Clinical update

Management of pericardial effusion

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Pericardial effusion is a common finding in clinical practice either as incidental finding or manifestation of a systemic or cardiac disease. The spectrum of pericardial effusions ranges from mild asymptomatic effusions to cardiac tamponade. The aetiology is varied (infectious, neoplastic, autoimmune, metabolic, and drug-related), being tuberculosis the leading cause of pericardial effusions in developing countries and all over the world, while concurrent HIV infection may have an important promoting role in this setting. Management is guided by the haemodynamic impact, size, presence of inflammation (i.e. pericarditis), associated medical conditions, and the aetiology whenever possible. Pericardiocentesis is mandatory for cardiac tamponade and when a bacterial or neoplastic aetiology is suspected. Pericardial biopsy is generally reserved for cases with recurrent cardiac tamponade or persistence without a defined aetiology, especially when a bacterial or neoplastic aetiology is suspected and cannot be assessed by other conventional and less invasive means. A true isolated effusion may not require a specific treatment if the patient is asymptomatic, but large ones are at risk of progression to cardiac tamponade (up to one third). Pericardiocenteses alone may be curative for large effusions, but recurrences are also common and pericardiectomy or less invasive options (i.e. pericardial window) should be considered with recurrent cardiac tamponade or symptomatic pericardial effusion (either circumferential or loculated). The aim of this paper was to summarize and critically evaluate current knowledge on the management of pericardial effusion.

Keywords: Pericardial effusion • Aetiology • Diagnosis • Management • Pericarditis

Introduction

Probably no serious disease is so frequently overlooked by the practitioner. Postmortem experience shows how often pericarditis is not recognized or goes to resolution and adhesion without attracting notice (Osler, The Principles and Practice of Modern Medicine, 1892).

Pericardial effusion is a common finding in clinical practice either as incidental finding or manifestation of a systemic or cardiac disease. The spectrum of pericardial effusions ranges from mild asymptomatic effusions to cardiac tamponade. Moreover, pericardial effusion may accumulate slowly or suddenly.1–3 Unfortunately, there are few epidemiological data on the incidence and prevalence of such effusions in the clinical setting. In Maria Vittoria hospital, an urban general hospital in Torino and an Italian referral centre for pericardial diseases, the mean annual incidence and prevalence of pericardial effusion have been, respectively, 3 and 9% in a 6 years experience of the echo laboratory (2000–05).4 Such data mainly depend on the epidemiological background (especially developed vs. developing country, where tuberculosis is a leading cause of pericardial disease and concurrent HIV infection may have an important promoting role),5 the institutional setting (tertiary referral centre vs. secondary and general hospitals), and the availability of specific subspecialties (especially nephrology, rheumatology, and oncology).

No specific guidelines and management recommendations have been issued by medical societies beyond the 2000 national Spanish guidelines6 and the 2004 European Society of Cardiology guidelines7 on the management of pericardial diseases, and some narrative reviews on the topic,4,8,9 whereas no specific guidelines have been issued from the American Heart Association (AHA) and American College of Cardiology (ACC).

It is the aim of this review to critically evaluate current knowledge on the management of pericardial effusion. A thorough literature review has been performed without language restriction with the MeSH term ‘pericardial effusion’ or ‘pericardial’[All Fields] and ‘effusion’[All Fields] or ‘pericardial effusion’[All Fields]. After the initial identification of 1520 papers, 139 papers were selected for detailed review based on novelty or important data leading to the final inclusion of 50 papers in the final reference list.

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Initial evaluation and pathophysiological issues

When a pericardial effusion is detected, the first step is to evaluate its size and haemodynamic importance, as well as the possible association with concomitant diseases. Echocardiography is the first diagnostic tool for this assessment as also acknowledged by the AHA/ACC guidelines on the use of echocardiography, that gave a class I indication for the use of echocardiography in any case of suspected pericardial disease.10

Pericardial effusion may be classified based on its onset (acute, subacute vs. chronic when dating >3 months), distribution (circumferential or loculated), haemodynamic impact (none, cardiac tamponade, effusive-constrictive), composition (exudates, transudate, blood, rarely air, or gas from bacterial infections), and especially by its size as mild, moderate, and large (Table 1) based on a simple semiquantitative echocardiographic assessment (Figure 1) that has been demonstrated useful also to estimate the risk of specific aetiology and complications during follow-up.4,7,9,11,12

The normal pericardial sac contains 10–50 mL of pericardial fluid acting as a lubricant between the pericardial layers. Surprisingly, little is known about the formation and removal of pericardial fluid, because of the paucity of comprehensive studies, especially in human subjects, and methodological difficulties to distinguish between the dynamics of normal pericardial fluid and those of a pathological effusion (Supplementary material online, Reference A). Nevertheless, normal pericardial fluid is generally considered an ultrafiltrate of plasma (Supplementary material online, Reference B). The arrangement of lymphatic vessels is complex and has been described in human cadavers (Supplementary material online, Supplementary material online, Reference D). The lymphatic vessels include different pathways according to ventral, lateral, and posterior surfaces, but, in any case, terminate to mediastinal, tracheobronchial, or iuxtacoesophageal lymph nodes. On the ventral surface, the lymphatics of the parietal pericardium connect to lymphatics in the pericardial fat and areolar tissue. On the lateral and posterior surfaces, the lymphatics of the parietal pericardium anastomose with lymphatics of the reflected mediastinal pleura (Supplementary material online, Reference C). Lymphatic drainage of the pericardium to the mediastinal and tracheobronchial lymph nodes and interactions with pleural lymphatic vessels (Supplementary material online, Reference D) provide the anatomical basis for pathological involvement of the pericardium in specific diseases (i.e. pulmonary tuberculosis and lung cancer).

