Pericardoscopy for primary management of pericardial effusion in cancer patients

Henri L. Porte a,*, Thérèse J. Janecki-Delebecq a, Laetitia Finzi a, David G. Métois a, Alain Millaire b, Alain J. Wurtz a

a Division of Thoracic Surgery, Calmette Hospital Lille University Hospital, Rue du Pr J. Leclerc 59037 Lille Cedex, France
b Division of Cardiology, Heart Hospital Lille University Hospital, Rue du Pr J. Leclerc 59037 Lille Cedex, France

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Abstract

Objective: To assess the usefulness of pericardoscopy via the subxyphoid route for the diagnosis and treatment of pericardial effusion in patients with a history of cancer. Methods: All patients with a recent or remote history of cancer and a pericardial effusion of unknown origin requiring drainage for diagnostic and therapeutic purposes were included in the study. They underwent complete exploration and cleansing of the pericardial cavity. Abnormal structures or deposits were biopsied under direct visual control, with a 24 cm long rigid pericardoscope. Results: Between 1985 and 1998, pericardoscopy was completed in 112 of the 114 patients included (feasibility 98%), resulting in the immediate relief of symptoms in all the cases. Peri-operative mortality was 3.5%, and post-operative morbidity, 6.1%. After pericardioscopy pericardial effusions were considered malignant in 43 cases. One more case (2.3%) due to a false negative result of perycardioscopy was diagnosed during follow-up. Overall, 44 of the 114 patients (38.6%) had a malignant effusion, and 70 (61.4%), a non-malignant effusion according the follow up. In 10 of the 44 patients with a malignant pericardial effusion (22.7%), pericardoscopy corrected the results of cytological pericardial fluid studies and pericardial window biopsy, both false negatives. The sensitivities of cytological studies of the pericardial fluid, pathological examinations of pericardial window biopsy and pericardioscopy were 75, 65 and 97%, respectively. One patient with a malignant effusion had a non-symptomatic recurrence 1 month after pericardioscopy (2.3%). Conclusion: We recommend pericardioscopy to ascertain the malignant nature of the effusion and to diminish the recurrence rate, this avoiding repeat procedures in patients with a short life expectancy. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Malignant pericardial effusion; Lung cancer; Non-Hodgkin lymphoma; Pericardioscopy

1. Introduction

In patients with a history of malignancy, it is essential for therapeutic management to assess the cause of a pericardial effusion (PE). When this is done, more than half the cases of (PE) prove to be benign. Furthermore, early recognition with successful treatment of malignant pericardial effusion (MPE) can prolong and improve the quality of life, especially in patients with a disease potentially responsive to current therapies. A wide variety of approaches have been reported to be effective in MPE. They include: repeat pericardiocentesis, surgical drainage of the pericardium with a pericardial window, indwelling catheter drainage with pericardial instillation of chemotherapeutic agents like tetracycline, thiopeta or bleomycin, partial or total pericardectomy, pericardioperitoneal shunt, thoracoscopy, radiotherapy and percutaneous balloon pericardiostomy [1].

Since the first description of pericardioscopy (PCS) by Santos and Frater [2], we and others have established its usefulness, combined with conventional subxyphoid pericardial drainage in increasing the diagnostic precision and reducing the relapse rate of PE [3–5]. However, despite these positive results, PCS is not widely employed and recent important studies or reviews of the management of MPE do not even mention the procedure [6–8]. We here report our experience of PCS since 1985 in patients who had a recent or remote history of malignancy and a PE of unknown origin which required a pericardial drainage for both diagnostic and therapeutic purposes.

