Constrictive Pericarditis: Etiology and Cause-Specific Survival After Pericardiectomy

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OBJECTIVES
We sought to determine the association of etiology of constrictive pericarditis (CP), pericardial calcification (CA), and other clinical variables with long-term survival after pericardiectomy.

BACKGROUND
Constrictive pericarditis is the result of a spectrum of primary cardiac and noncardiac conditions. Few data exist on the cause-specific survival after pericardiectomy. The impact of CA on survival is unclear.

METHODS
A total of 163 patients who underwent pericardiectomy for CP over a 24-year period at a single surgical center were studied. Constrictive pericarditis was confirmed by the surgical report. Vital status was obtained from the Social Security Death Index.

RESULTS
Etiology of CP was idiopathic in 75 patients (46%), prior cardiac surgery in 60 patients (37%), radiation treatment in 15 patients (9%), and miscellaneous in 13 patients (8%). Median follow-up among survivors was 6.9 years (range 0.8 to 24.5 years), during which time there were 61 deaths. Perioperative mortality was 6%. Idiopathic CP had the best prognosis (7-year Kaplan-Meier survival: 88%, 95% confidence interval [CI] 76% to 94%) followed by postsurgical (66%, 95% CI 52% to 78%) and postradiation CP (27%, 95% CI 9% to 58%). In bootstrap-validated proportional hazards analyses, predictors of poor overall survival were prior radiation, worse renal function, higher pulmonary artery systolic pressure (PAP), abnormal left ventricular (LV) systolic function, lower serum sodium level, and older age. Pericardial calcification had no impact on survival.

CONCLUSIONS
Long-term survival after pericardiectomy for CP is related to underlying etiology, LV systolic function, renal function, serum sodium, and PAP. The relatively good survival with idiopathic CP emphasizes the safety of pericardiectomy in this subgroup. (J Am Coll Cardiol 2004;43:1445–52) © 2004 by the American College of Cardiology Foundation

Constrictive pericarditis (CP) is a disease characterized by the encasement of the heart by a rigid non-pliable pericardium due to dense fibrosis and adhesions. This causes impaired diastolic cardiac function leading to heart failure manifested as systemic without pulmonary congestion (1). The natural history of this disorder remains unknown (2), and prospective studies comparing outcome for patients treated medically with patients undergoing pericardiectomy have never been performed. However, observational studies and case reports suggest that in most instances CP without surgical intervention causes a progression of symptoms and, frequently, early death (2). Furthermore, the overwhelming majority of operative survivors experience an improvement in functional class or quality of life (3–7). Hence, with rare exceptions, pericardiectomy is the treatment of choice for symptomatic CP.

In previous studies, long-term survival after pericardiectomy varied considerably (3,6,8–11). Moreover, even after the exclusion of patients with postradiation constriction, which is uniformly associated with poor outcome (3,6,12,13), data on long-term survival after pericardiectomy for CP remain inconsistent (3,5,6). This suggests that other etiologic subgroups may contribute to differences in survival.

Likewise, the impact of pericardial calcification (CA) on perioperative mortality and long-term outcome remains unclear. Ling et al. (14) found higher perioperative mortality for patients with CA, and in a study by Gimlette (15) CA was associated with poor postoperative outcome, whereas in other studies it was not (16,17).

Therefore, the purpose of this study was to determine long-term survival after pericardiectomy with particular emphasis on subgroup analysis, including the distinction of postsurgical and postradiation from idiopathic CP, and to determine the impact of CA on perioperative mortality and overall survival after pericardiectomy.

