



ESC Guidelines

# Guidelines on the Diagnosis and Management of Pericardial Diseases

## Full Text

### The Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology

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## Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by different organisations, the European Society of Cardiology (ESC) and by other related societies. By means of links to web sites of National Societies several hundred guidelines are available. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied within the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilisation of health resources.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups or consensus panels. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

## Introduction

The strength of evidence related to a particular diagnostic or treatment option depends on the available data: (1) *level of evidence A*. Multiple randomised clinical trials or meta-analyses; (2) *level of evidence B*. A single randomised trial or non-randomised studies; (3) *level of evidence C*. Consensus opinion of the experts. Indications for various tests and procedures were ranked in three classes:

*Class I*: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

*Class II*: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

*Class IIa*: Weight of evidence/opinion is in favour of usefulness/efficacy.

*Class IIb*: Usefulness/efficacy is less well established by evidence/opinion.

*Class III*: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

## Aetiology and classification of pericardial disease

The spectrum of pericardial diseases comprises congenital defects, pericarditis (dry, effusive, effusive-constrictive, constrictive), neoplasm, and cysts. The aetiological classification is shown in Table 1.<sup>1-3</sup>

### Pericardial syndromes

#### Congenital defects of the pericardium

Congenital defects of the pericardium (1/10.000 autopsies) comprise partial left (70%), right (17%) or total bilateral (extremely rare) pericardial absence. About 30% of patients have additional congenital abnormalities.<sup>4</sup> Most patients with a total absence of pericardium are asymptomatic. However, homolateral cardiac displacement and augmented heart mobility impose an increased risk for traumatic aortic type A dissection.<sup>5</sup> Partial left side defects can be complicated by cardiac strangulation caused by herniation of the left atrial appendage, atrium or left ventricle through the defect (chest pain, shortness of breath, syncope or sudden death). The chest X-ray is typical but the diagnosis is confirmed by echocardiography and CT/MRI.<sup>6,7</sup> Excision of the atrial appendage and surgical pericardioplasty (Dacron, Gore-tex, or bovine pericardium) is indicated for imminent strangulation.<sup>8</sup>

#### Acute pericarditis

Acute pericarditis is either dry, fibrinous or effusive, independent from its aetiology (Table 1).<sup>9</sup> A prodrome of fever (usually <39 °C), malaise, and myalgia is common, but elderly patients may not be febrile. Major symptoms are retrosternal or left precordial *chest pain* (radiates to the trapezius ridge, can be pleuritic or simulate ischaemia, and varies with posture), non-productive *cough*, and shortness of breath. *The pericardial friction rub* can be transient, mono-, bi- or triphasic. *Pleural effusion* may be present. Pericarditis is often accompanied by some degree of myocarditis (evidenced by global or regional myocardial dysfunction, myalgias or rhabdomyolysis, elevations of troponins I and T, MB creatine-kinase, serum myoglobin levels and tumour necrosis factor). Auscultation of a new S3 heart sound, convexly elevated J-ST segment in the ECG, fixation of Indium-111-labelled an-

**Table 1** Review of aetiology, incidence and pathogenesis of pericarditis<sup>1-3</sup>

Aetiology	Incidence (%)	Pathogenesis
<b>Infectious pericarditis</b>		
Viral (Coxsackie A9, B1-4, Echo 8, Mumps, EBV, CMV, Varicella, Rubella, HIV, Parvo B19...)	30–50 <sup>a</sup>	Multiplication and spread of the causative agent and release of toxic substances in pericardial tissue cause serous, serofibrinous or haemorrhagic (bacterial, viral, tuberculous, fungal) or purulent inflammation (bacterial)
Bacterial (Pneumo-, Meningo-, Gonococcosis, Hemophilus, Treponema pallidum, Borreliosis, Chlamydia, Tuberculosis...)	5–10 <sup>a</sup>	
Fungal (Candida, Histoplasma...)	Rare	
Parasitary (Entameba histolytica, Echinococcus, Toxoplasma...)	Rare	
<b>Pericarditis in systemic autoimmune dis.</b>		
Systemic lupus erythematosus	30 <sup>b</sup>	Cardiac manifestations of the basic disease, often clinically mild or silent
Rheumatoid arthritis	30 <sup>b</sup>	
Spondylitis ankylosans	1 <sup>b</sup>	
Systemic sclerosis	>50 <sup>b</sup>	
Dermatomyositis	Rare	
Periarthritis nodosa	Rare	
Reiter's syndrome	~2 <sup>b</sup>	
Familial Mediterranean fever	0.7 <sup>b</sup>	
<b>Type 2 (auto)immune process</b>		
Rheumatic fever	20–50 <sup>b</sup>	Secondary, after infection/surgery Mostly in acute phase 10–14 days after surgery DDg P. epistenocardica Common form
Postcardiotomy syndrome	~20 <sup>b</sup>	
Postmyocardial infarction syndrome	1–5 <sup>b</sup>	
Autoreactive (chronic) pericarditis	23.1 <sup>a</sup>	
<b>Pericarditis and pericardial effusion in diseases of surrounding organs</b>		
Acute MI (P. Epistenocardica)	5–20 <sup>b</sup>	1–5 days after transmural MI Accompanying epimyocarditis Dissection: haemorrhagic PE
Myocarditis	30 <sup>b</sup>	
Aortic aneurysm	Rare	No direct neoplastic infiltrate
Lung infarction	Rare	
Pneumonia	Rare	
Oesophageal diseases	Rare	
Hydropericardium in CHF	Rare	
Paraneoplastic pericarditis	Frequent	
<b>Pericarditis in metabolic disorders</b>		
Renal insufficiency (uraemia)	Frequent	Viral/toxic/autoimmune Serous, cholesterol rich PE Membranous leak?
Myxedema	30 <sup>b</sup>	
Addison's disease	Rare	Transudation of cholesterol (sterile serofibrinous PE)
Diabetic ketoacidosis	Rare	
Cholesterol pericarditis	Very rare	
Pregnancy	Rare	
<b>Traumatic pericarditis</b>		
Direct injury (penetrating thoracic injury, oesophageal perforation, foreign bodies)	Rare	Less frequent after introduction of topical convergent irradiation
Indirect injury (Non-penetrating thoracic injury, mediastinal irradiation)	Rare	
<b>Neoplastic pericardial disease</b>		
Primary tumours	35 <sup>a</sup>	Serous or fibrinous, frequently haemorrhagic effusion
Secondary metastatic tumours	Rare	
Lung carcinoma	40 <sup>c</sup>	Accompanying disease during the infiltration of malignant cells
Breast carcinoma	22 <sup>c</sup>	
Gastric and colon	3 <sup>c</sup>	
Other carcinoma	6 <sup>c</sup>	
Leukemia and lymphoma	15 <sup>c</sup>	
Melanoma	3 <sup>c</sup>	
Sarcoma	4 <sup>c</sup>	
Other tumours	7 <sup>c</sup>	

**Table 1** (continued)

Aetiology	Incidence (%)	Pathogenesis
Idiopathic	3.5 <sup>a</sup> , in other series >50 <sup>a</sup>	Serous, fibrinous, sometimes haemorrhagic PE with suspect viral or autoimmune sec- ondary immunopathogenesis

CHF, congestive heart failure; DDg, differential diagnosis; MI, myocardial infarction; P., pericarditis; PE, pericardial effusion.

<sup>a</sup> Percentage related to the population of 260 subsequent patients undergoing pericardiocentesis, pericardioscopy and epicardial biopsy (Marburg pericarditis registry 1988–2001).<sup>1</sup>

<sup>b</sup> Percentage related to the incidence of pericarditis in the specific population of patients (e.g., with systemic lupus erythematosus).

<sup>c</sup> Percentage related to the population of patients with neoplastic pericarditis.

timyosin antibodies, and structural changes in MRI are indicative.<sup>9</sup> However, only endomyocardial/epimyocardial biopsy findings are diagnostic.

The diagnostic algorithm can be derived from Table 2.<sup>10–21</sup> Heart rate is usually rapid and regular. Microvoltage and electrical alternans are reversible after effusion drainage.<sup>22</sup> Findings by chest X-ray, computer tomography (CT), and magnetic resonance imaging (MRI)

are shown in Table 3.<sup>23,24</sup> Echocardiography is essential to detect pericardial effusion and to check for concomitant heart disease or paracardial pathology.<sup>12,13</sup>

Hospitalisation is warranted for most patients to determine the aetiology, observe for tamponade, and start anti-inflammatory and symptomatic treatment. Nonsteroidal anti-inflammatory drugs (NSAID) are the mainstay (level of evidence B, class I). Ibuprofen is preferred for its

**Table 2** Diagnostic pathway and sequence of performance in acute pericarditis (level of evidence B for all procedures)

Technique	Characteristic findings	Reference
<i>Obligatory (indication class I)</i>		
Auscultation	Pericardial rub (mono-, bi-, or triphasic)	11
ECG <sup>a</sup>	<i>Stage I:</i> anterior and inferior concave ST segment elevation. PR segment deviations opposite to P polarity. <i>Early stage II:</i> ST junctions return to the baseline, PR deviated. <i>Late stage II:</i> T waves progressively flatten and invert <i>Stage III:</i> generalised T wave inversions <i>Stage IV:</i> ECG returns to prepericarditis state.	9
Echocardiography	Effusion types B-D (Horowitz) (Fig. 1) Signs of tamponade (see Section 3.5)	12, 13
Blood analyses	(a) ESR, CRP, LDH, leukocytes (inflammation markers) (b) Troponin I, CK-MB (markers of myocardial lesion) <sup>b</sup>	14
Chest X-ray	Ranging from normal to "water bottle" heart shadow. Revealing additional pulmonary/mediastinal pathology.	15
<i>Mandatory in tamponade (indication class I), optional in large/recurrent effusions or if previous tests inconclusive (indication class IIa) in small effusions (indication class IIb)</i>		
Pericardiocentesis and drainage	PCR and histochemistry for aetiopathogenetic classification of infection or neoplasia	2, 10, 16
<i>Optional or if previous tests inconclusive (indication class IIa)</i>		
CT	Effusions, peri-, and epicardium	17
MRI	Effusions, peri-, and epicardium	17
Pericardioscopy, pericardial biopsy	Establishing the specific aetiology	2, 10, 18, 19

<sup>a</sup> Typical lead involvement: I, II, aVL, aVF, and V3–V6. The ST segment is always depressed in aVR, frequently in V1, and occasionally in V2. Occasionally, stage IV does not occur and there are permanent T wave inversions and flattenings. If ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in EARLY REPOLARIZATION is very similar to stage I. Unlike stage I, this ECG does not acutely evolve and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves – large in early repolarisation pattern). Pericarditis is likely if in lead V6 the J point is >25% of the height of the T wave apex (using the PR segment as a baseline).

<sup>b</sup> Cardiac troponin I was detectable in 49% and >1.5 ng/ml in 22% of 69 patients with acute pericarditis (only in those with ST elevation in ECG) investigated by Bonnefoy et al.<sup>20</sup> In another study<sup>21</sup> troponin I was detected in 10/14 patients with a median peak concentration of 21.4 mg/ml (range 0.5 to >50 ng/ml). CK-MB was elevated in 8/14 patients with the median peak of 21 U/l (range 13–43), corresponding to the relative index of 10.2% of the total CK activity.

