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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Management of Acute and Recurrent Pericarditis

JACC State-of-the-Art Review

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) identify acute pericarditis signs and symptoms as well as those key risk factors for recurrences; 2) discuss the mainstay of treatment of acute and recurrent pericarditis; 3) discuss the role of multimodality imaging in terms of diagnostic accuracy, treatment response and prognosis of recurrent and constrictive pericarditis; 4) discuss the pharmacological treatment of recurrent pericarditis, in particular the role of immunomodulator therapy in patients with corticosteroid-dependent pericarditis; and 5) identify those patients with worse prognosis after complete pericardiectomy for constrictive pericarditis.

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ABSTRACT

Pericarditis refers to the inflammation of the pericardial layers, resulting from a variety of stimuli triggering a stereotyped immune response, and characterized by chest pain associated often with peculiar electrocardiographic changes and, at times, accompanied by pericardial effusion. Acute pericarditis is generally self-limited and not life-threatening; yet, it may cause significant short-term disability, be complicated by either a large pericardial effusion or tamponade, and carry a significant risk of recurrence. The mainstay of treatment of pericarditis is represented by anti-inflammatory drugs. Anti-inflammatory treatments vary, however, in both effectiveness and side-effect profile. The objective of this review is to summarize the up-to-date management of acute and recurrent pericarditis. (J Am Coll Cardiol 2020;75:76–92)

Pericarditis refers to the inflammation of the pericardial layers and is the most common form of pericardial disease (1). It may be associated with pericardial effusion that can result in impaired cardiac filling (tamponade). The disease can be either an isolated form or a cardiac manifestation of a systemic disorder (e.g., autoimmune or autoinflammatory diseases). Pericarditis may result from infectious and noninfectious causes, although it is often idiopathic (2,3). The clinical presentation of pericarditis can differ substantially in the timing of presentation, symptoms, and prognosis. In this review, we aim to summarize main updates concerning the pathophysiology, diagnosis, and management of acute and recurrent pericarditis and its related complications, such as cardiac tamponade and constrictive pericarditis.

DEFINITIONS

Pericarditis can be categorized as acute, incessant, recurrent, or chronic (**Table 1**). Acute pericarditis is complicated by recurrences in 20% to 30% of cases, and up to 50% of patients with a recurrent episode of pericarditis experience more recurrences (4).

ACUTE PERICARDITIS

EPIDEMIOLOGY. Exact epidemiological data for acute pericarditis are lacking. The incidence was reported as 27.7 cases per 100,000 person-years in an urban area in Northern Italy, with concomitant myocarditis in about 15% of cases (5). Acute pericarditis is diagnosed in 0.2% of all cardiovascular in-hospital admissions and is responsible for 5% of emergency room admissions for chest pain in North America and Western Europe (6–9).

ETIOLOGY. In developed countries, viruses are presumed to be the most prevalent etiologic agents as an acute episode of pericarditis is often preceded by a gastrointestinal or a flu-like syndrome (10,11). Indeed, an increased incidence of acute pericarditis was observed during the cold season (12). Maisch et al. (13) showed that only 14% of cases are of infectious origin, either viral or bacterial, with *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, Parvovirus B19, and Epstein-Barr virus as the most prevalent agents. In a prospective study conducted in France, no etiological diagnosis was provided for 55% of the cases, but one-fifth of pericarditis cases were classified as post-cardiac injury syndrome (14). The latter etiology is progressively increasing in

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ABBREVIATIONS AND ACRONYMS

CRP = C-reactive protein

ECP = effusive-constrictive pericarditis

ESR = erythrocyte sedimentation rate

LV = left ventricle/ventricular

NSAID = nonsteroidal anti-inflammatory drug

WBC = white blood cell

developed countries due to the increased number of cardiac procedures, such as cardiac surgery (especially coronary artery bypass grafting), pacemaker insertion, radiofrequency ablation, transcatheter aortic valve implantation, and, rarely, percutaneous coronary intervention (15–17). Other specific causes to consider are autoimmune diseases, hypothyroidism (both on autoimmune or post-surgical basis), and cancer, either as a metastasis from a primary source (lung and breast cancers and lymphomas) or as a result of radiotherapy for chest cancers (18–20). Recently, immune checkpoint inhibitor-associated pericarditis has been described in a small number of patients (21). This condition requires special attention due to its severity and the need for immunosuppressive therapy.

In developing countries, tuberculosis is the most frequent cause of acute pericarditis (22). The incidence of tuberculous pericarditis has been growing even further in the past few decades as a result of the human immunodeficiency virus epidemic (22,23).

