Current perspective

Clinical management of acute pericardial disease: a review of results and outcomes

Massimo Imazio, Rita Trinchero

Cardiology Department, Maria Vittoria Hospital, ASL 3 Turin, Italy

Key words:
Cardiac tamponade; Pericardial effusion; Pericarditis; Pericardium.

Acute pericardial diseases are common disorders in several clinical settings. The presentation may include acute pericarditis and its recurrences, incidental pericardial effusion, cardiac tamponade, and occasionally constrictive pericarditis. New diagnostic techniques have improved the sampling and analysis of pericardial fluid and allow a comprehensive diagnostic approach. Deciding on the extent of diagnostic evaluation in the individual patient requires good clinical judgment based on careful evaluation of the risk-benefit ratio of the planned diagnostic and therapeutic options. Most cases of acute pericarditis are viral or idiopathic and self-limited; however, other etiologies should also be considered. The diagnostic yield of extensive laboratory evaluation and pericardiocentesis is low, and invasive procedures should be limited mainly to patients in whom therapeutic intervention is necessary. Treatment should focus on symptomatic relief, usually through the administration of non-steroidal anti-inflammatory drugs, and patients should be carefully evaluated and monitored for common complications of the disease.

(Ital Heart J 2004; 5 (11): 803-817)

Received June 9, 2004; revision received October 12, 2004; accepted October 13, 2004.

Address:

Dr. Massimo Imazio

Dipartimento di Cardiologia Ospedale Maria Vittoria ASL 3 Torino Via Cibrario, 72 10149 Torino
E-mail: imazio@tin.it

Acute pericardial diseases are common disorders in several clinical settings, including primary care as well as emergency and subspecialty departments, such as cardiology, rheumatology, and nephrology. Their exact incidence and prevalence are unknown; however, acute pericardial diseases and their recurrences are quite common in everyday clinical practice and, even today, remain a challenging problem for the clinician. Acute pericardial diseases include acute pericarditis and its recurrences, pericardial effusion and cardiac tamponade.

The diagnosis of acute pericarditis in a young patient with typical chest pain is easy, but diagnosing the etiology may be quite more difficult. Deciding on the extent of diagnostic evaluation in the individual patient requires good clinical judgment based on careful evaluation of the risk-benefit ratio of planned diagnostic and therapeutic options.

Recently, a new direction in the diagnosis and treatment of pericardial disease has been proposed[1-4]. This approach is based on the comprehensive and systematic implementation of new techniques of pericardiocentesis, pericardial fluid analysis, pericardioscopy, epicardial and pericardial biopsy, as well as the application of molecular biology and immunology techniques for pericardial fluid and biopsy analyses in order to permit a specific diagnosis and treatment.

However, this strategy reported by the same authors in recently published guidelines[5] has not been employed in most academic and health care institutions and, in most cases, is not available. The clinician may wonder whether the usual "old" clinical approach must be changed and which clinical management is advisable. In order to provide an evidence-based guide for the clinical management of acute pericardial disease, we propose a review of the results and outcomes of the published papers and reviews.

A systematic review of all the published works on acute pericardial disease was performed. We did a comprehensive Medline search and included the MeSH terms "pericarditis", "pericardium", "pericardial effusion", "cardiac tamponade", and "pericardial constriction". Only papers published in English were considered. Papers with new or important contents as well as relevant abstracts are included in the reference list.

Acute pericarditis

Approach to the etiologic diagnosis. The true incidence and prevalence of acute pericarditis are unknown. As suggested by a

prevalence of about 1% in autopsy studies, pericarditis is frequently subclinical. However, it is a common disease that might account for up to 5% of presentations with non-ischemic chest pain[6].

Acute pericarditis may be due to several causes, owing to the fact that the pericardium may be involved in a large number of systemic disorders. Besides, acute pericarditis may also present as an isolated entity[7,8]. Acute pericarditis may be subdivided into infectious (more commonly viral) and non-infectious disease. A useful etiologic classification of acute pericarditis is reported in table I. However, in clinical practice a probabilistic approach seems to be reasonable. In Western countries most cases presenting in immunologically competent patients and not associated with apparent medical or surgical conditions have a viral etiology. In some cases an immunological response related to a previous viral infection may be found. However, in clinical practice many cases are classified as idiopathic pericarditis because an extensive diagnostic evaluation is not performed or is unsuccessful (Table II)[9-11]. Thus, most cases of the so-called idiopathic pericarditis are probably viral[8-11]. Acute viral or idiopathic pericarditis typically follows a brief and benign course after empiric treatment with salicylates or other non-steroidal anti-inflammatory drugs (NSAIDs)[9-11]. Some clinical features at presentation may be highly suggestive of a specific etiology or predictive of a high risk of complications. These include high fever, subacute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, severe pericardial effusion, and cardiac tamponade[11].

Table I. Etiology of acute pericarditis.

- Idiopathic pericarditis
- Infectious pericarditis: viral (echovirus and coxsackievirus are the most common), tuberculous, other bacterial and fungal (rare)
- Pericarditis in autoimmune disorders (pericardial injury syndromes including Dressler syndrome, postcardiotomy syndrome, autoreactive pericarditis, pericarditis in systemic autoimmune diseases: more common in systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Behçet syndrome, and familial Mediterranean fever)
- Neoplastic pericarditis: primary (rare, above all mesothelioma), secondary (common: lung and breast cancer, lymphoma)
- Pericarditis in metabolic disorders (more common: uremia and dyalisis-related, myxedema)
- Pericarditis in diseases of the surrounding organs (acute myocardial infarction, aortic aneurysm, lung infarction, pneumonia, paraneoplastic pericarditis)
- Traumatic pericarditis (direct and indirect injury including mediastinal irradiation)
- Other (rare: drug-related, etc.)

Specific issues. *Tuberculous pericarditis.* Tuberculous pericarditis is now rare in developed countries (up to 5% of all cases), but remains common in developing countries. It is also frequent among immigrants (above all from Africa and Eastern Europe) and immunodepressed patients[12]. The mortality rate in untreated effusive tuberculous pericarditis may be as high as 85% and pericardial constriction may be a delayed complication in up to 50% of all cases[5]. The symptoms of tuberculous pericarditis are non-specific and fever, weight loss, and night sweats generally precede cardiopulmonary complaints. While pericarditis in a patient with proven ongoing extracardiac tuberculosis is strongly suggestive of a tuberculous etiology, in many adults tuberculous pericarditis is due to reactivation of the disease. Thus, in such patients the primary focus of infection is often inapparent. In most cases tuberculous pericarditis is insidious in onset[13] and failure of empiric treatment with NSAIDs as well as disease persistence for more than 1 week are both common[9,10]. In such patients it is important to rule out a specific etiology[9-11]. Thus, it is necessary to ascertain whether the patient has a history of tuberculosis, tuberculosis exposure, PPD skin test reactivity, or immunodepression. Then, it is necessary to systematically perform an intermediate strength PPD skin test as well as a search for mycobacteria (both in stained smears and by culture) on three samples of sputum or, in patients not producing sputum, in gastric aspirates. The vast majority (over 85%) of immunocompetent patients with acute or chronic tuberculous pericarditis have a positive PPD skin test[14]. Thus, a negative PPD skin test indicates a low probability of tuberculous pericarditis. However, the PPD skin test is often negative in patients with HIV infection. Moreover, the tuberculin skin test has yielded false negative results in

Table II. Etiology of acute pericarditis in published clinical studies with unselected populations.

	Permanyer-Miralda et al.[9] (n=231)	Zayas et al.[10] (n=100)	Imazio et al.[11] (n=300)
Years (printed)	1977-1983 (1985)	1991-1993 (1995)	1996-2001 (2004)
Idiopathic	199 (86.0%)	88 (88.0%)	240 (80.0%)
Specific etiology	32 (14.0%)	22 (22.0%)	60 (20.0%)
Neoplastic	13 (5.6%)	7 (7.0%)	14 (4.7%)
Tuberculosis	9 (3.9%)	4 (4.0%)	14 (4.7%)
Autoimmune etiology	4 (1.7%)	3 (3.0%)	26 (10.2%)
Purulent	2 (0.9%)	1 (1.0%)	1 (0.3%)

up to 33% of cases due to anergy. Besides, it is positive in about 30 to 40% of patients with acute idiopathic pericarditis. Thus, the tuberculin skin test alone is not a reliable indicator of tuberculous pericarditis[5]. While in a minority of patients with pericarditis, a diagnosis may be made by culture or histological demonstration of tuberculosis outside the pericardium (sputum, gastric aspirate, pleural fluid), a definite diagnosis of tuberculous pericarditis is made by the identification of *Mycobacterium tuberculosis* in the pericardial fluid or tissue, and/or the presence of caseous granulomas in the pericardium[5,15]. The following analyses are useful in case of suspected tuberculosis: acid-fast bacilli staining, mycobacterium culture or radiometric growth detection, polymerase chain reaction analyses, adenosine deaminase (ADA), interferon (IFN)-γ. Pericardial fluid has a high specific gravity, high protein levels, and a high white cell count. A high ADA activity and IFN-γ levels in pericardial effusion are diagnostic. Using a cut-off value of ADA activity of 40 U/l, the sensitivity and specificity of ADA testing were 93 and 97% respectively. Using a cut-off of 30 U/l, the sensitivity was 94% and the specificity 68% with a positive predictive value of 80%. A cut-off value of 200 pg/l for pericardial IFN-γ resulted in a sensitivity and specificity of 100% for the diagnosis of tuberculous pericarditis[16]. Polymerase chain reaction analysis may identify the DNA of *Mycobacterium tuberculosis* in as little as 1 μl of pericardial fluid[5].