2. Patients and methods

Between July 1985 and March 1998, all patients who had
Table 1
Characteristics of the primary tumor in 114 patients who underwent pericardioscopy for diagnostic and therapeutic purpose

<table>
<thead>
<tr>
<th>Location of the primary tumor</th>
<th>Number of patients</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>114</td>
<td>100</td>
</tr>
<tr>
<td>Lung</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10</td>
<td>8.5</td>
</tr>
</tbody>
</table>

a past and/or present diagnosis of cancer with PE that required drainage for diagnostic or therapeutic purposes were included in the study. PE was classified as acute or subacute if the symptoms lasted less than 3 months, and as chronic if they lasted more than 3 months or were discovered incidentally. In all patients, the diagnosis of PE was confirmed by two-dimensional echocardiography and also evaluated by thoracic CT scan from January 1989. Hemodynamic tolerance of PE was assessed by clinical and echocardiographic criteria. The patients initially included in this study had also been included in previous series [3,4]. For short-term follow-up, hospital records were reviewed to determine the nature of the clinical presentation, the methods of diagnosis and treatment, procedure related morbidity and mortality and the length of the procedure related hospital stay. For long-term follow-up, the referring general practitioners and cardiologists were contacted, to ascertain whether PE had recurred, whether the diagnosis established by PCS was accurate, and the survival rate.

2.1. PCS technique

PCS was performed according to a technique which did not change throughout the study period. An incision was made over the distal sternum, xiphoid and upper abdomen. The anterior rectus fascia was opened and the xiphoid process was removed. A plane was dissected beneath the sternum by use of blunt dissection, and the pericardium was then identified. Needle aspiration of the fluid was performed for cytological, biochemical, bacterial and immunologic studies. Excision of a small portion of the subxiphoid pericardium was then performed for histological examination (called subxiphoid window biopsy).

However, as from September 1989, patients who had clinical signs of cardiac tamponade (i.e. combination of a paradoxical pulse above 12 mmHg, hyperpressure in the external jugular vein and/or hypotension with systolic pressure below 100 mmHg) and echocardiographic signs of tamponade (presence of right atrial and ventricular collapse) had initial transcutaneous pericardial drainage before PCS, to facilitate the induction of anesthesia.

All procedures were performed under general anesthesia via the subxiphoid approach (described above), except for the first cases at the beginning of our study period, which included patients with tamponade for whom local anesthesia was used. From 1988, we only used the 24 cm-long pericardioscope derived from the traditional 17 cm long mediastinoscope (Pericardoscope 24 cm 10970B, Karl Storz Tutlingen, Germany). The procedure was performed by eight surgeons, including young surgeons in training supervised by a senior surgeon (AW). In all patients, we performed a subxiphoid pericardial window biopsy for histopathological examination and for cytological, biochemical, bacterial and immunological studies of the pericardial fluid. Complete fluid aspiration and cleansing of the pericardial cavity was performed under visual control. PCS permitted direct inspection of the pericardial surface and made it possible to perform guided biopsies of areas with an abnormal appearance. Thus, for each patient, the results of the pericardial fluid analysis and subxiphoid biopsy could be compared with those of PCS. Two soft drains (Shirley AN30 Andersen Products, Haw River USA) were placed in the pericardial cavity anterior and posterior to the heart. These drains were attached to negative suction (40 cm H2O) and insured continuous opposition of the visceral and parietal pericardial surfaces, their were maintained on suction until the drainage yielded less than 50 ml per 24 h.

2.2. Evaluation of PCS

Pericardial fluid studies, subxiphoid window examination and guided biopsies under visual control were evaluated separately. If the biochemical, bacteriological, cytological or immunological analysis of the fluid supplied proof of a definite diagnosis it was considered to have been established pericardiocentesis. If pericardial biopsy or cytological studies of the pericardial fluid via the subxiphoid window permitted a definite diagnosis, it was considered to have been obtained by conventional subxiphoid surgical drainage.

If only direct visualization of the pericardial surfaces and/or guided biopsies of suspicious areas established the definite diagnosis, it was considered to have been made by PCS. False negative diagnoses by PCS were assessed when a PE diagnosed as non-neoplastic by PCS was shown to be neoplastic during the follow-up period, or when direct visualization or guided biopsies did not give an accurate result, whereas pericardial fluid or pericardial window biopsies confirmed the neoplastic nature of PE. A PE was considered idiopathic when the complete work-up revealed no specific cause, direct visualization showed either normal or only slightly inflamed pericardial surfaces and guided biopsies were negative.