Despite numerous attempts of identifying a precise cause, most cases are referred to as "idiopathic," although this term truly reflects an inability to establish a specific etiology (3). Indeed, many cases are considered to be of undiagnosed viral origin or related to an immune response to a virus or other pathogens.

HIGHLIGHTS

- Pericarditis is the most common disease of the pericardium. Generally self-limiting, pericarditis can be fraught by a significant risk of acute complications and of recurrences.
- Prompt diagnosis and appropriate treatment of acute pericarditis may reduce the risk of acute complications and recurrences.
- New therapies, such as IL-1 blockers, show promising results in patients with recurrent/refractory pericarditis.
- Future studies are needed to deepen the knowledge about pericarditis pathophysiology and provide targeted therapies.

CLINICAL FEATURES. Diagnosis.

Based on current European Society of Cardiology guidelines (1), at least 2 of 4 criteria are needed for the diagnosis of acute pericarditis: 1) chest pain; 2) pericardial rub; 3) electrocardiogram (ECG) changes; and 4) new or worsening pericardial effusion. Elevation of inflammatory markers (i.e., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and white blood cell [WBC] count elevation) and evidence of pericardial inflammation by an imaging technique (computed tomography [CT] scan, or cardiac magnetic resonance [CMR]) may help the diagnosis and the monitoring of disease activity (1).

Chest pain. Sharp chest pain with a rapid onset is the cardinal symptom of acute pericarditis. Although the pericardial pain may also be dull or throbbing, in many cases sitting up and leaning forward improves the pain. Likewise, the pain has a clear relationship with breath inspiration, coughing, and sometimes, hiccups. Pain radiating to the trapezius ridge is also common (24).

Physical examination. Patients with acute pericarditis often appear uncomfortable or anxious and may have sinus tachycardia and low-grade fever. A pericardial friction rub can be heard on the left sternal border with the patient leaning forward or resting on elbows and knees, caused by the friction between the 2 inflamed pericardial layers.

When a systemic disease is associated with pericarditis, noncardiac manifestations of these diseases may be present during clinical assessment (i.e., weight loss, night sweats, rash, arthritis).

Electrocardiogram. ECG changes derive from the inflammation of the epicardium and adjacent myocardium, because the parietal pericardium is electrically silent. Sequential changes are seen in only approximately 60% of patients and are summarized in **Figure 1** (25). PR segment depression with ST-segment elevation are rather specific for pericarditis, but up to 40% of the patients present atypical and nondiagnostic changes. ECG modifications can be diffuse or localized, with PR depression possibly being the only sign.

Biomarkers. Currently, no specific biomarker for pericarditis is available. At least 30% of patients with pericarditis have some degree of cardiac-specific troponin I or T elevation, which confirms the concomitant involvement of the subepicardial myocardium (26,27). Pericarditis with associated myocarditis is defined as myopericarditis. In this case, patients show elevation of troponin I or T or signs of myocardial involvement on CMR without new appearance of focal or diffuse abnormalities of left ventricle (LV) function (1). Perimyocarditis is used to describe the myopericardial inflammatory syndrome in which the evidence of the myocardial

TABLE 1 Definitions of Pericarditis According to the Time of Presentation

	Definition
Acute	Event lasting <4 to 6 weeks
Incessant	Event lasting >4 to 6 weeks without remission
Recurrent	New signs and symptoms of pericardial inflammation after a symptom-free interval of 4 to 6 weeks
Chronic	Pericarditis lasting >3 months

involvement is associated with a new onset or worsening of focal or diffuse depressed LV wall motion (1). Unlike acute coronary syndrome, troponin I or T elevation is not a negative prognostic marker in myopericarditis/perimyocarditis (27).