As reported by the current European Society of Cardiology (ESC) guidelines[5], we believe that only patients with proven or very probable tuberculous pericarditis should be treated. Various antituberculous drug combinations of different durations have been proposed[5]. A possible treatment of choice for all adults with tuberculous pericarditis (as for other forms of extrapulmonary tuberculosis) is an initial four-drug regimen: isoniazid (300 mg orally once daily), rifampicin (600 mg orally once daily), pyrazinamide (15 to 30 mg/kg/day up to 2 g/day given as a single dose, in Italy generally up to 1.5 g/day), and either ethambutol (15 to 25 mg/kg orally once daily) or streptomycin (20 to 40 mg/kg up to 1 g given intramuscularly once daily). After a daily therapy for 8 weeks, most patients may be switched to a daily or twice weekly two-drug regimen consisting of isoniazid and rifampicin until completion of a 6-month course of therapy. A meta-analysis of patients with effusive and constrictive tuberculous pericarditis suggested that the addition of corticosteroids to standard antituberculous treatment may reduce mortality and the need of subsequent pericardiocentesis and pericardiectomy. Thus, prednisone at the dose of 1 mg/kg for 1 month followed by a 2-month taper is recommended[17].

HIV infection. Pericardial involvement is seen in up to 20% of patients with HIV infection, but symptomatic pericarditis is frequently due to secondary infection (often mycobacterial) or neoplasia (particularly lymphoma or Kaposi's sarcoma)[18,19]. Nowadays, the incidence of pericardial involvement has decreased owing to effective antiretroviral therapy, but when present, it is associated with a worse prognosis[19].

Iatrogenic etiology. Due to the contemporary widespread use of invasive diagnostic and therapeutic options, radiation therapy, cardiac surgery and percutaneous procedures have become important causes of acute pericarditis[8].

Pericardial injury syndromes. Pericardial injury syndromes include the postpericardiotomy syndrome, the postmyocardial infarction syndrome, and traumatic pericarditis. The pericardial injury syndromes have many clinical and pathogenetic features in common, including: a prior injury of the pericardium, myocardium or both, followed by a latent period between the injury and the development of pericarditis, and their responsiveness to NSAIDs and corticosteroids.

The postpericardiotomy syndrome has been reported in up to 20% of cases at a median of 4 weeks after surgery. In these cases pericardial constriction is common and has been reported in about 0.2% of cases[20,21]. The most frequent complaint is chest pain occurring a few days to several weeks after a cardiac operation. Fever, leukocytosis and an elevated erythrocyte sedimentation rate are typically seen. The pathogenesis is thought to be autoimmune and is precipitated by pericardial injury during cardiac surgery.

After cardiac surgery, the baseline ECG is seldom normal. As a result, it is difficult to make a diagnosis of pericarditis by ECG. Serial echocardiography shows that postoperative pericardial effusion is considerably more common than is clinically obvious, being present in as many as 85% of patients[22]. The effusion usually develops by the second postoperative day but may not occur until day 10. In most cases, the effusion reaches its maximal size by the tenth postoperative day and then gradually resolves. The presence of pericardial effusion alone is not sufficient for the diagnosis of acute pericarditis.

The postmyocardial infarction and the postpericardiotomy syndromes are both treated with NSAIDs (ibuprofen, which increases coronary flow, may be the agent of choice). Anecdotal reports suggest that colchicine may be helpful. There are more data supporting benefit from colchicine in patients with recurrent pericarditis, which also appears to be mediated by immune mechanisms. A short course of steroids is effective when the patient does not respond to the above drugs. Owing to the widespread use of thrombolysis, pericarditis associated with transmural myocardial infarction is now less frequent and occurs in no more than 5 to 10% of cases[23,24]. It should be suspected in any patient with pleuropericardial pain. A pericardial friction rub may or may not be present. The differenti-

ation of pericarditis from recurrent angina may be difficult, but a careful history and evaluation of serial ECGs may help to distinguish the two entities. Dressler's syndrome, pericarditis that occurs at least 1 week following myocardial infarction, is now exceedingly rare[7,8]. Most cases of pericarditis have a benign course; however, because pericarditis is associated with larger infarcts, the overall long-term mortality rate is increased. Rare complications include hemopericardium, cardiac tamponade, and constrictive pericarditis.

Neoplastic pericarditis. Another important etiology to be considered in Western countries is neoplastic pericarditis. Neoplastic pericarditis is generally a secondary disorder caused by local tumor invasion or lymphatic or hematogenous spread (generally from breast or lung carcinoma, and lymphoma) while primary malignant disease is rare (generally pericardial mesothelioma)[8].

Most patients with a malignant pericardial disease are known to have a malignant tumor before evidence of pericardial involvement. However, some cases of pericardial disease as the first manifestation of cancer have been described. In a survey on 450 consecutive patients, an acute pericardial disease was the initial clue to malignancy in up to 4% of cases (in 3 out of 4 cases lung cancer was discovered in these patients). Malignancy must be excluded in every case of an acute pericardial disease with cardiac tamponade at presentation, an incessant or recurrent course, and in case of a lack of response to NSAIDs[25]. The patient with neoplastic pericarditis may have a mild, subtle presentation, as is often seen in the early stages of pericardial effusion, or may present with dramatic hemodynamic compromise, as is seen with cardiac tamponade and constrictive pericarditis. An effusion must be considered of proven malignant origin when specific supporting evidence is collected (e.g. positive cytology or positive biopsy). Cytology and tumor markers (carcinoembryonic antigen, α-feto protein, CA 125, CA 72-4, CA 15-3, CA 19-9) are mandatory in case of suspected neoplastic pericarditis. Moreover, in this subset low levels of ADA and high levels of carcinoembryonic antigen are highly suggestive of neoplastic pericarditis.

Many treatment options are available. These range from simple drainage to thoracic surgery. It is essential that the treating physician choose a treatment plan in the context of the cancer stage, the patient's prognosis, the success rates and risks of the various modalities, and also the local availability and expertise[26,27]. Given the poor prognosis of most patients presenting with malignant pericardial effusions, reducing symptoms and improving quality of life are the primary goals of treatment[28]. In cases with cardiac tamponade or significant effusion, initial relief may be easily obtained with percutaneous pericardiocentesis sometimes followed by drainage with an indwelling catheter. Effusion recurrences may occur, however, in up to 40% of cases if only simple pericardial drainage is performed[27,29]. Systemic antitumor therapy with chemotherapy or radiation therapy is effective in controlling malignant effusions in cases of sensitive tumors such as lymphomas, leukemias and breast cancer and must be considered whenever possible. Effective management may also be achieved by instillation in the pericardial sac of different agents, with sclerosing or cytostatic activity, such as tetracyclines, bleomycin, thiotepa, cisplatin or radionuclides[29]. Intrapericardial treatment tailored to the type of cancer indicates that cisplatin is more effective in secondary lung cancer while thiotepa is more effective in breast cancer[5,29]. Tetracyclines as sclerosing agents are effective in 80 to 90% of cases, but side effects and complications are common and include fever, chest pain, supraventricular arrhythmias, and above all fibrosis leading to constriction in long-term survivors.

Nowadays, radiation therapy for the treatment of mediastinal tumors and breast cancer is known as an increasingly frequent cause of pericarditis and pericardial constriction[30].

Diagnosis. Acute pericarditis is diagnosed when at least two of the following criteria are present: pericarditic chest pain, pericardial friction rub, and widespread ST-segment elevation on the ECG[7-9,11,31]. The presence of pericardial effusion confirms the clinical suspicion but is not necessary for the definite diagnosis.

Chest pain is the most common symptom and is typically sudden and severe in onset after a "viral illness" and may be preceded by low-grade fever (Table III). The pain is retrosternal and/or left precordial with possible referral to the back and trapezius ridge, and is often pleuritic and accentuated by inspiration, coughing and sometimes swallowing. It may be aggravated by some changes in posture (supine or left lateral decubitus posture) and relieved by others (upright posture).

