Constrictive Pericarditis in the Modern Era
Evolving Clinical Spectrum and Impact on Outcome
After Pericardiectomy

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Background—The clinical spectrum of constrictive pericarditis (CP) has been affected by a change in incidence of etiological factors. We sought to determine the impact of these changes on the outcome of pericardiectomy.

Methods and Results—The contemporary spectrum of CP in 135 patients (76% male) evaluated at the Mayo Clinic from 1985 to 1995 was compared with that of a historic cohort. Notable trends were an increasing frequency of CP due to cardiac surgery and mediastinal radiation and presentation in older patients (median age, 61 versus 45 years). Perioperative mortality decreased (6% versus 14%, \(P=0.011\)), but late survival was inferior to that of an age- and sex-matched US population (57±8% at 10 years). The long-term outcome was predicted independently by 3 variables in stepwise logistic regression analyses: (1) age, (2) NYHA class, and most powerfully, (3) a postradiation cause. Of 90 late survivors in whom functional class could be determined, functional status had improved markedly (2.6±0.7 at baseline versus 1.5±0.8 at latest follow-up \(P<0.0001\)), with 83% being free of clinical symptoms.

Conclusions—The evolving profile of CP, with increasingly older patients and those with radiation-induced disease in the past decade, significantly affects postoperative prognosis. Long-term results of pericardiectomy are disappointing for some patient groups, especially those with radiation-induced CP. By contrast, surgery alleviates or improves symptoms in the majority of late survivors. (Circulation. 1999;100:1380-1386.)

Key Words: pericarditis ■ prognosis ■ surgery

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Constrictive pericarditis (CP), although uncommon, commands substantial clinical interest because of the perceived potential for surgical cure. In the past 15 years, several reports have highlighted changes in the spectrum of CP in the United States, characterized chiefly by a declining incidence of tuberculous pericarditis and an increase in the frequency of cases resulting from therapeutic mediastinal radiation and cardiac surgery.1–3 Few data, however, exist on the impact of these changes on outcome after pericardiectomy. In addition, outcome analysis has focused predominantly on a mortality end point; markers for recurrent congestive heart failure (CHF) symptoms, for example, are unknown.

We hypothesized that the observed changes in the clinical spectrum of CP influence postoperative prognosis in the current era. Because the epidemiology of CP is strongly influenced by geography and referral bias, changes in disease patterns are most appropriately defined vis-à-vis a historic cohort from the same institution. Accordingly, we reviewed the cases of patients with proven CP evaluated at the Mayo Clinic in the past decade and identified contemporary trends in relation to 231 patients examined at our institution from 1936 through 1982.4

Methods

All patients with the diagnosis of CP in the medical and surgical indexes of the Mayo Clinic from January 1985 through June 1995 were screened. Only patients with CP confirmed at surgery or autopsy were included.

During this period, 135 patients were identified: 133 at surgery and 2 at autopsy. Case histories were reviewed, and clinical findings by a staff cardiologist were recorded. Follow-up of patients was done with a mailed questionnaire, hospital records, and telephone calls to the patients, their relatives, and their physicians. The circumstances and causes of death recorded in death certificates were verified whenever possible with the patient’s physician or the coroner who certified the death. Concomitant medical illnesses were assigned weights and summed as a comorbidity index for survival analyses.

Definitions

Radical pericardiectomy was defined as wide excision of the pericardium anteriorly between the 2 phrenic nerves and from the great arteries superiorly to the diaphragm inferiorly, posterior to the left phrenic nerve (which is left on a pedicle) to the left pulmonary veins, and including the pericardium on the diaphragmatic and posterior surfaces of the ventricles.4 Constricting layers of epicardium were also removed. The atria and venae cavae were decorticated only if the dissection could be accomplished easily, without risk of hemorrhage.6,5 Pericardiectomy was considered partial if both ventricles could not be decorticated completely because of dense myocardial adhesions or calcification.
For uniformity with other studies, perioperative death was defined as that occurring within 30 days after surgery. However, all deaths within the same hospitalization as for surgery were included in analysis of predictors of perioperative death. Cardiac-related death was defined as death due to cardiac causes, such as progressive CHF or sudden death. Sudden unexpected death was defined according to the criteria of Hinkle and Thaler,6 whereas sudden expected death was abrupt death occurring in the setting of progressive CHF or an episode of CHF in the preceding 12 months. A poor cardiovascular outcome was defined as any combination of the end points of perioperative death, late cardiovascular death, and new-onset or recurrent New York Heart Association (NYHA) class III to IV CHF.