**Table 3** Patterns of pericardial changes, their visualization and interpretation in chest X-ray, computer tomography (CT) and magnetic resonance imaging (MRI)<sup>23,24</sup>

Pattern	Patho-anatomic basis	Chest X-ray	CT	MR	Interpretation (Differential diagnosis)
Normal thickness	—	Lateral view between mediastinal and subepicardial fat	Thin line in front of the right atrium and right ventricle between mediastinum and subepicardial fat +++	Thin signal-free line round the heart as long subepicardial and mediastinal fat present (for delineation) ++	No pathology
Thickened and smooth	Acute inflammatory process, effusion	Thickened pericardial line on lateral chest X-ray view +	CT-values for DD +++	MR-signals for DD ++	Acute, subacute pericarditis, pericardial effusion, DD liquid, semiliquid, haemorrhagic, purulent, solid
Thickened irregular	Chronic inflammatory process	Irregular contours of cardiac silhouette +	+++	+++	Chronic pericarditis, pericardial fibrosis, tumour, metastasis post surgery
Thickened irregular, calcified	End-stage of inflammatory traumatic of haemorrhagic process	High density +	High CT value +++	Poor signal ++	Pericarditis calcarea, calcified tumours

+, visible; ++, good; +++, best visualization.

rare side effects, favourable effect on the coronary flow, and the large dose range.<sup>9</sup> Depending on severity and response, 300–800 mg every 6–8 h may be initially required and can be continued for days or weeks, best until the effusion has disappeared. Gastrointestinal protection must be provided in all patients. Colchicine (0.5 mg bid) added to an NSAID or as monotherapy also appears to be effective for the initial attack and the prevention of recurrences (level of evidence B, class IIa indication).<sup>25</sup> It is well tolerated with fewer side effects than NSAIDs. Systemic corticosteroid therapy should be restricted to connective tissue diseases, autoreactive or uremic peri-

carditis. Intrapericardial application avoids systemic side effects and is highly effective (level of evidence B, class IIa).<sup>2</sup> For tapering of prednisone, ibuprofen or colchicine should be introduced early (class IIa, level of evidence B).<sup>25</sup> Recovered patients should be observed for recurrences or constriction. If patients require anticoagulants, heparin is recommended under strict observation. *Pericardiocentesis* is indicated for clinical tamponade, high suspicion of purulent or neoplastic pericarditis (class I indication, level of evidence B), or for large or symptomatic effusions despite the medical treatment for more than one week<sup>9,26–37</sup> (Focus box 1).

#### Focus box 1 Pericardiocentesis

Pericardiocentesis is life saving in cardiac tamponade (level of evidence B, class I indication).<sup>27</sup> Aortic dissection is a major contraindication.<sup>28</sup> Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia <50,000/mm<sup>3</sup>, small, posterior, and loculated effusions. Pericardiocentesis in acute traumatic haemopericardium and purulent pericarditis is probably less appropriate than surgical drainage.<sup>9</sup> In effusions causing no haemodynamic compromise pericardiocentesis is indicated in effusions >20 mm in echocardiography in diastole<sup>29</sup> or for diagnostic purposes if additional procedures are available (e.g., pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy) which could reveal the etiology of the disease and permit further causative therapy (level of evidence B, class IIa indication).<sup>2,10,18,19</sup>

Pericardiocentesis guided by fluoroscopy is performed in the cardiac catheterisation laboratory with ECG monitoring. Direct ECG monitoring from the puncturing needle is not an adequate safeguard.<sup>30</sup> Right-heart catheterisation can be performed simultaneously with pericardiocentesis, allowing monitoring the improvement as the effusion is drained. The subxiphoid approach has been used most commonly, with a long needle with a mandrel (Tuohy or thin-walled 18-gauge) directed towards the left shoulder at a 30° angle to the skin. This route is extra-pleural and avoids the coronary, pericardial, and internal mammary arteries. The operator intermittently attempts to aspirate fluid and injects small amounts of contrast. If haemorrhagic fluid is freely aspirated a few millilitres of contrast medium may be injected under fluoroscopic observation. The appearance of sluggish layering of contrast medium inferiorly indicates that the needle is correctly positioned. A soft J-tip guidewire is introduced and after

dilatation exchanged for a multi-holed pigtail catheter. It is prudent to drain the fluid in steps of less than 1 l at a time to avoid the acute right-ventricular dilatation (“sudden decompression syndrome”).<sup>31</sup> It is essential to check the position of the guidewire in at least two angiographic projections. If the guidewire was erroneously placed intracardially, this should be recognized before insertion of the dilator and drainage catheter. If, despite the caution, the introducer set or the catheter have perforated the heart and are laying intracardially, the catheter should be secured and the patient promptly transferred to the cardiac surgery. Alternatively, a second puncture can be attempted. If successful, surgery may be avoided using autotransfusion of pericardial blood.

Echocardiographic guidance of pericardiocentesis is technically less demanding and can be performed in the intensive care unit at the bedside.<sup>16</sup> Echocardiography should identify the shortest route where the pericardium can be entered intercostally (usually in the sixth or seventh rib space in the anterior axillary line). Prolonged pericardial drainage is performed until the volume of effusion obtained by intermittent pericardial aspiration (every 4–6 h) fall to <25 ml per day.<sup>32</sup>

The feasibility is high (93%) in patients with anterior effusion  $\geq 10$  mm while the rate of success is only 58% with small, posteriorly located effusions. Fluoroscopic and haemodynamic monitoring improve feasibility (93.1% vs. 73.3%) in comparison to emergency pericardial puncture with no imaging control.<sup>33</sup> The tangential approach using the epicardial halo phenomenon in the lateral view<sup>34</sup> significantly increased the feasibility of fluoroscopically guided pericardiocentesis in patients with small effusions (200–300 ml) (92.6% vs. 84.9%) and very small effusions (<200 ml) (89.3% vs. 76.7%). Pericardiocentesis with echocardiography guidance was feasible in 96% of loculated pericardial effusions after cardiac surgery.<sup>35</sup> A rescue pericardiocentesis guided by echocardiography, successfully relieved tamponade after cardiac perforation in 99% of 88 patients, and was the definitive therapy in 82% of the cases.<sup>36</sup> 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 bradycardia), and puncture of the peritoneal cavity or abdominal viscera.<sup>33</sup> Internal mammary artery fistulas, 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 1.3–1.6%.<sup>16,32,35,36</sup> In a large series of fluoroscopy-guided percutaneous pericardiocenteses<sup>37</sup> cardiac perforations occurred in 0.9%, 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%. Incidence of major complications was further significantly reduced by utilizing the epicardial halo phenomenon for fluoroscopic guidance.<sup>34</sup>

## Chronic pericarditis

Chronic pericardial inflammation (>3 months) includes effusive, adhesive, and constrictive forms.<sup>9</sup> It is important to differentiate chronic inflammatory effusions from non-inflammatory hydropericardium (congestive heart failure). Symptoms are usually mild (chest pain, palpitations, fatigue), related to the degree of chronic cardiac compression and residual pericardial inflammation.

The diagnostic algorithm is similar as in acute pericarditis (Table 2). The detection of the curable causes (e.g., tuberculosis, toxoplasmosis, myxedema, autoimmune, and systemic diseases) allows specific therapy with high success rate. Symptomatic treatment is as in acute pericarditis. Intrapericardial instillation of crystalloid nonabsorbable corticosteroids is highly efficient in autoreactive forms.<sup>2</sup> Pericardiocentesis is indicated as diagnostic and therapeutic procedure. If the recurrences are frequent, pleuropericardial fenestration and percutaneous balloon pericardiectomy may be appropriate (level of evidence B, indication class IIb).<sup>38</sup> For chronic persistent/recurrent large effusions despite intrapericardial therapy or balloon pericardiectomy, pericardiectomy should be considered.<sup>29</sup>

## Recurrent pericarditis

The term recurrent pericarditis encompasses (1) the intermittent type (widely varying symptom-free interval

without therapy) and (2) the incessant type (discontinuation of anti-inflammatory therapy always ensures a relapse). Mechanisms suggested to explain recurrence include: (1) insufficient dose or/and insufficient treatment duration of antiphlogistics or corticoids in an autoimmune pericardial disease, (2) early corticosteroid treatment causing augmented viral DNA/RNA replication in pericardial tissue leading to increased viral antigen exposure, (3) reinfection, and (4) exacerbation of the connective tissue disease. Evidence for an immunopathological process includes: (1) the latent period lasting for months; (2) the presence of anti-heart antibodies; (3) the quick response to steroid treatment and the similarity and co-existence of recurrent pericarditis with other autoimmune conditions (lupus, serum sickness, polyserositis, postpericardiotomy/postmyocardial infarction syndrome, celiac disease, dermatitis herpetiformis, frequent arthralgias, eosinophilia, allergic drug reaction, and history of allergy). Evidence of a potential underlying genetic disorder in recurrent pericarditis is rare familial clustering with autosomal dominant inheritance with incomplete penetrance<sup>39</sup> and sex-linked inheritance (chronic recurrent pericarditis associated with ocular hypertension) suggested in two families.<sup>40</sup> Precordial pain, often with a pleuritic component, is characteristic. Fever, pericardial rub, dyspnoea, elevated erythrocyte sedimentation rate, and electrocardiographic changes may also occur. Massive pericardial effusion, cardiac tamponade, and pericardial constriction are rare.

Symptomatic management relies on exercise restriction and the regimen used in acute pericarditis. Indomethacin should be avoided in elderly patients due to its flow reduction in the coronaries.<sup>9</sup> *Colchicine* inhibits mitoses in the cell nucleus, binds to tubulin, inhibits various polymorphonuclear functions, interferes with transcellular movement of collagen. It was effective for recurrent pericarditis when NSAIDs and corticosteroids failed to prevent relapses.<sup>25,41–43</sup> During 1004 months of colchicine treatment, only 13.7% new recurrences occurred.<sup>25</sup> During the 2333 months of follow-up, 60.7% of the patients remained recurrence-free. The recommended dose is two mg/day for one or two days, followed by one mg/day (level of evidence B, indication class I). *Corticosteroids* should be used only in patients with poor general condition or in frequent crises<sup>9</sup> (level of evidence C, indication class IIa). A common mistake is to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen is: prednisone 1–1.5 mg/kg, for at least one month. If patients do not respond adequately, azathioprine (75–100 mg/day) or cyclophosphamide can be added.<sup>44</sup> Tapering of corticoids should occur over a three-month period. If symptoms recur during the taper, return to the last dose that suppressed the manifestations, maintain that dose for 2–3 weeks and then recommence tapering. Towards the end of the taper, introduce anti-inflammatory treatment with colchicine or NSAID. Renewed treatment should continue for at least three months. *Pericardiectomy* is indicated only in frequent and highly symptomatic recurrences resistant to medical treatment (level of evidence B, indication class IIa).<sup>45</sup> Before pericardiectomy, the patient should be on a steroid-free regimen for several weeks.<sup>46</sup> Post pericardiectomy recurrences were also demonstrated, possibly due to incomplete resection of the pericardium.

### Pericardial effusion and cardiac tamponade

Pericardial effusion may appear as transudate (hydropericardium), exudate, pyopericardium or haemopericardium. *Large effusions* are common with neoplastic, tuberculous, cholesterol, uremic pericarditis, myxedema, and parasitoses.<sup>47</sup> Effusions that develop slowly can be remarkably asymptomatic, while rapidly accumulating smaller effusions can present with tamponade. *Loculated effusions* are more common when scarring has supervened (e.g., postsurgical, posttrauma, postpurulent pericarditis). *Massive chronic pericardial effusions* are rare (2–3.5% of all large effusions).<sup>48</sup> *Cardiac tamponade* is the decompensated phase of cardiac compression caused by effusion accumulation and the increased intrapericardial pressure. In “surgical” tamponade intrapericardial pressure is rising rapidly, in the matter of minutes to hours (i.e., haemorrhage), whereas a low-intensity inflammatory process is developing in days to weeks before cardiac compression occurs (“medical” tamponade). The volume of fluid causing tamponade varies inversely with both parietal pericardial stiffness and thickness (150–2000 ml). In local compression, dyspnoea, dysphagia, hoarseness (recurrent laryngeal nerve), hiccups (phrenic nerve), or nausea

