GENERAL CARDIOLOGY

Management of pericardial effusion

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Pericardial effusion is a common finding in everyday practice. Sometimes, its cause is obviously related to an underlying general or cardiac disease, or to a syndrome of inflammatory or infectious acute pericarditis. On other occasions, pericardial effusion is an unexpected finding that requires specific evaluation. In these cases, the main issues are aetiology, the clinical course, and the possibility of evolution to haemodynamic embarrassment. This is especially relevant in cases of large pericardial effusions, in which echocardiographic recordings not infrequently show findings suggestive of subclinical haemodynamic derangement, mainly right atrial or right ventricular wall collapse. These uncertainties have led to a heterogeneous approach to the management of the syndrome of pericardial effusion by different groups of investigators.

The main goal of this article is to give a comprehensive review of aetiology, haemodynamic findings, and management of pericardial effusion. In addition, some comments on the management of neoplastic pericardial effusion are also provided.

Approach to mild pericardial effusion

In an asymptomatic patient, a pericardial effusion of less than 10 mm on the echocardiogram may be an incidental finding, especially in elderly women, as shown in the Framingham study.[1] In these patients, neither invasive studies nor treatment are required. A follow up echocardiogram is probably warranted to see if the echocardiographic findings are unchanged. Further investigation or treatment of these patients is not necessary if the echo findings are stable.

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Aetiologic spectrum and prognosis of moderate and large pericardial effusion

A wide variety of conditions may result in pericardial effusion. All types of acute pericarditis (inflammatory, infectious, immunologic or of physical origin) can be associated with pericardial effusion.[2] In addition, pericardial effusion of varying degrees can be seen in other conditions such as neoplasia (with or without direct pericardial involvement), myxoedema, renal insufficiency, pregnancy, aortic or cardiac rupture, trauma, chylopericardium, or in the setting of chronic salt and water retention of many causes, including chronic heart failure, nephrotic syndrome, and hepatic cirrhosis. Only three major studies[3-5] have addressed one of the most common clinical problems—the aetiology of large pericardial effusion of unknown origin. These three studies (table 1) are prospective and were done in general medical centres, but differ in respect to the criteria used to define a pericardial effusion as large, in the number of patients included and, in particular, in the study protocol applied to the patients.

Colombo and colleagues[3] consider effusions greater than 10 mm by M mode echocardiography as large, whereas Corey and associates[4] considered large effusions if they were greater than 5 mm. In the series by Sagristà-Sauleda and colleagues[5] moderate effusions were defined as an echo-free space of anterior plus posterior pericardial spaces of 10–20 mm during diastole, and severe effusions as a sum of echo-free spaces greater than 20 mm.

The series by Colombo and colleagues[3] included 25 male patients, all of whom were submitted to an invasive pericardial procedure. Of these patients, 44% presented with cardiac tamponade. The most frequent causes of pericardial effusion were: neoplastic (36%), idiopathic (32%), and uraemic (20%). The prognosis was strongly determined by the patients' underlying disease, and was particularly poor in patients with neoplastic pericardial effusion, none of whom survived longer than five months after the initial pericardial drainage.

Corey and associates[4] investigated the aetiology of pericardial effusion in 57 patients. The prevalence of cardiac tamponade was not reported. Each patient was assessed by a comprehensive preoperative evaluation followed by subxiphoid pericardiotomy. Microscopic examination of the samples of pericardial fluid and tissue was undertaken; the samples were also cultured for aerobic and anaerobic bacteria, fungi, mycobacteria, mycoplasma, and viruses. Aetiologic diagnosis was made in 53 patients (93%). The most common diagnoses were malignancy (23% of patients), viral infection (14%), radiation induced inflammation (14%), collagen–vascular disease (12%), and uraemia (12%). In only four patients was no diagnosis made. Prognosis was not assessed in this study.