Any pathological process usually causes an inflammatory process with the possible increased production of pericardial fluid (exudate). An alternative mechanism of the formation of pericardial fluid may be the decreased reabsorption due to increased systemic venous pressure generally as a result of congestive heart failure or pulmonary hypertension (transudate). If pericardial fluid is free to move within the pericardial sac following the gravity forces, it usually starts accumulating posteriorly to the left ventricle when the patient is laying on his/her left side for echocardiographic evaluation (mild effusion detected initially as posterior), then circumferentially in the case of moderate to large pericardial effusions. A mild pericardial effusion may also be detected close to the right atrium because this is the cardiac chamber with the lowest pressures within the cardiac cycle and thus pericardial fluid accumulation is easier in this position (Figure 2). An isolated mild anterior pericardial fluid is unusual on echocardiography without previous pericardial scarring as following surgery or chronic pericarditis, and should be regarded as fat rather than pericardial fluid.13 Computed tomography (CT) or cardiac magnetic resonance (CMR) may confirm the finding in specific cases, (Figure 3). On the contrary after pericardial scarring (i.e. after cardiac surgery or chronic pericarditis, or bacterial infections), pericardial fluid may not have a uniform distribution within the pericardial space and may give rise to loculated effusions that should be evaluated with multiple cardiac views.14,15

The pressure–volume curve of the normal pericardium is a J-shaped curve: after an initial short shallow portion that allows the pericardium to stretch slightly in response to physiological events, such as changes in posture or volume status, with minimal pressure increase, then the pericardium does not allow further sudden increases of the volume without a marked increase in the intrapericardial pressure. Thus a sudden increase of pericardial volume of 100–200 mL, as in haemopericardium, may elevate pericardial pressure till 20–30 mmHg with acute cardiac tamponade (acute or surgical cardiac tamponade). On the contrary a slowly accumulating pericardial fluid may allow pericardial distention till the accumulation of 1–2 L of pericardial fluid without the development of cardiac tamponade (Figure 4) till advanced stages often because of intermittent events (chronic cardiac tamponade or medical cardiac tamponade).1,3,16

Table 1 Classification of pericardial effusion

<table>
<thead>
<tr>
<th>Onset</th>
<th>Acute (&lt;1 week)</th>
<th>Subacute (&gt;1 week but &lt;3 months)</th>
<th>Chronic (&gt;3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Mild (&lt;10 mm)</td>
<td>Moderate (10–20 mm)</td>
<td>Large (&gt;20 mm)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Circumferential</td>
<td>Loculated</td>
<td></td>
</tr>
<tr>
<td>Haemodynamic effect</td>
<td>Without cardiac tamponade</td>
<td>With cardiac tamponade</td>
<td>Effusive-constrictive</td>
</tr>
<tr>
<td>Composition/type</td>
<td>Transudate</td>
<td>Exudate</td>
<td>Hydropericardium (transudate, plasma ultrafiltrate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Haemopericardium (blood in pericardial space)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyopericardium (purulent pericardial effusion)</td>
<td>Pneumopericardium (air in the pericardium)</td>
</tr>
</tbody>
</table>

No precise definition is available for acute and subacute pericardial effusion, while the definition of chronic as >3 months is more clearly defined.

Aetiology

A wide variety of aetologic agents may be responsible of pericardial effusions, since all known causes of pericardial disease may...
be causative agents (Table 2). The more common causes of pericardial effusions include infections (viral, bacterial, especially tuberculosis), cancer, connective tissue diseases, pericardial injury syndromes (post-myocardial infarction effusions, post-pericardiectomy syndromes, post-traumatic pericarditis either iatrogenic or not), metabolic causes (especially hypothyroidism, renal failure), myopericardial diseases (especially pericarditis, but also myocarditis, heart failure), aortic diseases, especially aortic dissection extending into the pericardium, and selected drugs (i.e. minoxidil). Hydropericardium, a non-inflammatory transudative pericardial effusion, may occur not only in heart failure, but also advanced hypoalbuminaemia, such as in cirrhosis and nephrotic

Figure 1 (A) The semiquantitative assessment of the pericardial effusion size in a case of idiopathic chronic pericardial effusion. A large pericardial effusion of >30 mm in diastole is shown in parasternal long-axis view. (B) Acute pleuroperticularitis with ST segment elevation and sinus tachycardia on ECG strip. A large pericardial effusion >20 mm with concomitant pleural effusion is also evident posteriorly to the aorta. Pe, pericardial effusion; pl, pleural effusion; Ao, aorta.

Figure 2. Presentation of a mild (A) vs. moderate to large pericardial effusions (B) on echocardiography. Mild pericardial effusion is evident adjacent to the right atrium in four-chambers view and only posterior in parasternal long-axis view (A). As fluid accumulates, the effusion becomes circumferential (B). Pe, pericardial effusion; RA, right atrium; Ao, aorta.
syndrome, when Starling forces promote the accumulation of a plasma ultrafiltrate across the pericardium as well as other membranes (e.g. pleura and peritoneum).