(diaphragm) can occur. Heart sounds are distant. Compression of the base of the lung results in a dullness under the left scapula (Bamberger–Pins–Ewart’s sign).<sup>9</sup> In tamponade chest discomfort, tachypnea and dyspnoea on exertion progress to orthopnoea, cough and dysphagia, occasionally also with episodes of unconsciousness. Insidiously developing tamponade may present with the signs of its complications (renal failure, abdominal plethora, shock liver and mesenteric ischaemia). In 60% of the patients, the cause of pericardial effusion may be a known medical condition.<sup>49</sup> Tamponade without two or more inflammatory signs (typical pain, pericardial friction rub, fever, diffuse ST segment elevation) is usually associated with a malignant effusion (likelihood ratio 2.9). Electrocardiography may demonstrate diminished QRS and T-wave voltages, PR-segment depression, ST-T changes, bundle branch block, and electrical alternans (rarely seen in the absence of tamponade).<sup>50</sup> In chest radiography large effusions are depicted as globular cardiomegaly with sharp margins (“water bottle” silhouette).<sup>15</sup> On well-penetrated lateral radiographies, or better on cine films, pericardial fluid is suggested by lucent lines within the cardiopericardial shadow (epicardial halo sign, or various other terms for this phenomenon).<sup>15,51,52</sup> Recently, it was suggested that this sign might be useful for fluoroscopic guidance of pericardiocentesis.<sup>34</sup> The separation of pericardial layers can be detected in echocardiography, when the pericardial fluid exceeds 15–35 ml (Fig. 1).<sup>50</sup> The size of effusions can be

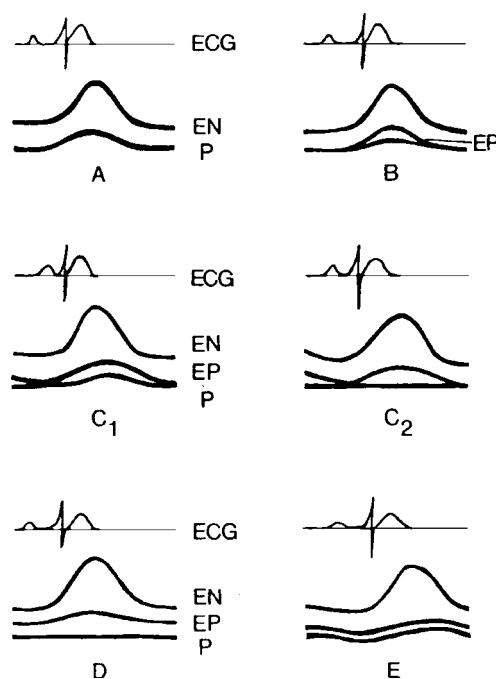


Fig. 1 Horowitz classification of pericardial effusions. Type A, no effusion; Type B, separation of epicardium and pericardium (3–16 ml = 1–3 mm); Type C 1, systolic and diastolic separation of epicardium and pericardium (small effusion >15 ml ≥ 1 mm in Diastole); Type C 2, systolic and diastolic separation of epicardium and pericardium with attenuated pericardial motion; Type D, pronounced separation of epicardium and pericardium with large echo-free space; Type E, pericardial thickening (>4 mm). (Horowitz, *Circulation* '74). Copyrights American Heart Association.

graded as: (1) small (echo-free space in diastole <10 mm), (2) moderate (at least  $\geq 10$  mm posteriorly), (3) large ( $\geq 20$  mm), or (4) very large ( $\geq 20$  mm and compression of the heart). In large pericardial effusions, the heart may move freely within the pericardial cavity ("swinging heart"). This exaggerated motion of the heart induces "pseudo" motions like pseudomitral valve prolapse, pseudosystolic anterior motion of the mitral valve, paradoxical motion of the interventricular septum, midsystolic aortic valve closure.<sup>53</sup> Importantly, effusion size is an overall predictor of prognosis: large effusions

generally indicate more serious disease.<sup>9</sup> Two-dimensional echocardiography also provides information about the nature of the fluid, suggesting the presence of fibrin, clot, tumour, air, and calcium. Intrapericardial bands, often found after radiation of the chest, are frequently combined with a thick visceral or parietal pericardium.<sup>54</sup> Rarely tumour masses, sometimes cauliflower-like, are found within or adjacent to the pericardium.<sup>55</sup> In parasternal long-axis view pericardial fluid reflects at the posterior atrioventricular groove, while pleural fluid continues under the left atrium, posterior to the de-

**Table 4** Diagnosis of cardiac tamponade

Clinical presentation	Elevated systemic pressure, <sup>a</sup> tachycardia, <sup>b</sup> pulsus paradoxus, <sup>c</sup> hypotension, <sup>d</sup> dyspnoea or tachypnoea with clear lungs
Precipitating factors	Drugs (cyclosporine, anticoagulants, thrombolytics, etc.), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicaemia <sup>e</sup>
ECG	Can be normal or non-specifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end-stage), Electromechanical dissociation (agonal phase)
Chest X-ray	Enlarged cardiac silhouette with clear lungs
M mode/2D echocardiogram	Diastolic collapse of the (1) anterior RV-free wall, <sup>62f</sup> RA collapse, <sup>63</sup> LA <sup>64</sup> and very rarely LV <sup>65</sup> collapse, increased LV diastolic wall thickness "pseudohypertrophy", <sup>66</sup> VCI dilatation (no collapse in inspiration), "swinging heart" <sup>67</sup>
Doppler	Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration) Systolic and diastolic flows are reduced in systemic veins in expiration and reverse flow with atrial contraction is increased <sup>68</sup>
M-mode colour Doppler	Large respiratory fluctuations in mitral/tricuspid flows <sup>69</sup>
Cardiac catheterisation	(1) Confirmation of the diagnosis and quantification of the haemodynamic compromise <sup>70</sup> <ul style="list-style-type: none"> <li>RA pressure is elevated (preserved systolic x descent and absent or diminished diastolic y descent)</li> <li>Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration)</li> <li>RV mid-diastolic pressure elevated and equal to the RA and pericardial pressures (no dip-and plateau configuration)</li> <li>Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure</li> <li>Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and right atrial pressure</li> <li>LV systolic and aortic pressures may be normal or reduced</li> </ul> (2) Documenting that pericardial aspiration is followed by haemodynamic improvement <sup>8</sup> (3) Detection of the coexisting haemodynamic abnormalities (LV failure, constriction, pulmonary hypertension) (4) Detection of associated cardiovascular diseases (cardiomyopathy, coronary artery disease)
RV/LV angiography	Atrial collapse and small hyperactive ventricular chambers
Coronary angiography	Coronary compression in diastole
Computer tomography	No visualisation of subepicardial fat along both ventricles, which show tube-like configuration and anteriorly drawn atrias

LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VCI, inferior vena cava.

<sup>a</sup> Jugular venous distension is less notable in hypovolemic patients or in "surgical tamponade". An inspiratory increase or lack of fall of the pressure in the neck veins (Kussmaul sign), when verified with tamponade, or after pericardial drainage, indicates effusive-constrictive disease.

<sup>b</sup> Heart rate is usually >100 beats/min, but may be lower in hypothyroidism and in uremic patients.

<sup>c</sup> Pulsus paradoxus is absent in tamponade complicating atrial septal defect<sup>71</sup> and in patients with significant aortic regurgitation.

<sup>d</sup> Occasional patients are hypertensive especially if they have pre-existing hypertension.<sup>72</sup>

<sup>e</sup> Febrile tamponade may be misdiagnosed as septic shock.

<sup>f</sup> Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy<sup>73</sup> or in right ventricular infarction.

<sup>g</sup> If after drainage of pericardial effusion intrapericardial pressure does not fall below atrial pressure, the effusive-constrictive disease should be considered.



scending aorta. Diagnostic pitfalls are: small loculated effusions, haematoma, cysts, tumours, foramen of Morgagni hernia, hiatus hernia, lipodystrophia with pericardial fat, inferior left pulmonary vein, left pleural effusion, mitral annulus calcification, giant left atrium, epicardial fat (best differentiated in CT), and left ventricular pseudoaneurysm.<sup>55</sup> Metastatic infiltration of the pericardium may masquerade pericardial tamponade in echocardiography in patients with no pericardial effusion.<sup>56</sup> After open-heart surgery, localized effusion at the posterior wall can be found with complete compression of the right atrium leading to cardiac tamponade. This may be misinterpreted as atrial myxoma or other cardiac tumour.<sup>57</sup> When bleeding into the pericardium occurs and thrombosis develops the typical echolucent areas may disappear, so that development of cardiac tamponade may be overlooked. Transesophageal echocardiography is particularly useful in postoperative loculated pericardial effusion or intrapericardial clot<sup>58</sup> as well as in identifying metastases and pericardial thickening.<sup>59</sup> CT, spin-echo and cine MRI can also be used to assess the size and extent of simple and complex pericardial effusions. The effusions measured by CT or by MRI may tend to be larger than by echocardiography.<sup>24,60</sup> Up to one-third of patients with asymptomatic large pericardial chronic effusion developed unexpected cardiac tamponade.<sup>29</sup> Triggers for tamponade include hypovolemia, paroxysmal tachyarrhythmia and intercurrent acute pericarditis; often no trigger is identifiable.<sup>61</sup> Major diagnostic findings in cardiac tamponade are noted in Table 4<sup>62–70</sup> and Focus box 2.<sup>71,72</sup>

Pericardiocentesis may not be necessary when the diagnosis can be made based on other systemic features or the effusions are very small or resolving under anti-inflammatory treatment. Where doubt remains, pericardiocentesis, pericardioscopy and epicardial and pericardial biopsy (including PCR, immunocytochemistry and immunohistochemistry) may be valuable (level of evidence B, class IIa indication).<sup>2,10,18,19</sup> (Focus box 1, 3–5) Haemodynamic compromise and cardiac tamponade is an absolute indication for drainage (class I indication). Patients with dehydration and hypovolemia may temporarily improve with intravenous fluids enhancing ventricular filling. Pericardiocentesis is not applicable in wounds, ruptured ventricular aneurysm, or dissecting aortic haematoma, when clotting makes needle evacu-

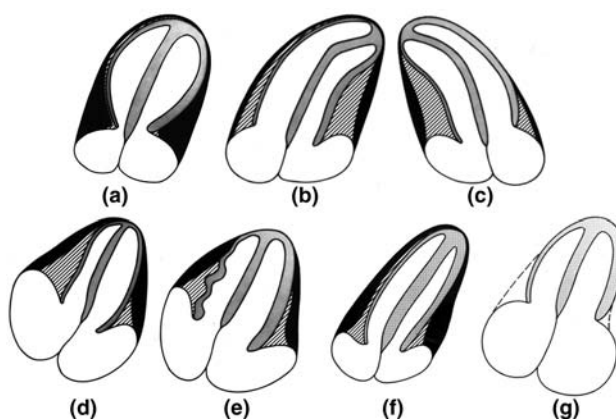
ation impossible so that surgical drainage with suppression of bleeding sources is mandatory. Loculated effusions may require thoracoscopic drainage, subxyphoid window or open surgery.<sup>45</sup> All patients should be monitored for postdrainage decompensation. Whenever possible, treatment should be aimed at the underlying aetiology rather than the effusion itself. However, even in idiopathic effusions extended pericardial catheter drainage ( $3 \pm 2$  days, range 1–13 days) was associated with a trend to lower recurrence rates (6% vs. 23%) than in those without catheter drainage during the follow-up of  $3.8 \pm 4.3$  years.<sup>32</sup> Resistant neoplastic processes require intrapericardial treatment,<sup>89</sup> percutaneous balloon pericardiectomy<sup>38</sup> or rarely pericardiectomy. Surgical approach is recommended only in patients with very large chronic effusion (with or without symptoms) in whom repeated pericardiocentesis and/or intrapericardial therapy were not successful.<sup>99</sup>

### Constrictive pericarditis

Constrictive pericarditis is a rare but severely disabling consequence of the chronic inflammation of the pericardium, leading to an impaired filling of the ventricles and reduced ventricular function. Tuberculosis, mediastinal irradiation, and previous cardiac surgical procedures are frequent causes of the disease, which can present in several pathoanatomical forms<sup>23</sup> (Fig. 2). Constrictive pericarditis may rarely develop only in the epicardial layer in patients with previously removed parietal pericardium.<sup>100</sup> Transient constrictive pericarditis is rare entity, distinguished by its self-limiting nature.<sup>101</sup> Patients complain about fatigue, peripheral oedema, breathlessness, and abdominal swelling, which may be aggravated by a protein-losing enteropathy. Typically, there is a long delay between the initial pericardial inflammation and the onset of constriction. In decompensated patients venous congestion, hepatomegaly, pleural effusions, and ascites may occur. Haemodynamic impairment of the patient can be additionally aggravated by a systolic dysfunction due to myocardial fibrosis or atrophy. Clinical, echocardiographic, and haemodynamic parameters can be derived from Table 5.<sup>23,59,103–106</sup> Differential diagnosis has to include acute dilatation of the heart, pulmonary embolism, right ventricular infarction, pleural effusion, chronic obstructive lung diseases<sup>102</sup> and

#### Focus box 2 Determination of pulsus paradoxus

Pulsus paradoxus is defined as a drop in systolic blood pressure  $>10$  mmHg during inspiration whereas diastolic blood pressure remains unchanged. It is easily detected by feeling the pulse.<sup>71,72</sup> During inspiration, the pulse may disappear or its volume diminishes significantly. Clinically significant pulsus paradoxus is apparent when the patient is breathing normally. When present only in deep inspiration it should be interpreted with caution. The magnitude of pulsus paradoxus is evaluated by sphygmomanometry. If the pulsus paradoxus is present, the first Korotkoff sound is not heard equally well throughout the respiratory cycle, but only during expiration at a given blood pressure. The blood pressure cuff is therefore inflated above the patients systolic pressure. Then it is slowly deflated while the clinician observes the phase of respiration. During deflation, the first Korotkoff sound is intermittent. Correlation with the patients respiratory cycle identifies a point at which the sound is audible during expiration, but disappears in inspiration. As the cuff pressure drops, another point is reached when the first blood pressure sound is audible throughout the respiratory cycle. The difference in systolic pressure between these two points is the measure of pulsus paradoxus.