The pericardial friction rub is considered the pathognomonic specific physical finding of acute pericarditis[7,31]. Classically described as triphasic (52%), with systolic and both early (passive ventricular filling) and late (atrial systole) diastolic components, it may be biphasic (33%) or monophasic (15%). The pericardial

Table III. Clinical findings in 300 consecutive cases of acute pericarditis[11].

Clinical finding	No. patients
Chest pain	295 (98.3%)
Pericardial friction rub	105 (35.0%)
ST-segment elevation	268 (89.3%)
Typical ECG evolution	161 (60.1%)
Pericardial effusion	180 (60.0%)
Cardiac tamponade	15 (5.0%)
Acute onset	267 (89.0%)

friction rub is frequently evanescent, positional, and may vary in intensity and characteristics even during a single day. Furthermore, it may occasionally disappear. Hence, adequate evaluation may sometimes require careful and repeated examination[11,31]. Although the presence of a pericardial rub guarantees the diagnosis, its absence does not exclude it.

ECG changes are common and typically evolve through four stages:

• stage I (first hours to days) is characterized by diffuse ST-segment elevation (typically concave up). There is also an atrial current of injury, reflected by elevation of the PR segment in lead aVR and depression of the PR segment in the other leads, principally V_5 and V_6. PR deviations are frequently overlooked and are recorded as the first and early ECG abnormalities[32];

• stage II is characterized by normalization of the ST and PR segments;

• stage III is characterized by the development of widespread T-wave inversions, generally after the ST segments have become isoelectric;

• stage IV is characterized by ECG normalization or by persistent T-wave inversion.

A typical ECG evolution is recorded in up to 60% of cases[11], while an atypical evolution is not rare and, especially in myopericarditis, may simulate an acute coronary syndrome. Therapy may accelerate or alter the progression of the ECG changes.

Patients with concomitant myocarditis may show ST and T changes resembling those of isolated pericarditis or acute ischemia. The ECG differential diagnosis must include acute coronary syndrome and early repolarization. The ECG features that may be used to distinguish the ECG changes in acute pericarditis from those in acute coronary syndromes and early repolarization are reported in tables IV and V.

Sustained arrhythmias are uncommon in acute pericarditis. They have been reported in only 7% of cases, were all atrial and occurred in patients with heart disease.

Acute pericarditis has also been associated with elevated biomarker serum levels. The MB fraction of creatine kinase may be modestly elevated in some cases of acute pericarditis, while the level of C-reactive protein is usually high. An elevation in serum cardiac troponin I (cTnI) is a sensitive and specific marker for myocardial injury and may also be seen in patients with acute pericarditis (Table VI)[33-35]. In two studies including 187 consecutive patients with acute idiopathic pericarditis, cTnI was detectable in the serum in 32 to 49% of cases and was above a threshold value of 1.5 ng/ml in 8 to 22%[33,35].

Features associated with a rise in cTnI are younger age, male gender, ST-segment elevation, a pericardial effusion at presentation and recent infection. Coronary angiography was performed in 16 patients with a cTnI level ≥ 1.5 ng/ml in the two studies and was normal in all[33,35]. The enzyme rise is transient, typically resolving within 10 days of presentation. Persistent cTnI elevations suggest myopericarditis. The rise in cTnI levels in acute pericarditis is roughly related to the extent of myocardial inflammation, and unlike acute coronary syndromes, is not a negative prognostic marker[35].

Clinical management. In three series including a total of 631 patients with primary acute pericardial disease who underwent conservative clinical evaluation, a specific diagnosis was established in 114 cases (18%)[9-11]. Among them, the most common diagnoses were neoplasia (29.8%), autoimmune disease (28.9%), and tuberculosis (23.7%), while purulent pericarditis (3.5%) was less common. The first study[9] was largely performed before the HIV era, while the second included only HIV-negative patients[10]. In the third study[11] HIV-infected patients were not excluded and accounted for about 5.0% of all cases.

In all these clinical studies a conservative diagnostic protocol was adopted considering that most cases had probably a viral or idiopathic etiology. The diagnosis of viral infection is strongly supported by the find-

Table V. ECG differential diagnosis between acute pericarditis and early repolarization.

Finding	Acute pericarditis	Early repolarization
Distribution	Generalized	V_3-V_6
PR depression	Yes	No
ST-segment evolution	Yes	No
ST/T ratio in V_6	≥ 0.24	< 0.24

Table IV. ECG differential diagnosis between acute pericarditis and ST-elevation myocardial infarction.

Finding	Acute pericarditis	Acute coronary syndrome
ST-segment elevation	Normal concavity, < 5 mm	Convex (dome-shaped), > 5 mm
Distribution	Generalized	Localized
Reciprocal ECG changes	No	Yes
T-wave inversion	Generally after ST-segment normalization	Before ST-segment normalization
ST-segment evolution	Asynchronous	Synchronous
PR depression	Yes	No
New Q waves	No	Yes
Prolonged QT interval	No	Yes

Table VI. Cardiac troponin (cTn) I elevation in viral or idiopathic acute pericarditis in published studies.

Study	Years	Study design	Setting	No. patients	cTn I assay	cTn I+	cTn I+ (≥ 1.5 ng/ml)
Bonnefoy et al.[33]	1996-1997	Single-center, retrospective	Hospital	69	Dade, Stratus	34 (49%)	15 (22%)
Brandt et al.[34]	1998-1999	Single-center, observational	Hospital	14	Abbott Lab	10 (71%)	ND
Imazio et al.[35]	2000-2002	Single-center, prospective	Hospital, day-hospital, ambulatory	118	Dade, Stratus	38 (32%)	9 (7.6%)

ND = not determined.

ing of a greater than 4-fold rise in serial antiviral antibody titers during the initial 3 weeks of illness, while it is rarely productive to attempt to isolate the virus from blood, pericardial fluid, pleural fluid or stool. However, treatment is not influenced by a specific viral diagnosis; thus, the diagnosis is frequently presumed to be viral, but evidence for this is often not sought because of the expense involved and the time required before the results of viral titers are available. This approach may change with the introduction of new methods for the diagnosis and treatment of specific viral infections.

The number of "idiopathic" cases may be substantially reduced with an invasive approach including a comprehensive and systematic implementation of new techniques of pericardiocentesis, pericardial fluid analysis, pericardioscopy, epicardial and pericardial biopsy, as well as the application of molecular biology and immunology techniques for pericardial fluid and biopsy analyses in order to permit a specific diagnosis and treatment. In this setting true idiopathic cases are reduced to less than 5% of all cases[1-5]. However, these techniques are expensive, not universally available and require invasive interventions in patients with a possible brief and benign course after NSAIDs.

Recently, a clinical approach for the triage of acute pericarditis has been proposed[11]. After literature review, the clinical features that had previously been more frequently associated with an increased risk of short-term complications or a high likelihood of a specific disease were identified as "poor prognostic predictors". These clinical features included fever > 38°C, subacute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, severe pericardial effusion and cardiac tamponade. Patients without poor clinical or echocardiographic prognostic predictors were considered at low risk and assigned to outpatient treatment with high-dose oral aspirin (800 mg orally every 6 or 8 hours for 7-10 days with gradual tapering over 2-3 weeks and gastroprotection with omeprazole 20 mg/day). A clinical and echocardiographic follow-up was performed at 48-72 hours, 7 to 10 days, 1 month, 6 months and 1 year in non-complicated cases.

Patients with poor clinical and echocardiographic prognostic predictors or patients who did not respond to aspirin were considered high-risk patients to be studied and treated after hospitalization. In these cases a complete search for specific causes was performed.

Aspirin failure was considered in case of an unfavorable clinical reaction with persistence of fever, pericardial effusion appearance or worsening and generalized illness lasting more than 7 days despite treatment with full-dose aspirin[9-11].

In this study a low recurrence rate was observed (16.9%) in the low-risk group and was attributed to the application of a conservative management protocol and to the gradual tapering of aspirin, while the reported recurrence rate after an initial attack of idiopathic pericarditis may be as high as 30 to 50%[5,36]. Moreover, authors[1-5] who usually perform a thorough invasive approach have reported the highest frequency of recurrence (up to 50%) while the recurrence rate is lower in clinical studies where a conservative management strategy was adopted[9-11]. It is not clear whether this is to be attributed to a selection bias (surveys from tertiary referral centers) or whether it is related to other causes.

The implementation of the protocol led to a specific diagnosis in 60 out of 300 cases (20.0%) in the un-selected group (previous literature data ranged from 14 to 22% of cases)[9,10], but in 36 out of 46 moderate-high-risk patients (78.3%) who were hospitalized. This suggests the importance and utility of patient selection to initiate a search for a specific etiologic diagnosis. Outpatient treatment was efficacious in 221 out of 254 cases (87%) without serious complications during follow-up.

In all studies, features that predicted the finding of a specific etiology were tamponade at presentation and lack of resolution after 7 to 10 days. No patient with seemingly idiopathic pericarditis had persistent disease or an adverse outcome.