Table 1 Moderate-large pericardial effusion trials

	Corey[4]	*Colombo*[3]	*Sagristà*[5]
Effusion	> 5 mm	> 10 mm	> 10 mm
n	57	25	322
Tamponade	Not reported	44%	37%
Idiopathic	7%	32%	20%*
Chronic idiopathic effusion	?	?	9%
Neoplastic	23%	36%	13%
Uraemia	12%	20%	6%
Iatrogenic	0%	0%	16%
Post-acute myocardial infarction	0%	8%	8%
Viral	14%	0%	0%
Collagen vascular disease	12%	0%	5%
Tuberculosis	0%	0%	2%
Other	9%	4%	21%

*Acute idiopathic pericarditis; ? no distinction between acute idiopathic pericarditis and idiopathic chronic pericardial effusion.

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The study by Sagristà-Sauleda and colleagues[5] included 322 patients, 132 with moderate and 190 with severe pericardial effusion. Cardiac tamponade was present in 37%. The patients were studied following our own protocol for the management of pericardial diseases,[6] in which invasive pericardial procedures were not systematically performed but were only undertaken under precisely defined indications. In this series, the most common diagnosis was acute idiopathic pericarditis which accounted for 20% of patients. The next most prevalent diagnoses were iatrogenic effusion (16%), neoplastic effusion (13%), and chronic idiopathic pericardial effusion (9%). As in the series by Colombo and colleagues,[3] the prognosis was related to the underlying disease, deaths occurring mainly among patients with malignancy.

Other series are limited to patients with clinical[7] or echocardiographic[8] tamponade. Among the 56 patients with tamponade included in the study of Guberman and colleagues,[7] the most common diagnoses were metastatic cancer in 18 patients, idiopathic pericarditis in eight patients, and uraemia in five. Once again, the worst prognosis was in the group of patients with cancer. Finally, in the study by Levine and associates[8] involving 50 patients, the most frequent aetiologies of pericardial effusion were malignancy (58%), idiopathic effusion (14%), and uraemia (14%). The ultimate survival of patients identified in this study did not correlate with initial haemodynamic status, but with the underlying aetiology, with a 17% cumulative probability of survival at one year for the group with malignancy and 91% for the group without malignancy.

Therefore, the main causes of large pericardial effusion in general medical centres are idiopathic pericarditis and malignancy. Remarkably, iatrogenic effusion accounted for 16% and chronic idiopathic pericardial effusion for 9% of patients in the largest series.[5] Nowadays tuberculosis is a rare cause of pericardial effusion in western societies (table 1), although this may not be the case in developing countries with a high prevalence of tuberculosis. In fact, the aetiologic spectrum of pericardial effusion largely depends on the source of the patients, the relative size and activity of the different departments in general hospitals (especially the different number of patients with neoplastic disease who attend each hospital), and, of course, on the frequency distribution of the different aetiologies of pericardial diseases in each geographical area.

Clinical clues to aetiology

When a clinician is faced with a patient who presents with large pericardial effusion, the challenge is to identify its aetiology. In some instances, it can be easily related to an associated condition or iatrogenic procedure, but often the aetiology may be difficult to establish. Agner and Gallis,[9] in a retrospective

Aetiology of moderate and large pericardial effusion

- A wide variety of conditions may result in pericardial effusion. The aetiologic spectrum in different series largely depends on the source of the patients, the characteristics of the centre, and on the frequency distribution of the different aetiologies in each geographic area

- In many cases, pericardial effusion is associated with a previous known condition or underlying cardiac disease, which are finally proven to be the cause of the pericardial effusion

- In patients with no apparent cause of pericardial effusion, the presence of inflammatory signs is predictive of acute (idiopathic) pericarditis; on the other hand, severe effusion with absence of inflammatory signs and absence of tamponade is predictive of chronic idiopathic pericardial effusion. Tamponade without inflammatory signs is suspicious for neoplastic pericardial effusion

- The prognosis of pericardial effusion is related to the underlying disease, being especially poor in patients with malignancy

series of 133 patients, observed that haemodynamic compromise, cardiomegaly, pleural effusion, and large pericardial effusion were more common in patients with tuberculous or malignant disease than in patients with idiopathic pericarditis. In the series of Posner and colleagues,[10] dealing with 31 patients with cancer and pericardial disease, patients with malignant pericardial disease had tamponade more frequently, whereas fever, a pericardial friction rub, and improvement following treatment with non-steroidal anti-inflammatory drugs characterised patients with idiopathic pericarditis. Haemorrhagic pericardial effusion has been associated with neoplasia and a poor survival in some studies,[3] but haemorrhagic effusions can be seen in patients with idiopathic pericarditis. The predictive value of these different clinical findings for assessing the aetiology of pericardial effusion has not been established.