**Fig. 2** Pathoanatomical forms of constrictive pericarditis vs. restrictive cardiomyopathy. (a) *Annular form* of pericardial constriction with bilateral thickening of the pericardium along the atrial ventricular grooves with normal configuration of both ventricles and enlargement of both atria. (b) *Left sided form* of pericardial constriction with thickened pericardium along the left ventricle and right sided bending of the interventricular septum with tube-like configuration of mainly left ventricle and enlargement of both atria (lateral sternotomy and partial pericardiectomy is indicated). (c) *Right sided form* of pericardial constriction with thickened pericardium along the right ventricle and left sided bending of the interventricular septum with tube-like configuration of mainly right ventricle and enlargement of both atria (median sternotomy and partial pericardiectomy is indicated). (d) *Myocardial atrophy and global form of pericardial constriction* with bilateral thickening of the pericardium along both ventricles separated from the right myocardial wall by a thin layer of subepicardial fat. Tube-like configuration of both ventricles and enlargement of both atria, however, thinning of the interventricular septum and posterolateral wall of the left ventricle below 1 cm is suggesting myocardial atrophy (pericardiectomy is contraindicated). (e) *Perimyocardial fibrosis and global form of pericardial constriction* with bilateral thickening of the pericardium along both ventricles, however, the right sided thickened pericardium cannot be separated from the wave-like thin form of right sided ventricular wall suggesting perimyocardial fibrosis (pericardiectomy is contraindicated). (f) *Global form of pericardial constriction* with bilateral thickening of the pericardium along both ventricles separated from the right myocardial wall by a thin layer of subepicardial fat. Tube-like configuration of both ventricles and enlargement of both atria (median sternotomy and pericardiectomy is indicated). (g) *Restrictive cardiomyopathy* with normal thin pericardium along both ventricles that show normal configuration and with enlargement of both atria.

restrictive cardiomyopathy. The best way to distinguish constrictive pericarditis from restrictive cardiomyopathy is the analysis of respiratory changes with or without changes of preload by Doppler and/or tissue Doppler echocardiography,<sup>107</sup> but physical findings, ECG, chest radiography, CT and MRI, haemodynamics, and endomyocardial biopsy may be helpful as well (Table 6).<sup>9</sup>

Pericardiectomy is the only treatment for permanent constriction. The indications are based upon clinical symptoms, echocardiography findings, CT/MRI, and heart catheterisation. There are two standard approaches, both aiming at resecting the diseased pericardium as far as possible:<sup>108–111</sup> (1) The *antero-lateral thoracotomy* (fifth intercostal space) and (2) *median sternotomy* (faster access to the aorta and right atrium for extracorporeal circulation). A primary installation of cardiopulmonary bypass is not recommended, due to the enhanced diffuse bleeding during dissection of the pericardium, following systemic heparinisation. If severe calcified adhesions between peri- and epicardium or a general affection of the epicardium (“outer porcelain heart”) are present surgery carries a high risk of either incomplete success or severe myocardial damage. An alternative approach in such cases may be a “laser shaving” using an Excimer laser.<sup>109</sup> Areas of strong calcification or dense scarring may be left as islands to avoid major bleeding. Pericardiectomy for constrictive pericarditis has a mortality rate of 6%–12% in the current series.<sup>109,111</sup> The complete normalization of cardiac haemodynamics is reported in only 60% of the patients.<sup>108,110</sup> The deceleration time (DT) may remain

prolonged<sup>112</sup> and postoperative respiratory variations of mitral/tricuspid flow are found in 9–25%.<sup>110,113</sup> Left ventricular ejection fraction increases due to a better ventricular filling<sup>110, 112</sup> but consistent changes of the left and right atrial sizes were not reported. Major complications include acute perioperative cardiac insufficiency and ventricular wall rupture.<sup>114</sup> Cardiac mortality and morbidity at pericardiectomy is mainly caused by the pre-surgically unrecognised presence of myocardial atrophy or myocardial fibrosis (Fig. 2).<sup>23</sup> Myocardial atrophy in CT is characterized by: (1) Thinning of the interventricular septum and posterolateral wall (<1 cm); (2) Reduction of the wall thickening during the cardiac cycle (<40%); and (3) Reduction of the left-ventricular muscle mass (LVMM)/end-diastolic volume (EDV) ratio (<1). Myocardial fibrosis should be considered whenever the thickened/calcified pericardium is not separated from the myocardium by subepicardial fat and when the myocardial wall is showing wave-like appearance with wall thinning. Exclusion of patients with extensive myocardial fibrosis and/or atrophy led to a reduction of the mortality rate for pericardiectomy to 5%.<sup>23</sup> Postoperative low cardiac output<sup>114</sup> should be treated by fluid substitution and catecholamines, high doses of digitalis, and intraaortic balloon pump in most severe cases. If indication for surgery was established early, long-term survival after pericardiectomy corresponds to that of the general population.<sup>109,110</sup> However, if severe clinical symptoms were present for a longer period before surgery, even a complete pericardiectomy may not achieve a total restitution.

**Table 5** Diagnostic approach in constrictive pericarditis

Clinical presentation	Severe chronic systemic venous congestion associated with low cardiac output, including jugular venous distension, hypotension with a low pulse pressure, abdominal distension, oedema and muscle wasting.
ECG	Can be normal, or reveal low QRS voltage, generalized T-wave inversion/flattening, LA abnormalities, atrial fibrillation, atrioventricular block, intraventricular conduction defects, or rarely pseudoinfarction pattern
Chest X-ray	Pericardial calcifications, pleural effusions
M mode/2D echocardiogram	Pericardial thickening and calcifications <sup>a</sup> as well as the indirect signs of constriction: RA & LA enlargement with normal appearance of the ventricles, and normal systolic function. Early pathological outward and inward movement of the interventricular septum (“dip-plateau phenomenon”) <sup>102</sup> Fluttering waves at the LV posterior wall LV diameter is not increasing after the early rapid filling phase. VCI and the hepatic veins are dilated with restricted respiratory fluctuations. <sup>b</sup>
Doppler	Restricted filling of both ventricles with respiratory variation >25% over the AV-valves. <sup>103c</sup>
TEE	Measurement of the pericardial thickness <sup>59</sup>
CT/MRI	Thickened and/or calcified pericardium, tube-like configuration of one or both ventricles, enlargement of one or both atria, narrowing of one or both atrio-ventricular grooves, congestion of the caval veins <sup>23</sup>
Cardiac catheterisation	“Dip and plateau” or “square route” sign in the pressure curve of the right and/or left ventricle Equalisation of LV/RV end-diastolic pressures in the range of 5 mmHg or less. <sup>102d</sup>
RV/LV angiography	The reduction of RV & LV size and increase of RA & LA size During diastole a rapid early filling with stop of further enlargement (“dip-plateau”)
Coronary angiography	In all patients over 35 years and in patients with a history of mediastinal irradiation, regardless of the age

LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VCI, inferior vena cava; TEE, transoesophageal echocardiography.

<sup>a</sup> Thickening of the pericardium is not always equal to constriction (absent in 18% of 143 surgically proven cases). When clinical, echocardiographic, or invasive haemodynamic features indicate constriction, pericardiectomy should not be denied on the basis of normal pericardial thickness.<sup>64</sup>

<sup>b</sup> Diagnosis is difficult in atrial fibrillation. Hepatic diastolic vein flow reversal in expiration is observed even when the flow velocity pattern is inconclusive.<sup>103</sup>

<sup>c</sup> Patients with increased atrial pressures or mixed constriction and restriction demonstrate <25% respiratory changes.<sup>102</sup> A provocation test with head-up tilting or sitting position with decrease of preload may unmask the constrictive pericarditis.<sup>105</sup>

<sup>d</sup> In the early stage or in the occult form, these signs may not be present and the rapid infusion of 1–2 l of normal saline may be necessary to establish the diagnosis. Constrictive haemodynamics may be masked or complicated by valvular- and coronary artery disease.

<sup>e</sup> In chronic obstructive lung disease mitral in-flow velocity will decrease nearly 100% during inspiration and increase during expiration. The mitral E-velocity is highest at the end of expiration (in constrictive pericarditis mitral E-velocity is highest immediately after start of expiration).<sup>106</sup> In addition, superior vena cava flow increases with inspiration in chronic obstructive lung disease, whereas it does not change significantly with respiration in constrictive pericarditis.

**Table 6** Differential diagnosis: constrictive pericarditis vs. restrictive cardiomyopathy

Method	Restrictive cardiomyopathy	Constrictive pericarditis
Physical findings	Kussmaul's sign $\pm$ , apical impulse +++ S <sub>3</sub> (advanced), S <sub>4</sub> (early disease), regurgitant murmurs ++	Kussmaul's sign +, apical impulse – pericardial knock+, regurgitant murmurs –
ECG	Low voltage, pseudoinfarction, left-axis deviation, AF, conduction disturbances	Low voltage (<50%)
Chest radiography	No calcifications	Calcifications may be present (low diagnostic accuracy)
2D-echocardiography	Small LV cavity with large atria Increased wall thickness sometimes present (especially thickened interatrial septum in amyloidosis) Thickened valves and granular sparkling (amyloidosis)	Normal wall thickness Pericardial thickening, prominent early diastolic filling with abrupt displacement of IVS
Doppler studies		
Mitral inflow	No respiration variation of mitral inflow E wave velocity, IVRT E/A ratio $\geq 2$ , short DT, diastolic regurgitation	Inspiration: decreased inflow E wave velocity, prolonged IVRT Expiration: opposite changes, short DT, diastolic regurgitation
Pulmonary vein	Blunted S/D ratio (0.5), prominent and prolonged AR No respiration variation, D wave	S/D ratio = 1, <i>Inspiration</i> : decreased PV S and D waves <i>Expiration</i> : opposite changes
Tricuspid inflow	Mild respiration variation of tricuspid inflow E wave velocity, E/A ratio $\geq 2$ , TR peak velocity, no significant respiration change	Inspiration: increased tricuspid inflow E wave velocity, increased TR peak velocity, <i>Expiration</i> : opposite changes
Hepatic veins	Short DT with inspiration, diastolic regurgitation Blunted S/D ratio, increased inspiratory reversals	Short DT, diastolic regurgitation Inspiration: minimally increased HV S and D Expiration: decreased diastolic flow/increased reversals
Inferior vena cava	Plethoric	Plethoric
Colour M-mode	Slow flow propagation	Rapid flow propagation ( $\geq 100$ cm/s)
Mitral annular motion	Low-velocity early filling (<8 cm/s)	High-velocity early filling ( $\geq 8$ cm/s)
Tissue Doppler echocardiography	Peak early velocity of longitudinal expansion (peak Ea) of $\geq 8.0$ cm/s (89% sensitivity and 100% specificity) <sup>107</sup>	Negative
Cardiac catheterisation	Dip and plateau LVEDP often >5 mmHg greater than RVEDP, but may be identical, RV systolic pressure >50 mmHg RVEDP <1/3 RVSP	Dip and plateau, RVEDP and LVEDP usually equal, Inspiration: Increase in RV systolic pressure Decrease in LV systolic pressure, <i>with Expiration</i> , opposite
EMB CT/MRI (Fig. 2)	May reveal specific cause of restrictive cardiomyopathy Pericardium usually normal	May be normal or show nonspecific hypertrophy or fibrosis Pericardium must be thickened or calcified.