Statistical Analysis
Categorical data, expressed as percentages, were compared by the t test or χ2 test, as appropriate. Continuous variables, expressed as mean±SD or median values, were compared by the 2-sample Wilcoxon rank sum test. The rates of all-cause mortality, perioperative death, late survival, late cardiac-related death, recurrent NYHA class III to IV CHF, and a poor late cardiovascular outcome were estimated by the Kaplan-Meier method. Late survival curves were compared with those of a normal 1990 US population matched for age and sex by the log-rank test. Baseline predictors of subsequent sudden death were identified by univariate Cox proportional hazards analysis initially performed on candidate variables (Table 1). Variables univariately significant on the basis of a threshold value of P<0.15 were entered stepwise into a multivariable logistic regression model to confirm independent predictive value. A value of P<0.05 was considered statistically significant.

Results
Incidence and Causes
The causes of CP in the 135 study patients and the 231 patients of the historic series are depicted in Figure 1. An indeterminate cause of CP was significantly less common in the contemporary cohort (33% versus 73%, P<0.0001). The 3 most common identifiable causes were cardiac surgery (18%), pericarditis (16%), and mediastinal irradiation (13%).

Patients who had received radiotherapy most commonly had Hodgkin’s lymphoma (8 patients) or breast cancer (7 patients), a median of 13.1 years (range, 1.0 to 40.6 years) before pericardiectomy. Of the patients with connective tissue disease or arthritides, 6 had rheumatoid arthritis and 1 each had rheumatic fever (with myopericarditis), polymyalgia rheumatica, psoriatic arthropathy, and Still’s disease. Infectious causes identified were fungal pericarditis (histoplasmosis and candidiasis) in 2 patients and tuberculosis and Whipple’s disease in 1 patient each. Miscellaneous causes included myeloproliferative disorders, malignancy, trauma, asbestososis, drug-induced causes, and complicated pacemaker lead replacement. CP was diagnosed in 2 patients at autopsy: 1 had had cardiac surgery and the other had tumor encasement by non-Hodgkin’s lymphoma.

Clinical Characteristics
Clinical characteristics of the study population are shown in Table 2. The presentation was CHF in 90 patients (67%), chest pain in 11 (8%), abdominal symptoms in 8 (6%), cardiac tamponade in 7 (5%), atrial arrhythmia in 6 (4%), and frank liver disease in 5 (4%). In the other 8 patients, the initial presentation included postoperative low cardiac output state, recurrent pleural effusion, transient ischemic attack, and syncope. The median symptomatic duration before pericardiectomy was 11.7 months (range, 3 days to 29.1 years). Chronicity of symptoms characterized patients with an indeterminate cause of CP (mean, 17.4 months).

Surgery
Pericardiectomy was performed in 132 of the 135 patients. One patient who had previously had radiotherapy underwent triple coronary artery bypass graft surgery and a tricuspid annuloplasty, but the patient’s condition deteriorated intraoperatively and pericardiectomy was not performed. Radical pericardiectomy was performed in 117 patients (89%). Pericardial resection was deemed incomplete in the other 15 patients (11%). Ultrasonic debridement of calcified pericardium was performed in 12 patients (9%), coronary artery bypass grafting was performed in 10 patients (8%), valve replacement or repair in 5 (4%), and a combined coronary artery-valve procedure, atrial septal defect closure, resection of subaortic stenosis, and right ventricular outflow tract enlargement in 1 patient (0.8%) each. Cardiopulmonary bypass was used in 45 patients; the mean extracorporeal circulation time was 88±58 minutes.
Overall Survival
Information about death was available for all except 1 patient (99%) and for other end points in 129 patients (98%). In patients dismissed from the hospital, the mean follow-up period was 3.9±3.0 years (maximum, 12.2 years). There were 39 deaths (30%), of which 26 occurred after hospital dismissal. At 5 and 10 years, overall survival was 71±6 and 52±8%, respectively. Independent determinants of overall survival were age, previous radiotherapy, NYHA class, and serum concentration of sodium (Table 3).

Perioperative Deaths
The 30-day perioperative mortality was 6% (8 of 132). This compares favorably with the 14% perioperative mortality in the historic cohort (χ²=6.40, P=0.011). A total of 13 patients died in hospital. The principal causes of death were low output state in 6 patients, sepsis in 3, uncontrolled hemorrhage in 2, and renal failure and respiratory insufficiency in 1 each. Of these 13 patients, pericardiectomy was incomplete in 6 (univariate P<0.0001 for prediction of perioperative death), and cardiopulmonary bypass was required in 9.

