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Constrictive Pericarditis after Open Heart Surgery: A 20-Year Case Controlled Study

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ABSTRACT

Background: Constrictive pericarditis is a rare complication of open heart surgery (OHS), but little is known regarding the etiologic determinants, and prognostic factors. The purpose of this study was to investigate clinical predictors and long term prognosis of post-operative constrictive pericarditis (CP).
Methods: Using the Myocardial Infarction Data Acquisition System database, we analyzed records of 142,837 patients who were admitted for OHS in New Jersey hospitals between 1995 and 2015. Ninety-one patients were hospitalized with CP 30 days or longer after discharge from OHS. Differences in proportions were analyzed using Chi square tests. Controls were matched to cases for demographics, surgical procedure type, history of OHS, and propensity score. Cox proportional hazard models were used to evaluate the risk of all-cause death. Log-rank tests and Cox models were used to assess differences in the Kaplan-Meier survival curves with and without adjustments for comorbidities.
Results: Patients with CP were more likely to have history of valve disease (VD, $p < 0.001$), atrial fibrillation (AF, $p = 0.024$) renal disease (CKD, $p = 0.028$), hemodialysis (HD, $p = 0.008$), previous OHS ($p < 0.001$). Patients with CP compared to matched controls had a higher 7-year mortality ($p < 0.001$). This difference became statistically significant at 1-year after surgery.
Conclusion: CP is a rare complication of OHS that occurs more frequently in patients with VD, AF, CKD, HD, multiple OHS, and it is associated with an unfavorable long-term prognosis. Given the large number of OHS performed every year, the results highlight the need for clinicians to recognize and properly manage this complication of OHS.

1. Introduction

First described in 1669 by Richard Lower, constrictive pericarditis (CP) is a syndrome of pericardial inflammation and fibrosis that results in impaired ventricular filling and reduced cardiac output [1,2]. In 1972, Kendall and colleagues first reported CP as a complication following coronary artery bypass graft surgery (CABG) [3]. Since then, CP has become a well-recognized, albeit rare, clinical phenomenon following open heart surgery (OHS) resulting from scarring and consequent loss of the normal elasticity of the pericardial sac. It is estimated that OHS accounts for approximately 20% of all cases of CP [4–6].

The annual number of US adult cardiac surgeries exceeds 200,000, and although the percentage of patients who develop CP is small, the recognition and management of these patients is clinically relevant [7]. Little is known regarding the etiologic determinants, and prognostic factors for postoperative CP. The aim of this study was to investigate risk factors associated with this condition, and the long-term prognosis of CP after OHS.

2. Methods

Using the previously validated Myocardial Infarction Data Acquisition System (MIDAS) database, a case-control comparison study was

Abbreviation: AF, atrial fibrillation; CABG, coronary artery bypass graft surgery; CKD, chronic renal disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HD, hemodialysis; HF, heart failure; HTN, hypertension; ICD-9, international classification of diseases, ninth revision; IHD, ischemic heart disease; OHS, open-heart surgery; CP, constrictive pericarditis; VD, valve disease.

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conducted analyzing the records of 142,837 patients who had OHS in New Jersey hospitals between 1995 and 2015. MIDAS is a database that includes demographics, co-morbidities, procedures, length of stay, and disposition in patients who were discharged with a cardiovascular diagnosis from non-Federal NJ hospitals [8]. Cases were patients (n = 91) who did not have a history of CP of any etiology, and had open heart surgery (coronary bypass graft, valve surgery or both; ICD-9 procedural codes 35 and 36), developing CP 30 days or longer after discharge from OHS requiring hospitalization. Controls were patients based on demographics, history of OHS, type of surgical procedure, and propensity score, who did not develop CP at any time after discharge. Patients were excluded from the study if they had: history of cancer, history of radiation to the chest, OHS and CP diagnosis at the same admission, CP diagnosed less than 30 days after OHS, or were younger than 18 years old.

Means, medians and standard deviations were calculated for continuous variables, and frequency distributions were used for categorical variables. Differences in proportions among the categorical variables were analyzed using Chi-square tests and Fisher's exact test for low expected counts. A Cox proportional hazard model was used to identify factors associated with time to develop CP development that was calculated from the OHS date to admission date for CP. The survival curves were compared by bootstrapping the area under the curves.