In the last 20 years, five major surveys have been published on the characteristics of moderate to large pericardial effusions (Table 3).\(^{17–21}\) Obviously, the relative frequency of different causes depends on the local epidemiology (especially the prevalence of tuberculosis), the hospital setting, and the diagnostic protocol that has been adopted. Many cases still remain idiopathic in developed countries (up to 50%), while other common causes include especially cancer (10–25%), pericarditis and infectious causes (15–30%), iatrogenic causes (15–20%), and connective tissue disease (5–15%), whereas tuberculosis is the dominant cause in developing countries (60%), where tuberculosis is endemic.\(^{22}\) In the setting of pericarditis with pericardial effusion, the prevalence of malignant or infectious aetiologies ranges from 15 to 50% depending on published series.\(^{12,17–21}\)

At present, the largest cohort of patients with moderate (echo-free space of 10–20 mm during diastole) and large pericardial effusions (echo-free space >20 mm) comes from Spain and includes 322 cases (mean age 56 years, 52% males). Cases were collected retrospectively from 1990 to 93 and then prospectively from 1994 to 96 in a 637-bed university general hospital in Barcelona. The authors adopted a three-stage protocol including a basic evaluation for all (stage I including clinical history, physical examination, electrocardiography, chest X-ray, echocardiography, evaluation for tuberculosis, measurement of serum antinuclear antibodies and thyroid hormones, and other targeted studies according to specific presentation), followed by stage II with pericardiocentesis and pericardial fluid analysis for those with cardiac tamponade, suspicion of purulent pericarditis, or chronic large pericardial effusions. Stage III (surgical biopsy of the pericardium) was limited to those with persistent or recurring tamponade after pericardiocentesis, and when the effusion lasted for >3

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**Figure 3** Differential diagnosis of pericardial effusion vs. epicardial fat. (A) Echocardiographic view. Anterior pericardial echo-free space. No effusion was evident adjacent to the right atrium in four-chambers view. (B) Epicardial fat and thickened pericardium with contrast enhancement on CT scan.

**Figure 4** Pressure/volume curve of the pericardium with fast accumulating pericardial fluid leading to cardiac tamponade with a smaller volume (A) compared with the slowly accumulating pericardial fluid reaching cardiac tamponade only after larger volumes (B).
weeks after admission and without an aetiologic diagnosis. The most common diagnoses included: acute idiopathic pericarditis (20%), iatrogenic effusions (16%), cancer (13%), and chronic idiopathic pericardial effusion (9%). In 60% of cases, the cause of pericardial effusion was a known medical condition.18

**Clinical presentation**

The clinical presentation of pericardial effusion is varied according to the speed of pericardial fluid accumulation as mentioned in the introduction, and the aetiology of the effusion with possible symptoms that may be related to the causative disease. The rate of pericardial fluid accumulation is critical for the clinical presentation. If pericardial fluid is quickly accumulating such as for wounds or iatrogenic perforations, the evolution is dramatic and only small amounts of blood are responsible of a quick rise of intrapericardial pressure and overt cardiac tamponade in minutes. On the contrary a slowly accumulating pericardial fluid allows the collection of a large effusion in days to weeks before a significant increase in pericardial pressure becomes responsible of symptoms and signs.3

Classical symptoms include dyspnoea on exertion progressing to orthopnoea, chest pain, and/or fullness. Additional occasional symptoms due to local compression may include nausea (diaphagm), dysphagia (oesophagus), hoarseness (recurrent laryngeal nerve), and hiccup (phrenic nerve). Non-specific symptoms include also cough, weakness, fatigue, anorexia and palpitations and reflect the compressive effect of the pericardial fluid on contiguous anatomic structures or reduced blood pressure and secondary sinus tachycardia.23

The classical findings of cardiac tamponade have been described by the thoracic surgeon Beck in 1935.24 Beck identified a triad including hypotension, increased jugular venous pressure, and a small and quiet heart. This triad was classically identified in 'surgical tamponade' with acute cardiac tamponade due to intrapericardial haemorrhage because of trauma, myocardial or aortic rupture. The Beck triad may be lacking in patients with 'medical tamponade' with slowly accumulating pericardial fluid. Hypotension is absolute or relative. Acute cardiac tamponade is usually associated with low blood pressure (<90 mmHg) but may be only slightly reduced in subacute, chronic tamponade. Hypertensive patients may have normal to mildly elevated blood pressure concomitant to cardiac tamponade.25 Fever is a non-specific sign that may be associated with pericarditis either infectious or immune-mediated (i.e. systemic inflammatory diseases).

On physical examination classical signs include neck vein distension with elevated jugular venous pressure at bedside examination, pulsus paradoxus, and diminished heart sounds on cardiac auscultation. Pericardial friction rubs are rarely reported, they can be usually detected in patients with concomitant pericarditis. Rubs which occur during the maximal movement of the heart within its pericardial sac, are said to be generated by friction between the two inflamed layers of the pericardium. However, this commonly offered explanation for its mechanism may be an oversimplification as patients with a pericardial effusion may also have an audible friction rub, and there is no precise correlation between pericardial rubs and size of the effusion, although pericardial rubs may be easier to hear in patients without a pericardial effusion, but this finding is not universal and is not well-documented (Supplementary material online, Reference E). In a report of 100 patients with acute pericarditis, a pericardial rub was present in 85% of cases without an effusion (Supplementary material online, Reference F). This prevalence is considerably higher than the 35% incidence of friction rubs reported in another series (Supplementary material online, Reference G).