METHODS
All 163 patients who underwent pericardiectomy for surgically confirmed CP at the Cleveland Clinic Foundation from January 1, 1977, to December 31, 2000, and who had a valid U.S. Social Security number were identified through...
Abbreviations and Acronyms
- CA = pericardial calcification
- CAD = coronary artery disease
- CI = confidence interval
- CP = constrictive pericarditis
- LV = left ventricular
- PAP = pulmonary artery systolic pressure

the Cardiovascular Information Registry, a computer–based surgical registry. In addition to the information routinely collected for the registry, surgical reports and charts were systematically reviewed for data relating to etiology, presenting history, lab studies, and surgical details. Patients with recurrent pericarditis, pericardial effusion or tamponade, or tumor invasion into the pericardium were excluded. Survival was obtained through query of the Social Security Death Index, which has been shown to be highly specific (99.5%) and unbiased (18). The high sensitivity of this index has been reported elsewhere (19). The Cleveland Clinic Foundation institutional review board approved the study. The Cleveland Clinic Foundation institutional review board approved the study.

Definitions. Postsurgical constriction was defined as CP after prior cardiac surgery, postradiation constriction as CP associated with a history of mediastinal radiation, and miscellaneous constriction as constriction with a history of one or more conditions that have been associated with CP other than prior viral pericarditis, radiation, or surgery. Patients were classified into the idiopathic group if they did not qualify for any of the previous subgroups. Perioperative mortality was defined as death during the initial hospitalization or within 30 days following surgery. Phrenic-to-phrenic pericardiectomy was defined as wide excision of the pericardium anteriorly extending to both phrenic nerves and including the diaphragmatic pericardium. Incomplete pericardiectomy was defined as any pericardial excision that did not meet criteria for phrenic-to-phrenic pericardiectomy. Pericardial calcification was defined as calcification seen either with fluoroscopy or on chest x-ray. Left ventricular systolic function was determined by cineangiography or, if not available, by echocardiography. Function was defined as abnormal if it was reported to be abnormal by either cineangiography or echocardiography or if the ejection fraction was reported to be below 50%.

Statistical analysis. Categorical data, presented as frequencies and percentages, were compared using the chi-square or exact tests as appropriate. Exact tests were used if ≥25% of cells had expected counts of <5. Continuous variables, expressed as mean ± SD or median values, were compared by the Kruskall–Wallis test. Survival was estimated using the Kaplan–Meier method (20).

Cox proportional-hazards regression analyses were performed to assess the association of various causes of CP, CA, and other possible predictors on long-term survival. Because of the small number of deaths during follow-up, we were concerned about the possibility of model overfitting. This can occur when there are substantially fewer than 10 events per variable considered (21). Therefore, we used serial bootstrapping along with cluster analyses to reduce the number of candidate variables in an unbiased way.

Bootstrapping involves the generation of many new data sets by random sampling and replacement of the main cohort set (22,23). We generated 1,000 bootstrap resampled data sets with replacement and performed a stepwise Cox regression analysis on each one, identifying those variables that were retained at p < 0.05 level. Candidate variables included etiology of CP (with idiopathic as the reference group) and the variables listed in Table 1. Clusters of related variables were defined to allow for model reduction. Those variables or clusters of variables that entered at least 50% of models were considered for a second set of 1,000 bootstrap-based analyses. The resulting variables that entered at 50% of these models were then systematically assessed for important interactions along with other biologically plausible interactions. A final set of 1,000 bootstrap-based analyses used fixed Cox modeling to generate parameter estimates and a risk score for mortality.

The Cox proportional hazards assumption was confirmed by examination of weight Schoenfeld residuals (24). For all continuous variables, logarithmic, quadratic, and inverse transformations were tested for improved fit.

Impact of CA on survival was performed as a subgroup analysis. The many differences between the two groups were accounted for by using the propensity score analysis. We constructed a logistic regression model in which CA was the dependent variable and outcome played no part. This generated a propensity score: the probability that a person would have CA given the information provided by the variables. The propensity score was then included in a proportional hazards model (25), hence simultaneously adjusting for all the variables in the propensity score, to determine the true independent association of CA with mortality.

All data were analyzed with SAS version 8.2 (SAS Institute, Cary, North Carolina). Bootstrapping macros were written by one of us (E.H.B.) and are available from the authors upon request.