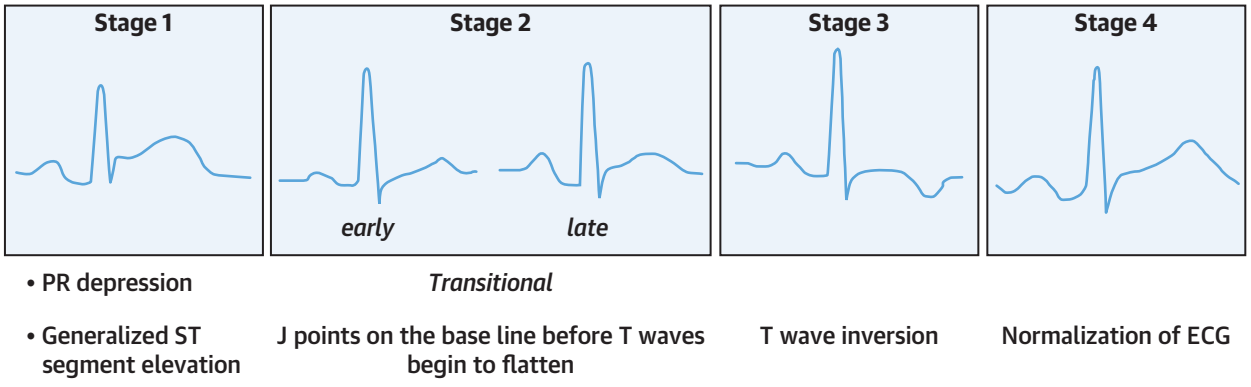
Markers of inflammation (WBC, ESR, and CRP) are elevated in up to 80% of cases, but these markers are not sensitive or specific for acute pericarditis. However, high-sensitivity CRP identifies patients with higher risk of recurrences (28).

Imaging. Cardiac imaging is an integral part of the diagnostic and staging process of pericarditis (29,30), as indicated by the European Association of Cardiovascular Imaging position statement on multimodality imaging in pericardial disease (31) and in the American Society of Echocardiography Clinical Recommendations for Multimodality Cardiovascular Imaging of Patients with Pericardial Disease (32).

Echocardiography is the first and often the only necessary imaging test in patients with acute pericarditis. Although normal in 40% of cases, this test is essential to identify complications, such as tamponade or constrictive pericarditis, and could be useful for monitoring the evolution of pericardial effusion over time and the response to medical therapy (32). As well, echocardiography allows for an indirect quantification of the pericardial effusion, which is semiquantitatively described based on the echo-free space size between pericardial layers at the end of the diastole: trivial (only seen in systole), small (<10 mm), moderate (10 to 20 mm), large (21 to 25 mm), and very large (>25 mm) (32). Large pericardial fluid could identify patients with acute pericarditis who are at higher risk of complications (18). Additionally, echocardiography can result useful in providing a real-time assessment when performing a pericardial drainage in the setting of severe pericardial effusion or cardiac tamponade. It may also aid in the determination of concomitant ventricular dysfunction that may suggest a component of myocarditis (33). Patients presenting with myocardial involvement have lower longitudinal and circumferential strain in all of the 3 myocardial layers and at the basal, midventricular, and apical levels. LV twist is also lower than in normal subjects due to lower apical rotation (34). Transesophageal echocardiography may be considered when transthoracic echocardiography is suboptimal. Limitations of the echocardiography include detection of loculated effusions or the presence of a clot, as well as the difficulty for a precise characterization and quantification of the amount of pericardial fluid (32). The use of 3-dimensional echocardiography may, however, help in identifying and characterizing loculated effusions.