## Pericardial cysts

*Congenital* pericardial cysts are uncommon, may have both unilocular and multilocular forms, with the diameter from 1 to 5 cm.<sup>115</sup> *Inflammatory* cysts comprise pseudocysts as well as encapsulated and loculated pericardial effusions, caused by rheumatic pericarditis, bacterial infection, particularly tuberculosis, trauma and cardiac surgery. *Echinococcal* cysts usually originate from ruptured hydatid cysts in the liver and lungs. Most patients are asymptomatic and cysts are detected incidentally on chest roentgenograms as an oval, homogeneous radiodense lesion, usually at the right cardiophrenic angle.<sup>116</sup> However, the patients can also present with chest discomfort, dyspnoea, cough or palpitations, due to the compression of the heart. Echocardiography is useful, but additional imaging by computed tomography (density readings) or magnetic resonance is often needed.<sup>117</sup>

The treatment for congenital and inflammatory cysts is percutaneous aspiration and ethanol sclerosis.<sup>118,119</sup> If this is not feasible, video assisted thoracotomy or surgical resection may be necessary. The surgical excision of echinococcal cysts is not recommended. Percutaneous aspiration and instillation of ethanol or silver nitrate after pre-treatment with Albendazole (800 mg/day 4 weeks) is safe and effective.<sup>119</sup>

## Specific forms of pericarditis

### Viral pericarditis

Viral pericarditis is the most common infection of the pericardium. Inflammatory abnormalities are due to direct viral attack, the immune response (antiviral or an-

ticardiac), or both.<sup>3,120,121</sup> Early viral replication in pericardial and epimyocardial tissue elicits cellular and humoral immune responses against the virus and/or cardiac tissue. Viral genomic fragments in pericardial tissue may not necessarily replicate, yet they serve as a source of antigen to stimulate immune responses. Deposits of IgM, IgG, and occasionally IgA, can be found in the pericardium and myocardium for years.<sup>3,120</sup> Various viruses cause pericarditis (entero-, echo-, adeno-, cytomegalo-, Epstein Barr-, herpes simplex-, influenza, parvo B19, hepatitis C, HIV, etc). Attacks of enteroviral pericarditis follow the seasonal epidemics of Coxsackie virus A+B and Echovirus infections.<sup>122</sup> Cytomegalovirus pericarditis has an increased incidence in immunocompromised and HIV infected hosts.<sup>123–125</sup> Infectious mononucleosis with sore throat, adenopathy, and positive Mumps or EBV serology may also present with pericarditis.

The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by PCR or in-situ hybridisation (level of evidence B, class IIa indication) (Focus box 3–5). A fourfold rise in serum antibody levels is suggestive but not diagnostic for viral pericarditis (level of evidence B, class IIb indication).

Treatment of viral pericarditis is directed to resolve symptoms (see acute pericarditis), prevent complications, and eradicate the virus. In patients with chronic or recurrent symptomatic pericardial effusion and confirmed viral infection the following specific treatment is under investigation: (1) CMV pericarditis: hyperimmunoglobulin – 1 time per day 4 ml/kg on day 0, 4, and 8; 2 ml/kg on day 12 and 16; (2) Coxsackie B pericarditis: Interferon  $\alpha$ : 2.5 Mio. IU/m<sup>2</sup> surface area s.c. 3 $\times$  per week; (3) adenovirus and parvovirus B19 perimyocarditis: immunoglobulin treatment: 10 g intravenously at day 1 and 3 for 6–8 h.<sup>126</sup>

#### Focus box 3 Analyses of pericardial effusion

Analyses of pericardial effusion can establish the diagnosis of viral, bacterial, tuberculous, fungal, cholesterol, and malignant pericarditis.<sup>9</sup> It should be ordered according to the clinical presentation. Cytology and tumour markers (carcinoembryonic antigen (CEA),  $\alpha$ -feto protein (AFP), carbohydrate antigens CA 125, CA 72-4, CA 15-3, CA 19-9, CD-30, CD-25, 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).<sup>14,61,73–84</sup> Differentiation of tuberculous and neoplastic effusion is virtually absolute with low levels of ADA and high levels of CEA.<sup>78</sup> In addition, very high ADA levels have prognostic value for pericardial constriction.<sup>79</sup> However, it should be noted that PCR is as sensitive (75% vs. 83%), but more specific (100% vs. 78%) than ADA estimation for tuberculous pericarditis.<sup>83</sup> In suspected bacterial infection at least three cultures of pericardial fluid for aerobes and anaerobes as well as the blood cultures are mandatory (level of evidence B, indication class I). PCR analyses for cardiotropic viruses discriminate viral from autoreactive pericarditis (indication class IIa, level of evidence B).<sup>2</sup> 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 (exudates vs. transudates = 77.9  $\pm$  41.9 vs. 96.1  $\pm$  50.7 mg/dl) can separate exudates from transudates but are not directly diagnostic (class IIb).<sup>14</sup> However, purulent effusions with positive cultures have significantly lower fluid glucose levels (47.3  $\pm$  25.3 vs. 102.5  $\pm$  35.6 mg/dl) and fluid to serum ratios (0.28  $\pm$  0.14 vs. 0.84  $\pm$  0.23 mg/dl), than non-infectious effusions.<sup>14</sup> White cell count (WBC) is highest in inflammatory diseases, particularly of bacterial and rheumatologic origin. A very low WBC count is found in myxedema. Monocyte count is highest in malignant and effusions in hypothyroidisms (79  $\pm$  27% and 74  $\pm$  26%), while rheumatoid and bacterial effusions have the highest proportions of neutrophils (78  $\pm$  20% and 69  $\pm$  23%). Compared with controls, both bacterial and malignant pericardial fluids have higher cholesterol levels (49  $\pm$  18 vs. 121  $\pm$  20 and 117  $\pm$  33 mg/dl).<sup>14</sup>

The real nature of the cells found in the pericardial effusion can be difficult to recognize. Grams stains in pericardial fluid have a specificity of 99%, but a sensitivity of only 38% for exclusion of the infection in comparison to bacterial cultures.<sup>14</sup> Combination of epithelial membrane antigen, CEA and vimentin immunocytochemical staining can be useful to distinguish reactive mesothelial and adenocarcinoma cells.<sup>85</sup> Antimyolemmal and antisarcolemmal antibodies, as well as complement fixation, were seen predominantly in viral and autoreactive effusions.<sup>10</sup> In vitro cardiocytolysis of isolated rat heart cells by the pericardial effusion fluid, with or without addition of a fresh complement source, was seen primarily in autoreactive effusions. Mediators of inflammation such as IL-6, IL-8 and IFN- $\gamma$  in pericardial fluids may be also helpful in the discrimination of autoreactive effusions.<sup>75,86</sup> A cut-off value of 200 pg/L for pericardial IFN- $\gamma$  resulted in a sensitivity and specificity of 100% for the diagnosis of tuberculous pericarditis.<sup>84</sup>

Pericardial manifestation of *human immunodeficiency virus* (HIV) infection can be due to infective, non-infective and neoplastic diseases (Kaposi sarcoma and/or lymphoma). Infective (myo)pericarditis results from the local HIV infection and/or from the other viral (cytomegalovirus, herpes simplex), bacterial (*S. aureus*, *K. pneumoniae*, *M. avium*, and tuberculosis) and fungal coinfections (cryptococcus neoformans).<sup>127–130</sup> In progressive disease the incidence of echocardiographically detected pericardial effusion is up to 40%.<sup>131, 132</sup> Cardiac tamponade is rare.<sup>133</sup> During the treatment with retroviral compounds, lipodystrophy can develop (best demonstrated by MRI) with intense paracardial fat deposition leading to heart failure. Treatment is symptomatic, while in large effusions and cardiac tamponade pericardiocentesis is necessary. The use of corticoid therapy is contraindicated except in patients with secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment (level of evidence A, indication class I).<sup>134</sup>

### Bacterial pericarditis

Purulent pericarditis in adults is rare (Table 7),<sup>135–147</sup> but always fatal if untreated. Mortality rate in treated patients is 40%, mostly due to cardiac tamponade, toxicity, and constriction. It is usually a complication of an infection originating elsewhere in the body, arising by contiguous spread or haematogenous dissemination.<sup>148</sup> Predisposing conditions are: pre-existing pericardial effusion, immunosuppression, chronic diseases (alcohol abuse, rheumatoid arthritis, etc), cardiac surgery and chest trauma. Rarely, left ventricular pseudoaneurysm may complicate bacterial pericarditis.<sup>149</sup>

The disease appears as an acute, fulminant infectious illness with short duration. Percutaneous pericardiocentesis must be promptly performed. Obtained pericardial fluid should undergo urgent Gram, acid-fast and fungal staining, followed by cultures of the pericardial and body fluids (level of evidence B, indication class I).

Rinsing of the pericardial cavity, combined with effective systemic antibiotic therapy is mandatory (combination of antistaphylococcal antibiotic and aminoglycoside, followed by tailored antibiotic therapy according to the results of pericardial fluid and blood cultures).<sup>136</sup> Intrapericardial instillation of antibiotics (e.g., gentamycin) is useful but not sufficient. Frequent irrigation of the pericardial cavity with urokinase or streptokinase, using large catheters, may liquefy the

purulent exudate,<sup>137,138</sup> but open surgical drainage through subxiphoid pericardiotomy is preferable.<sup>135</sup> Pericardiectomy is required in patients with dense adhesions, loculated and thick purulent effusion, recurrence of tamponade, persistent infection, and progression to constriction.<sup>136</sup> Surgical mortality up to 8% was reported for pericardiectomy combined with antibiotic treatment but the total mortality is higher.

### Tuberculous pericarditis

In the last decade TBC pericarditis in the developed countries has been primarily seen in immunocompromised patients (AIDS).<sup>140</sup> The mortality rate in untreated acute effusive TBC pericarditis approaches 85%. Pericardial constriction occurs in 30–50%.<sup>139,142</sup> The clinical presentation is variable: acute pericarditis with or without effusion; cardiac tamponade, silent, often large pericardial effusion with a relapsing course, toxic symptoms with persistent fever, acute constrictive pericarditis, subacute constriction, effusive-constrictive, or chronic constrictive pericarditis, and pericardial calcifications.<sup>3, 73</sup> The diagnosis made by the identification of *Mycobacterium tuberculosis* in the pericardial fluid or tissue, and/or the presence of caseous granulomas in the pericardium.<sup>3,140</sup> Pericarditis in a patient with proven extracardiac tuberculosis is strongly suggestive of TBC aetiology (several sputum cultures should be taken).<sup>3,143</sup> The tuberculin skin test may be false negative in 25–33% of patients<sup>139</sup> and false positive in 30–40% (elderly patients).<sup>140</sup> A more accurate enzyme-linked immunospot (ELISPOT) test was recently developed,<sup>150</sup> detecting T-cells specific for *Mycobacterium tuberculosis* antigen. Perimyocardial TBC involvement is also associated with high titres of antimyolemmal and antimyosin antibodies in the sera.<sup>151</sup> The diagnostic yield of pericardiocentesis in TBC pericarditis ranges from 30–76% according to the methods applied for the analyses of pericardial effusion.<sup>139,144</sup> Pericardial fluid demonstrates high specific gravity, high protein levels, and high white-cell count (from 0.7–54  $\times 10^9$ /l).<sup>140</sup> Importantly, PCR can identify DNA of *Mycobacterium tuberculosis* rapidly from only 1  $\mu$ L of pericardial fluid.<sup>144,145</sup> High adenosine deaminase activity and interferon  $\gamma$  concentration in pericardial effusion are also diagnostic, with a high sensitivity and specificity (Focus box 4): Both pericardioscopy and pericardial biopsy have also improved the diagnostic accuracy for TBC pericarditis.<sup>18</sup> Pericardial biopsy enables rapid diagnosis with better sensitivity than pericardiocentesis (100 vs. 33%).