We performed propensity score matching cases to 3 controls using logistic regression and verified that the matching was balanced in the covariates. The model included demographics, procedures, and the following comorbid conditions ischemic heart disease (IHD), hypertension (HTN), atrial fibrillation (AF), diabetes mellitus (DM), chronic renal disease (CKD), chronic obstructive pulmonary disease (COPD), valve disease (VD), anemia, heart failure (HF), and hemodialysis (HD). The matching procedure consisted of a combination of exact matching on gender, race, history of OHS, and type of surgical procedure, and approximate matching on age (±3 years) and admission year (±2 years) and propensity score (±0.0005). The controls were matched to cases with the condition that they were still alive at the time the cases developed CP in order to account for the bias caused by the cases surviving until the development of CP.

To compare the survival curves between the matched cases and controls a log-rank test was applied using all-cause death as response. Time to death was calculated starting from the OHS date. A cox proportional hazard model was used to adjust for the 10 comorbid conditions and was clustered by the matching group.

3. Results

The incidence of CP after OHS in this study was 0.06%. For the unmatched dataset, the mean age for the case group was 66 (±11) years, and for the control group 66 (±12) years. Age, gender, and race were not statistically different between the groups. Among the comorbidities, AF, CKD, VD, HD and the number of OHS procedures showed significant difference between the groups (Table 1). Similar results were observed using a Cox model.

Table 2 compares the type of surgical procedures between cases and unmatched controls. From this table, the odds of developing CP after a valve procedure were 2.8 times higher (95% C.I. (1.7–4.5), $p < 0.001$) than the odds of CABG alone. If the procedure was CABG and valve, the odds were 2.4 times higher than of developing CP after CABG alone (95% C.I. (1.2–4.3), $p = 0.003$). There was no statistically significant difference between CABG with valve versus valve alone. If the patient had more than one OHS, the odds were 3.8 (95% C.I. (1.9–7.1), ($p < 0.001$) times more likely to develop CP. The median number of days (n = 1225) from CABG to CP admission was twice as long as the median number of days from valve (n = 616) and four time as long as both (n = 283).

Matched patients with CP compared to matched controls had a higher 7-year mortality (unadjusted $p < 0.001$; adjusted $p < 0.001$) and these differences started to be seen at 1 year after OHS (unadjusted $p < 0.002$; adjusted $p < 0.009$, Fig. 1A). Once patients were admitted with CP diagnosis, profound differences in mortality were seen at 30 days (unadjusted $p < 0.001$; adjusted $p = 0.001$, Fig. 1B). The rates of comorbid conditions between the cases and controls were similar (Table 3).

Of the 91 cases with CP, seventeen had pericardiectomy, 5 died in the hospital, and 8 died within 7-years after discharge. Out of the 74 who did not have pericardiectomy, 5 died in the hospital, 37 died within 7-years after discharge ($X^2 = 1.498$, p-value+0.221). The median number of days from CP admission to the pericardiectomy was 7 days. The median number of days from CP admission to death was 975 days (1369 days) for the patients who did not have a pericardiectomy (bootstrap p-value-0.263). However, the sample size limits the statistical power to come to valid conclusions of survival after pericardiectomy.

Table 1
Demographics, comorbidities and procedures of patients Who Developed vs. those Who Did Not Develop CP after OHS.

	CP	No CP	P-Value
	(n = 91)	(n = 142,746)	
Mean Age (±SD) (Years)	66 ± 11.3	66 ± 12.1	0.965
GENDER			
Male	61 (67%)	95,180 (67%)	>0.999
Female	30 (33%)	47,566 (33%)	>0.999
RACE			
White	79 (87%)	115,693 (81%)	0.204
Black	6 (7%)	9638 (7%)	>0.999
Other	6 (7%)	17,415 (12%)	0.141
Ischemic heart disease	71 (77%)	119,488 (84%)	0.185
Hypertension	48 (53%)	83,806 (59%)	0.294
Atrial fibrillation	37 (41%)	41,883 (29%)	0.024
Diabetes mellitus	32 (35%)	40,385 (28%)	0.181
Renal disease	17 (17%)	15,632 (11%)	0.028
Chronic lung disease	14 (15%)	20,148 (14%)	0.844
Valve disease	56 (62%)	46,332 (32%)	<0.001
Anemia	27 (30%)	39,200 (27%)	0.723
Heart failure	26 (29%)	35,049 (25%)	0.442
Drug abuse	5 (5%)	10,838 (8%)	0.577
Hemodialysis	5 (5%)	2177 (2%)	0.008
One OHS Procedure	80 (87%)	137,351 (96%)	<0.001
Two or more OHS	12 (13%)	5395 (4%)	<0.001

CP = constrictive pericarditis; OHS = open heart surgery.