The invasive nature of pericardiocentesis and pericardial biopsy must be weighed against their low diagnostic yield in some studies and against the demonstration that many patients may be safely and effectively managed without examination of the pericardial fluid[8-11]. Thus, in a clinical setting it is not appropriate to perform a full diagnostic evaluation in all patients with acute pericarditis. Acute pericarditis triage may be possible on a clinical basis and hospitalization and a full diagnostic evaluation may be safely restricted to high-risk cases (Fig. 1).

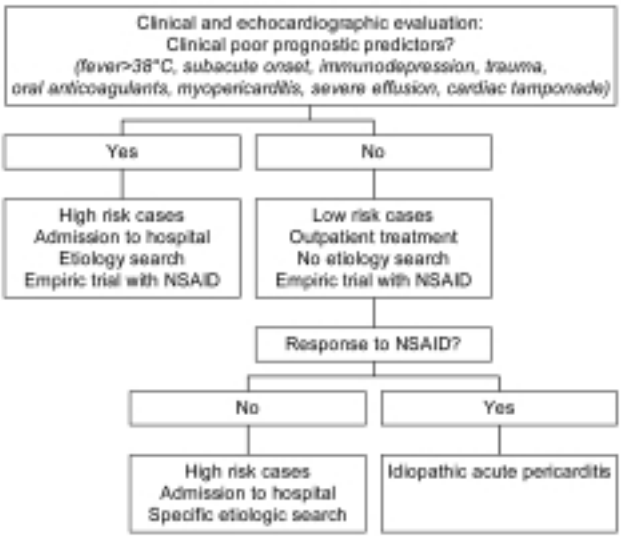


Figure 1. *Acute pericarditis triage (see text for details). NSAID = non-steroidal anti-inflammatory drug.*

Indications to invasive procedures. At this point a clinician may wonder when to resort to invasive approaches in a manner which effectively contributes to the clinical management. A traditional approach[9,37] has been thoroughly studied by Spanish authors (the so-called "Barcelona experience") and is summarized in table VII.

In the current ESC guidelines[5], pericardiocentesis is indicated for clinical tamponade, a high suspicion of purulent or neoplastic pericarditis (class I indication), or for large or symptomatic effusions despite medical treatment for more than 1 week. Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia (< 50 000/mm^3) and small, posterior, and loculated effusions. In acute traumatic hemopericardium and purulent pericarditis, surgical drainage is more appropriate than pericardiocentesis. The subxiphoid approach is used most commonly because it is extrapleural and avoids the coronary arteries. Pericardiocentesis may be guided by fluoroscopy or echocardiography. Direct ECG monitoring from the puncturing needle is not an adequate safeguard.

If hemorrhagic fluid is aspirated, one should remember that clotting is prevented in pericardial fluid; on the contrary, clotting readily occurs when blood is collected from a cardiac chamber. Fibrinolytic activity in the pericardium prevents blood clotting in subacute and chronic effusion. However, acute hemorrhage into the pericardium overwhelms fibrinolysis and blood clotting may occur in such cases. If the answer is not clear, contrast medium may be injected under fluoroscopic guidance, or agitated saline under echocardiographic guidance, to exclude cardiac puncture.

It is prudent to drain the fluid in steps of < 1 liter at a time to avoid acute right ventricular dilation (the so-called sudden decompression syndrome). The feasibility is high (> 90%) in patients with an anterior effusion > 10 mm while the success rate falls to about 60% in case of small, posterior effusions. The most serious complications of pericardiocentesis are lacerations and perforation of the myocardium and the coronary vessels. The incidence of major complications is < 1.6%[5].

In previous studies[9-11,37] pericardial biopsy was generally performed as a part of a therapeutic procedure (surgical drainage) in patients with cardiac tamponade relapsing after pericardiocentesis (therapeutic biopsy), and as a diagnostic procedure in patients with disease lasting > 3 weeks without a definite diagnosis.

Technical advances in instrumentation with the introduction of pericardioscopy, and in contemporary pathology, virology and molecular biology have improved the diagnostic value of epicardial/pericardial biopsy[1-5]. Targeted biopsy during pericardioscopy was particularly useful in the diagnosis of neoplastic pericarditis.

Although, according to some authors, pericardioscopy may offer an advantage in selected patients, the available evidence does not seem to justify increasing the indications for pericardial drainage. Probably a more appropriate approach might be a compromise between performing too many unnecessary invasive studies and missing too many specific diagnosis[38,39]. Thus, in current ESC guidelines pericardioscopy and pericardial biopsy have a class IIa indication[5]. This approach may change with the introduction of new treatments for specific viral infections. Still, nowadays the old clinical management with a wise use of invasive procedures seems to be appropriate in most cases.

Table VII. Management protocol for acute pericarditis in the "Barcelona experience".

Step	Procedures
I	General clinical and laboratory evaluation including ECG, chest X-ray and echocardiography was performed in all patients. For persistent illness (> 1 week) a specific etiology search is recommended
II	Pericardiocentesis was performed in patients who had tamponade, suspected purulent pericarditis or clinical activity with effusion persisting > 1 week after NSAID therapy. Pericardial studies are performed according to laboratory facilities
III	Pericardial biopsy was performed if the illness lasted > 3 weeks without an apparent etiologic diagnosis
IV	Empiric antituberculosis therapy was instituted if the diagnosis was not established by means of the above measures

NSAID = non-steroidal anti-inflammatory drug.

Recurrent pericarditis

Recurrent pericarditis is a syndrome in which pericarditis recurs after the original etiologic agent has dis-

appeared or has ceased to be active[7,40,41]. It is one of the most troublesome complications of acute pericarditis. Recurrent pericarditis may be a prolonged and frustrating disease with disabling pain and malaise. Because of this and the need to maintain compliance, effective communication with the patient is very important. The precise recurrence rate after the initial attack is unknown, but may be as high as 15 to 32%[36,40] and even up to 50% in some recent reports[3,5]. Recurrences may occur during the phase of drug reduction (incessant pericarditis) or after treatment discontinuation (recurrent pericarditis)[36].

Recurrent pericarditis is considered an autoimmune phenomenon and therefore should respond well to anti-inflammatory or immunosuppressive drugs[40,41]. The optimal method for preventing and treating recurrences has not been established. Therapeutic modalities are non-specific and include NSAIDs, corticosteroids, immunosuppressive agents, and pericardiectomy[7,36,40-43]. The majority of cases respond to NSAIDs. Others have a prolonged course and respond only to corticosteroids[41]. In this setting prolonged or frequent administration of corticosteroids may be necessary, possibly leading to corticosteroid-dependence and adverse side effects[36,41,42]. It is therefore recommended that the use of steroids for recurrent pericarditis should be restricted[36,44]. Several small studies[36,44-47] have successfully used colchicine to prevent recurrences of acute pericarditis after failure of conventional treatment. NSAIDs plus colchicine is a reasonable first choice, even for the first episode, before steroid therapy is attempted[5,7,44,48]. When corticosteroid therapy is chosen, the dose and duration of treatment are critical factors in treating and preventing recurrent pericarditis. High-dose prednisone (1.0-1.5 mg/kg) should be considered in the treatment of recurrent pericarditis resistant to anti-inflammatory therapy, adding aspirin or another NSAID during gradual tapering of the steroid. Cyclophosphamide or azathioprine should be reserved for patients who do not respond to high-dose prednisone or who present with severe complications[41]. Recurrent cases resistant to prednisone, colchicine and other immunosuppressive drugs have been successfully treated with high-dose intravenous immunoglobulins[49]. A possible management strategy for recurrence is reported in figure 2, while commonly used drugs are reported in table VIII.

Data on recurrent pericarditis in children and adolescents are controversial[42,50]. A previous study showed that children might respond remarkably well to colchicine, which was administered for 6 months with no adverse reactions[50]. On the other hand, in a more recent study colchicine did not prevent relapses[42].

In the management of patients with a previous attack of acute pericarditis, recurrent pain without objective evidence of a recurrence is a common and often annoying problem for physicians as well as recurrent pericarditis itself[51,52]. About 10% of patients with a previous acute pericarditis attack might present with recurrent pain but no clinical evidence of disease. This is actually a difficult and not uncommon problem that is most likely to appear in more chronic cases in which numerous recurrences have occurred and have been suppressed by corticosteroids. The reason for this phenomenon is unknown but it seems reasonable to suggest that a new course of corticosteroids should not be started. Therefore, the pain must be treated by simple analgesic remedies (paracetamol with a starting dose of 500 mg every 8 hours). Sometimes it can precede clinical evidence of a recurrence and thus patient re-examination is mandatory. Female gender, previous use of corticosteroids, and frequent recurrences were found to be risk factors for this syndrome[52].