In our recent prospective study of 322 patients with moderate and severe pericardial effusion,[5] we investigated the value of selected clinical data (underlying disease, development of cardiac tamponade, and presence or absence of inflammatory signs) for inclusion of the patients in a likely major aetiologic diagnostic category. In 60% of the patients a known previous condition that could cause pericardial effusion was present. The pericardial effusion was shown to be related to the underlying disease in all but seven of these patients. In the patients with no apparent cause of pericardial effusion at the time of diagnosis (40%) we found that the presence of inflammatory signs (characteristic chest pain, pericardial friction rub, fever or typical electrocardiographic
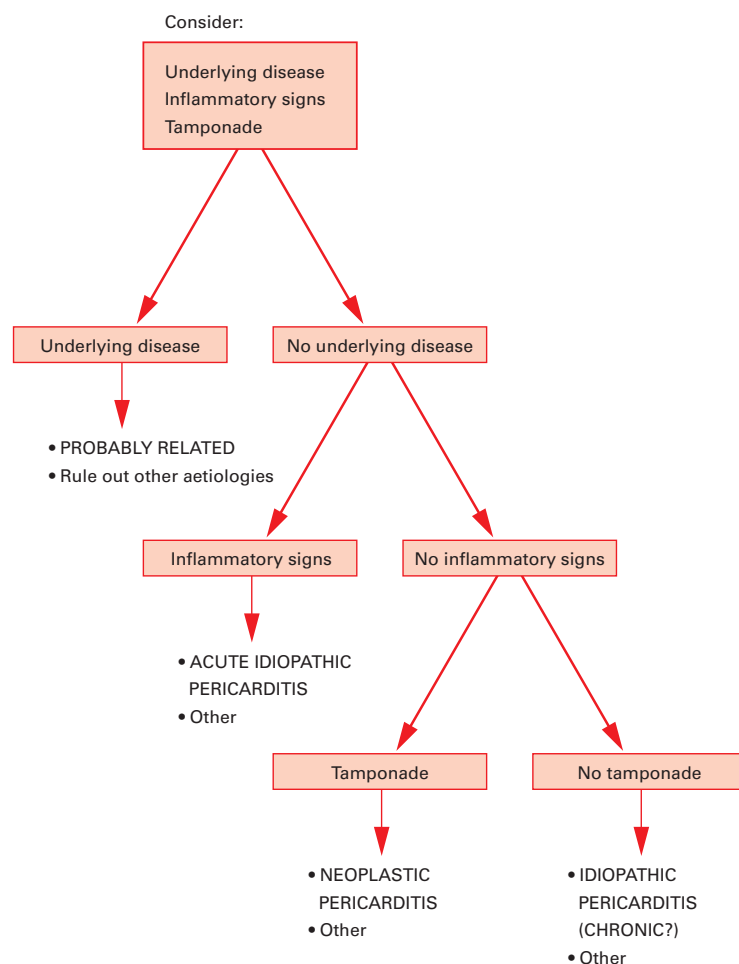
Consider:

Underlying disease
Inflammatory signs
Tamponade

→ Underlying disease
  → • PROBABLY RELATED
    • Rule out other aetiologies

→ No underlying disease
  → Inflammatory signs
    → • ACUTE IDIOPATHIC PERICARDITIS
      • Other
  → No inflammatory signs
    → Tamponade
      → • NEOPLASTIC PERICARDITIS
        • Other
    → No tamponade
      → • IDIOPATHIC PERICARDITIS (CHRONIC?)
        • Other