Table 2
Type of surgical procedure in patients Who Developed vs. those Who Did Not Develop CP after OHS.

Variable	Total n = 142,837	CP	No CP	P-Value
		n = 91	n = 142,746	
CABG*	96,279	40 (44%)	96,239 (67%)	<0.001
Valve**	28,522	33 (36%)	28,489 (20%)	<0.001
CABG + Valve	18,036	18 (20%)	18,018 (13%)	0.058

* CABG – coronary artery bypass graft surgery; CP-constrictive pericarditis.
** Repair or replacement of valves; OHS-open heart surgery.

4. Discussion

Constrictive pericarditis is a rare complication of OHS. The estimated incidence of CP after OHS has reported rates of 0.2% to 3%, recognizing that the true incidence is difficult to ascertain [5,6,9,10]. In this large, contemporary, case-controlled study, we found an incidence of 0.06%, a rate significantly lower than the previously reported. The low incidence may be related because in this study we only included patients requiring hospitalization, and the possibility that mild cases were treated as outpatients. The disease has an indolent nature, and not infrequently mistaken as congestive heart failure. Cases of transient constrictive physiology after OHS have been recently reported, but most of these cases resolve spontaneously [11,12].

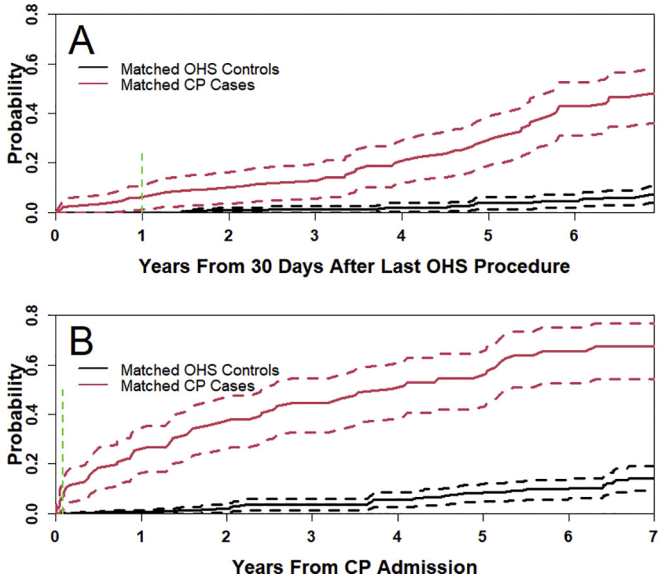

Fig. 1. A Kaplan Meier mortality curve for matched cases/controls from 30 days after last open heart surgery procedure. Cox Proportional Hazard: HR: 11.2; 95% C.I.: (5.9–21.1); p-value < 0.001. Green vertical line-differences in mortality curves at 1-year. B. Kaplan Meier mortality curve for matched cases/controls from CP admission date. Cox Proportional Hazard: HR: 9.8; 95% C.I.: (6.5–14.8); p-value < 0.001. Green vertical line-differences in mortality curves at 30 days. CP-constrictive pericarditis; OHS-open heart surgery.

Table 3
Demographics and clinical characteristics of matched pair Who Developed vs. those Who Did Not Develop CP after OHS.

	Matched CP Patients (n = 85)	Matched OHS Patients (n = 255)	P-Value
Mean Age (±SD) (Years)	68 ± 10.4	68 ± 10.4	0.967
GENDER			
Male	59 (69%)	177 (69%)	>0.999
Female	26 (31%)	78 (31%)	>0.999
RACE			
White	225 (88%)	75 (88%)	>0.999
Black	15 (6%)	5 (6%)	>0.999
Other	15 (6%)	5 (6%)	>0.999
Ischemic heart disease	68 (80%)	181 (71%)	0.137
Hypertension	47 (55%)	148 (58%)	0.752
Atrial fibrillation	36 (42%)	92 (36%)	0.366
Diabetes mellitus	31 (36%)	74 (29%)	0.249
Chronic lung disease	11 (13%)	37(15%)	0.857
Valve disease	52 (61%)	126 (48%)	0.052
Anemia	26 (31%)	68 (27%)	0.575
Heart failure	22 (26%)	71 (28%)	0.833
Drug abuse	5 (6%)	11 (4%)	0.767
Hemodialysis	4 (5%)	3 (1%)	NA
One OHS Procedure	78 (92%)	234 (92%)	>0.99
Two or more OHS	7 (8%)	21 (8%)	<0.099

CP = constrictive pericarditis; OHS = open heart surgery.

