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Contemporary Etiologies, Risk Factors, and Outcomes after Pericardiectomy

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Abstract

Background—The leading causes of constrictive pericarditis have changed over time leading to a commensurate change in the indications and complexity of surgical pericardiectomy. We evaluated our single-center experience to define the etiologies, risk factors, and outcomes of pericardiectomy in a modern cohort.

Methods—We retrospectively reviewed our institutional database for all patients who underwent total or partial pericardiectomy. Demographic, co-morbid, operative, and outcome data were evaluated. Survival was assessed by the Kaplan-Meier method. Multivariable Cox proportional hazards regression models examined risk factors for mortality.

Results—From 1995–2010, 98 adults underwent pericardiectomy for constrictive disease. The most common etiologies were idiopathic (n=44), postoperative (n=30), and post-radiation (n=17). Total pericardiectomy was performed in 94 cases, most commonly through a sternotomy (n=93). Thirty-three cases were redo sternotomies, 34 underwent a concomitant procedure, and 34 required cardiopulmonary bypass. Overall in-hospital, 1-year, 5-year, and 10-year survival rates were 92.9%, 82.5%, 64.3%, and 49.2%, respectively. Survival differed sharply by etiology with idiopathic, postoperative, and post-radiation 5-year survivals of 79.8%, 55.9%, and 11.0%, respectively (p<0.001). On multivariable analysis, only the need for cardiopulmonary bypass (HR: 21.2, p=0.02) was predictive of 30-day mortality while post-radiation etiology (HR: 3.19, p=0.02) and hypoalbuminemia (HR: 0.57, p=0.03) were associated with increased 10-year mortality.

Conclusions—Although survival varies significantly by etiology, pericardiectomy continues to be a safe operation for constrictive pericarditis. Post-radiation pericarditis and hypoalbuminemia are significant risk factors for decreased long-term survival.

Keywords

Pericardium

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INTRODUCTION

Severe inflammation of the pericardium can result in constrictive pericarditis. The resulting cardiac dysfunction can lead to varying degrees of heart failure and eventually death.[1–3] Although there are no prospective studies comparing medical and surgical management, pericardiectomy is an accepted treatment to improve patient hemodynamics.[4] Additionally, pericardiectomy has been shown to improve patient symptoms and prevent disease progression and death.[1,3,5]

Pericarditis requiring pericardiectomy can result from a number of diverse etiologies. Several studies have shown that long-term survival is dramatically affected by etiology. [1,3,6–8] One study reported that 7-year survival ranged from 88% for patients with an idiopathic etiology to 27% for those with a post-radiation etiology.[3] Additionally, recent studies suggest that the most common causes of pericarditis requiring pericardiectomy continue to change.[1,3,4,8,9] In particular, the incidence of tuberculosis-related pericarditis has declined dramatically, while the incidence of postoperative and post-radiation pericarditis continue to increase.[8] We undertook this study to characterize our modern pericardiectomy experience and better define the impact of etiology on survival. Additionally, we sought to characterize how the etiology of pericarditis is changing and its impact on outcomes.

MATERIAL AND METHODS

Study Design

We conducted a retrospective review of our prospectively maintained cardiac surgery database. Our study included all patients who underwent a total or partial pericardiectomy for constrictive pericarditis from January 1995 through December 2010. Patients with effusive disease and those who underwent pericardial window procedures were excluded. Our institutional review board approved this study.

We examined pertinent variables in our database, including: demographics and comorbidities (age, gender, race, hypertension, diabetes, and coronary artery disease); preoperative laboratory results (sodium, creatinine, total bilirubin, albumin, and liver function tests); etiology of pericarditis; and operative data (total or partial pericardiectomy, concomitant procedure, need for cardiopulmonary bypass, and operative approach).