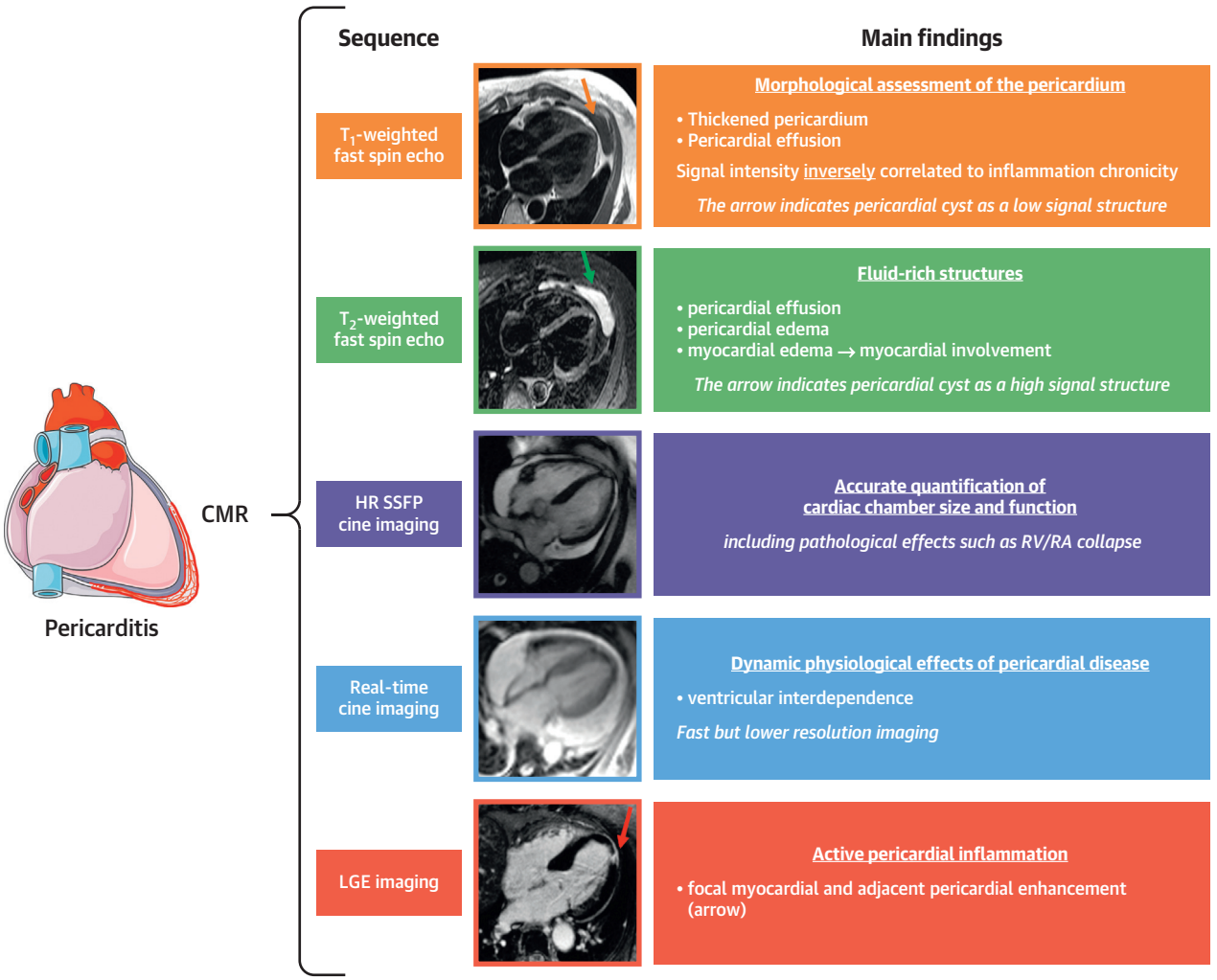
CMR is an adjuvant test in patients with pericarditis (30) and is particularly useful when echocardiographic images are ambiguous or in case of suspicion for myocardial involvement (35). CMR provides both morphological and hemodynamic information. The characteristics of the pericardium

FIGURE 1 ECG Changes in Acute Pericarditis



In the first stage, a PR-segment depression and generalized ST-segment elevation are seen. The second stage is the normalization of these findings. In the third stage, a T-wave inversion predominates. The fourth stage is represented by the normalization of all of these changes. ECG = electrocardiogram.

FIGURE 2 Major Findings at CMR in Patients With Pericarditis



The different sequences acquired through cardiac magnetic resonance (CMR) can greatly help in the diagnosis of pericarditis, starting from the morphological assessment until the individuation of the area of active inflammation of the pericardium. This figure was partially created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License. CMR = cardiac magnetic resonance; HR SSFP = high-resolution steady-state-free-precession; LGE = late gadolinium enhancement; RA = right atrium; RV = right ventricle.

evaluated through CMR and case images are detailed in **Figure 2**. Late gadolinium enhancement (LGE) can provide accurate information on the presence and severity of pericardial inflammation, with a sensitivity of nearly 94% (36). LGE is absent or minimal under physiological conditions because the normal pericardium is not vascularized, whereas acute pericarditis is associated with neovascularization. Interestingly, a correlation between LGE and histological markers of inflammation and neovascularization was found (37). LGE measurement can help identify subjects who are at high risk of complications, as patients with multiple recurrences and higher LGE experience a reduced clinical remission rate (38). The modulation of therapy according to inflammation level is another intriguing application of LGE evaluation along with CRP reduction. CMR can be performed in case of doubt or in patients with multiple recurrences showing to reduce the incidence of recurrences and decrease the administration of drugs, especially of corticosteroids (39). In a recent study in patients with recurrent pericarditis, pericardial thickening seen through CMR performed within 4 weeks from symptom onset has been shown to predict adverse outcomes independently from CRP levels, whereas LGE was associated with a lower risk (40). Whether