RESULTS

Etiology and clinical characteristics. Patients were classified into four subgroups based on etiology. Constrictive pericarditis was idiopathic or viral in 75 patients (46%), postsurgical in 60 patients (37%), secondary to prior mediastinal irradiation in 15 patients (9%), and miscellaneous in 13 patients (8%). Miscellaneous causes for constriction were tuberculosis in six patients, rheumatoid arthritis in two, systemic lupus erythematosus in two, prior chest trauma in one, Wegener’s granulomatosis in one, and purulent pericarditis in one. In patients with postsurgical constriction, the preceding surgery was coronary artery bypass surgery in
28 patients (47%), valve surgery in 14 patients (23%), a combination of both in 6 patients (10%), and miscellaneous in 12 patients (20%).

Miscellaneous surgeries were heart transplantation in three patients, Beck procedure in two, and open atrial septal defect repair, surgical interruption of Wolfe-Parkinson-White bypass tract, combined automatic implantable cardiac defibrillator implantation and coronary artery bypass surgery, and combined open atrial septal defect repair and valve surgery in one patient, respectively.

Baseline clinical characteristics according to the etiologic subgroup are listed in Table 1. Of note, idiopathic CP patients had lower rates of coronary artery disease (CAD) and higher rates of CA, whereas postsurgical CP patients were older and had higher rates of CAD and hypertension. Postradiation CP patients were younger. In patients with postradiation constriction, the median duration between pericardiectomy and preceding surgery was 16 months (range 2 months to 25 years). The majority of patients with postradiation constriction had radiation for Hodgkin’s disease (9 patients). The remainder underwent radiation for non-Hodgkin’s lymphoma (2 patients), breast cancer (2 patients), esophageal cancer (1 patient), and metastatic testicular cancer (1 patient). The median duration between prior radiation and pericardiectomy was 11 years (range 2 to 30 years). There was no significant association of pericardial calcification on fluoroscopy or chest X-ray and the presence of pericardial knock.

**Surgery.** Surgical approach is listed in Table 1. The majority (119 patients, 73%) underwent complete (phrenic-to-phrenic) pericardiectomy. Patients least likely to be treated with complete pericardiectomy were patients with postradiation constriction. The favored surgical approach (146 patients, 90%) was median sternotomy. Alternative approaches were bilateral thoracotomy in eight patients (5%), left anterolateral thoracotomy in seven patients (4%), sub-
mammary approach that was extended into a right lateral thoracotomy and eventually median sternotomy in two patients (1%) and left posterolateral thoracotomy in one patient (1%). Surgery or procedures in addition to pericardectomy were performed in 35 patients, coronary artery bypass surgery in 11 patients (7%), valve surgery in 4 patients (3%), combined coronary artery bypass surgery and valve surgery in 4 patients (3%), and miscellaneous in 16 patients (10%).

**Perioperative mortality.** One patient who had postradiation constriction was lost to follow-up after hospital discharge. Perioperative mortality, defined as death either within the hospital or within 30 days of surgery, was 6.1% (10 patients). By etiologic subgroup it was 2.7% in idiopathic constriction, 8.3% in postsurgical constriction, and 21.4% in postradiation constriction. Miscellaneous constriction had no deaths. Nine patients (5.5%) died in hospital and the causes of death were progressive heart failure in four patients, sepsis and renal failure in two patients, sepsis and respiratory failure in two patients, and arrhythmia in one patient.

**Long-term survival.** Median follow-up among survivors was 6.9 years (range 0.8 to 24.5 years). There were 61 deaths. A strong association was noted between presumed etiology of CP and mortality (Fig. 1). Patients with idiopathic disease had an excellent outcome (7-year Kaplan-Meier survival: 88%, 95% confidence interval [CI] 76% to 94%), whereas patients with postsurgical and postradiation disease had substantially worse survival rates (7-year survival rates 66% [95% CI 52% to 78%] and 27% [95% CI 9% to 58%], respectively).