Pulsus paradoxus has been described for the first time by Kussmaul in 1873 as a palpable reduction of radial pulse on inspiration in patients with cardiac tamponade.26 The so-called paradox was the ‘waxing and waning’ of the peripheral pulse, in contrast to the unvarying strength of the apical cardiac impulse. Pulsus paradoxus is classically defined as an inspiratory reduction of at least 10 mmHg of the systolic blood pressure (Figure 5). It can be
easily detected recording the systolic pressure at which Korotkoff sounds are first audible and the systolic pressure at which they are audible through the whole respiratory cycle. Pulsus paradoxus is due to exaggerated ventricular interdependence occurring in cardiac tamponade when overall volume of cardiac chambers becomes fixed and any change in the volume of one side of the heart causes the opposite changes in the other side (i.e. inspiratory increase of venous return and right chambers with decreased left chambers volume and reduced systemic blood pressure).

In the absence of cardiac tamponade reported symptoms and signs are non-specific and may include: shortness of breath, dyspnoea on exertion, fever, chills, chest pain, paroxysmal nocturnal dyspnoea, orthopnoea, cough, and oedema. All these symptoms, and signs may be secondary to the underlying cause of the effusion (i.e. systemic disease and pericarditis) or the initial mechanical interference of pericardial fluid with cardiac function or surrounding anatomical structures.

### Diagnosis

The diagnosis of pericardial effusion is generally performed by echocardiography, that also allows the semiquantitative assessment of the pericardial effusion size and its haemodynamic effects as outlined in the paragraph on the initial approach to pericardial effusion. The diagnosis of cardiac tamponade is essentially a clinical diagnosis requiring echocardiographic confirmation of the initial diagnostic suspicion. In most patients, cardiac tamponade should be diagnosed by a clinical examination that shows elevated systemic venous pressure, tachycardia, dyspnoea, and paradoxical arterial pulse. Systemic blood pressure may be normal, decreased, or even elevated. The diagnosis is confirmed by an echocardiographic demonstration of moderately large or large circumferential pericardial effusion and in most instances, of right atrial compression, abnormal respiratory variation in right and left ventricular dimensions, and in tricuspid and mitral valve flow velocities usually associated with inferior vena cava plethora (Table 4 and Figure 6) (Supplementary material online, Reference H).

However, a more complex task is the evaluation of the aetiology. Different diagnostic protocols have been proposed.

### Table 3: Aetiologic diagnosis of moderate to large pericardial effusions according to major published series

<table>
<thead>
<tr>
<th>Feature</th>
<th>Corey et al.17</th>
<th>Sagrista-Sauleda et al.18</th>
<th>Levy et al.19</th>
<th>Reuter et al.20</th>
<th>Ma et al.21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>57</td>
<td>322</td>
<td>204</td>
<td>233</td>
<td>140</td>
</tr>
<tr>
<td>Country</td>
<td>USA</td>
<td>Spain</td>
<td>France</td>
<td>South Africa</td>
<td>China</td>
</tr>
<tr>
<td>Effusion size</td>
<td>&gt;5 mm</td>
<td>&gt;10 mm</td>
<td>NR</td>
<td>NR</td>
<td>Moderate to large*</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>NR</td>
<td>37</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Subxiphoid pericardiomy</td>
<td>TB, ANA, TSH, pericardiocentesis, and biopsy</td>
<td>BCx, TSH, ANA, Q fever, viral rectal, and throat swabs</td>
<td>HIV, sputum, TB, BCx, blood chemistry, and serology</td>
<td>Pericardiocentesis</td>
</tr>
<tr>
<td>Idiopathic (%)</td>
<td>7</td>
<td>29</td>
<td>48</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>23</td>
<td>13</td>
<td>15</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>Infections (%)</td>
<td>27</td>
<td>2</td>
<td>16</td>
<td>72</td>
<td>29</td>
</tr>
<tr>
<td>Connective tissue diseases (%)</td>
<td>12</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Metabolic (%)</td>
<td>24</td>
<td>6</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Iatrogenic (%)</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

A selection of the most frequent aetiological diagnoses is reported (thus overall sum in columns may be <100%).
NR, not reported; TB, aetiology search for tuberculosis; BCx, blood cultures.
*All effusions requiring pericardiocentesis.

[Figure 5](#): The femoral artery pressure curve showing pulsus paradoxus during cardiac tamponade. A systolic blood pressure decline is >10 mmHg during inspiration.
Nevertheless, the diagnostic work-up should be guided by the epidemiology and the clinical presentation to avoid performing an extensive and blinded testing. As already remarked, developing countries have a high rate of pericardial effusions correlated to tuberculosis (>60, and >80% with HIV infection) that should be ruled out in such context, as well as in immigrants and HIV-infected patients. Non-idiopathic and non-viral aetiologies (especially bacterial and neoplastic) are associated with an increased risk of cardiac tamponade and large effusion, and pericardiocentesis is mandatory when cardiac tamponade or such aetiologies are suspected.