TABLE 2 Differential Diagnosis for Acute Pericarditis

Diagnosis	Clinical Presentation	ECG Findings	Echocardiography	Coronary Angiography	CMR	Biomarkers
Takotsubo syndrome	Chest pain, dyspnea, syncope, arrhythmias, sudden cardiac death. Usually in older female patients triggered by an emotional event or exertion.	ST-segment elevation, T-wave inversion, QTc segment prolongation.	Apical, midventricular, basal, or focal hypokinesia/ akinesia.	Absence of obstructive CAD or angiographic evidence of acute plaque rupture.	Transmural ventricular edema in the areas of ventricular dysfunction; regional wall motion abnormalities according to the anatomical patterns. No LGE.	BNP markedly elevated, troponin I/T levels mildly increased.
Myocardial infarction	Chest pain, dyspnea, arrhythmias, sudden cardiac death.	ST-segment elevation, ST-segment depression, and/or T-wave inversion.	Regional wall motion abnormalities according to epicardial coronary artery distribution.	Coronary artery disease with acute plaque rupture, thrombus formation, and coronary dissection.	Subendocardial or transmural edema at sites of wall motion abnormalities. Regional wall motion abnormalities according to epicardial coronary artery distribution. Bright LGE typically subendocardial or transmural in an epicardial coronary artery distribution.	Troponin I/T levels significantly elevated. BNP mildly increased.
Myocarditis	Chest pain, dyspnea, acute heart failure, sudden cardiac death. Usually in young or middle-aged populations, often preceded by an upper respiratory infection or enteritis.	Nonspecific ST-segment and T-wave changes (diffuse ST-segment elevation is usually seen in myopericarditis/ perimyocarditis).	Global systolic dysfunction (sometimes regional or segmental). Pericardial involvement may be also present.	Absence of obstructive CAD or angiographic evidence of acute plaque rupture.	Subepicardial basal and lateral edema. Usually global dysfunction unless regional edema/ LGE is severe. Low intensity or bright LGE is often present with a focal "patchy" subepicardial or midventricular noncoronary distribution.	Troponin I/T levels significantly elevated. BNP mildly increased.
Acute pericarditis	Chest pain, with changes according to position (worse leaning back), pericardial rub, pericardial effusion.	PR-segment depression, concave ST-segment elevation, T-wave inversion.	Pericardial effusion, cardiac tamponade, constrictive physiology.	Absence of obstructive CAD or angiographic evidence of acute plaque rupture.	LGE of the pericardium. In cine imaging, constrictive physiology can be seen. Edema and LGE of myocardium is generally absent.	Troponin I/T mildly elevated at times. BNP levels generally normal

BNP = brain natriuretic peptide; CAD = coronary artery disease; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; QTc = corrected QT interval.

repeating a CMR after treatment has additional prognostic value is, however, unknown.

The combined evaluation of pericardial inflammation with LGE and of pericardial edema in T_2-weighted sequences can determine the stage of inflammation. A prominent LGE with an increased signal in T_2-weighted sequences is associated with acute inflammation, whereas the absence of elevated T_2 signal represents the chronic phase. An increased LGE with a normal T_2 signal is suggestive of a subacute phase of inflammation, characterized by edema resolution (41).

CMR may define the eventual presence and the extent of myocardial involvement with myocardial LGE. CMR also has a role in the evaluation of stable patients with suspected constrictive pathophysiology and inconclusive evidence on echocardiography, whereas its use in case of hemodynamic impairment is discouraged (31).

CMR is not without limitations: cost and availability may limit use, and both a stable heart rhythm and breath hold are needed for an adequate diagnostic image quality. Finally, although the use of CMR at 1.5-T in patients with pacemakers/defibrillators is increasing, the use of gadolinium is contraindicated in case of advanced renal dysfunction (41,42).

The CT scan has the advantage of a short acquisition time and a very high spatial resolution. Following the administration of intravenous contrast, enhancement of thickened pericardium can be observed in case of suspected pericarditis or tumor infiltration (32). It is particularly sensitive for identifying pericardial calcification and may enable the initial characterization of the pericardial fluid better than echocardiography. Unfortunately, the pericardium can only be clearly visualized where it is surrounded by fat and not immediately adjacent to the myocardium. Another limitation is the inability to make real-time hemodynamic assessment by using respiratory maneuvers to test ventricular interdependence.

Differential diagnosis and management. During the evaluation of chest pain, diagnoses other than pericarditis should be ruled out (**Table 2**). Fever (>38°C), subacute onset, large pericardial effusion (>20 mm in echocardiography), cardiac tamponade, and lack of response to anti-inflammatory therapy after 1 week of treatment (11,28) are associated with a worse prognosis. Patients with these characteristics

as well as those with an increased risk for tamponade and constriction should be hospitalized (18). Other minor predictors of worse prognosis are immunosuppression, trauma, and oral anticoagulation (8,18).

TREATMENT. Anti-inflammatory therapy is the cornerstone of acute pericarditis (**Central Illustration**). In **Figure 3**, we describe treatment algorithms for acute and recurrent pericarditis as well as their complications (i.e., cardiac tamponade and constrictive pericarditis).