Pericardial effusion and cardiac tamponade

Pericardial effusion may occur as a result of a variety of clinical conditions, including infections (viral,

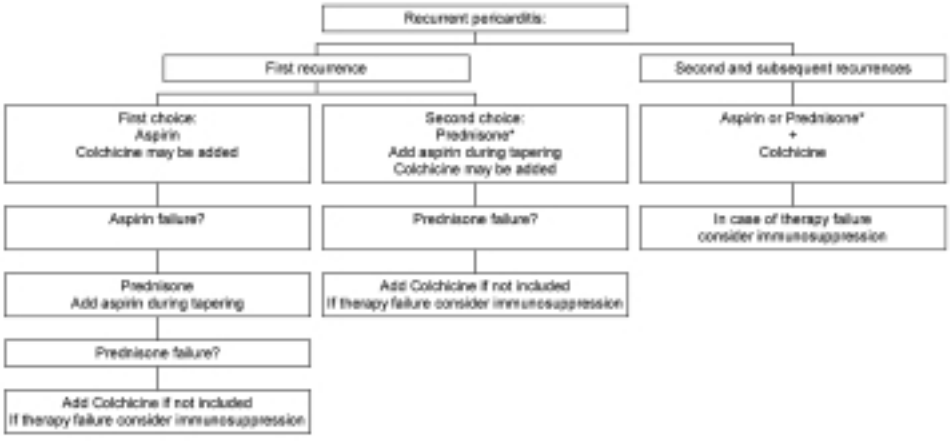


Figure 2. *Recurrent pericarditis management (see text for details).*

Table VIII. Common drugs in acute pericarditis and its recurrences.

Drug	Acute pericarditis	Recurrence
Aspirin	800 mg every 6 to 8 hours subsequent gradual tapering (reduction of 800 mg every week)	Idem
Ibuprofen	300-800 mg every 6 to 8 hours until clinical resolution	ND
Prednisone	1-1.5 mg/kg for 7-14 days then gradual tapering*	1-1.5 mg/kg for 1 month, then gradual tapering within 3 months*
Colchicine	1 mg/day (0.5 mg × 2/day) for 3 months (?)**	Idem for 6 months

ND = not determined. * add aspirin or another non-steroidal anti-inflammatory drug during tapering (for instance: aspirin 800 mg bid until prednisone discontinuation and then reduced to 800 mg/day for a further 1 to 4 weeks); ** not studied extensively.

bacterial, or fungal), inflammatory, postinflammatory, autoreactive, and neoplastic processes. Moreover, pericardial effusion may be an incidental and silent finding in a number of systemic disorders. Although pericardial effusion is common in patients with connective tissue disease, cardiac tamponade is rare. Among medical patients, malignant disease is the most common cause of pericardial effusion with tamponade. The more common causes reported in clinical studies[53,54] are shown in table IX.

The diagnosis of pericardial effusion/tamponade relies on a strong clinical suspicion and is confirmed by echocardiography. Echocardiography is the primary method for documenting the presence of a pericardial effusion because of its high degree of specificity and sensitivity, even when available only in M-mode. For these reasons, the use of echocardiography for the evaluation of all patients with suspected pericardial disease was given a class I recommendation by a 2003 task force of the American College of Cardiology (ACC), the American Heart Association (AHA) and the American Society of Echocardiography (ASE)[55,56]. A detailed list of recommendations in pericardial diseases is reported in table X.

Table IX. Main surveys on pericardial effusion.

	Corey et al.[53] (n=53)	Sagrista-Sauleda et al.[54] (n=322)
Effusion size (mm)	> 10	> 10
Cardiac tamponade (%)	NR	37
Etiology (%)		
Idiopathic	7	20
Neoplastic	23	13
Uremic	12	6
Iatrogenic	0	16
Post-AMI	0	8
Viral	14	0
Collagen vascular disease	12	5
Tuberculosis	0	2
Other	9	21

AMI = acute myocardial infarction; NR = not reported.

A commonly used classification of pericardial effusion is that reported by Weitzman et al.[22]: a small effusion is an echo-free space (anterior plus posterior) < 10 mm during diastole, a moderate effusion is an echo-free pericardial space 10 to 20 mm, and a severe effusion is an echo-free space > 20 mm. Pericardial effusion echo-free spaces are measured at the onset of the QRS complex (end of diastole) (Fig. 3).

Once the diagnosis of pericardial effusion has been made, it is important to determine whether the effusion is creating significant hemodynamic compromise. Asymptomatic patients without hemodynamic compromise, even with large pericardial effusions, do not need to be treated with pericardiocentesis unless fluid analysis is necessary for diagnostic purposes (e.g., in acute bacterial pericarditis, tuberculosis and neoplasia). Although tamponade is a clinical diagnosis, two-dimensional and Doppler echocardiography play a major role in the identification of pericardial effusion and in the assessment of its hemodynamic significance. Except in hyperacute cases, a moderate to large effusion is usually present and swinging of the heart within the effusion may be seen.

Other echocardiographic findings suggesting hemodynamic compromise are the result of transiently reversed right atrial and right ventricular diastolic transmural pressures (Table XI).

Echocardiography is also very useful as a guidance to pericardiocentesis. Even though to date fluoroscopic guidance has been the most widely employed technique, echocardiographic guidance is becoming increasingly popular and may be equally effective in good hands[57,58]. It has the added advantage of allowing the physician to monitor the position of the needle during the initial puncture; moreover, it is easier and more convenient than fluoroscopy.

The 2003 ACC/AHA/ASE task force gave a class IIa recommendation to echocardiographic guidance and monitoring of pericardiocentesis[55,56].

Table X. Summary of the recommendations for the use of echocardiography by a 2003 task force of the American College of Cardiology, the American Heart Association, and the American Society of Echocardiography[55,56].

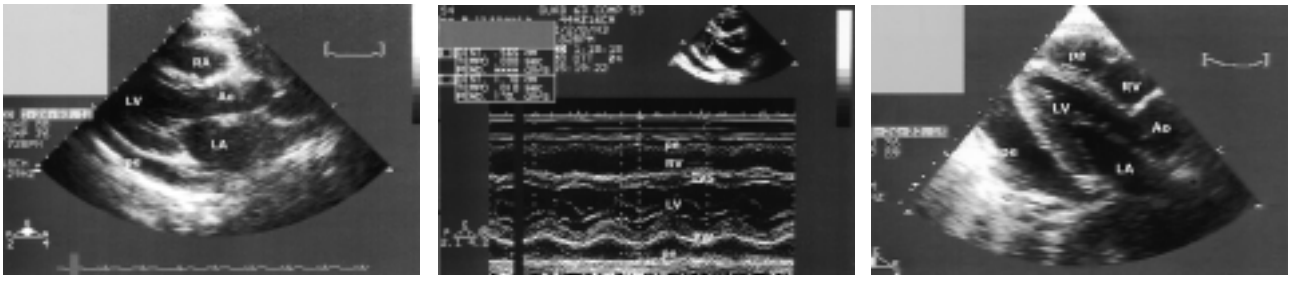
Recommendations	Class
1. All patients with suspected pericardial disease 2. Patients with suspected bleeding in the pericardial space 3. Follow-up study to evaluate the recurrence of effusion or to diagnose early constriction Repeat studies directed to answer a specific clinical question 4. Pericardial friction rub developing in acute myocardial infarction accompanied by symptoms	I
1. Follow-up studies to detect early signs of tampotamponade in the presence of large or rapidly accumulating effusions 2. Echocardiographic guidance and monitoring of pericardiocentesis	IIa
1. Postsurgical pericardial disease 2. Strong clinical suspicion and non-diagnostic TTE, TEE; assessment of pericardial thickness to support a diagnosis of constrictive pericarditis	IIb
1. Routine follow-up of small stable pericardial effusion 2. Follow-up studies in patients with cancer or other terminal illness for whom management would not be influenced 3. Assessment of pericardial thickness without clinical evidence of constriction 4. Pericardial friction rub in early uncomplicated myocardial infarction or during the early postoperative period after cardiac surgery	III

TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

Although not always performed, cardiac catheterization may confirm the diagnosis and document that pericardial aspiration is followed by hemodynamic improvement. Patients who are hypovolemic at presentation may have low-pressure tamponade in which the intracardiac diastolic pressures are 6 to 12 mmHg. Such patients may not have a pulsus paradoxus. A fluid challenge with 1 liter of isotonic saline may reveal typical tamponade dynamics[58].

Tamponade may occur acutely (e.g., due to rupture of the heart or aorta, trauma, or as a complication of catheter or pacemaker procedures) or subacutely (e.g., due to neoplasm, uremia or idiopathic pericarditis). Acute cardiac tamponade is generally sudden in onset, may be associated with chest pain and dyspnea, and is life-threatening if not promptly treated. The jugular venous pressure is typically markedly elevated, while hypotension is common due to the decline in cardiac output. The heart sounds are often muted. In the most acute cases, the effusion is small because the pericardium cannot stretch rapidly. Subacute cardiac tamponade is a less dramatic process. Patients may be asymptomatic or complain of dyspnea, chest discomfort or fullness, fatigue or other symptoms referable to increased filling pressures and limited cardiac output[58,59].