Late Survival
At last follow-up, 93 of the 119 operative survivors (78.2%) were alive. Survival at 5 and 10 years was 78±5% and 57±8%, respectively, and was inferior to that of an age- and sex-matched US population (log-rank P=0.001) (Figure 2). This difference was not observed for the historic cohort, which had an identical proportion of patients with advanced NYHA symptoms.4 In stepwise multivariate analysis, independent predictors of late survival were age, NYHA class, and previous radiation (Table 3 and Figure 3). The difference from expected survival was still statistically significant even when patients with radiation disease were excluded (log-rank P=0.016) (Figure 2).

Late Cardiovascular Deaths
The late deaths in 26 patients resulted from cardiac-related causes in 17, pleuropulmonary disease in 2, noncardiac illness in 6, and an unknown cause in 1. None of the patients who had radiation therapy died of recrudescent neoplastic disease.


| Characteristic                | 1985–1995 Cohort (n=135) | 1936–1982 Cohort (n=231) | P  
|------------------------------|--------------------------|--------------------------|-----
| Age, y                       | 56±16 NA                 | 60±16 60±16              |     
| Median                       | 61 45                    | 63 70                    |     
| Range                        | 11–78 0.8–83             | 1.0–349 1.0–348          | 0.63
| Male                         | 103 76 171 74            |                         |     
| Symptom duration, mo         | 11.7 14.0                |                         |     
| Median                       | 11.7 14.0                |                         |     
| Range                        | 0.1–349 1.0–348          |                         |     
| NYHA class                   |                          |                         |     
| I–II                         | 40 30 72 31              |                         |     
| III–IV                       | 93 69 159 69             |                         | 0.83
| Indeterminate                | 2 1 0 0                 |                         |     
| Elevated JVP                 | 119* 93* 229 99         |                         | 0.001
| Peripheral edema             | 103 76 162 70           |                         | 0.20
| Hepatomegaly                 | 71 53 169 73            |                         | <0.0001
| Pericardial knock or S₂      | 63 47 106 46            |                         | 0.89
| Ascites                      | 50 37 139 60            |                         | <0.0001
| Pleural effusion             | 47 35 NA                |                         |     
| Kussmaul’s sign              | 28 21 NA                |                         |     
| Pulsum paradoxus             | 25 19 NA                |                         |     
| Pericardial rub              | 22 16 NA                |                         |     
| Known CAD                    | 26 20 NA                |                         |     
| Diuretic use                 | 68 50 NA                |                         |     
| Atrial arrhythmia            | 22 16 68 29            |                         | <0.0001
| Low QRS voltage              | 37 27 92 40            |                         | 0.083
| Pericardial calcification    | 34 25 92 40            |                         | 0.0017

JVP indicates jugular venous pressure; CAD, coronary artery disease; and NA, not available.
*Indeterminate in 7 of 135 patients.
Cardiac-related deaths were due to progressive CHF in 14 patients (4 terminated in sudden expected death) and were sudden and unexpected in 3. The cumulative incidence of cardiovascular deaths was 14±4% and 35±9% at 5 and 10 years, respectively. Independent predictors of late cardiac-related deaths were previous radiotherapy, NYHA class III to IV symptoms, and age (Table 3).

**Late NYHA Class III to IV CHF Symptoms**

Recurrent or new NYHA class III to IV symptoms supervened in 37 of 119 patients (31%) at some stage of late follow-up. The median time to onset of new or recurrent CHF symptoms was 7.1 months (range, 0.4 to 137.1 months). Three patients were reoperated on for recurrent CP. The 5- and 10-year incidence of late NYHA class III to IV CHF, 25±5% and 41±9%, respectively, parallels that of late cardiovascular deaths, consistent with the observation that most severely symptomatic patients died eventually of a cardiac-related cause. Multivariate predictors of late CHF were age, radiation, and the presence of ascites (Figure 4). Mean functional class was 2.6±0.7 at baseline, compared with 1.5±0.8 after pericardiectomy (mean change, 1.1±0.9, P<0.0001).

