study performed by Massarrat *et al.* (2001) (12.5% in men and 24.5% in women).

Furthermore, our study revealed that the prevalence of male gender, hyperlipidemia and biliary colic was significantly higher in patients with gallstones. Bortnichak *et al.* (1985) suggested that the higher prevalence of gallstones in men can be due to inappropriate lipid profile. They also concluded that male patients with gallstones might be at a greater risk for coronary artery disease and have to be monitored for this. Zhou (1990) also stated that synergistic effects of lipid metabolism imbalance and prescription of certain drugs in patients with gallstones imposes a great risk of cardiovascular diseases on them.

On the contrary to the study performed by Inoue and Mishima (1988) that indicated a prevalence of 90% for acalculus cholecystitis, 83.33% of the patients with cholecystitis had gallstones in our study.

Male to female ratio was 5:1 in our study which was similar to the results of Inoue and Mishima (1988) which was 2.8:1.

This study did not find a significant difference in demographic variables including mean age, gender and BMI in patients with and without acute cholecystitis.

There have been a variety of studies investigating the GI complications following cardiac surgeries suggesting different risk factors including history of GI disorders, long CPB time, decrease in visceral perfusion due to hypotension, valvular surgery and using vasopressors (Gonzalez Ojeda *et al*., 1999; Ohri *et al*., 1991).

The results of the present study revealed no significant differences in mean of CPB time and cross clamp time in patients with or without cholecystitis Musleh *et al.* (2003) indicated that use of CPB does not alter the incidence of GI complications. Moreover, Simic *et al.* (1997) showed that the type of surgery and use of CPB cannot change the incidence of post-op GI complications. However, prevalence of diabetes mellitus, hyperlipidemia and biliary colic was significantly higher in patients with acute cholecystitis which is congruent with other studies that suggest the increased risk with diabetes mellitus and hyperlipidemia.

Our results also revealed that although the GI complications might be masked by use of narcotics (to induce analgesia after operation) and muscle relaxants and sedatives in patients undergoing mechanical ventilation, biliary colic and rise of liver enzymes were observed in all patients with cholecystitis.

This study indicated that inotropic drugs were used in all patients with cholecystitis which is congruent with studies that assume inotropic drugs as an important factor in pathogenesis of cholecystitis (Gonzalez Ojeda *et al*., 1999; Ohri *et al*., 1991) Furthermore, use of IABP was significantly (33.33 vs. 2.86%) higher in patients with cholecystitis. This fact in addition with higher use of inotropic drugs suggests a more compromised hemodynamics in patients with cholecystitis. These results are in accordance with other studies. Other studies have also presented ischemia of abdominal viscera as an influential factor in pathogenesis of cardiac post-op complications (Christenson *et al*., 1994; D'Ancona *et al*., 2003; Zacharias *et al*., 2000).

Since, all of the patients with cholecystitis in this study, after 12 h of experiencing NPO situation have been recovered; we could not assess the effect of NPO duration on the management of cholecystitis. However, some researchers including Kelm *et al.* (1991) assume cholecystitis as a multi-factorial complication whose risk factors include transfusion, dehydration, narcotics, shock and PEEP (Positive end expiratory pressure).

Gately and Thomas (1983) have also indicated that long fasting, transfusion, mechanical ventilation and vascular disorders are predisposing factors for cholecystitis. Moreover Musleh *et al.* (2003) have introduced renal dysfunction, advanced age, prior history of GI surgery and use of CPB as risk factors of GI complications after cardiac surgeries.

Cholecystitis can be managed conservatively (using IV fluids, bowel rest and broad-spectrum antibiotics), though it mainly needs surgery because of high risk of ischemic damage (Sakakibara *et al*., 1998). Some studies have yielded successful results using medical treatment. For example Gately and Thomas (1983) managed a small group of cholecystitis patients conservatively with great success. There were no patients in need of surgery in our study. Although cholecystitis is a severe complication with a mortality rate of 10-50%, all our patients were treated successfully by conservative therapy. But Kelm *et al*. (1991) had 2 cases of death among their 6 patients.

The findings of our survey however, should be interpreted within the limitations of the study. The lack of cholecystitis cases compared with controls was the main limitation of the current study, although the low frequency of cholecystitis after CABG reported in the literatures (0.2-0.5%) could be a reason for this situation. Regarding the prospective method of our cohort, to have more cases for evaluation, maybe a retrospective study should be designed.

However, the higher frequency of cholecystitis after CABG as a surgical complication which was revealed in our survey compared with other studies (1.2 vs. 0.2-0.5%), could be attributed to the following reasons; first, maybe our patients with coronary artery disease that being affected by cholecystitis after CABG, had some risk factors more than diabetes mellitus which could not be assessed in this survey and further studies should be performed in the future to find them. Second, may be more diagnostic evaluation for post CABG cholecystitis such as laboratory and ultrasonographic investigations as well as accurate physical examinations in the current study could lead to increase the sensitivity of diagnosis.

Finally, the present study revealed that prevalence of diabetes mellitus, hyperlipidemia, post-op biliary colic, rise of liver enzymes and use of inotropic drugs and IABP are significantly higher in patients with cholecystitis. Although in multivariable analysis a

significant association was only observed between diabetes mellitus and post CABG cholecystitis. Furthermore, the patients with cholecystitis were successfully treated by medical therapy.

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