In about 60% of patients, the effusion is due to a known underlying condition[54]. Specific clinical information may be helpful to establish the etiology of a pericardial effusion. Inflammatory signs, the size of the effusion, and the presence or absence of tamponade are useful to establish the cause of the effusion in clinical practice. The presence of inflammatory signs was associated with acute idiopathic pericarditis (likelihood ratio 5.4). On the other hand, a large effusion without inflammatory signs or tamponade was associated with chronic idiopathic pericardial effusion (likelihood ratio 20), while tamponade without inflammatory signs was associated with a malignant effusion (likelihood ratio 2.9)[54]. A possible diagnostic strategy for the evaluation of pericardial effusion based on a probabilistic approach is reported in figure 4. The etiology of the effusion as well as its biochemical, immunologic, cytologic, and bacteriologic characteristics may, in some cases, be established by examination of the pericardial fluid. The invasive nature of pericardiocentesis and pericardial biopsy must be weighed against their low diagnostic yield in some studies, and the demonstration that many patients may be safely and effectively managed without examination of the



A B C

Figure 3. *Evaluation of pericardial effusion (pe) by means of echocardiography.* Panels A *and* B: *severe pe according to the Weitzman criteria (echo-free space [anterior plus posterior] 23 mm as measured at the end of diastole) with evolution to cardiac tamponade with a swinging heart* (panel C). *Ao = aortic valve; IVS = interventricular septum; LA = left atrium; LV = left ventricle; PW = posterior wall; RA = right atrium; RV = right ventricle.*

Table XI. Diagnostic approach in cardiac tamponade.

Clinical presentation	Tachycardia, pulsus paradoxus, hypotension, dyspnea
ECG	Electrical alternans, low QRS voltage
Chest X-ray	Enlarged cardiac silhouette with clear lungs
Echocardiography	1) Large effusion, swinging heart, 2) diastolic collapse of the right atrium (sensitivity 55%, specificity 88%) and right ventricle (sensitivity 48%, specificity 88%), 3) left atrial collapse, 4) dilation and < 50% reduction in the diameter of the IVC (IVC plethora: sensitivity 97%, specificity 66%), 5) reciprocal changes in the left and right ventricular volumes with respiration (during inspiration, the ventricular and atrial septa move leftward, a process reversed with expiration. These changes play a central role in the pathogenesis of pulsus paradoxus)
Cardiac catheterization	Equilibration of the average diastolic pressures (usually between 10 and 30 mmHg), an inspiratory increase in the right-sided pressures and a reduction in the left-sided pressures that are responsible for pulsus paradoxus

IVC = inferior vena cava.

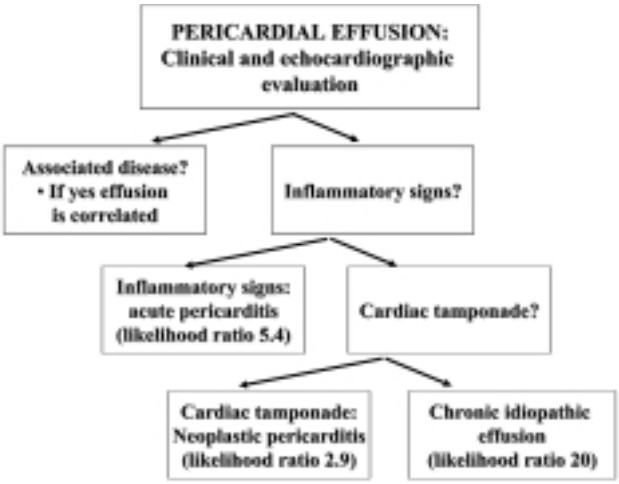


Figure 4. *A possible evaluation of pericardial effusion based on a probabilistic approach.*

pericardial fluid[39,60]. Routine pericardial drainage procedures have a very low diagnostic yield in patients with a large pericardial effusion without tamponade or suspected purulent pericarditis, and no clear therapeutic benefit is obtained with this approach. The clinical outcomes depend on the underlying diseases and do not appear to be influenced by drainage of the pericardial fluid[60]. The main indications for pericardiocentesis or surgical drainage of a pericardial effusion are moderate to severe tamponade, suspected purulent (infectious) or tuberculous pericarditis, or persistence of a large effusion.

A large idiopathic chronic pericardial effusion may be defined as a collection of pericardial fluid that persists > 3 months and has no apparent cause. During follow-up overt tamponade was found in up to 29% of cases. Large idiopathic chronic pericardial effusion is well tolerated for long periods in most patients, but severe tamponade may develop unexpectedly at any time. Pericardiocentesis alone frequently results in the resolution of large effusions, but recurrence is common and pericardiectomy should be considered whenever a large effusion recurs after pericardiocentesis[61].

Other complications: constrictive pericarditis

The normal pericardium is ≤ 3 mm in thickness. With chronic constriction, especially tuberculous constriction, the pericardium may thicken to ≥ 10 mm, calcify, and intimately involve the epicardium. Constrictive pericarditis is an uncommon disorder with various causes. In less developed countries, tuberculosis remains the most common cause of chronic constrictive pericarditis, whereas in developed countries constriction is more common after cardiac surgery, mediastinal irradiation, and purulent or recurrent pericarditis. In many patients a specific cause cannot be identified.

The encasement of the heart by a rigid, non-pliable pericardium results in characteristic pathophysiologic effects, including impaired diastolic filling of the ventricles, exaggerated ventricular interdependence, and dissociation of the intracardiac and intrathoracic pressures during respiration. Constrictive pericarditis typically presents with chronic insidious signs and symptoms of predominantly systemic venous congestion[62,63].

In patients with heart failure symptoms, the presence of pericardial calcification on a plain radiograph strongly suggests constrictive pericarditis. It is often associated with idiopathic disease and other markers of disease chronicity and is an independent predictor of increased perioperative mortality rates[64]. The diagnosis is made on the basis of the clinical presentation, echocardiography and/or computed tomography/magnetic resonance imaging and right heart catheterization (Tables XII and XIII).

Echocardiography may be particularly helpful to establish the diagnosis as well as to make a correct differential diagnosis[65,66]. Invasive hemodynamic evaluation

Table XII. Diagnostic approach in constrictive pericarditis.

Clinical presentation	Insidious signs and symptoms of systemic venous congestion
ECG	Often abnormal: low QRS voltage, non-specific ST-T wave changes. Atrial fibrillation may be present in 33 to 50%
Chest X-ray	Pericardial calcification on a plain radiograph in patients with heart failure symptoms strongly suggests constrictive pericarditis
Echocardiography	*M- and B-mode:* pericardial thickening/calcification, abrupt posterior deflection of the interventricular septum at end-diastole, and posterior wall "flat tiring"; inferior vena cava and hepatic veins often markedly dilated with blunted respiratory variability *Doppler:* enhanced transmitral and transtricuspid E-wave variation. Respiratory variations of the mitral inflow peak early (peak E) velocity ≥ 10% (sensitivity 84%, specificity 91%) and variation in the pulmonary venous peak diastolic (peak D) flow velocity ≥ 18% (sensitivity 79%, specificity 91%)
Cardiac catheterization	1) "Dip and plateau" or "square root" sign in the pressure curve of the right and/or left ventricle* 2) Elevation and virtual equalization (within 5 mmHg) of the right atrial, right ventricular diastolic, left atrial (pulmonary capillary wedge) and left ventricular diastolic pressures** 3) Discordance between the right ventricular and peak left ventricular systolic pressures during inspiration (a sign of increased ventricular interdependence)
CT/MRI	Thickened pericardium (> 3.5 mm) with or without calcifications

CT = computed tomography; MRI = magnetic resonance imaging. * since filling, and therefore the diastolic pressure, in both ventricles is constrained by the inelastic pericardium. This finding reflects rapid early diastolic filling of the ventricles, followed by lack of additional filling due to compression in late diastole. It may be obscured by the presence of tachycardia and by the damping effect of the connecting tubes or bubbles within the catheters and transducers; ** in some patients, this finding is seen only during inspiration. This statement may be an oversimplification because the pulmonary wedge pressure falls during inspiration while the systemic venous pressure remains constant. Thus, it is not reasonable to expect the two pressures to be precisely equal throughout the respiratory cycle, and frequently equilibration is present only during inspiration. Furthermore, equilibration of the diastolic pressures occurs in some patients who have heart failure or an acute volume overload, but who do not have constrictive pericarditis.

Table XIII. Constrictive pericarditis vs restrictive cardiomyopathy.