The results of serial bootstrap-based Cox proportional hazards analyses are shown in Table 2. Independent predictors of death were radiation-induced disease, worse renal function, abnormal left ventricular (LV) systolic function, higher pulmonary artery systolic pressure (PAP), lower serum sodium level, and older age. The final Cox model performed well for risk stratification using the formula shown under Table 2. Figure 2 shows mortality according to tertiles of predicted risk, with a score of <9.9 having lowest risk, a score between 9.9 and 11.2 an intermediate risk, and those >11.2 the highest risk.

### Table 2. Multivariable Model of Mortality After Surgery for Constrictive Pericarditis: Results of Sequential Bootstrapping Cox Proportional Hazards Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Models Entered (1,000 Possible)</th>
<th>β Coefficient (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>998</td>
<td>3.3 (2.3 to 4.7)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)*</td>
<td>956</td>
<td>−1.6 (−2.4 to −1.0)</td>
</tr>
<tr>
<td>PA systolic pressure (mm Hg)†</td>
<td>786</td>
<td>0.6 (0.2 to 1.1)</td>
</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>708</td>
<td>0.8 (0.2 to 1.4)</td>
</tr>
<tr>
<td>Sodium (mg/dl)‡</td>
<td>639</td>
<td>0.9 (−0.1 to 2.4)</td>
</tr>
<tr>
<td>Age (yrs)§</td>
<td>522</td>
<td>0.6 (0.01 to 1.3)</td>
</tr>
</tbody>
</table>

*Postsurgical patients only, 1/creatinine. †(PA systolic pressure/40)², 410/(Sodium/140), §[(Age/50)²]. The precise model for predicting risk is: $h_i(t) = A_i(t) \exp{(3.04080 \times \text{radiation where } 0=\text{no and } 1=\text{yes}) + (-1.59094 \times \text{1/creatinine} \times \text{post-surgical disease where } 0=\text{no and } 1=\text{yes}) + (0.644457 \times \text{PA systolic pressure/40})^2 + (0.803423 \times \text{LV systolic dysfunction present where } 0=\text{no and } 1=\text{yes}) + (0.945918 \times [10/(\text{sodium/140})]) + (0.579352 \times [(\text{Age/50})^2])}$.

LV = left ventricular; PA = pulmonary artery.
The five-year death rate for patients who underwent pericardiectomy before 1990 was 19% and not significantly different from the five-year death rate of patients who underwent pericardiectomy thereafter (21%, log-rank chi-square 0.5, p = 0.48).

**Pericardial calcification and survival.** Complete radiologic records were obtained in 159 of the 163 patients. Of these 159 patients, there were 50 patients (31%) with and 109 patients (69%) without evidence of CA. Of the 50 patients with CA, 41 (82%) had idiopathic, 6 (12%) postsurgical, one (2%) postradiation, and 2 (4%) miscellaneous constriction. In contrast, of the 109 patients without CA, only 33 (30%) had idiopathic, 51 (47%) postsurgical, 11 (10%) postradiation, and 14 (13%) miscellaneous constriction. On univariate analysis, there was no significant difference in perioperative mortality in the two groups (p > 0.4). Patients with CA had better late survival (log-rank chi-square 6.09, p = 0.014, hazard ratio 0.442, 95% CI 0.227 to 0.860, p = 0.016). However, by Cox proportional hazards analysis, adjusting for the propensity score generated from the logistic model and the most important covariates, CA was not found to have an independent effect on survival (hazard ratio 0.913, 95% CI 0.408 to 2.043, p = 0.824).

**DISCUSSION**

Our study is one of the largest current series determining survival after pericardiectomy for CP. The results demonstrate that the etiology of CP has an important impact on long-term survival. It was excellent in the idiopathic and miscellaneous subgroups. In patients with postsurgical CP, survival was inferior to that of patients with idiopathic constriction but significantly better than that of patients with postradiation constriction. Apart from etiology, other independent predictors of overall survival include age, LV systolic dysfunction, PAP, creatinine, and serum sodium. By using these parameters, it is possible to assess outcome after pericardiectomy for constrictive pericarditis. Pericardial calcification was not an independent predictor of survival.