Figure 1. Initial approach to aetiologic diagnosis of large pericardial effusion. This flow chart shows the aetiologic likelihood of large pericardial effusion depending on simple clinical data (presence of underlying disease, inflammatory signs, and tamponade). Modified from Sagristà-Sauleda *et al*.[5]

changes) was predictive for acute idiopathic pericarditis (p < 0.001, likelihood ratio 5.4), irrespective of the size of effusion and presence or absence of tamponade. Furthermore, a large effusion with absence of inflammatory signs and absence of tamponade was predictive of chronic idiopathic pericardial effusion (p < 0.001, likelihood ratio 20), and tamponade without inflammatory signs predictive of neoplastic pericardial effusion (p < 0.001, likelihood ratio 2.9). The search for evidence of a previous effusion can be particularly helpful, as it may help to distinguish neoplastic disease from chronic idiopathic pericardial effusion, which sometimes presents with tamponade. Therefore, although the final aetiologic diagnosis should certainly be based on specific clinical data in individual patients, we think that the data afforded by this study (fig 1) may be helpful in the initial assessment and in the decision to perform invasive pericardial studies.

Special attention should be given to tuberculous pericarditis. Most patients with acute pericarditis will turn out to have idiopathic pericarditis, but a few cases will be tuberculous in origin. Identification of these cases is important because of the obvious therapeutic implications.

The diagnosis can be established through general examination, including the search of tubercle bacilli in sputum or gastric aspirate (which provided the diagnosis in four of our eight cases[5]), or by means of pericardial fluid or pericardial tissue examination (indicated in patients with tamponade or with persistent active illness for more than three weeks).

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Clinical correlation of echocardiographic and catheterisation findings

Before the advent of echocardiography and cardiac catheterisation, the haemodynamic compromise caused by pericardial effusion could be recognised only through physical findings such as jugular venous distension, hepatomegaly, hypotension, or pulsus paradoxus. These clinical findings defined the condition known as classical clinical tamponade. With the availability of echocardiography it was soon realised[11 12] that some patients with pericardial effusion but without clinical tamponade show findings suggesting raised intra-pericardial pressure—namely, collapse of the right sided cardiac chambers. Cardiologists were puzzled about the clinical relevance of these findings, especially regarding the indication of pericardial drainage, since these findings were interpreted as "impending" cardiac tamponade. Studies correlating clinical, echocardiographic, and catheterisation data helped to clarify this problem, although some doubts remain.

In the study by Levine and colleagues,[8] 50 consecutive patients with pericardial effusion and echocardiographic findings suggestive of tamponade (defined as the presence of right heart chamber collapse) underwent combined right sided cardiac catheterisation and percutaneous pericardiocentesis. Right atrial collapse was present in 92%, and right ventricular collapse in 57% of patients, respectively. The initial pericardial pressure was raised in all patients (range 3–27 mm Hg) and was equal to right atrial pressure in 84% of patients. However, many patients had minimal evidence of haemodynamic compromise. For example, systolic blood pressure was higher than 100 mm Hg in 94% of patients, elevation of the jugular venous pressure was found in only 74%, hepatomegaly was present in 28%, and pulsus paradoxus was found in only 36% of patients. In comparison with the series of Guberman and associates,[7] which included patients with classical clinical tamponade, the patients in the series of Levine and colleagues[8] had a significantly lower prevalence of hypotension, abnormal pulsus paradoxus, jugular venous pressure elevation, and hepatomegaly. In fact, in 25 patients (50%) tamponade had not been suspected before the echocardiographic study. Pericardiocentesis was associated with reduction of mean (SD) pericardial pressure in all patients (15 (5) to 1 (5) mm Hg), but frequently did not alleviate dyspnoea or correct tachycardia.

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These findings suggest that echocardiography can identify patients with pericardial effusion causing elevation of pericardial pressure before overt haemodynamic embarrassment develops, as the majority of these patients had only mild to moderate clinical tamponade. Subsequent studies have also shown that some patients with moderate or severe pericardial effusion and without any sign of clinical tamponade have chamber collapse at echocardiographic examination. For example, in the study by Mercé and colleagues,[13] which included 110 patients with moderate or severe pericardial effusion, 34% of 72 patients without clinical tamponade showed collapse of one or more cardiac chambers. Specifically, right atrial collapse had a low positive predictive value (50%) for clinical cardiac tamponade. However, these patients consistently show elevation of intrapericardial pressure when they undergo catheterisation study. Patients with asymptomatic large pericardial effusions without echocardiographic collapse show elevation of intrapericardial pressure, which equalises with right atrial pressure and becomes normal after pericardiocentesis. This situation is often found in patients with chronic massive pericardial effusion, as discussed below. Experimental[14–17] and clinical[18 19] studies have shown that cardiac tamponade is not an "all or nothing" phenomenon but a continuum that goes from slight elevation of intrapericardial pressure with subtle haemodynamic changes to severe haemodynamic embarrassment and even death.