Definitions

The distinction between constrictive and effusive pericarditis was based on operative findings. Pericarditis etiology was determined by the patient's history. Patients with a history of prior chest radiation were defined as having post-radiation pericarditis. Patients with a history of prior cardiac surgery were defined as having postoperative pericarditis. Additional possible etiologies included infectious (bacterial or fungal), asbestos-related, autoimmune, hemopericardium, tumor-related, metabolic, pneumopericardium, and tuberculosis. Patients who could not be classified in any of these groups were considered to have idiopathic pericarditis.

Similar to previous studies, pericardial calcification was defined as any calcification seen on preoperative imaging including chest x-rays, computed tomography, fluoroscopy, or cardiac magnetic resonance imaging (MRI).[3,8]

Surgical Technique

In accordance with previous literature, a total pericardiectomy was defined as the removal of all anterior pericardium between the phrenic nerves from the great vessels superiorly down to and including the diaphragmatic surface.[1,3,4,8] Both the parietal and visceral pericardial peels were removed. Removal of less pericardium constituted a partial pericardiectomy. Total pericardiectomy was attempted in all cases unless it was not technically feasible. The same approach was utilized regardless of etiology.

Outcomes

Three etiologies of pericarditis predominated (idiopathic, postoperative, and post-radiation) and provided the basis for primary stratification. The primary outcome examined was survival (in-hospital, 1-year, 5-year, and 10-year). Institutional survival data was supplemented with data from the Social Security Death Index. Secondary outcome measures included the need for cardiac reoperation, prolonged mediastinal drainage, stroke, renal failure, cardiac arrhythmias (atrial fibrillation, junctional rhythms, heart block), and infectious complications (sternal wound infection, pneumonia, septicemia).

Statistical Analysis

We compared baseline characteristics by etiology using the Student's t-test or analysis of variance (ANOVA) for continuous variables and Chi-square or Fisher's exact test for categorical variables as appropriate. For associations found to be significant according to ANOVA, post hoc pair-wise comparisons were performed using the Tukey-Kramer method. For associations found to be significant by Chi-square testing, post hoc pair-wise comparisons were performed using univariate logistic regression.

Survival was calculated by the Kaplan-Meier method and survival comparisons were performed using the log-rank test. To further analyze survival, multivariable Cox proportional hazards regression models were constructed. To construct our multivariable models, all independent covariates were tested in univariate fashion. Variables associated with the outcome measure on exploratory analysis ($p < 0.20$), those with biological plausibility, and those previously reported in the literature to be significant were incorporated in a forward and backward stepwise fashion into the multivariable models. The likelihood ratio test and Akaike's information criterion were utilized in a nested model approach to identify which model had the greatest explanatory power. Since different covariates may affect short and long-term survival differently, one model was constructed for short-term survival (30-days) and one model was constructed for longer survival (1, 5, and 10-years).

For all analyses, values of $p < 0.05$ (2-tailed) were considered statistically significant. Mean values are displayed with standard deviations and median values are displayed with their interquartile ranges (IQR). Hazard ratios (HR) are presented with their 95% confidence intervals (CI). Statistical analysis was performed using Stata 12.0 (StataCorp, College Station, TX).

RESULTS

Cohort Statistics

From 1995 through 2010, 111 adult patients underwent a pericardiectomy, 98 (88.3%) for constrictive and 13 (11.7%) for effusive pericarditis. Patients with effusive disease were excluded, leaving 98 patients in our final cohort. The mean age of the cohort was 50 ± 16 years and 60 (61.2%) were male. The most common etiologies were idiopathic ($n=44$, 48.4%), postoperative ($n=30$, 33.0%), and post-radiation ($n=17$, 18.7%; Table 1).

All patients had an echocardiogram as part of their work up. Thoracic CT scanning was utilized selectively. Cardiac MRI was utilized in 31 (32.0%) patients when the diagnosis was still unclear. Twenty-nine of these MRIs revealed characteristic findings of pericarditis: a variable degree of pericardial thickening, evidence of pericardial-cardiac adhesions, and characteristics of constrictive cardiac physiology.