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended based on clinical experience, although no randomized clinical trial has proven their efficacy in acute pericarditis.

During an acute episode, the recommended dose of oral ibuprofen is 600 to 800 mg every 8 h. Oral indomethacin at a dose of 50 mg every 8 h may also be used (1,54). Ketorolac may be used as an alternative for patients who are unable to take oral medication or who have severe pain, however, its use should be limited to a maximum of 5 days (43). Aspirin 750 to 1,000 mg 3 times per day is preferred in patients with concomitant coronary artery disease (44). NSAIDs have been shown to increase the risk of gastrointestinal ulcers by 3.8-fold compared with patients without NSAIDs (45). Other toxicities include bleeding (46), arterial hypertension (47), and kidney failure (48).

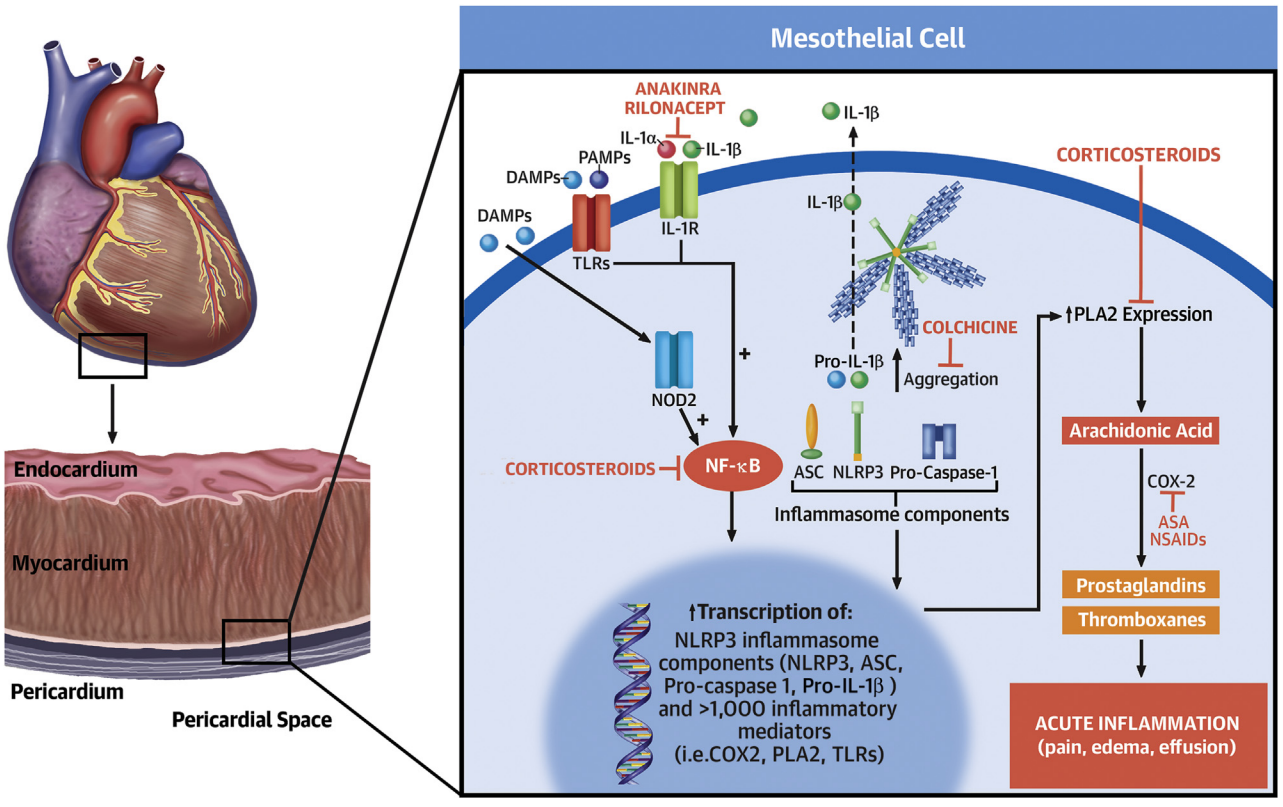
Colchicine. Colchicine has a known anti-inflammatory effect blocking tubulin polymerization with consequent impaired microtubule assembly, thus inhibiting inflammasome formation and cytokine release in WBCs, especially granulocytes (49). Weight-adjusted dosing is recommended in patients with acute pericarditis in addition to aspirin or another NSAID (4). Although NSAIDs are gradually discontinued when pain resolves and CRP normalizes, longer continuation with or without tapering of colchicine may be considered to prevent persistence of symptoms and recurrence. At the point of symptom resolution and normalization of CRP (<3.0 mg/l), the dose of the agent may be tapered accordingly (50). The benefit of colchicine is well established in both acute and recurrent pericarditis (**Table 3**) (4,51–54). The COPE (COlchicine for acute PEricarditis) trial, including patients with a first episode of acute pericarditis, showed that colchicine significantly reduced symptom persistence at 72 h and recurrence rate (51). These results were confirmed in the ICAP (Investigation on Colchicine for Acute Pericarditis) trial, where colchicine also significantly reduced the hospitalization rate (4). In a recent open-label trial of patients with acute idiopathic pericarditis (not previously treated with corticosteroids), colchicine, however, failed to show an improvement over standard anti-inflammatory treatment (55). The study, therefore, had some limitations: it was underpowered to test colchicine efficacy; diagnostic criteria for pericarditis did not include the standard ones (1), and colchicine was started late.