**Freedom From Poor Cardiovascular Outcome**

Of 129 patients with complete follow-up information, 75 (58%) were alive and free of CHF at latest follow-up. At 5 and 10 years, 70±5% and 43±8% of patients, respectively, were free of a poor cardiovascular outcome. This end point occurred in 15 of 17 patients (88%) who had received radiation, including 13 deaths, and in 31 of 112 patients (28%) without a radiation basis for CP (P<0.0001). The dismal outcome for patients with radiation disease was reflected in a 12±6% freedom from any cardiovascular event by 5 years.

**Discussion**

In comparing our contemporary patients with a historical cohort that had pericardiectomy at the Mayo Clinic—a total experience spanning nearly 6 decades—several trends were observed: (1) patients in the last decade were older (median age, 61 years versus 45 years), (2) previous open heart surgery and mediastinal irradiation emerged as important causes of CP, (3) operative mortality was significantly lower, but (4) late survival was not as good as expected.

The increasing importance of iatrogenic causes of CP2,3,7–9 is reflected in the marked decline in the proportion of indeterminate causes in the present series. Postoperative CP may not be as uncommon as previously believed.2,7,9,10 At the current level of 725 000 such procedures performed annually in the United States, a conservative 0.3% incidence could yield up to 2200 new cases annually. Therapeutic radiation could also remain a significant cause of pericardial disease. Cardiac structures are exquisitely sensitive to the effects of radiation, which often become manifest decades later.11,12 In addition, improved cancer cure rates have resulted in greater longevity and thus the likelihood of developing cardiovascular sequelae.13 Active tuberculous CP, present in 6.1% of patients in the series of McCaughan et al,4 was rare in our patients (0.7%). This declining trend is in contradistinction to recent reports from other geographic regions,14–16 emphasizing again the heterogeneity of disease patterns.

**Operative Mortality**

The decline in operative mortality at our institution from 25% in the earlier half of this century9 to 6% at present probably is related to improvements in surgical technique, anesthesia, and postoperative care. Despite the inclusion of older patients and those with radiation-induced CP, our results compare favorably with the 6% to 19% rate of larger series published after 1985.1–3,14,15,17

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**TABLE 3. Multivariate Predictors of Outcome After Pericardiectomy in 132 Patients With CP**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.04–1.10</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.43</td>
<td>1.22–4.86</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Previous radiation</td>
<td>5.13</td>
<td>2.49–10.56</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Serum sodium</td>
<td>1.11</td>
<td>1.04–1.18</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Late survival</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.04–1.12</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.99</td>
<td>1.76–9.08</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Previous radiation</td>
<td>11.80</td>
<td>4.57–30.44</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Late CV death</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.03–1.12</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.38</td>
<td>1.25–9.19</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Previous radiation</td>
<td>20.74</td>
<td>6.77–63.52</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Late NYHA class III–IV CHF</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.01–1.07</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Previous radiation</td>
<td>9.47</td>
<td>4.19–21.39</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>2.19</td>
<td>1.03–4.67</td>
<td>0.042</td>
<td></td>
</tr>
</tbody>
</table>

CV indicates cardiovascular; CHF, congestive heart failure.

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**Figure 2. Late survival (perioperative deaths excluded) after pericardiectomy for CP compared with that of an age- and sex-matched US population (left) and after patients with radiation-induced disease were excluded (right). Numbers at bottom represent percentage of expected survival for specified intervals.**
Late Survival
Unlike our earlier experience, late survival was inferior to that of an age- and sex-matched control population. The difference in survival was not entirely explained by the increased prevalence of radiation-induced CP. Two reasons may account for this observation. First, patients with CP often have systemic or pleuropulmonary disease that increases the risk of non-cardiac-related deaths. However, comorbidity was not a significant predictor of late survival in our study. Second, improved perioperative management and medical therapy could have deferred attrition in patients with associated myocardial disease. This latter possibility is supported by 2 observations: (1) preoperative NYHA class independently predicted late cardiac-related deaths and (2) the survival curves diverged early, after only 18 months.

Late death occurred suddenly in 6 patients. Sudden death has been reported in the setting of CP and after pericardiectomy. Occult atherosclerotic coronary artery disease may be suspected, but the pericardial process can also obliterate epicardial vessels and cause myocardial ischemia. This is unlikely after pericardiectomy unless it was incomplete. In 2 of our patients with radiation disease, sudden death could have resulted from accelerated coronary atherosclerosis.

Predictors of Late Events
All long-term outcomes were predicted consistently by 3 baseline variables: age, NYHA class, and a radiation cause for CP.