3. Results

From July 1985 to February 1998, we performed 210 PCS in 209 patients.
Among them 114 patients had a history of malignancy. In 45 cases, it was remote (more than 3 months before the study) and in 69 cases, recent (less than 3 months before the study). These 114 patients are the subject of the present report. The histological nature of the primary tumor was known before PCS in 103 cases (90%). The remaining 11 cases included supraclavicular lymphadenopathy \((n = 1)\), mediastinal lymphadenopathy \((n = 1)\) and mediastinal tumor of unknown origin \((n = 9)\). The characteristics of the primary tumor (including 4 diagnoses obtained after PCS) are given in Table 1. The 114 patients comprised 89 men and 35 women whose mean age was 57 years (range: 24–82). Thoracic CT scan was performed in 97 patients (85%). PE was acute or subacute in 32 patients (28%) and chronic in 31 (28%).

Pericardial effusions were symptomatic in 77 patients (67%), including 19 with pericardial tamponade (16%), and non-symptomatic in 37 (32%). PCS was performed under general anesthesia in all but three patients (2.5%). Ten patients with pericardial tamponade (9%) underwent echo-guided transfuscaneous pericardial drainage before PCS.

The mean duration of PCS was 36 min (range: 21–74), the mean duration of drainage was of 5 days (range 4–6 days), the mean hospital stay related to PCS was of 5 days (range: 4–9) and the mean amount of fluid withdrawn was 750 ml (range 50 ml in a patient with previous transcuscaneous drainage, to 1600 ml).

### 3.1. PCS feasibility, per and post-operative morbidity and mortality

PCS was complete in 112 of the 114 patients (98%). The two incomplete explorations were due to a cardiac arrest during the induction of anesthesia in one case, and to the presence of neoplastic tissue hindering introduction of the pericardioscope in the other.

In these two patients, cytolological studies of the pericardial fluid revealed the presence of malignant cells.

Four of the 114 patients died during the perioperative period (3.5%). One patient died during the induction of anesthesia (i.e. before PCS), one near the end of operation, from electromechanical dissociation, and two during the hours following drainage, from acute respiratory distress caused by severe bronchospasm in one case and ventricular fibrillation in the other. All four deaths occurred in patients with very poor general health status and advanced metastatic processes including pericardial metastases in two cases.

The peroperative morbidity consisted of the occurrence of ventricular or supraventricular arrhythmias which had no hemodynamic consequences in 36 patients (31%) and resolved spontaneously after withdrawal of the pericardioscope. PCS was complete in all patients with peroperative arrhythmias. Post-operative morbidity consisted of lung infection necessitating assisted ventilation for 3 days in two patients with a poor respiratory function who could be discharget on the 9th post-operative day (1.7%) and superficial wound suppuration without a prolonged hospital stay in five (4.4%). The overall complication rate related to PCS was 6.1%.

### 3.2. Diagnosis after PCS

After PCS, pericardial effusions were considered to be malignant in 43 cases and non-malignant in 71. Of the 43 malignant pericardial effusion (MPE) established by PCS, 32 were due to neoplastic involvement of the pericardial cavity which was either diffuse or localized following a hematogeneous spread, and 11 were due to localized involvement after a direct contiguous invasion by the underlying malignancy. In four of these 11 patients histology of the underlying malignancy, unknown before PCS, was identified (i.e. non-Hodgkin lymphoma \(n = 3\), germ cell tumor \(n = 1\)). In 10 of the 43 patients (23%) with MPE diagnosed by PCS (23%), results of pericardial fluid analysis and pericardial window biopsy were both negative. PCS corrected the diagnosis of these patients by showing a typical aspect of intrapericardial neoplastic proliferation, which was biopsied.