**Etiology.** In our current series, 45% of patients had idiopathic, 36% postsurgical, 9% postradiation, and 9% had miscellaneous CP (including 6 patients with tuberculous CP). This compares with 55% with idiopathic, 13% with postsurgical, 10% with postradiation, and 22% of patients with miscellaneous CP in previous studies (3-12,26-32) between 1977 and 2001 including a total of 1,129 patients. The high proportion of postsurgical CP (36%) in our study is due to the large number of cardiac surgeries performed at our institution (approximately 68,000 cardiac surgeries were performed between 1977 and 2000). Constrictive pericarditis as a complication of prior cardiac surgery occurred in 0.09% and is similar to prior estimates of 0.025% to 0.35% (5,27,29). In the postradiation subgroup, 11 patients (73%) received mediastinal radiation for lymphomas and 2 patients (13%) for breast cancer, which is similar to previous studies (3,5,6,8,10-13). The long duration between prior radiation and the need for pericardiectomy reflects the general experience. The median range between radiation and pericardiectomy was 13 years in the study by Ling et al. (3). Cameron
et al. (26) and McCaughan et al. (5) report a mean of seven years and a range of 15 months to 44 years, respectively.

Of note, there were three patients in our study who developed pericardial constriction after prior heart transplantation, which may reflect the comparatively large number of transplants performed at our institution. This complication has been described by Copeland et al. (33). Further, Roca et al. (34) describe two cases of CP after cardiac transplantation. Pericardial complications after heart transplantation, including CP, are uncommon but not unusual (35,36). Therefore, this complication should be recognized in the care of heart transplant patients.

**Perioperative mortality.** Perioperative mortality is 6% in our series. This is similar to a perioperative mortality of 5% in recent studies (3,4,7,9,31,37), including a total of 429 patients. The most frequent cause of death in the perioperative period in our study as well as in most prior studies is low-output heart failure (3,5,6,10,16,26,37). Perioperative mortality appears to be clearly related to etiology. The higher mortality associated with pericardiectomy for postradiation (21.4%) and postsurgical constriction (8.3%) is probably related to the fact that constriction is not the sole factor producing cardiac failure in these subgroups. Thus, even successful pericardiectomy does not always relieve their cardiac failure. Cardiac failure has been attributed to myocardial atrophy from prolonged constriction (2,5,38), residual constriction (2,39), or a concomitant myocardial process (5). However, myocardial atrophy secondary to constriction alone is uncommon, given the usually favorable outcome after pericardiectomy for idiopathic constriction. The best surgical approaches, partial versus total pericardiectomy and median sternotomy versus lateral thoracotomy, as well as the need for cardiopulmonary bypass, have been discussed with controversy (5,6,16,31,40). In our series there is no clear benefit for any particular surgical approach with regard to perioperative mortality or long-term survival.

**Overall survival.** Seven-year survival in the idiopathic and miscellaneous subgroups was excellent. Survival for patients with postsurgical constriction was inferior to that of patients with idiopathic constriction but significantly better than that of patients with postradiation constriction. The effects of radiation on cardiac structures, including premature CAD, concomitant myocardial constriction, and valvular abnormalities, are likely to have an adverse impact on perioperative mortality as well as overall survival irrespective of constriction. Furthermore, mediastinal fibrosis from prior radiation limits the extent of pericardial removal, frequently requires alternative surgical approaches, and complicates surgery and increases the likelihood of residual constriction. Other studies have also noticed an inferior long-term survival with postradiation constriction (3,6). Postsurgical CP patients, by virtue of their initial condition warranting heart surgery, are more likely to have CAD, valvular heart disease, and systolic LV dysfunction. These, in addition to the technical challenge of a reoperation, may adversely affect perioperative mortality and overall survival in postsurgical CP patients. By contrast, most patients with idiopathic CP have isolated pericardial constriction, and once pericardectomy is successfully done, the perioperative mortality and overall survival are excellent. Previous studies with patient populations having the smallest proportion of both postradiation and postsurgical constriction patients had the best overall survival (5,7,9).