Analyses of pericardial effusion can establish the diagnosis of infectious and neoplastic pericardial effusions. Cytology and tumour markers (carcinoembryonic antigen (CEA), alfetoprotein, carbohydrate antigens CA 125, CA 72-4, CA 15-3, CA 19-9, etc.) should be performed in suspected malignant disease. In suspected tuberculosis acid-fast bacilli staining, mycobacterium culture or radiometric growth detection (e.g. BACTEC-460), adenosine deaminase (ADA), interferon (IFN)-gamma, pericardial lysozyme, and as well as PCR analyses for tuberculosis should be performed (indication class I, level of evidence B). Differentiation of tuberculous and neoplastic effusion is virtually absolute with low levels of ADA and high levels of CEA. In addition, high ADA levels may predict the evolution towards pericardial constriction. In suspected bacterial infections, at least three cultures of pericardial fluid for aerobes and anaerobes as well as the blood cultures are mandatory (indication class I, level of evidence B). PCR analyses for cardiotropic viruses have been suggested (indication class IIa, level of evidence B), but are rarely used in clinical practice. Analyses of the pericardial fluid specific gravity (>1015), protein level (>3.0 g/dL), fluid/serum ratio >0.5, LDH >200 mg/dL, serum/ fluid >0.6, and glucose can separate exudates from transudates, but are not directly diagnostic (class IIb). Nevertheless, purulent effusions with positive cultures have significantly lower fluid glucose levels than non-infectious effusions. White cell count is highest in inflammatory and infectious diseases, and lowest in myxedema. Technical advances in instrumentation, introduction of pericardiography and contemporary pathology, virology, and molecular biology techniques have improved the diagnostic value of epicardial/pericardial biopsy. Pericardiography performed through air instead of fluid, make it possible to inspect large areas of pericardial surface, select the biopsy site, and take numerous samples. Targeted pericardial/pericardial biopsy during pericardiography was particularly useful in the diagnosis of neoplastic pericarditis. No major complications were reported with the use of flexible pericardioscopies (Supplementary material online, References I and J). Such techniques and approaches are warranted in skilled tertiary referral centres for selected cases, when a specific diagnosis, that may require a targeted therapy (i.e. neoplastic pericardial effusion), is suspected and cannot be diagnosed by traditional diagnostic means.

In the 2004 ESC guidelines, a specific definition is provided for autoreactive pericarditis/pericardial effusion. The diagnosis of autoreactive pericarditis is established using the following criteria: (i) increased number of lymphocytes and mononuclear cells (>5000/mm³ (autoreactive lymphocytic), or the presence of antibodies against heart muscle tissue (antisarcocennmal) in the pericardial fluid (autoreactive antibody mediated); (ii) signs of myocarditis on epicardial/endomyocardial biopsies by >14 cells/mm³; (iii) exclusion of active viral infection both in pericardial effusion and endomyocardial/epimyocardial biopsies (no virus isolation, no IgM titer against cardiotropic viruses in pericardial effusion, and negative PCR for major cardiotropic viruses); (iv) tuberculosis; (v) Borrelia burgdorferi, Chlamydia pneumoniae, and other bacterial infection excluded by PCR and/or cultures; (v) neoplastic infiltration absent in pericardial effusion and biopsy samples; (vii) exclusion of systemic, metabolic disorders, and uraemia. This is essentially a diagnosis of exclusion for pericardial effusions with an autoimmune pathogenesis not related to a known systemic inflammatory disease, and that may be efficiently treated by corticosteroids.

A standard recommended approach for the analysis of pericardial fluid is reported in Table 5.

Among specific causes of pericardial effusion, tuberculosis is especially important to be recognized, because it is a dangerous disease with a high mortality if untreated, and a high risk of evolution towards constrictive pericarditis (30–50% of cases). A previous history of tuberculosis, an origin from an area, where tuberculosis is endemic (i.e. Africa and India), a subacute course, low grade fever, weight loss, night sweats, a moderate to large pericardial effusion are all features associated with a high risk of a tuberculous cause of the effusion. A definite diagnosis of tuberculous effusion requires the demonstration of tuberculosis bacilli in pericardial fluid or tissue. However, the diagnosis is probable if tuberculosis is shown in patients with the diagnosis of tuberculosis elsewhere in the body (i.e. pulmonary), or with a lymphocytic pericardial exudate with elevated ADA levels. The empiric response to antituberculosis therapy as ex-juvantibus diagnosis may be acceptable only in countries, where tuberculosis is endemic, but not in Western Europe and North America.

| Table 4 Major echocardiographic signs of cardiac tamponade (Supplementary material online, Reference H) |

<table>
<thead>
<tr>
<th>Sign</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large pericardial effusion with swinging heart</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Diastolic collapse of right atrium (RA)</td>
<td>50–100%</td>
<td>33–100%</td>
</tr>
<tr>
<td>Duration of RA inversion by the RA inversion time index (duration of inversion/cardiac cycle length); for values &gt;0.34</td>
<td>&gt;90%</td>
<td>100%</td>
</tr>
<tr>
<td>Diastolic collapse of right ventricle (RV)</td>
<td>48–100%</td>
<td>72–100%</td>
</tr>
<tr>
<td>Variations in E velocities during respiration across the mitral valve, tricuspid valve, and pulmonary outflow that are greater than 25, 50, and 30%</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Inferior vena cava (IVC) plethora (dilatation &gt;20 mm and &lt;50% reduction in the diameter of IVC with respiratory phases)</td>
<td>97%</td>
<td>40%</td>
</tr>
</tbody>
</table>