A total pericardiectomy was performed in 94 (95.9%) patients. The operative approach was a median sternotomy in 93 (94.9%) patients, a left anterolateral thoracotomy in 6 (6.1%) patients, and a bilateral thoracotomy in 2 (2.0%) patients. Thirty-three (33.7%) patients had undergone at least one prior sternotomy and 34 (34.7%) patients underwent a concomitant procedure (coronary artery bypass grafting (CABG), n=6; valve repair/replacement, n=13; combined CABG/valve procedure, n=3; tumor resection, n=6; maze procedure, n=2; combined aortic valve replacement and septal myectomy, n=1; surgical ventricular restoration, n=1; and other, n=2). The majority of patients did not require cardiopulmonary bypass (n=64, 65.3%) and of the 34 who did, 27 (79.4%) underwent a concomitant procedure.

Although the numbers are small, when we divide the study period into 2 eras of equal length, the proportion of patients with post-radiation pericarditis has declined relative to patients with an idiopathic or postoperative diagnosis (Figure 1).

In the entire cohort, there were 42 (42.9%) deaths with a median follow-up of 4.0 [IQR: 1.3–7.4] years. Overall in-hospital survival was 92.9%. 1, 5, and 10-year survival were 82.5%, 64.3%, and 49.2%, respectively (Figure 2).

Baseline Characteristics

When stratified by the three primary etiologies, there were some notable differences in baseline characteristics (Table 2). Patients with idiopathic pericarditis tended to have less hypertension and less coronary artery disease than patients with postoperative or post-radiation pericarditis. Idiopathic patients were also more likely to have calcific pericarditis. Patients with post-radiation pericarditis were more likely to undergo a concomitant procedure with their pericardiectomy and thus also more likely to need cardiopulmonary bypass. Not surprisingly, patients with postoperative pericarditis were more likely to have undergone prior cardiac surgery though nearly a quarter of post-radiation patients also underwent a redo sternotomy at the time of the pericardiectomy.

Outcomes

Regardless of etiology, unadjusted short-term survival was similar at 30-days (Idiopathic: 95.5%, postoperative: 96.7%, and post-radiation: 94.1%, p=0.9). However, at 1-year, although survival was similar between patients with an idiopathic or postoperative etiology, post-radiation patients had significantly lower survival (Idiopathic: 90.9%, postoperative: 86.7%, and post-radiation: 58.8%, p=0.005). Unadjusted long-term survival differed sharply by etiology at both 5-years (Idiopathic: 79.8%, postoperative: 55.9%, and post-radiation: 40.3%, p=0.004) and 10-years (Idiopathic: 66.5%, postoperative: 55.9%, and post-radiation: 11.0%, p<0.001; Figure 3). Again, post hoc analysis revealed that post-radiation pericarditis was associated with significantly lower survival compared to both idiopathic and postoperative pericarditis at both time points. Although postoperative pericarditis tended to have lower survival than idiopathic pericarditis, this difference did not reach statistical significant at 30-days (p=0.9), 1-year (p=0.6), 5-years (p=0.06), or 10-years (p=0.2).

On multivariable analysis, pericarditis etiology was also not associated with increased 30-day mortality (Table 3). Only the need for cardiopulmonary bypass (HR: 21.2 [1.81 – 248.4], p=0.02) was associated with increased early mortality. Compared to idiopathic

pericarditis, post-radiation pericarditis was associated with a significantly increased hazard of mortality at 1-year (HR: 4.50 [1.01 – 20.17], $p=0.049$), 5-years (HR: 3.40 [1.11 – 10.44], $p=0.03$), and 10-years (HR: 3.19 [1.19 – 8.55], $p=0.02$; Table 4). Although postoperative pericarditis tended to be associated with an increased hazard of mortality, these differences did not reach statistical significance at 1-year (HR: 1.75 [0.35 – 8.79], $p=0.5$), 5-years (HR: 1.79 [0.63 – 5.11], $p=0.3$), or 10-years (HR: 1.51 [0.59 – 3.93], $p=0.4$). At all three later time points, only lower serum albumin levels were also associated with increased mortality. There was also a strong trend toward increased mortality in patients with elevated total bilirubin levels. No factors were protective.