The factors leading to the encasement of the heart by a thick pericardium are not well known. Possible explanations have been 1) accumulation of blood in the pericardium, with fibrous degradation triggering an inflammatory response with development of fibrosis of the pericardium 2) use of warfarin 3) undrained pericardial effusions causing friction between the pericardium and epicardium particularly in patients with normal ejection fraction 4) pericardial irrigation with povidine-iodine which, similar to all antiseptics, may cause tissue injury 5) exposure to cardiopulmonary bypass causing the release of proinflammatory factors (tumor necrosis factor-alpha and interleukin) and growth factors (transforming growth factor β) [6,13–16] These studies have addressed surgical features and biological factors that might lead to the development of CP, however, the clinical predictors of CP after OHS are not well known. We found AF to be higher in the CP patients (41% versus 29% in OHS patients without CP). AF is an arrhythmia that requires the use of anticoagulation therefore increasing the risk of bleeding in the pericardial space. Another interesting finding is that CKD was an independent predictor of CP. The link may be related to the generalized inflammatory state associated with CKD [17,18]. Previous studies did not associate CP with any particular cardiac surgery. We found that valve procedures had 2.8 times higher odds of developing CP than CABG alone. Combined CABG and valve surgery had 2.4 times higher odds than CABG alone. Similar to other studies, we found that patients exposed to repeated OHS procedures had an increased risk of developing CP probably related to build-up of adhesions and fibrous tissue [6].

CP is considered a slowly progressing disease, and this concept arises from the time that tuberculosis and other infectious disease were the most common causes. However, CP after OHS is different, and the time of occurrence is variable. In the series of CP cases reported by Gaudino et al. the time elapsed between surgery to the presentation of CP varied from 3 weeks to 54 months (average 336 days) [6]. In our study, the range from CABG to CP development was 39 to 5644 days (median 1225); for valve it was 59 to 5322 days (median 616); and for both it was 35 to 3271 days (median 283). Therefore, it appears that it takes longer to develop CP after CABG compared to valve or combined surgery, and the reason for this difference is unclear.

Although CP is uncommon, when it occurs it was associated with an ominous prognosis. We found that compared to matched controls, patients that developed CP had significantly higher 7-year mortality, and these differences started as early as 1 year after OHS. When we consider the first hospitalization for CP compared to controls, the difference in mortality was seen much earlier starting at 30 days. At 7-years of follow-up, the group of patients undergoing pericardiectomy had 76% mortality and the ones treated with conservative management was 57%. One explanation for higher mortality in patients requiring pericardiectomy could be that they were a sicker population, and the delay in the surgical intervention. Perioperative mortality for pericardiectomy for CP has been reported between 2.3% to 16% however, this relatively low perioperative risk changes to a poor prognosis in the long term [16–26]. For example, Gillespie et al. in 98 patients that had pericardiectomy after CABG reported an early mortality of 3% with a 5-year and 10-year mortality of 38% and 59% respectively [27]. This demonstrates that although in recent years the results for pericardiectomy have improved, the long-term prognosis is of concern, thus this procedure should be considered only for those patients that are highly symptomatic.

Although this study is a case-controlled matched study, it has the limitations of retrospective studies. The administrative database on which the study is based does not include surgical details, medications, echocardiography, and hemodynamic data. On the other hand, it has the strengths of including all adult patients age 18 years and older, in New Jersey who had OHS, long follow-up, and the analyses of clinical variables that might influence the development of CP. This is the first case-controlled study of patients with CP after OHS.

5. Conclusion

Constrictive pericarditis is a rare complication of OHS that occurs more frequently in patients with multiple OHS, valve surgery, AF, CKD, HD, and it is associated with an unfavorable long-term prognosis. The large number of OHS performed every year highlights the need for clinicians to recognize and properly manage this complication of OHS.

Declaration of Competing Interest

None.

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