n.a. not available.
The presence of elevated inflammatory markers and other criteria for pericarditis (chest pain, pericardial rubs, and ECG changes) suggests pericarditis and management should follow the triage and management recommended for pericarditis. Integrated cardiovascular imaging, including echocardiography, CT, and CMR may provide valuable aid in the search for the cause of pericardial effusions. Although echocardiography remains the primary diagnostic tool for the study of pericardial diseases because of its widespread availability, portability, and limited costs, CT and CMR provide a larger field of view, allowing the detection of loculated pericardial effusion, pericardial thickening and masses, as well as associated chest abnormalities. Cardiac magnetic resonance may also provide a combined morphological and functional evaluation. For both CT and CMR, the pericardium is ideal for imaging studies, because of a high natural contrast between pericardial layers separated by pericardial fluid, and contiguous fat tissue in the mediastinal and subepicardial space. Computed tomography density measurements and the analysis of CMR signals may enable the initial characterization of pericardial fluid better than echocardiography. With inflamed pericardium, the patient usually has the combination of effusion and pericardial thickening. On CT, generally, pericardial effusions are of low density in the range of 0–20 Hounsfield units (HU). When the effusion contains higher amounts of protein, such as in bacterial infections, or when it is haemorrhagic, its density may rise to 50 HU and more. Inflamed pericardium may also show contrast enhancement. In CT imaging of the pericardium, difficulty may be encountered in differentiating fluid from thickened pericardial tissue. Cardiac magnetic resonance is superior to CT in differentiating fluid, especially highly proteinaceous exudative effusions, from thickened pericardium. On the contrary, CT may detect even minimal amounts of pericardial calcium, whereas CMR may miss significant deposits. Computed tomography requires less time than echocardiography and CMR. However, CT requires the use of intravenously administered iodinated contrast materials and ionizing radiation. Moreover, if performed without ECG gating, CT may lead to cardiac motion artefacts, that limit the evaluation of pericardial thickness. However, the use of more recent and updated CT scanners with a greater spatial and temporal resolution and more sophisticated algorithms for image reconstruction may allow a significant reduction in CT imaging artefacts. Cardiac magnetic resonance has a superior ability to characterize pericardial effusions and masses with the use of a combination of T1-weighted, T2-weighted, and gradient-recalled echo cine sequences without the use of either iodinated contrast material or ionizing radiation. However, a possible disadvantage of CMR with ECG gating is that arrhythmias, often associated with

### Table 5 Routine analyses to be performed on pericardial fluid

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Test</th>
<th>Aetiology or feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>General chemistry</td>
<td>Specific gravity &gt; 1015, protein level &gt; 3 g/dL, protein fluid/serum ratio &gt; 0.5, LDH &gt; 200 mg/dL, fluid/serum ratio &gt; 0.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose, blood cell count</td>
<td>Exudate</td>
</tr>
<tr>
<td>Cytology</td>
<td>Cytology (higher volumes of fluid, centrifugation, and rapid analysis improve diagnostic yield)</td>
<td>Cancer</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Tumour markers (i.e. CEA &gt; 5 ng/mL or CYFRA 21-1 &gt; 100 ng/mL)</td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Adenosine deaminase &gt; 40 U/L, IFN-gamma</td>
<td>TBC</td>
</tr>
<tr>
<td>Polymerase chain reaction (PCR)</td>
<td>PCR for specific infectious agents (i.e. TBC)</td>
<td>TBC</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Acid-fast bacilli staining, mycobacterium cultures, aerobic, and anaerobic cultures</td>
<td>TBC Other bacteria</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase; TBC, tuberculosis.

*These chemical features have been especially validated for pleural fluid and not pericardial fluid, although generally used also for pericardial effusion.
myopericardial diseases, may cause artefacts. Another disadvantage of CMR is related to its limited availability and higher costs. Use of i.v. injected gadolinium may be useful for pericarditis detection, because gadolinium has been reported to enhance inflamed pericardium (Figure 7), as well as for the detection of concomitant myocardial involvement in myopericarditis.4,7,14,34–37

**Therapy**

The therapy of pericardial effusion should be targeted at the aetiology as much as possible.37–41 In ~60% of cases, the effusion is associated with a known disease,18 and the essential treatment is that of the underlying disease. When pericardial effusion is associated with pericarditis, management should follow that of pericarditis.30,37 Nevertheless, when diagnosis is still unclear or idiopathic, and inflammatory markers are elevated, a trial of aspirin or a non-steroidal anti-inflammatory drug (NSAID) can be prescribed also to evaluate the response (Table 6). A viral or idiopathic form is often responsive to such empiric therapy. For the management of recurrent inflammatory cases, the first step is considering the combination of aspirin or a NSAID plus colchicine,42 while corticosteroids at low to moderate doses may be considered for specific indications (i.e. systemic inflammatory diseases and pregnancy),43 and in case of intolerance, contraindications, or failure of aspirin/NSAID; other therapies are based on less solid evidence: less toxic and less expensive drugs (e.g. azathioprine or methotrexate) should be preferred, tailoring the therapy for the individual patient and the physician experience.44

In the 2004 ESC guidelines, ibuprofen is proposed as the favourite first choice for empiric anti-inflammatory therapy of pericarditis, due to rare side effects, favourable effect on the coronary flow, and the large dose range.7 However, other approaches have been published, and aspirin is used as first favourite choice in several clinical trials in the setting of acute and recurrent pericarditis.4,37,38,42 For patients who already are taking or need aspirin, such drug is the best anti-inflammatory choice.7

In the setting of post-myocardial infarction pericarditis, ibuprofen, which increases the coronary flow, is the preferred agent of choice according to 2004 ESC guidelines.7 Aspirin has been also successfully applied.