Perioperatively, 6 (6.1%) patients required reoperation for bleeding and 8 (8.2%) developed prolonged mediastinal drainage. One (1.2%) patient suffered a stroke and 12 (12.2%) patients developed renal failure. Twenty-seven (27.6%) patients developed a cardiac arrhythmia requiring treatment and 12 (12.2%) developed an infectious complication, with some patients having multiple infections (2 sternal wound infections, 8 pneumonias, 5 septicemia).

COMMENT

In this study, we report our contemporary indications, risk factors, and outcomes for pericardiectomy. In this modern, 16-year experience, we found intermediate and long-term outcomes differed dramatically by etiology with post-radiation patients continuing to have a dismal outcome. Moreover, hypoalbuminemia and hyperbilirubinemia were predictors of adverse short and long-term outcomes. Additionally, although the etiologic distribution of our patients has changed over time, with a decreasing number of post-radiation patients, short and long-term survival appears to be similar regardless of the era of operation.

Previous studies have reported widely ranging outcomes following pericardiectomy, with perioperative mortality ranging from 5.6% to as high as 11%. [1,3,4,8,10] In our series, we report an in-hospital mortality of 7.1% which is similar to several modern series. [1,3,4,8] As has been previously reported, [3] we found dramatically different intermediate and long-term survival depending on etiology. When stratified by etiology, on both univariate and multivariable analysis, post-radiation pericarditis was associated with significantly lower 1, 5, and 10-year survival than idiopathic or postoperative pericarditis. Additionally, although it did not reach statistical significance, postoperative pericarditis tended to be associated with lower survival than idiopathic pericarditis but better survival than post-radiation pericarditis. These findings are consistent with previous studies suggesting poor long-term survival for patients with post-radiation pericarditis. [1,3,8] The outcomes of radiation-induced pericarditis are so dismal, that some have suggested pericardiectomy is futile for this patient population. [6,7] However, our series demonstrates acceptable perioperative mortality with a 1-year survival over 50%, despite a higher percentage requiring CPB, suggesting that at least half of these patients may benefit from this operation. Therefore, in carefully selected patients with radiation-induced pericarditis we still offer pericardiectomy.

On multivariable analysis, post-radiation pericarditis was significantly associated with an increased hazard of intermediate and long-term mortality. Not surprisingly, the need for cardiopulmonary bypass was also associated with increased 30-day mortality, likely denoting either a more difficult pericardiectomy or a sicker patient requiring a concomitant procedure. Interestingly, our models found increasing bilirubin and hypoalbuminemia to also be predictive of mortality. Increasing bilirubin is likely a surrogate for the degree of heart failure caused by severe pericarditis. Such heart failure likely results in cardiac cirrhosis secondary to a combination of decreased hepatic perfusion and increased hepatic congestion. Several previous studies have found increased total bilirubin to be predictive of

mortality after heart transplantation and thus its association with increased mortality after pericardiectomy is not surprising.[11,12] Similarly, several previous reports have suggested that hypoalbuminemia may be a powerful predictor of malnutrition and overall poor health in the cardiac surgery population.[13,14] Thus patients with severe hypoalbuminemia have increased perioperative and long-term mortality.

The impact of pericardial calcification on outcomes is controversial. Although some studies have identified pericardial calcification as a significant risk factor for increased mortality, several have not.[8,10,15,16] In the largest US series to date, Bertog et al.[3] did not find pericardial calcification to be associated with increased mortality. In our study, calcific pericarditis was not a risk factor for either early or late mortality.

In analyzing our case mix over the study period, we found that post-radiation pericarditis has comprised a decreasing percentage of our population over time. Although there has certainly been an increase in the number of cases of postoperative pericarditis in our series and others, [8] we also observed a decrease in the absolute numbers of radiation-induced pericarditis requiring pericardiectomy. Whether this represents an actual decrease in the incidence of post-radiation pericarditis, secondary to increasingly narrow fields of radiation and better shielding, or whether this represents some type of selection or referral bias warrants further investigation. Interestingly, this change in case mix has not resulted in a change in overall survival.