The lack of clinical evidence in patients with concomitant myocarditis indicates the need for cautious advancement with regard to treatment. Preclinical studies showed an increase in mortality after administration of a single dose of colchicine (2 mg/kg) at day 3 after viral infection in a mouse model of myocarditis (56). However, the dose of colchicine used in that study would likely be toxic in the clinical setting (therapeutic range in humans: 0.5 to 4.8 mg/day/60 kg) (57). This would explain why sicker animals could not tolerate a high single dose compared with the noninfected group. This limitation is also strengthened by the evidence that the continuous administration of colchicine in a mouse model of pericarditis was lethal when given at the daily dose of 1 mg/kg (58).

The most common adverse event with colchicine is gastrointestinal intolerance leading to discontinuation in 5% to 8% of patients (51,53,54). Myelosuppression and aplastic anemia are rare at the recommended doses (0.5 to 1.2 mg daily). Neuromuscular toxicity has been documented at an increased risk with drugs inhibiting P-glycoprotein (59). Patients older than 70 years and those weighing <70 kg should receive a tailored dose (50).

Corticosteroids. Systemic corticosteroids (i.e., prednisone) have been used mostly as second- or third-line treatments. In retrospective studies, their use has been associated with a more prolonged disease course and a higher recurrence risk. In the COPE trial (52), a history of corticosteroid use was an independent risk factor for recurrences with a 4.3-fold increase in risk. A meta-analysis confirmed the association of corticosteroid use with the risk of recurrences and showed that low-dose corticosteroids proved to be superior to high-dose corticosteroids, suggesting therefore a potential cause-effect link (60) probably due to a deficit in viral particle clearance within the pericardial space (61). Indeed, low-dose, weight-based corticosteroid treatment therapy (i.e., prednisone 0.2 to 0.5 mg/kg) was associated with lower rates of recurrence or treatment failure, hospitalizations, and adverse effects compared with high-dose corticosteroids (i.e., prednisone 1.0 mg/kg/day) (62). Another key element in recurrence rates is the rapid tapering of corticosteroid treatment. In our experience, the tapering should be done very slowly,

CENTRAL ILLUSTRATION **Pathophysiology of Acute Pericarditis**



Chiabrando, J.G. et al. J Am Coll Cardiol. 2020;75(1):76–92.

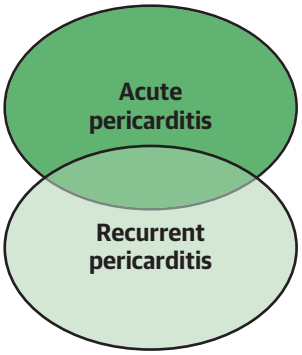
Injury to the pericardium leads to the release of DAMPs and PAMPs and induces NF-kB synthesis, which increases the transcription of precursors of inflammatory molecules and associated cytokines (NLRP3, ASC, pro-caspase-1) required for the polymerization of the NLRP3 inflammasome, ultimately releasing IL-1β and IL-18. NF-κB stimulates the synthesis of phospholipase-A2 required for promoting the arachidonic acid pathway and the subsequent synthesis of prostaglandins and thromboxanes. The IL-1 receptor (IL-1R) occupies a central role as IL-1α functions as an alarmin or DAMP being released during tissue injury, and IL-1β is processed and released by the inflammasome leading to amplification of the process. ASA = acetylsalicylic acid; ASC = apoptosis-associated speck-like protein containing a carboxy-terminal caspase-recruiting domain; DAMP = damage-associated molecular pattern; IL = interleukin; IL-1R = interleukin-1 receptor; NF-κB = nuclear factor kappa-light-chain enhancer of activated B cells; NLRP3 = NACHT, leucine-rich repeat, and pyrin domain-containing protein 3; NOD = nucleotide-binding oligomerization domain. NSAID = nonsteroidal anti-inflammatory drug; PAMP = pathogen-associated molecular pattern; PLA2 = phospholipase A2; TLR= toll-like receptor.