**Table 7** Differential diagnosis of the specific forms of pericarditis<sup>135–147</sup>

	Viral	Bacterial	Tuberculous	Auto reactive
Cardiotropic microbial agents	Enterovirus, echovirus, adenovirus, cytomegalovirus, Epstein Barr virus, herpes simplex virus, influenza, parvovirus B19, hepatitis A, B, C virus, HIV	Staphylococci, pneumococci, streptococci, Neisseria, proteus, gram negative rods, Legionella	Mycobacterium tuberculosis	Autoimmune process in the absence of viral and bacterial agents
Etiological evidence by PCR or in situ hybridisation (evidence level B, indication IIa)	PCR or in situ hybridisation (evidence level B, indication IIa)	Gram-stain, bacterial culture, PCR for Borrelia & chlamydia pneumoniae (evidence level B, indication I)	Ziehl-Neelsen, auramin O stain, culture, PCR (evidence level B, indication I)	Ig-binding to peri- and epicardium, negative PCR for cardiotropic agents, epicarditis (evidence level B, indication IIa)
Incidence (%) Western countries	30	5–10	<4 (much more in Africa & South America)	20–30
Male:female ratio	3:1	5 per 100 000 patients	1:1	1:1
Predisposition	Unknown	Chronic alcohol abuse, immuno-suppression, Spiking fever, fulminant, tachycardia, pericardial rubs	Alcohol abuse, HIV infection	Association to autoimmune disorders
Clinical features	Identical to acute pericarditis, often subfebrile	Variable	Subfebrile, chronic	Subfebrile, chronic
Effusion size	Variable, mostly small	Variable	Variable, mostly large	Variable
Tamponade	Infrequent	80%	Frequent	Infrequent
Spontaneous remission	Frequent	None	None	Rare
Recurrence rate	30–50%	Rare	Frequent	Frequent ; >25%
Aspect of PE	Serous/serosanguinous	Purulent	Serosanguinous	Serous
Protein content	> 3 g/dl	High	High/intermediate	Intermediate
Leukocyte count (PE)	>5000/ml	≥10,000/ml	Intermediate > 8000	Intermediate <5000
Pericardial fluid analyses	Activated lymphocytes & macrophages (sparse)	Granulocytes & macrophages (massive)	Granulocytes & macrophages (intermediate)	Activated lymphocytes & macrophages (sparse)
	Adenosine deaminase (ADA) – negative	ADA-negative	ADA positive (>40 U/ml)	ADA-negative
Peri- & epicardial biopsy	Lymphocytic peri-/epicarditis, PCR positive for cardiotropic virus	Leukocytic epicarditis	Caseous granuloma, PCR	Lymphocytic peri-/epicarditis, PCR negative
Mortality if untreated	Depending on agent and tamponade	100%	85%	In untreated tamponade
Intrapericardial treatment	Drainage, if needed, no intrapericardial corticoids	Drainage and rinsing (saline) gentamycin 80 mg i.p., Promptly needed (evidence level B, indication I)	Drainage, if needed	Drainage, i.p. triamcinolon (evidence B, indication IIa)
Pericardiectomy/Pericardiectomy	Rarely needed	I.V. antibiotics	Rarely needed	Rarely needed
Systemic treatment	I.V. immunoglobulins, IFN (in enteroviral P) s.c.	Frequent	Tuberculostatic + prednisone	NSAIDs, Colchicine, prednisolone/Azathioprin
Constriction	Rare	Frequent	Frequent (30–50%)	Rare

**Focus box 4** Pericardioscopy and epicardial/pericardial biopsy

Technical advances in instrumentation, introduction of pericardioscopy and contemporary pathology, virology, and molecular biology techniques have improved the diagnostic value of epicardial/pericardial biopsy.<sup>2,10,18,19,87–62,90–93</sup> Pericardioscopy performed through air instead of fluid, made it possible to inspect large areas of pericardial surface, select the biopsy site, and take numerous samples safely.<sup>19</sup> Targeted pericardial/epicardial biopsy during pericardioscopy was particularly useful in the diagnosis of neoplastic pericarditis.<sup>18,19, 87,88,89</sup> No major complications occurred in any of the flexible pericardioscopy studies. Mortality reported in the studies with rigid endoscopes was 2.1%,<sup>18</sup> and 3.5%<sup>88</sup> due to induction of anaesthesia in patients with very large pericardial effusions.

Various antituberculous drug combinations of different lengths (6, 9, 12 months) have been applied.<sup>78,139,140,143</sup> However, only patients with proven or very likely TBC pericarditis should be treated. Prevention of constriction in chronic pericardial effusion of undetermined aetiology by “*ex iuvantibus*” antitubercular treatment was not successful.<sup>152</sup> The use of steroids remains controversial.<sup>143, 147,153</sup> A meta analysis of patients with effusive and constrictive TBC pericarditis<sup>154</sup> suggested that tuberculostatic treatment combined with steroids might be associated with fewer deaths, less frequent need for pericardiocentesis or pericardiectomy (level of evidence A, indication class IIa).<sup>143,146</sup> If given, prednisone should be administered in relatively high doses (1–2 mg/kg per day) since rifampicin induces its liver metabolism.<sup>9</sup> This dose is maintained for 5–7 days and is progressively reduced to discontinuation in 6–8 weeks. If, in spite of combination therapy, constriction develops pericardiectomy is indicated (level of evidence B, class I indication).

**Pericarditis in renal failure**

Renal failure is a common cause of pericardial disease, producing large pericardial effusions in up to 20% of patients.<sup>155</sup> Two forms have been described: (1) *Uremic pericarditis* – in 6–10% of patients with advanced renal failure (acute or chronic) before dialysis has been instituted or shortly thereafter.<sup>156</sup> It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotemia (the BUN is usually >60 mg/dl). (2) *Dialysis-associated pericarditis* – in up to 13% of patients on maintenance haemodialysis,<sup>157</sup> and occasionally with chronic peritoneal dialysis due to inadequate dialysis and/or fluid overload.<sup>158</sup> Pathologic examination of the pericardium shows adhesions between the thickened pericardial membranes (“bread and butter” appearance). The clinical features may include fever and pleuritic chest pain but many patients are asymptomatic. Pericardial rubs may persist even in large effusions or may be transient. Due to autonomic impairment in uremic patients, heart rate may remain slow (60–80 beats/min) during tamponade, despite fever and hypotension. Anaemia, due to induced resistance to erythropoietin<sup>159</sup> may worsen the clinical picture. The ECG does not show the typical diffuse ST/T wave elevations observed with other causes of acute pericarditis due to the lack of the myocardial inflammation.<sup>160</sup> If the ECG is typical of acute pericarditis, intercurrent infection must be suspected.

Most patients with uremic pericarditis respond rapidly to haemo- or peritoneal dialysis with resolution of chest

pain and pericardial effusion. To avoid haemopericardium heparin-free haemodialysis should be used. Care should be taken since acute fluid removal with haemodialysis can lead to cardiovascular collapse in patients with tamponade or pretamponade. Hypokalemia and hypophosphatemia should be prevented by supplementing the dialysis solution when appropriate.<sup>161</sup> Intensified dialysis usually leads to resolution of the pericarditis within 1–2 weeks.<sup>162</sup> Peritoneal dialysis, which does not require heparinisation, may be therapeutic in pericarditis resistant to haemodialysis, or if heparin-free haemodialysis cannot be performed. NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective.<sup>163–165</sup> Cardiac tamponade and large chronic effusions resistant to dialysis must be treated with pericardiocentesis (level of evidence B, class IIa indication). Large, non-resolving symptomatic effusions should be treated with instillation of intrapericardial corticosteroids after pericardiocentesis or subxiphoid pericardiectomy (triamcinolone hexacetonide 50 mg every 6 h for 2–3 days).<sup>157, 166</sup> Pericardiectomy is indicated only in refractory, severely symptomatic patients due to its potential morbidity and mortality. Within two months after renal transplantation pericarditis has been reported in 2.4% of patients.<sup>167</sup> Uraemia or infection (CMV) may be the causes.

**Autoreactive pericarditis and pericardial involvement in systemic autoimmune diseases**

The diagnosis of autoreactive pericarditis is established using the following criteria:<sup>2</sup> (1) increased number of lymphocytes and mononuclear cells >5000/mm<sup>3</sup> (autoreactive lymphocytic), or the presence of antibodies against heart muscle tissue (antisarcolemmal) in the pericardial fluid (autoreactive antibody-mediated); (2) signs of myocarditis on epicardial/endomyocardial biopsies by  $\geq 14$  cells/mm<sup>2</sup>; (3) 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); (4) tuberculosis, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, and other bacterial infection excluded by PCR and/or cultures; (5) neoplastic infiltration absent in pericardial effusion and biopsy samples; (6) exclusion of systemic, metabolic disorders, and uraemia. Intrapericardial treatment with triamcinolone is highly efficient with low incidence of side effects.<sup>2</sup>

Pericarditis, with or without effusion, is also a component of a multiserositis in systemic autoimmune dis-



eases: rheumatoid arthritis, systemic lupus erythematosus (SLE), progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behçet syndrome, Wegener granulomatosis and sarcoidosis.<sup>9</sup> Intensified treatment of the underlying disease and symptomatic management are indicated (level of evidence B, indication class I). Treatment should focus on pericardial symptoms, management of the pericardial effusion, and the underlying systemic disease.

### The post-cardiac injury syndrome: postpericardiotomy syndrome

Post-cardiac injury syndrome develops within days to months after cardiac, pericardial injury or both.<sup>9,168</sup> It resembles the post-myocardial infarction syndrome, both appearing to be variants of a common immunopathic process. Unlike post-myocardial infarction syndrome, post-cardiac injury syndrome acutely provokes a greater antiheart antibody response (antisarcolemmal and antifibrillary), probably related to more extensive release of antigenic material.<sup>168,169</sup> Pericardial effusion also occurs after orthotopic heart transplantation (21%). It is more frequent in patients receiving aminocaproic acid during the operation.<sup>170</sup> Cardiac tamponade after open heart surgery is more common following valve surgery (73%) than coronary artery bypass grafting (CABG) alone (24%) and may be related to the preoperative use of anticoagulants.<sup>171</sup> Constrictive pericarditis may also occur after cardiac surgery. Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion.<sup>172</sup> Symptomatic treatment is as in acute pericarditis (NSAIDs or colchicine for several weeks or months, even after disappearance of effusion).<sup>173</sup> Long term (3–6 months) oral corticoids or preferably pericardiocentesis and intrapericardial instillation of triamcinolone (300 mg/m<sup>2</sup>) are therapeutic options in refractory forms. Redo surgery and pericardiectomy are very rarely needed. Primary prevention of postpericardiotomy syndrome using short-term perioperative steroid treatment or colchicine is under investigation.<sup>174</sup>

### Postinfarction pericarditis

Two forms of postinfarction pericarditis can be distinguished: an “early” form (pericarditis epistenocardica) and a “delayed” form (Dressler’s syndrome).<sup>175</sup> *Epistenocardic pericarditis*, caused by direct exudation, occurs in 5–20% of transmural myocardial infarctions but is clinically discovered rarely. *Dressler’s syndrome* occurs from one week to several months after clinical onset of myocardial infarction with symptoms and manifestations similar to the post-cardiac injury syndrome. It does not require transmural infarction<sup>176</sup> and can also appear as an extension of epistenocardic pericarditis. Its incidence is 0.5–5%<sup>177</sup> and is still lower in patients treated

with thrombolytics (<0.5%),<sup>178</sup> but was more frequent in cases of pericardial bleeding after antithrombotic treatment.<sup>175,179</sup> Of note, ECG changes are often overshadowed by myocardial infarction changes. Stage I ECG changes are uncommon and suggest “early” post-myocardial infarction syndrome whereas failure to evolve or “resurrection” of previously inverted T waves strongly suggest myocardial infarction pericarditis.<sup>180,181</sup> Postinfarction pericardial effusion >10 mm is most frequently associated with haemopericardium, and two thirds of these patients may develop tamponade/free wall rupture.<sup>182</sup> Urgent surgical treatment is life saving. However, if the immediate surgery is not available or contraindicated pericardiocentesis and intrapericardial fibrin-glue instillation could be an alternative in subacute tamponade.<sup>182,183</sup>

Hospitalisation to observe for tamponade, differential diagnosis, and adjustments of treatment is needed. Ibuprofen, which increases coronary flow, is the agent of choice.<sup>184</sup> Aspirin, up to 650 mg every 4 h for 2–5 days has also been successfully applied. Other nonsteroidal agents risk thinning the infarction zone.<sup>185</sup> Corticosteroid therapy can be used for refractory symptoms only but could delay myocardial infarction healing (level of evidence B, class IIa indication).