Diagnostic approach	Constrictive pericarditis	Restrictive cardiomyopathy
Physical findings	Kussmaul sign, pericardial knock	Regurgitant murmurs, Kussmaul sign ± S3 (advanced)
ECG	Low-voltage, non-specific ST-T wave changes, AF	Low-voltage, pseudoinfarction, left-axis deviation, AF
Chest X-ray	Pericardial calcifications	No calcifications
Echocardiography	Pericardial thickening and calcification, normal wall thickness Respiratory variation of the mitral peak E velocity ≥ 10% and variation in the pulmonary venous peak D flow velocity ≥ 18% Tissue Doppler: peak Ea ≥ 8.0 cm/s	Small left ventricle with large atria, increased wall thickness (occasionally) E/A ratio ≥ 2, short deceleration time, significant respiratory variations of the mitral inflow are absent Tissue Doppler: peak Ea < 8.0 cm/s
Cardiac catheterization	"Dip and plateau" or "square root" sign, LVEDP and RVEDP usually equal, ventricular interdependence	Marked right ventricular systolic hypertension (> 50 mmHg) and LVEDP > RVEDP at rest or during exercise by ≥ 5 mmHg (RVEDP < 1/3 RVSP)
CT/MRI	Pericardial thickness ≥ 3.5 mm (up to 10-15 mm)	Normal pericardial thickness (≤ 3.0 mm)

AF = atrial fibrillation; CT = computed tomography; LVEDP = left ventricular end-diastolic pressure; MRI = magnetic resonance imaging; RVEDP = right ventricular end-diastolic pressure; RVSP = right ventricular systolic pressure.

may be useful for the assessment of patients suspected of having constrictive pericarditis to document the presence of elevation and equilibration of the diastolic filling pressure, and to assess the effect of constriction on the stroke volume and cardiac output. Catheterization of both the right and left ventricles should be performed to permit simultaneous recording of the right and left filling pressures, also taking into account possible limitations and pitfalls (Table XII). When the baseline hemodynamics are unremarkable, the rapid infusion of about 1000 ml of saline solution over 5 to 10 min may unmask these findings in rare cases with occult constrictive pericarditis. Invasive hemodynamic evaluation is also useful to assist in the difficult discrimination between constrictive and restrictive cardiomyopathy (Table XIII). However, in a significant proportion of patients with restrictive cardiomyopathy, the hemodynamic profiles at rest and during exercise may be indistinguishable from

those of constrictive pericarditis with equalization of the right and left ventricular diastolic pressures and a dip-and-plateau pattern in the ventricular waveforms as well as in constrictive pericarditis. Thus, the differential diagnosis must be made on the basis of data obtained at echocardiography and computed tomography or magnetic resonance imaging.

Traditionally, an increased pericardial thickness has been considered an essential diagnostic feature of constrictive pericarditis. The pericardial thickness was not increased in up to 20% of patients with surgically proven constrictive pericarditis, although the histopathological appearance was focally abnormal in all cases[67].

An increased pericardial thickness is most reliably diagnosed at and computed tomography or magnetic resonance imaging. Both modalities provide a larger field of view than echocardiography, allowing the examination of the entire chest and the detection of associated abnormalities in the mediastinum and lungs[68]. A clinical study showed that a pericardial thickness ≥ 3 mm at transesophageal echocardiography was 95% sensitive and 86% specific for the detection of a thickened pericardium[69]. It must be acknowledged that the pericardial thickness as assessed by transesophageal echocardiography has not yet been validated in clinical practice.

The standard therapy is an extended pericardiectomy performed to restore an unlimited inflow and outflow as well as an unrestricted diastolic function of both ventricles. The risks of this procedure are related to the presence of dense adhesions between the two pericardial layers and to the presence of severe calcifications especially of the epicardium. Incomplete removal results in persistent diastolic restriction while lacerations of the underlying myocardium may lead to diffuse and severe bleeding and finally to myocardial dysfunction, that might be already present in more advanced cases. The operative mortality is generally low but may exceed 5 to 15% in the most advanced cases. Idiopathic constrictive pericarditis had the best prognosis followed by postsurgical and postradiation constrictive pericarditis. Predictors of poor overall survival were prior radiation, worse renal function, a higher pulmonary artery systolic pressure, an abnormal left ventricular systolic function, lower serum sodium levels, and older age[70].

When it develops in the setting of acute pericarditis, constrictive pericarditis may occasionally reverse spontaneously. In some patients with acute constrictive pericarditis, the symptoms and constrictive physiologic features resolve with medical therapy alone, a phenomenon that has been labeled "transient constrictive pericarditis"[71]. However, more commonly the natural history of this disease is one of progression with a declining cardiac output and progressive renal and hepatic failure.

Effusive-constrictive pericarditis is an uncommon pericardial syndrome characterized by concomitant tamponade, caused by a tense pericardial effusion, and constriction, caused by the visceral pericardium[72]. Effusive-constrictive pericarditis is uncommon but may be missed in some patients who present with tamponade. The causes of effusive-constrictive pericarditis are the same as those associated with constriction, and the clinical features resemble those of both tamponade and constriction. Although evolution to persistent constriction is frequent, idiopathic cases may resolve spontaneously.

Surface echocardiography may demonstrate an "echo-filled" pericardial effusion with a thickened pericardium and fibrinous pericardial bands. Although this echocardiographic appearance should increase suspicion, the diagnosis is generally made after successful pericardiocentesis. Rather than normalizing after pericardiocentesis, the intracardiac pressures remain elevated with a "square root" sign in the ventricular tracings and the development of a prominent y descent in the atrial and jugular venous pressure pulses. A Kussmaul sign may also be evident. Extensive epicardiectomy is recommended as the procedure of choice in patients requiring surgery[72].

Conclusions

Acute pericardial diseases are common disorders in several clinical settings. New diagnostic techniques have improved the sampling and analysis of pericardial fluid and allow a comprehensive diagnostic approach. Deciding on the extent of diagnostic evaluation in the individual patient requires a good clinical judgment based on a careful evaluation of the risk-benefit ratio of planned diagnostic and therapeutic options. Most cases are viral or idiopathic and self-limited; however, numerous causes should be taken into consideration. The diagnostic yield of extensive laboratory evaluation and pericardiocentesis is low, and invasive procedures should be limited mainly to patients in whom therapeutic intervention is necessary.

The management of uncomplicated pericarditis is based on NSAIDs with the addition of colchicine for recurrences. The management of pericardial effusion must include its clinical background. Constrictive pericarditis is an infrequent complication that must be considered and that can be diagnosed using a combination of modern imaging methods.

References

1. Maisch B, Ristic AD, Rupp H, Spodick DH. Pericardial access using the PerDUCER and flexible percutaneous pericardioscopy. Am J Cardiol 2001; 88: 1323-6.
2. Maisch B, Ristic AD, Pankuweit S. Intrapericardial treatment of autoreactive pericardial effusion with triamcinolone; the way to avoid side effects of systemic corticosteroid therapy. Eur Heart J 2002; 19: 1503-8.