During follow-up, one false negative result of PCS was identified. In this patient, who had Hodgkin’s disease, a rhabdomyosarcoma was not detected during PCS and cytolological and histological studies were also both negative. Consequently, there were three false negative results, including the two patients with MPE who had an incomplete PCS exploration. Overall, there were 44 final diagnosis of MPE and 70 of non-malignant pericardial effusions (NMPE) including: idiopathic effusions \((n = 33)\), radiation induced effusions \((n = 20)\), infectious effusions \((n = 10)\) and hemopericardium as a result of coagulation disorders \((n = 8)\). The sensitivities and specificities of cytolological studies, pericardial window biopsy and PCS are given in Table 2.
3.3. Late recurrence and mortality

In the NMPE group complete follow up was available in 66/70 patients (94%) and no patient was lost by follow up before 9 months. The expected mean follow up period in this group was 60 months (range: 9–137). Mortality was 58% (41 patients). PE relapses occurred in 4 patients without symptoms. In the MPE group a complete follow up was available for all 44 patients with an expected mean follow up period of 50 months (range: 10–145). Mortality was 93% (40 patients), all death resulted from the progression of the underlying malignancy, and half of them occurred during the 3 months after PCS. PE relapse occurred in one patient (2.3%) 1 month after PCS. Overall mortality in the NMPE and MPE groups was 81/114 patients (71%) and the overall relapse rate for PE, 4.3% (5 patients).

4. Discussion

Most cases of MPE are diagnosed in patients with a previous diagnosis of cancer at a late stage of malignancy, but in some cases the pathological nature of the underlying malignancy is unknown. Defining the cause of a pericardial effusion in patients with cancer is important for prognosis. Accordingly, we and others previously demonstrated that patients with MPE have a poorer prognosis than patients with NMPE in a malignant context, and that the histology of the underlying malignancy is the crucial factor determining the survival of patients with MPE [3,6,9,10]. Clinical and echographic features cannot reliably distinguish malignant from non-malignant causes [11]. The cytology of the pericardial fluid was found positive or suggestive of malignancy in only 58% of the 112 patients with MPE reported by Wilkes and colleagues [12]. The present study confirmed that cytology is not reliable to ascertain the diagnosis of MPE, as its sensitivity was 75%. Our study also confirmed that the diagnostic yield of pericardial biopsy was even lower than that of cytology, due to the presence of patients with non-diffuse MPE, i.e. MPE resulting from invasion of the pericardium by contiguous thoracic tumors. Our experience with PCS clearly demonstrates that the diagnostic quality was improved by direct visualization of the pericardial surfaces and by guided biopsies of suspicious areas or intrapericardial deposits. Accordingly, PCS permitted access to parts of the pericardial cavity that would not have been reached by digital palpation or direct visualization through the subxyphoid window. Therefore, 10 of our 44 patients with MPE would have been misdiagnosed if the conventional pericardial procedure had been used. In these 10 patients PCS identified the mechanism of pericardial involvement with consequences for the therapeutic management.

Many authors believe that subxyphoid drainage remains the first line procedure for the management of MPE including the prevention of relapses which is evaluated between 8 and 10% [1,12–16]. In the present study, PCS diminished the recurrence rate to 2.3%. This reduction was due to the complete cleansing of the pericardial cavity under visual control followed by prolonged suction drainage which insures continued opposition of the visceral and parietal pericardial surfaces. We believe that continuous anteroposterior drainage of a pericardial cavity is a much more important factor in reducing recurrence rates than the surface of the resected pericardial window [15]. Furthermore, the inflammatory response to the trauma created by pericardial cleansing under visual control leads to the complete clogging of the pericardial cavity with adhesions such as those found after open heart surgery. This inflammatory response can also explain the lower recurrence rate in the MPE group than in the NMPE group.