Other non-steroidal agents may increase the risk of thinning the infarction zone. Corticosteroid therapy can be used for refractory symptoms only, but could delay myocardial infarction healing (class IIIa indication, level of evidence B). Post-infarction pericardial effusion >10 mm may be associated with haemopericardium, and up to two-thirds of these patients may develop tamponade/free wall rupture. In this setting, urgent surgical treatment is life saving. However, if the immediate surgery is not available or contraindicated, pericardiocentesis, and intrapericardial fibrin-glue instillation could provide an alternative immediate treatment, as proposed in the 2004 ESC guidelines.7

In the setting of autoreactive pericardial effusion, growing evidence supports the possible use of intrapericardial therapies to reduce side effects related to the oral use of corticosteroids.
Management of pericardial effusion

( Supplementary material online, Reference K). Systemic corticosteroids offer an effective treatment option for autoreactive pericarditis; however, their use is limited by adverse effects and they are an independent risk factor for pericarditis recurrence. In a recently published systematic review (Supplementary material online, Reference L), one case series and three open-label trials evaluating intrapericardial triamcinolone for the management of autoreactive pericarditis were reviewed. Included studies were limited by small sample sizes (n = 2–84), lack of control groups, short durations of follow-up (24 h–12 months), use of adjuvant agents, lack of patient demographic data, subjective report of symptom relief, and lack of consistent dose of intrapericardial triamcinolone. Despite these limitations, available data suggest symptom resolution and reduced pericarditis recurrence with the administration of intrapericardial triamcinolone to patients with autoreactive pericarditis (Supplementary material online, Reference L).

When a pericardial effusion becomes symptomatic without evidence of inflammation or when empiric anti-inflammatory drugs are not successful, drainage of the effusion should be considered. Pericardiocentesis with prolonged pericardial drainage till <30 mL/24 h is recommended to promote adherence of pericardial layers and prevent further accumulation of fluid, although evidence to support this indication is based on case reports, retrospective studies, and expert opinion. If pericardiocentesis is not feasible or fails, the creation of a so-called pericardial window should be considered either by conventional heart surgery or video-assisted thoracoscopy. Balloon pericardiectomy is an alternative to surgical creation of a pericardial window, which has been shown successful especially in the setting of neoplastic pericardial disease. The technique involves inserting a deflated single catheter or double balloon catheters into the pericardial space using a subxiphoid approach under fluoroscopic or echocardiographic guidance. Although successful in preventing recurrence in >80% of cases, stretching of the pericardium is often painful so appropriate analgesia is recommended.

The 2004 ESC guidelines gave a class Ila recommendation to pericardiectomy for frequent and highly symptomatic recurrences resistant to medical treatment. Other reported indications include repeated recurrences with cardiac tamponade, and evidence of serious steroid toxicity. Although surgical experiences are not always concordant, pericardiectomy is generally considered as a therapeutic option of doubtful efficacy in recurrent idiopathic pericarditis or pericardial effusion and should be considered only in exceptional cases. Chronic permanent constriction remains the major indication for such intervention. However, incessant pericarditis, as distinguished from recurrent intermittent pericarditis, may respond favourably to surgical removal, especially in the presence of recurrent pericardial effusion. An idiopathic chronic pericardial effusion is defined as a collection of pericardial fluid that persists for >3 months and has no apparent cause; large effusions have a risk of progression to cardiac tamponade (up to one-third, according to a Spanish study). On this basis some authors have advocated the need for pericardiectomy for such cases, whenever a large effusion recurs after pericardiocentesis. Since drainage is relatively safe and easy in some cases with guided pericardiocentesis, drainage has been recommended for large subacute effusions, that do not respond to empiric therapy, and are stable after several weeks (e.g. 6–8 weeks), especially when there are signs of rightsided collapse, in order to prevent the possible progression of the effusion towards tamponade following additional events (e.g. pericarditis, bleeding following chest trauma).

Unfortunately, there are no proven effective medical therapies to reduce an isolated effusion; in the absence of inflammation, NSAID as well as colchicine and corticosteroids are generally not efficacious. Pericardiocentesis alone may be necessary for the resolution of large effusions but recurrences are also common and pericardiectomy or less invasive options (i.e. pericardial window) should be considered whenever fluid reaccumulates, becomes loculated, or biopsy material is required. The feasibility of pericardiocentesis is high (>90%) in patients with anterior effusion, while the rate of success is <60% with small, posteriorly located effusions. Pericardiocentesis with echocardiography guidance is feasible in >95% of cases. The most serious complications of pericardiocentesis are laceration and perforation of the myocardium and the coronary vessels. In addition, patients can experience air embolism, pneumothorax, arrhythmias (usually vasovagal brady-cardia), and puncture of the peritoneal cavity or abdominal viscera. Internal mammary artery fistulae, acute pulmonary oedema, and purulent pericarditis were rarely reported. The safety was improved with echocardiographic or fluoroscopic guidance. Recent large echocardiographic series reported an incidence of major complications of 1–1.6%. In a large series of fluoroscopy-guided percutaneous pericardiocenteses, cardiac perforations occurred in <1%, serious arrhythmias in 0.6%, arterial bleeding in 1.1%, pneumothorax in 0.6%, infection in 0.3%, and a major vagal reaction in 0.3%. The need for intervention in all cases remains controversial and requires the understanding of the possible benefit/risk ratio (i.e. possible trigger of recurrences).