The optimal surgical approach is controversial. While some authors have suggested that complete pericardiectomy is best performed via a median sternotomy,[17,18] others have argued in favor of a left anterolateral thoracotomy.[4,10,19,20] In our series, a median sternotomy was utilized in over 90% of cases and a total pericardiectomy was performed in over 95% of the cases. In the largest series to date, Chowdhury et al.[4] found that total pericardiectomy was associated with increased survival compared to partial pericardiectomy. In their series, the predominant surgical approach was an anterolateral thoracotomy. Thus, as others have suggested, it is not the surgical approach but rather the extent of pericardiectomy that is important.[1] We agree with previous reports that a total pericardiectomy should be performed whenever possible since it is associated with improved outcomes and prevents recurrence.[4] Therefore, although surgical approach is largely a matter of surgeon preference, we favor a median sternotomy as it facilitates excellent exposure to adequately perform a complete pericardiectomy.[3,4,19] Moreover, in cases requiring a concomitant procedure, a median sternotomy permits easy access for cardiopulmonary bypass. Although many of our patients required cardiopulmonary bypass, this was mostly secondary to a concomitant procedure. Thus we agree with others who have suggested that cardiopulmonary bypass is not necessary for a total pericardiectomy.[4,18] However, dense epicardial scarring can result in incidental ventriculotomies and thus preparation for emergent cardiopulmonary bypass is prudent.

Limitations

Our study is a retrospective study and despite our efforts to control for confounding data and selection bias, it is not possible to control for all confounders. Additionally, as a single-center study, our sample size is relatively small and thus susceptible to a type II error. Our findings should be considered in light of these limitations.

Although our cardiac surgery database is extensive, some variables are not captured well. In particular, tuberculosis skin test results cannot be extracted in a retrospective fashion. Tuberculosis is an uncommon etiology of pericarditis in the Western world. None of our patients showed clinical evidence for tuberculosis and the final pathology of all the patients

was negative for acid fast staining organisms and granulomatous inflammation. However, the absence of tuberculosis skin testing results is a limitation.

Conclusion

In conclusion, although survival varies significantly by etiology, pericardiectomy continues to be a safe operation for constrictive pericarditis. Post-radiation pericarditis, hypoalbuminemia, and hyperbilirubinemia are significant risk factors for decreased long-term survival. Finally, while the etiologic spectrum has changed over time, these changes have not affected outcomes.

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Figure 1. Etiologic distribution of pericardiectomy cases by era. Idiopathic etiology is depicted by the solid black bars. Postoperative etiology is depicted by shaded red bars. Post-radiation etiology is depicted by shaded blue bars. P-value determined by chi-square test.

Figure 2.
10-year Kaplan-Meier survival for all pericardiectomy patients.

time (years)											
<u>Number at risk</u>											
Idiopathic	44	39	34	29	27	23	20	15	13	12	10
Postoperative	30	26	19	18	12	11	10	9	7	7	6
Post-radiation	17	10	8	6	6	6	6	2	2	2	1

Figure 3. Kaplan-Meier survival stratified by etiology of pericarditis. Idiopathic etiology is depicted with a solid black line. Postoperative etiology is depicted with a dashed red line. Post-radiation etiology is depicted with a dashed blue line. P-value determined by the log-rank test.