Non-surgical management of MPE includes the placement of a pig-tail catheter under echocardiographic guidance (i.e. pericardocentesis) [17]. This procedure may be life saving in acute situations, but is associated with a high rate of recurrence and must be followed by instillations of a sclerosing agent to obtain a symphysis of the parietal and visceral pericardium. The more widely employed sclerosing agent has been tetracycline. Maher et al. [6], reported their experience of this method for the management of 85 patients with MPE which was controlled in 75 of them (88%) after a mean five days of sclerosis. The same authors compared the results of medical management and those of surgical treatment published during the years 1984–1995 including the creation of a pericardial window via the subxyphoid approach and via video-assisted thoracoscopic surgery (VATS). They concluded that in terms of survival, the results of pig-tail drainage followed by sclerosis with tetracycline instillations are identical to those obtained by surgery and that for morbidity, mortality, and recurrence rates, the results are better than with surgery. Subsequently, Girardi et al. [8] compared the results of pericardocentesis followed by the injection of thiotepa with those of conventional surgical drainage, and found no significant difference between the complication and survival rates for the two methods, but the cost of surgical drainage exceeded those of pericardocentesis by nearly 40-fold. However, because of the small number of patients and the multiple procedures carried out in their series, no significant conclusion as to the most effective therapy can be made. The most important problem concerning sclerosis is the nature of the sclerosing agent itself. As stated above, the most widely used was formally tetracycline which is no longer available in is powdered form in many western countries including the USA. Alternative agents like bleomycin, doxyccycline or thiotepa are still under evaluation [7,18,19].

We agree that a minimum of 4 days of surgical drainage after PCS increases the cost of the procedure. Nevertheless, after diagnosis, the main objective in the management of MPE is to prevent recurrence, in order to avoid repeat procedures during what is expected to be a short period of survival. After pericardial sclerosis, 8–13% [6,7,8] of patients will require further intervention. As shown here, PCS
reduced recurrence to 2.3%, and gave immediate relief of symptoms.

VATS was recently used for the diagnosis and treatment of MPE. However, its superiority for diagnosis has not yet been clearly proved by recent reports, as the latter were relatively limited series [20–25]. We believe that VATS does not offer any advantage over PCS via the subxyphoid route, except when the pleural cavity has to be explored [25], when PCS cannot be performed because of previous retrosternal gastro or coloplasty, or in the presence of neoplastic tissue hindering the progress of the pericardioscope along the subxyphoid route. Also VATS is a more time consuming procedure than PCS, only one side of the pericardial cavity can be explored, and it is only appropriate for patients in hemodynamically stable condition [7].

Certain parts of the pericardial cavity cannot be completely explored with the rigid pericardioscope, especially around the lateral wall of the left ventricle. However, the rigid, pericardioscope allows more complete emptying of the cavity and larger tissue biopsies for pathological studies than a flexible pericardioscope. The perioperative mortality rate of 3.5% reported in the present study for patients with advanced metastatic processes who underwent PCS at the beginning of the period covered shows that these patients were not good candidates for the procedure. In such cases, echo-guided pericardiocentesis followed by instillation of sclerosing agents is certainly the procedure of choice when cytological examinations are positive. However, its superiority for diagnosis has not yet been clearly proved by recent reports, as the latter were relatively limited series [20–25]. We believe that VATS does not offer any advantage over PCS via the subxyphoid route, except when the pleural cavity has to be explored [25], when PCS cannot be performed because of previous retrosternal gastro or coloplasty, or in the presence of neoplastic tissue hindering the progress of the pericardioscope along the subxyphoid route. Also VATS is a more time consuming procedure than PCS, only one side of the pericardial cavity can be explored, and it is only appropriate for patients in hemodynamically stable condition [7].

In order to reduce the recurrence rate of symptomatic PE, we recommend PCS when cytological examinations are positive. However, except in these particular situations, we recommend PCS for the diagnosis of PE especially when the histology of the underlying malignancy is unknown. We also recommend it for patients in whom PE has already been diagnosed in order to reduce the recurrence rate of symptomatic PE.

References