Indications for invasive pericardial procedures in the absence of clinical tamponade

The prognosis of pericardial effusion mainly depends on the underlying aetiology, provided that haemodynamic compromise is not life threatening. The optimal management of large pericardial effusion without clinical tamponade is controversial. Some authors[3 4] advise routine pericardial drainage by pericardiocentesis or surgical pericardiotomy, claiming diagnostic and therapeutic benefits. However, these procedures are not innocuous and some fatalities have been reported. Our opinion is that in patients without haemodynamic compromise, routine pericardial drainage would only be justified if it might provide relevant diagnostic information or help to avoid further tamponade. In a study by our group,[20] which included 71 patients with large pericardial effusion without clinical tamponade or suspected purulent pericarditis, we found that pericardial drainage procedures (performed in 26 patients) had a diagnostic yield of only 7%. On the other hand, no patients developed cardiac tamponade or died as a result of pericardial disease, nor did any new diagnosis become apparent in the 45 patients who did not have pericardial drainage initially. Furthermore, moderate or large effusions persisted in only two of 45 patients managed conservatively. In

> **Indications for pericardiocentesis/surgical drainage**
>
> - Pericardiocentesis is indicated in patients with overt clinical tamponade, in patients with suspicion of purulent pericarditis, and in patients with idiopathic chronic large pericardial effusion
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> - The indications for surgical drainage are tamponade, either unresolved or relapsing after pericardiocentesis, and persistent active illness three weeks after hospital admission
>
> - Pericardial drainage does not seem warranted in the initial management of patients with large pericardial effusion without clinical tamponade because of its low diagnostic yield and its poor influence on the evolution of pericardial effusion. Even the presence of echocardiographic right chamber collapse (suggesting raised intrapericardial pressure) does not warrant by itself pericardial drainage as most of these patients do not evolve to overt tamponade

another study by our group,[12] we found that even patients with echocardiographic collapse rarely require pericardial drainage for therapeutic purposes during initial admission. Accordingly, we think that routine pericardial drainage is not justified in the initial management of patients with large pericardial effusion without clinical tamponade, especially if the aetiology is known. The exceptions would be those patients with suspected purulent or tuberculous pericarditis.

Idiopathic chronic pericardial effusion

When a large pericardial effusion persists for more than three months, the prognosis, even in asymptomatic patients, is less good. Sagristà-Sauleda and colleagues[21] have reported that up to 29% of such patients may develop unexpected, overt cardiac tamponade. In these patients medical treatment, particularly corticosteroids or antituberculous therapy, is not useful. The trigger of tamponade is unknown, but hypovolaemia, paroxysmal tachyarrhythmias, and intercurrent acute pericarditis may precipitate tamponade; accordingly, these events should be vigorously managed.

Role of pericardiocentesis
Pericardiocentesis is the first option in patients with overt tamponade. Elective pericardiocentesis is warranted in asymptomatic patients as well, as a prophylactic measure to prevent unexpected tamponade. In these patients pericardiocentesis may result in the disappearance of chronic pericardial effusion as was the case in eight of 19 patients with effusions present for at least four years.[21] Pericardiocentesis should drain as much pericardial fluid as possible. In

Idiopathic chronic pericardial effusion

- Large (echo-free spaces > 20 mm), chronic (longer than three months) idiopathic pericardial effusion may evolve to unexpected clinical tamponade in spite of a previous prolonged (years) good clinical tolerance

- Anti-inflammatory drugs and corticosteroids are unsuccessful. Pericardiocentesis may allow the resolution of effusion in a third of patients. When large effusion reappears after two pericardiocenteses, wide anterior pericardiectomy has to be considered

some cases with a relapsing effusion, it has been shown that a second pericardiocentesis is usually followed by complete resolution of the effusion.