Table 1

Etiology of Pericarditis

Cause	Constrictive
Idiopathic	44
Postoperative	30
Post-radiation	17
Autoimmune	1
Tumor	3
Infectious	1
Hemopericardium	1
Asbestos	1
Total	98

Table 2

Baseline Characteristics Stratified by Etiology

Variable	Idiopathic (n=44)	Postoperative (n=30)	Post- Radiation (n=17)	P-value*
Demographics and Co-Morbidities				
Age (years)	48 ± 17	52 ± 16	51 ± 13	0.6
Male gender, n (%)	30/44 (68%)	19/30 (63%)	7/17 (41%)	0.1
White ethnicity, n (%)	34/44 (77%)	25/30 (83%)	17/17 (100%)	
Black ethnicity, n (%)	9/44 (20%)	5/30 (17%)	0/17 (0%)	
Other ethnicity, n (%)	1/44 (2%)	0/30 (0%)	0/17 (0%)	0.3
Hypertension, n (%)	10/41 (24%)	17/30 (57%)	6/17 (35%)	0.02 ^a
Diabetes, n (%)	4/41 (10%)	9/30 (30%)	0/17 (0%)	0.01 ^{a,b}
Coronary artery disease, n (%)	2/42 (5%)	15/30 (50%)	4/17 (24%)	<0.001 ^{a,c}
Creatinine (mg/dL)	1.2 ± 1.2	1.8 ± 1.5	1.0 ± 0.3	0.1
Total bilirubin (mg/dL)	1.4 ± 1.6	1.1 ± 0.9	1.0 ± 0.8	0.5
Albumin (g/dL)	3.9 ± 0.6	4.0 ± 0.7	3.9 ± 0.8	0.7
Calcific, n (%)	17/44 (39%)	3/30 (10%)	6/17 (35%)	0.02 ^{a,b}
Operative data				
Total pericardiectomy, n (%)	42/44 (95%)	28/30 (93%)	17/17 (100%)	0.6
Concomitant procedure, n (%)	5/44 (11%)	13/30 (43%)	11/17 (65%)	<0.001 ^{a,c}
Need for CPB, n (%)	7/44 (16%)	14/30 (47%)	12/17 (71%)	<0.001 ^{a,c}
Median sternotomy, n (%)	43/44 (98%)	27/30 (90%)	15/17 (88%)	0.3
Redo sternotomy, n (%)	2/44 (5%)	27/30 (90%)	4/17 (24%)	<0.001 ^{a,b,c}

* P-value determined by ANOVA or chi-square or Fisher's exact test

^a Idiopathic different than postoperative by post hoc Tukey-Kramer test

^b Postoperative different than post-radiation by post hoc Tukey-Kramer test

^c Idiopathic different than post-radiation by post hoc Tukey-Kramer test

Abbreviation: CPB, cardiopulmonary bypass.

Table 3

Multivariable Cox Proportional Hazards Regression Model for 30-Day Mortality

Variable	Hazard Ratio [95% Confidence Interval]	P-Value
Idiopathic pericarditis	1 (Reference)	
Postoperative pericarditis	0.25 [0.02–3.51]	0.3
Post-radiation pericarditis	0.84 [0.06–12.75]	0.9
Other pericarditis	5.11 [0.31–84.36]	0.3
Age (per year)	1.01 [0.94–1.08]	0.9
Creatinine (per mg/dL)	1.30 [0.74–2.29]	0.4
Albumin (per g/dL)	0.30 [0.08–1.10]	0.07
Need for cardiopulmonary bypass	21.20 [1.81–248.44]	0.02

Table 4

Multivariable Cox Proportional Hazards Regression Model of 10-Year Mortality

Variable	Hazard Ratio [95% Confidence Interval]	P-Value
Idiopathic pericarditis	1 (Reference)	-
Postoperative pericarditis	1.51 [0.59–3.93]	0.4
Post-radiation pericarditis	3.19 [1.19–8.55]	0.02
Other pericarditis	1.95 [0.50–7.62]	0.3
Age (per year)	0.99 [0.98–1.03]	0.9
Male gender	0.72 [0.37–1.43]	0.3
Creatinine (per mg/dL)	1.03 [0.80–1.34]	0.8
Total bilirubin (per mg/dL)	1.26 [0.95–1.66]	0.1
Albumin (per g/dL)	0.57 [0.34–0.95]	0.03
Calcific pericarditis	0.62 [0.26–1.46]	0.3
Need for cardiopulmonary bypass	1.87 [0.84–4.14]	0.1