A correlation between NYHA class and overall or late survival has been observed by us and others and is the basis for advocating early pericardiectomy. However, the effect of age on survival after pericardiectomy has not previously been apparent because of the uniformly young populations studied, especially from regions in which tuberculosis is endemic. The median age of our patients is at least a decade older than that in other series. Greater physician awareness and a comprehensive Doppler echocardiographic examination could have been instrumental in diagnosing CP in these older patients.

Previous radiotherapy was the most powerful predictor of all outcome measures. The deleterious late effects of radiation on cardiac structures other than the pericardium have been well described. Pericardiectomy is more challenging because of mediastinal fibrosis, which limits complete resection and postoperative recovery may be prolonged because of chest wall fibrosis. Long-term survival is also compromised by pulmonary interstitial disease, impaired immunological responses, and recurrent primary tumor or secondary neoplasms from chemotherapy. However, all deaths in our patients with radiation pericarditis were cardiac-related. Our study confirms the guarded long-term outcome of these patients, even if some derived initial symptomatic relief after pericardiectomy. The recognition of such poor-risk subgroups also facilitates objective comparisons of survival data. For instance, although Tirilomis et al reported a 5-year overall survival of 85% after pericardiectomy, the mean age of their patients was 44 years, and only 1 patient had radiation-induced CP.

Late Functional Status
Pericardiectomy provided excellent relief of symptoms in most late survivors in our study. However, nearly one third of these patients experienced either new or recurrent NYHA class III to IV symptoms at some time during follow-up. This could be due to incomplete surgical resection. In our study, incomplete pericardiectomy was significantly associated with recurrence of late CHF in univariate analysis. However, the majority of patients in whom recurrent symptoms developed had had radical surgery. The culprit pathophysiological mechanisms in these instances are not well characterized but include immobilization atrophy, myoperi-

Figure 3. Late survival stratified by age ≤55 years versus >55 years (left), NYHA class I to III versus class IV (middle), and nonradiation versus radiation causes (right). Baseline NYHA class was indeterminate in 2 patients.

Figure 4. Change in NYHA functional class in 93 late survivors, showing marked symptomatic improvement in most patients after pericardiectomy. NYHA class was indeterminate in 1 patient before surgery and unknown in 3 patients at latest follow-up.
cardiac involvement by the same pathological process (exemplified by radiation disease), or physical extension of pericardial calcification into the myocardium.20,30–41 Residual myocardial fibrosis was likely in our patients who had recurrent CHF symptoms, because (1) many had radiation-induced disease and (2) restrictive left ventricular filling could be documented by serial Doppler echocardiography in some patients.31,42

Involvement of adjacent pleuropulmonary structures by the constrictive disease process39 and concomitant chronic obstructive lung disease limited functional recovery in nearly a fifth of patients. Clearly, these mechanisms are not mutually exclusive in individual cases.

Limitations

Selecting cases of CP on the basis of thoracotomy findings to reflect incidence represents a bias of all surgical studies. It is likely that more cases remain unoperated on, because of underdiagnosis, minimal symptoms, or high operative risk. However, inspection of the pericardium remains the gold standard for the diagnosis of CP and may be the only way to prove the diagnosis in relation to restrictive cardiomyopathy.31,43

Incomplete functional recovery in some patients may be the result of gradual adaptation of the released ventricles to loading conditions and may not represent the permanent functional state. However, nearly all our patients had follow-up of at least 1 year, and myocardial recovery should have occurred by that time.44,45

Unlike other investigators,1 we did not include cardiac catheterization variables for prediction of outcome. This test, which was done in 65 of the 132 patients, is currently not performed routinely in the workup of CP at our institution unless echocardiographic findings are nondiagnostic.

Because patients who had concomitant surgical procedures were excluded from our historic cohort, a direct comparison of outcome between the historic and contemporary patient groups may preferentially favor the former. However, the occasional need for concomitant coronary artery bypass graft surgery and valvular procedures did not have significant impact on early and late mortality in univariate analyses, consistent with the findings of other studies.29,36

Conclusions

CP is a heterogeneous disease. Increasingly important causes in the current era include previous mediastinal irradiation and cardiac surgery. Although pericardiectionomy is often performed, it may not offer a cure or good long-term result for patients with CP that is advanced or due to radiation disease. Cardiac transplantation could be considered in selected patients without recurrent tumor and with good pulmonary reserve, particularly if severe valvular disease coexists. However, postoperative prognosis and functional outcomes remain good for most other patients with CP and excellent for younger patients without radiation pericarditis.

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References


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