Role of pericardiectomy

Surgical drainage with wide anterior pericardiectomy is very effective in the long term.[21 22] At the present time, we recommend this procedure only in patients, with or without symptoms, in which repeat pericardiocentesis is not followed by notable or complete diminution of the effusion.

Management of neoplastic pericardial effusion

Symptoms and signs suggestive of pericardial involvement may be the presenting clinical feature of either primary[23] or secondary[24] malignant cardiac disease, but they are much more frequently present in patients under treatment for advanced malignancy. Life expectancy is short as concomitant metastases are nearly always present elsewhere. In these instances, adequate management of pericardial effusion may contribute to palliation of the symptoms—in a significant number of

patients—and possibly to prolonged survival (in an undefined number of cases). Although the main causes of death in patients with malignancy are unrelated to cardiac involvement, in some necropsy series pericardial metastases are commonly found, particularly in lung cancer (35%)[25] and breast cancer (25%)[26]; on the other hand, cardiac symptoms are mainly related to the presence of tamponade, which is present in a significant number of patients, although it has no negative impact on survival if it is correctly managed.

In patients with malignancy and pericardial effusion the first step is to determine whether the effusion is secondary to neoplastic pericardial involvement or if it is an epiphenomenon (non-malignant effusion) related to the management of the cancer (such as previous thoracic irradiation) or effusions of unknown origin. In these two latter situations, an invasive procedure may be warranted in the absence of tamponade as the diagnostic yield of both pericardial fluid and tissue is high for malignancy.[27]

The management of cardiac tamponade in patients with secondary neoplastic pericardial involvement has two targets—relief of symptoms, and prevention of recurrences. Pericardiocentesis alleviates symptoms in most cases. It is a safe, simple, and widely available procedure with few complications if it is done under echocardiographic guidance. Probably it is the procedure of choice in end stage patients, when recurrence of effusion is not a real issue. In patients surviving longer the pericardial fluid may re-accumulate, and isolated pericardiocentesis prevents this in only about 50% of cases.[28] In such patients a more aggressive approach with surgery may be warranted. Patient management has to be individualised (type and stage of neoplasm, general condition, etc)[28 29] as even the best possible treatment for responsive types of tumour (for example, lymphoma) with neoplastic pericardial involvement is associated with survival of only about one year.

Procedures to prevent tamponade

Among the several procedures suggested to prevent tamponade, none has emerged as the treatment of choice (fig 2)[28]; adequate controlled trials for the different procedures in the several types of neoplasm are not available. The rate of success (defined as a procedure without mortality, no recurrent cardiac symptoms, and no additional pericardial procedure) of the above mentioned treatment modalities is depicted in fig 2. Taking into consideration the poor prognosis of these patients we favour the less invasive procedures, although a surgical approach may occasionally be indicated.
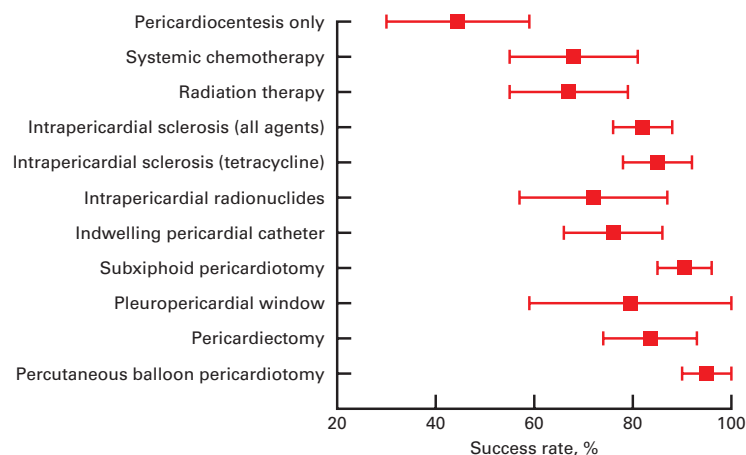

Figure 2. Success rates with 95% confidence intervals for different treatment modalities of malignant pericardial effusions to prevent further pericardial complications. Reproduced form Vaitkus et al[28] (Treatment of malignant pericardial effusion. *JAMA* 1994;**272**:59–64). Copyrighted (1994), American Medical Association.

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