Despite the long period covered, five-year outcomes were not significantly different between patients treated before and after 1990. This may reflect the unchanged surgical treatment in both time periods.

**Predictors of overall survival.** Independent predictors of overall survival include postradiation etiology, age, LV systolic dysfunction, PAP, creatinine, and serum sodium. We have explained the effects of radiation on the heart. High PAP may reflect the severity of constriction, concomitant myocardial dysfunction, or pulmonary pathology. The presence of abnormal LV systolic function may result from concomitant CAD, hypertension, or valvular heart disease. Previous studies have shown age (3), preoperative New York Heart Association class (4,6,7,11), and hepatic (11) and renal dysfunction (7) as predictors of overall survival.

We demonstrate that using age, prior radiation, LV systolic function, renal function, and serum sodium, it is possible to stratify patients with pericardial constriction undergoing pericardiectomy into three distinct risk groups with regard to survival. This emphasizes that, although etiology is a very important predictor of overall survival, other predictors need to be taken into account when predicting survival in patients with CP after pericardiectomy.

**Pericardial calcification and survival.** In our series, 31% of patients had radiographically demonstrated CA. This is similar to 38% in seven previous studies (3,5,7,9,27,31,32) with a total of 640 patients. Pericardial calcification was more commonly associated with idiopathic CP. This was shown previously (14), but its role in postoperative outcome remains unclear. Although CP was not associated with postoperative outcome in two studies (16,17), it has been implicated in other studies as a predictor of perioperative mortality (14) and postoperative outcome (15). In our analysis we found that CP was not a predictor of perioperative mortality. Likewise, after accounting for baseline differences between patients with and without calcification, it was not an independent predictor of overall survival.

**Study limitations.** Pericardial constriction is defined on the basis of physiologic findings demonstrated by echocardiographic parameters, magnetic resonance imaging, and right heart catheterization findings. To allow comparison with prior studies, we defined constriction by surgical findings that are difficult to quantify. Therefore, patients whose preoperative evaluation suggested CP might have been disqualified on the basis of surgical findings. Moreover, knowledge of preoperative findings may have biased the operator's findings and assessment at surgery. Second, it is conceivable that differences in physiologic properties...
among the etiologic subgroups, such as coexistent restriction, focal constriction, or different severity of constriction, may have accounted for differences in survival rather than etiology itself. However, this is difficult to evaluate in retrospect and, because of the long study interval (1977 to 2000), sophisticated imaging studies, such as cardiac magnetic resonance imaging, conventional and tissue Doppler imaging, and color M-mode Doppler imaging necessary to characterize these aspects were not available in all patients (41). Third, endomyocardial biopsy findings were not available in patients with postradiation constriction. This, in addition to physiologic parameters acquired by imaging, may be important to determine the contribution of a restrictive myocardial component in patients with prior mediastinal radiation and may help to predict outcome in this group. Furthermore, LV systolic function was determined by cineangiography or echocardiography in a semiquantitative fashion. A quantitative assessment with a uniform method may have more accurately predicted its impact on outcome.

Finally, the distribution of etiologies is specific to our institution, and therefore data may not be extrapolated to other settings such as developing countries. Moreover, there may be a selection bias because of the retrospective nature of the study.

Conclusions. Our results demonstrate that overall survival after pericardiectomy for CP differs significantly among the major etiologic subgroups and is best for patients with idiopathic and miscellaneous constriction, intermediate for postsurgical constriction, and poor for postradiation constriction. Using parameters such as LV systolic function, PAP, serum sodium, and creatinine, it may be possible to predict long-term survival after pericardiectomy. The excellent survival after pericardiectomy for idiopathic constriction emphasizes that, when an isolated entity, pericardial constriction can be treated safely with pericardiectomy. These results should be considered in the clinical management of patients with CP.

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