### Traumatic pericardial effusion and haemopericardium in aortic dissection

Direct pericardial injury can be induced by accidents or iatrogenic wounds.<sup>9,186–189</sup> Blood loss, vasoconstriction, and haemothorax leading to severe hypotension and shock may mask pulses paradoxus.<sup>189</sup> Thoracotomy and surgical repair should be performed to stabilize the haemodynamics.

Iatrogenic tamponade occurs most frequently in percutaneous mitral *valvuloplasty*, during or after transseptal puncture, particularly, if no biplane catheterisation laboratory is available and a small left atrium is present. Whereas the puncture of the interatrial septum is asymptomatic, the passage of the free wall induces chest-pain immediately. If high-pressure containing structures are punctured, rapid deterioration occurs. However, if only the atrial wall is passed, the onset of symptoms and the tamponade may be delayed for 4–6 h. Rescue pericardiocentesis is successful in 95–100% with a mortality of less than 1%<sup>36</sup> (Table 8).

Transection of the coronary artery and acute or subacute cardiac tamponade may occur during *percutaneous coronary interventions*.<sup>191,192</sup> A breakthrough in the treatment of coronary perforation are membrane-covered graft stents.<sup>196,197</sup> Perforation of the coronary artery by a guidewire is not infrequent and causes very rarely a relevant pericardial haemorrhage.

During right ventricular *endomyocardial biopsy*, due to the low stiffness of the myocardium, the catheter may pass the myocardium, particularly, when the biptome has not been opened before reaching the endocardial border. The rate of perforation is reported to be in the range of 0.3–5%, leading to tamponade and circulatory

**Table 8** Traumatic pericardial effusion <sup>186-213</sup>

Effusion due to	Incidence (%)	Mortality (%)	Management	Comment/reference
<b>Iatrogenic</b>				
Transseptal puncture	1–3	<1%	Rescue pericardiocentesis, if needed	Use biplane angio-graphy <sup>190</sup>
Coronary artery perforation during PTCA (guidewire only)	Not infrequent	Not available	Watchful waiting by withdrawal of guidewire	Reverse anticoagulation
Coronary artery transection during PTCA	0.3–3.2	Not available	Sealing by graft stents (best) or perfusion catheters with balloon occlusion of perforated vessel, if pericardial puncture is need reinfusion of recovered blood in vein avoids anaemia.	Surgery only if >30% of myocardium at stake or bleeding cannot be stopped <sup>191,192</sup>
Rotablation	0.1–3	Not available	See above	See above <sup>191,192</sup>
Transluminal extraction atherectomy (atherocath)	0–2%	Not available	See above	See above
Excimer laser angioplasty	1.7–3%	Not available	See above	See above <sup>192</sup>
High pressure stenting	<2% (?)	Not available	See above	See above <sup>192</sup>
Mitral valvuloplasty	1–3%	<1%		<sup>190,198</sup>
Left ventricular biopsy (LV-EMB)	0.1–3.3%	0%	Routine echocardiography post EMB, pericardiocentesis, if needed; reverse anticoagulation	<sup>199,200,213</sup>
Right ventricular biopsy (RV-EMB)	0.3–5%	0–0.05%	Routine echocardiography post EMB, pericardiocentesis, if needed; reverse anticoagulation	<sup>199,200,213</sup>
Pacemaker leads	0.3–3.1%	0.1%	Routine echocardiography post implantation, pericardiocentesis, if needed	Pericardial effusion with/without tamponade, <sup>209,210</sup> postpericardiotomy syndrome, <sup>211</sup> constrictive pericarditis <sup>212</sup>
<b>Other causes</b>				
Injury (direct: e.g., stabbing; indirect: compression, closed chest massage)	Not available	Often lethal	Direct: surgery (see text) indirect: pericardiocentesis or surgery	
Aortic dissection	48% post mortem, 17–45% in clinical series	Lethal if not operated	Transoesophageal echo, CT or MRI, immediate surgery	Particularly in De-Bakey I + II = Stanford type A <sup>203-208</sup>

collapse in less than half of the cases.<sup>199,200,213</sup> The incidence of pericardial haemorrhage in left ventricular endomyocardial biopsy is lower (0.1–3.3%). Frank cardiac perforations seem to be accompanied by sudden bradycardia and hypotension.<sup>199</sup> Severe complications, leading to procedure related mortality were reported in only 0.05% in a worldwide survey of more than 6000 cases<sup>200</sup> and in none of the 2537 patients from the registry of an experienced reference centre.<sup>213</sup>

*Pacemaker leads* penetrating the right ventricle or epicardial fixed electrodes may cause pericarditis with tamponade, adhesions, or constriction. A right bundle branch block instead of a usually induced left bundle branch block can be a first clue.<sup>209–212</sup>

*Blunt chest trauma* is the major risk of car accidents. The deceleration force can lead to myocardial contusion with intrapericardial haemorrhage, cardiac rupture, pericardial rupture, or herniation. Transesophageal echocardiography in the emergency room<sup>202</sup> or immediate computed tomography should be performed. Indirect injury of the pericardium is more difficult to detect. Pericardial laceration and partial extrusion of the heart into the mediastinum and pleural space may also occur after injury.<sup>187</sup>

In *dissection of the ascending aorta* (pericardial effusion can be found in 17–45% of the patients and in 48% of the autopsy cases (Table 8).<sup>203</sup> In a clinical series of aortic dissection, pericardial tamponade was found by CT,<sup>204</sup> MRI,<sup>205</sup> or echocardiography<sup>206</sup> in 17–33% of patients with type I dissection and 18–45% in type II dissection and 6% in type III dissection.<sup>204</sup> Pericardiocentesis is contraindicated, due to the risk of intensified bleeding and extension of the dissection.<sup>207,214</sup> Surgery should be performed immediately after the diagnosis is established by echocardiography and/or CT/MRI, even if no coronary angiography or aortography is available (level of evidence B, indication class I).

### Neoplastic pericarditis

Primary tumours of the pericardium are 40 times less common than the metastatic ones.<sup>9</sup> Mesothelioma, the most common of the primary tumours, is almost always incurable. Metastatic tumours of the pericardium are found in 15–30% of all autopsies performed in patients

with malignant disease and in 4% in general autopsies.<sup>215</sup> The most common secondary malignant tumours are lung cancer, breast cancer, malignant melanoma, lymphomas, and leukemias. Effusions may be small or large with an imminent tamponade (frequent recurrences) or constriction. It even may be the initial sign of malignant disease.<sup>216</sup> The majority of patients with malignant pericardial effusion are asymptomatic, particularly if the accumulation of pericardial effusion is gradual. The onset of dyspnoea, cough, chest pain, tachycardia, jugular venous distension is observed when the volume of fluid exceeds 500 ml. Orthopnea, weakness, dysphagia, syncope, palpitations, pericardial friction rub, hiccups, distant heart sounds, pleural effusion, hepatomegaly, oliguria, and oedema can also be present.<sup>9</sup> Pulsus paradoxus, hypotension, cardiogenic shock and paradoxical movement of the jugular venous pulse are important signs of cardiac tamponade.

The diagnosis is based on the confirmation of the malignant infiltration within pericardial sac. Of note, in almost two thirds of the patients with documented malignancy pericardial effusion is caused by non-malignant diseases, e.g., radiation pericarditis, or opportunistic infections.<sup>87, 88</sup> The chest roentgenogram, CT, and MRI may reveal mediastinal widening, hilar masses, and pleural effusion.<sup>9</sup> The analyses of pericardial fluid, pericardial or epicardial biopsy are essential for the confirmation of malignant pericardial disease (level of evidence B, indication class I) (Focus box 3–5).

Treatment of cardiac tamponade is a class I indication for pericardiocentesis. The following steps are recommended in suspected neoplastic pericardial effusion without tamponade: (1) systemic antineoplastic treatment as baseline therapy which can prevent recurrences in up to 67% of cases<sup>216</sup> (level of evidence B, class I indication); (2) pericardiocentesis to relieve symptoms and establish diagnosis (level of evidence B, class IIa indication); (3) intrapericardial instillation of cytostatic/sclerosing agent (level of evidence B, class IIa indication). Pericardial drainage is recommended, when technically possible, in all patients with large effusions because of the high recurrence rate (40–70%) (level of evidence B, indication class I).<sup>217–223</sup> Prevention of recurrences, may be achieved by intrapericardial instillation of: sclerosing, cytotoxic agents, or immunomodulators. Intrapericardial treatment tailored to the type of the tumour indicate

#### Focus box 5 Epicardial/pericardial tissue analyses

Histology of epicardial/pericardial biopsies can establish the diagnosis in patients with neoplastic pericarditis and tuberculosis.<sup>19,89,91</sup> Diagnosis of viral pericarditis can be established by PCR techniques with much higher sensitivity and specificity in comparison to viral isolation from fluid and tissue.<sup>93,94–97</sup> Immunohistochemistry, especially IgG-, IgM- and IgA- and complement fixation contribute significantly to the diagnostic value of epicardial biopsy.<sup>2</sup> Specificity of immunoglobulin fixation in autoreactive pericarditis is 100%. Complement fixation was found primarily in patients with the autoreactive form and rarely in patients with neoplastic pericarditis.<sup>10</sup>

Malignant mesotheliomas can be distinguished from pulmonary adenocarcinomas by immunohistochemical staining for CEA, surfactant apoprotein, Lewis a, and Tn antigen.<sup>98</sup> The majority (78%) of the malignant mesotheliomas expressed keratin, but CEA and surfactant apoprotein were not detected in any mesotheliomas. On the other hand, pulmonary adenocarcinomas expressed not only keratin (100%), but also CEA (62%) and surfactant apoprotein (62%). The expression of Lewis a blood group antigen and Tn antigen was detected in 76% and 62% of the pulmonary adenocarcinomas, respectively, but only one mesothelioma was stained for Lewis a antigen.

that administration of cisplatin is most effective in secondary lung cancer and intrapericardial instillation of thiotepa was more effective in breast cancer pericardial metastases.<sup>224–226</sup> No patient showed signs of constrictive pericarditis (for both agents level of evidence B, indication class IIa). Tetracycline as sclerosing agents also control the malignant pericardial effusion in around 85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%), and atrial arrhythmias (10%) (level of evidence B, indication class IIb).<sup>216,222,223</sup> Although classic sclerotherapy after intrapericardial instillation of tetracycline, doxycycline, minocycline and bleomycin is an effective procedure, constrictive pericarditis secondary to fibrosis remains a severe problem in long-term survivors.<sup>223</sup> Although intrapericardial administration of radionuclides has yielded very good results, it is not widely accepted because of the logistic problems connected with their radioactivity<sup>227</sup> (level of evidence B, indication IIa). Radiation therapy is very effective (93%) in controlling malignant pericardial effusion (level of evidence B, indication class IIa) in patients with radiosensitive tumours such as lymphomas and leukemias. However, radiotherapy of the heart can cause myocarditis and pericarditis by itself.<sup>216</sup> Subxyphoid pericardiectomy is indicated when pericardiocentesis cannot be performed (level of evidence B, indication IIb).<sup>228</sup> The procedure can be carried out in local anaesthesia, but complications include myocardial laceration, pneumothorax, and mortality.<sup>216,229–233</sup> Pleuropericardiectomy allows drainage of malignant pericardial fluid into the pleural space (level of evidence C, indication IIb). It is associated with a higher complications rate and offers no advantage over pericardiocentesis or subxyphoid pericardiectomy. Pericardiectomy is rarely indicated, mainly for pericardial constriction or complications of previous procedures.<sup>216</sup>

Percutaneous balloon pericardiectomy creates a pleuro-pericardial direct communication, which allows fluid drainage into the pleural space (level of evidence B, indication class IIa). In large malignant pericardial effusions and recurrent tamponade, it seems to be effective (90–97%) and safe<sup>38,234</sup> but has the potential risk of dissemination of neoplastic cells.