Special considerations should be done for the management of neoplastic pericardial effusions (Supplementary material online, References L and M–Q). Malignant pericardial effusion and cardiac tamponade are known complications of many advanced malignancies, such as breast cancer, lung cancer, lymphomas, and leukaemias. There are many treatment options available, ranging from simple drainage to thoracic surgery. It is essential that treating physicians 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 local availability and expertise. Given the poor prognosis of most patients presenting with malignant pericardial effusions, reducing symptoms and improving the quality of life are the primary goals of treatment. Management of these patients requires multidisciplinary approaches with cooperation between cardiologists, cardiac surgeons, oncologists, radiotherapists, and palliative care physicians. Immediate relief of symptoms may be obtained with percutaneous drainage or with a surgical approach. For long-term prevention of recurrences, various approaches have been proposed: extended drainage, pericardial window (either surgical or percutaneous balloon pericardiostomy), sclerosing local therapy, local and/or systemic chemotherapy, or radiation therapy. The outcomes of various therapeutic approaches vary for different tumour types. Lymphoma and leukaemias can be successfully treated with systemic chemotherapy; for solid tumours, percutaneous drainage and the use of systemic and/or local sclerosing and antineoplastic therapy seems to offer the best chance of...
success. The use of ‘pure’ sclerosing agents has been replaced by agents with both sclerosing and antineoplastic activity (bleomycin or thiotepa), which seems to be quite effective in breast cancer, at least when associated with systemic chemotherapy. Local chemotherapy with platinum, mitoxantrone, and other agents may lead to good local control of the disease, but the addition of systemic chemotherapy is probably relevant to improve survival. The rationale of local instillation of antineoplastic agents is to cure the metastases, rather than simply prevent effusion by mechanical means. Intrapericardial treatment tailored to the type of cancer indicates that cisplatin is more effective in secondary lung cancer, whereas thiotepa seems to be effective in breast cancer.7 Surgical or percutaneous pericardiostomy and radiation therapy may be useful in recurring effusions or cases not responding to other treatments (Supplementary material online, References P and Q).40

**Prognosis and follow-up**

The prognosis of pericardial effusion is essentially related to the aetiology, and, thus, it is important to identify specific aetiologies that require targeted therapies. The size of the effusion is correlated to the prognosis, because moderate to large effusions are more common for specific aetiologies, such as bacterial, neoplastic or related to a systemic inflammatory disease.4,12,30 Bacterial aetiologies as well as post-radiation pericardial diseases, pericardial injury syndromes have an increased risk of developing complications either early or intermediate (cardiac tamponade, recurrences) or late (constrictive pericarditis).59 Idiopathic pericardial effusion and pericarditis have an overall good prognosis with a very low risk of complications especially if the effusion is mild to moderate. In contrast with these observations, a recently published prospective study has shown that even with mild pericardial effusion the overall prognosis may be worse than in age- and sex-matched controls.50

Large idiopathic chronic effusion (>3 months) have a 30–35% risk of progression to cardiac tamponade.46 Also subacute (4–6 weeks) large effusions not responsive to conventional therapy and with echocardiographic signs of right chambers collapse may have an increased risk of progression according to some authors who recommend preventive drainage in such cases.47

Idiopathic pericarditis has a very low documented risk of constrictive pericarditis despite even several recurrences: here the risk is related to the aetiology and not the number of recurrences.49

The follow-up of pericardial effusion is mainly based on the evaluation of symptoms and the echocardiographic size of the effusion, as well as additional features such as inflammatory markers (i.e. C-reactive protein). There are no specific recommendations from pericardial diseases guidelines. A mild idiopathic effusion (<10 mm) is usually asymptomatic, has generally a good prognosis and does not require specific monitoring. Moderate to large effusions (>10 mm) may worsen and especially severe effusions may evolve towards cardiac tamponade in up to one-third of cases as

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**Figure 8** A simplified algorithm for pericardial effusion triage and management. CRP, C-reactive protein.
already mentioned. We usually recommend to tailor the follow-up to the aetiology, adopted therapies (usually a control after 1–2 weeks and then after 1 month and 6 months), and monitoring the possible evolution towards worsening pericardial effusion, cardiac tamponade, and constrictive pericarditis. For idiopathic pericardial effusions, an appropriate timing for echocardiographic follow-up may be an echocardiogram every 6 months. For a severe effusion, an echocardiographic follow-up may be every 3–6 months. A tailored follow-up is warranted also considering the relative stability or evolution of the size (i.e. a worsening effusion may require a closer timing also guided by symptoms).\(^4\)

**Conclusions**

Relatively, few data have been published on the management of pericardial effusion and there is a lack of contemporary prospective series with unselected patients with pericardial effusions of different entity (small vs. moderate vs. large). Ongoing prospective studies, registries, and new updated guidelines from medical societies will provide more evidence based data to guide the management of pericardial effusion. A simplified algorithm for the triage and management of pericardial effusion is illustrated in Figure 8.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Conflict of interest:** none declared.

**References**