3. Maisch B, Ristic A. Practical aspects of the management of pericardial disease. Heart 2003; 89: 1096-103.
4. Seferovic PM, Ristic AD, Maksimovic R, et al. Diagnostic value of pericardial biopsy: improvement with extensive sampling enabled by pericardioscopy. Circulation 2003; 107: 978-83.
5. Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary. The Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2004; 25: 587-610.
6. Launbjerg J, Fruergaaard P, Hesse B, et al. Long-term risk of death, cardiac events and recurrent chest pain in patients with acute chest pain of different origin. Cardiology 1996; 87: 60-6.
7. Spodick DH. Acute pericarditis: current concepts and practice. JAMA 2003; 239: 1150-3.
8. Troughton R, Asher CR, Klein AL. Pericarditis. Lancet 2004; 363: 717-27.
9. Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J. Primary acute pericardial disease: a prospective series of 231 consecutive patients. Am J Cardiol 1985; 56: 623-30.
10. Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. Am J Cardiol 1995; 75: 378-82.
11. Imazio M, Demichelis B, Parrini I, et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. J Am Coll Cardiol 2004; 43: 1042-6.
12. Wragg A, Strang JI. Tuberculous pericarditis and HIV infection. Heart 2000; 84: 127-8.
13. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000; 161 (Part 1): 1376-95.
14. Cegielski JP, Lwakatare J, Dukes CS, et al. Tuberculous pericarditis in Tanzanian patients with and without HIV infection. Tuber Lung Dis 1994; 75: 429-34.
15. Fowler NO. Tuberculous pericarditis. JAMA 1991; 266: 99-103.
16. Burgess LJ, Reuter H, Carstens ME, Taljaard JJ, Doubell AF. The use of adenosine deaminase and interferon-gamma as diagnostic tools for tuberculous pericarditis. Chest 2002; 122: 900-5.
17. Mayosi BM, Ntsekhe M, Volmink JA, et al. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev 2002; (4): CD000526.
18. Barbaro G, Klatt EC. HIV infection and the cardiovascular system. AIDS Rev 2002; 4: 93-103.
19. Barbaro G. Evolution of the involvement of the cardiovascular system in HIV infection. Adv Cardiol 2003; 40: 15-22.
20. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation 1999; 100: 1380-6.
21. Kutcher MA, King SB 3rd, Alimurung BN, et al. Constrictive pericarditis as a complication of cardiac surgery: recognition of an entity. Am J Cardiol 1982; 50: 742-8.
22. Weitzman LB, Tinker WP, Kronzon I, Cohen ML, Glassman E, Spencer FC. The incidence and natural history of pericardial effusion after cardiac surgery - an echocardiographic study. Circulation 1984; 69: 506-11.
23. Tofler GH, Muller JE, Stone PH, et al. Pericarditis in acute myocardial infarction: characterization and clinical significance. Am Heart J 1989; 117: 86-92.
24. Correale E, Maggioni AP, Romano S, et al. Comparison of frequency, diagnostic and prognostic significance of pericardial involvement in acute myocardial infarction treated with and without thrombolytics. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). Am J Cardiol 1993; 71: 1377-81.
25. Imazio M, Demichelis B, Parrini I, et al. Acute pericardial disease as initial clue to malignancy. (abstr) Eur Heart J 2004; 25 (Suppl): 628.
26. Retter AS. Pericardial disease in the oncology patient. Heart Dis 2002; 4: 387-91.
27. Vaitkus PT, Herrmann HC, LeWinter MM. Treatment of malignant pericardial effusion. JAMA 1994; 272: 59-64.
28. DeCamp MM, Mentzer SJ, Swanson SJ, Sugarbaker DJ. Malignant effusive disease of the pleura and pericardium. Chest 1997; 112 (Suppl 4): 291S-295S.
29. Martinoni A, Cipolla CM, Civelli M, et al. Intrapericardial treatment of neoplastic pericardial effusions. Herz 2000; 25: 787-93.
30. Piovaccari G, Ferretti RM, Prati F, et al. Cardiac disease after chest irradiation for Hodgkin's disease: incidence in 108 patients with long follow-up. Int J Cardiol 1995; 49: 39-43.
31. Shabetai R. Acute pericarditis. Cardiol Clin 1990; 8: 639-44.
32. Baljepally R, Spodick DH. PR-segment deviation as the initial electrocardiographic response in acute pericarditis. Am J Cardiol 1998; 81: 1505-6.
33. Bonnefoy E, Godon P, Kirkorian G, et al. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. Eur Heart J 2000; 21: 832-6.
34. Brandt RR, Filzmaier K, Hanrath P. Circulating cardiac troponin I in acute pericarditis. Am J Cardiol 2001; 87: 1326-8.
35. Imazio M, Demichelis B, Cecchi E, et al. Cardiac troponin I in acute pericarditis. J Am Coll Cardiol 2003; 42: 2144-8.
36. Adler Y, Finkelstein Y, Guindo J, et al. Colchicine treatment for recurrent pericarditis. A decade of experience. Circulation 1998; 97: 2183-5.
37. Soler-Soler J, Permanyer-Miralda G, Sagrista-Sauleda J. A systematic diagnostic approach to primary acute pericardial disease. The Barcelona experience. Cardiol Clin 1990; 8: 609-20.
38. Soler-Soler J. Mini-symposium. Pericardial disease: introduction. Heart 2004; 90: 251.
39. Permanyer-Miralda G. Acute pericardial disease: approach to the aetiologic diagnosis. Heart 2004; 90: 252-4.
40. Fowler NO. Recurrent pericarditis. Cardiol Clin 1990; 8: 621-6.
41. Marcolongo R, Russo R, Laveder F, Noventa F, Agostini C. Immunosuppressive therapy prevents recurrent pericarditis. J Am Coll Cardiol 1995; 26: 1276-9.
42. Raatikka M, Pelkonen PM, Karjalainen J, Jokinen EV. Recurrent pericarditis in children and adolescents. J Am Coll Cardiol 2003; 42: 759-64.
43. DeValeria PA, Baumgartner WA, Casale AS. Current indications, risks, and outcome after pericardiectomy. Ann Thorac Surg 1991; 52: 219-24.
44. Imazio M, Demichelis B, Cecchi E, Giuggia M, Forno D, Trinchero R. Recurrent pericarditis: follow-up of 55 cases. (abstr) Circulation 2002; 106 (Suppl II): II-323.
45. Guindo J, Rodriguez de la Serna A, Ramio J, et al. Recurrent pericarditis: relief with colchicine. Circulation 1990; 82: 1117-20.
46. Millaire A, de Groote P, Decoulx E, Goullard L, Ducloux G. Treatment of recurrent pericarditis with colchicine. Eur Heart J 1994; 15: 120-4.
47. Cacoub P, Sbai A, Wechsler B, Amoura Z, Godeau P, Piette JC. Efficacy of colchicine in recurrent acute idiopathic pericarditis. Arch Mal Coeur Vaiss 2000; 93: 1511-4.
48. Imazio M, Demichelis B, Cecchi E, et al. Is colchicine the initial mode of treatment for acute pericarditis? (abstr) Eur Heart J 2003; 24 (Suppl): 250.
49. Tona F, Bellotto F, Laveder F, Meneghin A, Sinagra G, Marcolongo R. Efficacy of high-dose intravenous immunoglobulins in two patients with idiopathic recurrent pericarditis

refractory to previous immunosuppressive treatment. Ital Heart J 2003; 4: 64-8.
50. Yazigi A, Abou-Charaf LC. Colchicine for recurrent pericarditis in children. Acta Paediatr 1998; 87: 603-4.
51. Shabetai R. Often neglected yet important: the pericardium and its disease. Herz 2000; 25: 717-9.
52. Imazio M, Demichelis B, Parrini I, et al. Recurrent pericarditic pain without objective evidence of disease in patients with previous acute pericarditis. Am J Cardiol 2004; 94: 973-5.
53. Corey GR, Campbell PT, van Trigt P, et al. Etiology of large pericardial effusions. Am J Med 1993; 95: 209-13.
54. Sagrista-Sauleda J, Merce J, Permanyer-Miralda G, Soler-Soler J. Clinical clues to the causes of large pericardial effusions. Am J Med 2000; 109: 95-101.
55. Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA guidelines for the clinical application of echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on clinical application of echocardiography). Circulation 1997; 95: 1686-744.
56. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to update the 1997 guidelines for the clinical application of echocardiography). Circulation 2003; 108: 1146-62.
57. Tsang TS, Freeman WK, Sinak LJ, Seward JB. Echocardiographically guided pericardiocentesis: evolution and state-of-the-art technique. Mayo Clin Proc 1998; 73: 647-52.
58. Spodick DH. Acute cardiac tamponade. N Engl J Med 2003; 349: 684-90.
59. Shabetai R. Pericardial effusion: haemodynamic spectrum. Heart 2004; 90: 255-6.
60. Merce J, Sagrista-Sauleda J, Permanyer-Miralda G, Soler-Soler J. Should pericardial drainage be performed routinely in patients who have a large pericardial effusion without tamponade? Am J Med 1998; 105: 106-9.
61. Sagrista-Sauleda J, Angel J, Permanyer-Miralda G, Soler-Soler J. Long-term follow-up of idiopathic chronic pericardial effusion. N Engl J Med 1999; 341: 2054-9.
62. Myers RB, Spodick DH. Constrictive pericarditis: clinical and pathophysiologic characteristics. Am Heart J 1999; 138: 219-32.
63. Sagrista-Sauleda J. Pericardial constriction: uncommon patterns. Heart 2004; 90: 257-8.
64. Ling LH, Oh JK, Breen JF, et al. Calcific constrictive pericarditis: is it still with us? Ann Intern Med 2000; 132: 444-50.
65. Rajagopalan N, Garcia MJ, Rodriguez L, et al. Comparison of new Doppler echocardiographic methods to differentiate constrictive pericardial heart disease and restrictive cardiomyopathy. Am J Cardiol 2001; 87: 86-94.
66. Sengupta PP, Mohan JC, Mehta V, Arora R, Pandian NG, Khandheria BK. Accuracy and pitfalls of early diastolic motion of the mitral annulus for diagnosing constrictive pericarditis by tissue Doppler imaging. Am J Cardiol 2004; 93: 886-90.
67. Talreja DR, Edwards WD, Danielson GK, et al. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. Circulation 2003; 108: 1852-7.
68. Wang ZJ, Reddy GP, Gotway MB, Yeh BM, Hetts SW, Higgins CB. CT and MR imaging of pericardial disease. Radiographics 2003; 23 (Special Number): S167-S180.
69. Ling LH, Oh JK, Tei C, et al. Pericardial thickness measured with transesophageal echocardiography: feasibility and potential clinical usefulness. J Am Coll Cardiol 1997; 29: 1317-23.
70. Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. J Am Coll Cardiol 2004; 43: 1445-52.
71. Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. J Am Coll Cardiol 2004; 43: 271-5.
72. Sagrista-Sauleda J, Angel J, Sanchez A, Permanyer-Miralda G, Soler-Soler J. Effusive-constrictive pericarditis. N Engl J Med 2004; 350: 469-75.