## Rare forms of pericardial disease

### Fungal pericarditis

Fungal pericarditis occurs mainly in immunocompromised patients or in the course of endemic-acquired fungal infections.<sup>235</sup> The clinical picture comprises the full spectrum of pericardial diseases including fungal myocarditis.<sup>3</sup> Fungal pericarditis is mainly due to endemic fungi (*Histoplasma*, *Coccidioides*), or nonendemic – opportunistic fungi (*Candida*, *Aspergillus*, *Blastomyces*) and semifungi (*Nocardia*, *Actinomyces*).<sup>236–238</sup> Diagnosis is obtained by staining and culturing pericardial fluid or tissue. Antifungal antibodies in serum are also helpful in establishing the diagnosis of fungal infection.<sup>3</sup> Antifungal treatment with fluconazole, ketoconazole, itraconazole, amphotericin B, liposomal amphotericin B or amphotericin B lipid complex is indicated in patients with docu-

mented fungal pericarditis (level of evidence B, indication class I). Corticosteroids and NSAIDs can support the treatment with antifungal drugs (level of evidence C, indication class IIa). Patients with pericarditis in the course of histoplasmosis do not need antifungal therapy, but respond to nonsteroidal anti-inflammatory drugs given during 2–12 weeks. Sulfonamides are the drugs of choice for a nocardiosis infection. Combination of three antibiotics including penicillin should be given for actinomycosis (level of evidence C, indication class I). Pericardiocentesis or surgical treatment is indicated for haemodynamic impairment. Pericardiectomy is indicated in fungal constrictive pericarditis (level of evidence C, indication class I).

### Radiation pericarditis

The probability to develop radiation-induced pericarditis is influenced by the applied source, dose, its fractionation, duration, radiation exposed volume, form of mantle field therapy, and the age of the patients.<sup>239</sup> Radiation induced pericarditis may occur already during the therapy or months and years later – with latency of up to 15–20 years. The effusion may be serous or haemorrhagic, later on with fibrinous adhesions or constriction, typically without tissue calcification. The symptoms may be masked by the underlying disease or the applied chemotherapy. Imaging should start with echocardiography, followed by cardiac CT or MRI if necessary. Pericarditis without tamponade may be treated conservatively or by pericardiocentesis for diagnostic purposes or if haemodynamic compromise/tamponade occurs. Pericardial constriction may happen in up to 20% of patients, requiring pericardiectomy. The operative mortality is high (21%) and the postoperative five years survival rate is very low (1%)<sup>240</sup> mostly due to myocardial fibrosis.

### Chylopericardium

Chylopericardium refers to a communication between the pericardial sac and the thoracic duct, as a result of trauma, congenital anomalies, or as a complication of open-heart surgery,<sup>241</sup> mediastinal lymphangiomas, lymphangiomatous hamartomas, lymphangiectasis, and obstruction or anomalies of the thoracic duct.<sup>242</sup> Infection, tamponade or constriction may aggravate the prognosis.<sup>243</sup> The pericardial fluid is sterile, odourless, and opalescent with a milky white appearance and the microscopic finding of fat droplets. The chylous nature of the fluid is confirmed by its alkaline reaction, specific gravity between 1010 and 1021,<sup>244,245</sup> Sudan III stain for fat, the high concentrations of triglycerides (5–50 g/l) and protein (22–60 g/l). Enhanced computed tomography,<sup>246</sup> alone or combined with lymphography, can identify not only the location of the thoracic duct but also its lymphatic connection to the pericardium.<sup>247</sup> Treatment depends the aetiology and the amount of chylous accumulation.<sup>248</sup> Chylopericardium after thoracic or cardiac operation without signs of tamponade is preferably treated by pericardiocentesis and diet (medium chain triglycerides).<sup>249,250</sup> If further production of chylous effusion continues, surgical treatment is man-

datory (level of evidence B, indication class I). When conservative treatment and pericardiocentesis fail, pericardio-peritoneal shunting by a pericardial window is a reasonable option.<sup>251,252</sup> Alternatively, when the course of the thoracic duct was precisely identified, its ligation and resection just above the diaphragm is the most effective treatment.<sup>253</sup> In secondary chylopericardium the underlying disease, e.g., mediastinal tumour should be treated.

#### Drug- and toxin-related pericarditis

Pericardial reactions to drugs are rare. However, several medications and toxic substances can induce pericarditis, tamponade, adhesions, fibrosis, or constriction (Table 9).<sup>9,254</sup> Mechanisms include drug induced lupus reactions, idiosyncrasy, “serum sickness”, foreign substance reactions, and immunopathy. Management is based on discontinuation of the causative agent and symptomatic treatment.

#### Pericardial effusion in thyroid disorders

Pericardial effusion occurs in 5–30% of patients with hypothyroidism.<sup>9</sup> Fluid accumulates slowly and tamponade occurs rarely. In some cases cholesterol pericarditis may be observed. The diagnosis of hypothyroidism is based on serum levels of thyroxin and thyroid stimulating

hormone. Bradycardia, low-voltage of the QRS and T wave inversion or flattening in the ECG, cardiomegaly in the roentgenogram and pericardial effusion in echocardiography, as well as a history of radiation induced thyroid dysfunction,<sup>255</sup> myopathy, ascites, pleural effusion and uveal oedema may be observed.<sup>255–259</sup> Therapy with thyroid hormone decreases pericardial effusion (level of evidence B, indication class I).

#### Pericardial effusion in pregnancy

There is no evidence that pregnancy affects susceptibility to pericardial disease. However, many pregnant women develop a minimal to moderate clinically silent hydropericardium by the third trimester. Cardiac compression is rare.<sup>260</sup> ECG changes of acute pericarditis in pregnancy should be distinguished from the slight ST-segment depressions and T-wave changes seen in normal pregnancy (Table 10).<sup>260–275</sup> Occult constriction becomes manifest in pregnancy due to the increased blood volume.<sup>261</sup> Most pericardial disorders are managed as in nonpregnant. Caution is necessary while high-dose aspirin may prematurely close the ductus arteriosus, and colchicine is contraindicated in pregnancy. Pericardiotomy and pericardiectomy can be safely performed if necessary and do not impose a risk for subsequent pregnancies.<sup>262,263</sup> Foetal pericardial fluid can be de-

**Table 9** Drug- and toxin-related pericardial disease<sup>9,254</sup>

A. Drug-induced lupus erythematosus		
Procainamide	Methyldopa	Isoniazid
Tocainide	Mesalazine	Hydantoins
Hydralazine	Reserpine	
B. Hypersensitivity reaction		
Penicillins	Tryptophan	Cromolyn sodium
C. Idiosyncratic reaction or hypersensitivity		
Methysergide	Amiodarone	Cyclophosphamide
Minoxidil	Streptokinase	Cyclosporine
Practolol	p-Aminosalicylic acid	Mesalazine
Bromocriptine	Thiazides	5-Fluorouracil
Psicofuranine	Streptomycin	Vaccines (Smallpox, Yellow fever)
Polymer fume inhalation	Thiouracils	GM-CSF
Cytarabine	Sulfa drugs	
Phenylbutazone		
D. Anthracycline derivatives		
Doxorubicin	Daunorubicin	
E. Serum sickness		
Foreign antisera (e.g., antitetanus)	Blood products	
F. Venom		
Scorpion fish sting		
G. Foreign-substance reactions (direct pericardial application)		
Talc (Mg silicate)	Tetracycline/other sclerosants	Iron in $\beta$ -thalassemia
Silicones	Asbestos	
H. Secondary pericardial bleeding/haemopericardium		
Anticoagulants	Thrombolytic agents	
I. Polymer fume fever – inhalation of the burning fumes of polytetrafluoroethylene (Teflon)		

Table 10 Diagnostic approach to pericardial effusion in pregnancy.<sup>260-275</sup>

Procedure	Indications	Interpretation in pregnancy
Pulsus paradoxus	Diagnosis of cardiac tamponade	Can be also noted in Normal late pregnancy with no pericardial effusion Chronic constrictive pericarditis (~50%) Bronchial asthma/emphysema Pulmonary embolism Extreme obesity Hypovolemic shock
Electrocardiogram	Acute pericarditis Myopericarditis	ECG changes of acute pericarditis <sup>9</sup> should be distinguished from changes in normal pregnancy QRS axis shift to left or right <sup>268</sup> ST-segment depressions <sup>269</sup> and T-wave changes A small Q wave and an inverted P wave in lead III that vary with respiration, greater R-wave amplitude in V2 Sinus tachycardia, atrial and/or ventricular premature beats <sup>270</sup>
Chest radiography <sup>a</sup>	Suspected cardiac tamponade or haemopericardium in aortic dissection if echocardiography is not available Chest trauma Suspected tuberculous/neoplastic disease	The heart may seem enlarged (horizontal positioning)  An increase in lung markings may simulate a pattern of flow redistribution (LV failure in perimyocarditis) Small pleural effusion is often found early post partum <sup>271</sup> resolving spontaneously 1–2 weeks after delivery
Echocardiography	Pericardial effusion/tamponade Haemopericardium in aortic dissection Haemopericardium in aortic dissection <sup>273</sup> Confirmation of cardiac tamponade or constriction <sup>274</sup>	Enlarged right chambers (left lateral position) <sup>272</sup> LV systolic dimensions unchanged/slightly increased
Magnetic resonance imaging <sup>b</sup> Swan-ganz catheterization	Constrictive pericarditis <sup>d274</sup> Haemopericardium in aortic dissection Only in tamponade or diagnostic pericardiocentesis in critically ill patients Only in vital indications <sup>10,19</sup>	Brachial approach preferred (to minimize radiation exposure) Appropriate shielding (exposure kept to a minimum) Echocardiography guidance to avoid foetal radiation exposure whenever possible
Cardiac catheterisation <sup>c</sup> Pericardiocentesis Pericardioscopy and epicardial/pericardial biopsy		Foetal radiation exposure similar as during cardiac catheterisation

<sup>a</sup> Estimated radiation to the uterus is low (0.2–43.0 mrad)<sup>267</sup> but is best avoided in pregnancy.

<sup>b</sup> Safety has not been fully established.<sup>274</sup>

<sup>c</sup> High dose of radiation (~500 mrad to the conceptus, even with an appropriate pelvic shield) (488).

<sup>d</sup> When cardiac decompensation occurs during pregnancy in patients with constrictive pericarditis, particularly if cardiac surgery is being considered, cardiac catheterisation is required to: (1) confirm the diagnosis and (2) to exclude accompanied coronary artery disease in patients with several risk factors for coronary artery disease and of age >35 years.

tected by echocardiography after 20 weeks' gestation and is normally 2 mm or less in depth. More fluid should raise questions of hydrops foetalis, Rh disease, hypoalbuminemia, and immunopathy or maternally transmitted mycoplasmal or other infections, and neoplasia.<sup>264</sup>

## Acknowledgements

Members of the Task Force have the pleasure to acknowledge participation of Prof. Dr. Annalisa Angelini (Padua, Italy), Chairperson of the ESC WG Developmental Anatomy and Pathology, and Dr. Steffen Lamparter (Marburg, Germany) in preparation of the sections of the Guidelines on pericardial pathology and analyses of pericardial effusion. We also highly appreciate kind technical assistance of Ms. Veronica Dean (European Heart House).

*Special thanks to Prof. Dr. Eloisa Arbustini for her significant contribution to the review process of these guidelines.*

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