and every decrease in dose should be performed only in asymptomatic patients with CRP levels <3.0 mg/l (28). In case of recurrences, every effort should be made to not increase the dose or to reinstitute corticosteroid therapy (1). Hence, corticosteroids should be used for cases with incomplete response, with failure to other anti-inflammatory therapies, or for specific indications (e.g., immune checkpoint inhibitor-associated pericarditis, pericarditis associated with autoimmune diseases) (1).

IL-1 blockers. IL-1 receptor antagonist (i.e., anakinra [Kineret, Sobi, Stockholm, Sweden]) has proven beneficial in recurrent pericarditis in a randomized clinical trial (63). Data for IL-1 blockade in acute pericarditis are not so robust and are limited to a single case (64). A randomized controlled trial is ongoing to determine the efficacy of anakinra in acute pericarditis (NCT03224585). A case report of 3 patients showed that a fully human monoclonal antibody selectively binding IL-1β (canakinumab [Ilaris, Novartis, Basel, Switzerland]) was effective in patients with pericarditis due to adult-onset Still's disease (65). However, as described in a case report of a pediatric patient with corticosteroid-dependent recurrent pericarditis, canakinumab was associated with treatment failure, whereas symptom resolution occurred with the initiation of anakinra, which blocks the action of both IL-1α and IL-1β (66).

Antimicrobial therapy. A specific antimicrobial treatment according to the causative etiologic agent is

FIGURE 3 Treatment for Acute and Recurrent Pericarditis and Their Complications



DRUG	DOSE	DURATION
Aspirin	750-1,000 mg every 8 h	1-2 weeks
Ibuprofen	600-800 mg every 8 h	1-2 weeks
Colchicine	0.5-1.2 mg in one or divided doses	3 months
Aspirin	750-1,000 mg every 8 h	Weeks-months
Ibuprofen	600-800 mg every 8 h	Weeks-months
Indomethacin	25-50 mg every 8 h	Weeks-months
Colchicine	0.5-1.2 mg in one or divided doses	At least 6 months
Prednisone	0.2-0.5 mg/kg/daily	Months
Anakinra	1-2 mg/kg/daily up to 100 mg/daily	Months
Rilonacept	320 mg once, then 160 mg weekly	Months
Azathioprine	1 mg/kg/daily up to 2-3 mg/kg/daily	Months
Methotrexate	10-15 mg weekly	Months
MMF	2,000 mg daily	Months
IVIGs	400-500 mg/kg/day	5 days

Pericardiocentesis

Pericardial window

Active inflammation
- Yes → Anti-inflammatory therapy as first line, pericardiectomy for refractory cases
- No → Pericardiectomy

Different treatments, their dosing, and duration according to clinical presentation are summarized. IVIGs = intravenous immunoglobulins; MMF = mycophenolate mofetil.

indicated in purulent pericarditis, a rare but potentially life-threatening disease (67). *Staphylococcus aureus* and various streptococci are the most common pathogens (1). Nevertheless, micro-organisms of the normal skin flora, such as *Propionibacterium acnes,* may be implicated, especially when risk factors, such as immunosuppression, chest wall trauma, and increased alcohol intake, are present (68). Local fibrinolytic therapy may be considered as a less invasive alternative (69) and should be provided in the early phase of the disease to prevent pericardial effusion organization and the development of constriction.

The treatment of tuberculous pericarditis requires a multidrug regimen to be continued for several months (70). Given the regional differences in practices and resistance of the pathogens, it is advisable that cardiologists work closely with infectious disease specialists and the local department of health, if applicable, to determine the best regimen. A regimen consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol is recommended for ≤2 months, followed by isoniazid and rifampicin for 4 months. The goal of the prolonged therapy is to eradicate the mycobacterium and prevent the development of constrictive pericarditis (71). Corticosteroids and pericardiectomy are to be considered in selected patients (72). Specific antiviral treatment is indicated in case of pericarditis associated with documented viremia, particularly in immunocompromised patients.

Lifestyle modifications. Current U.S. and European guidelines are mostly focused on athletes recommending they return to competitive sports only after symptoms are resolved and diagnostic tests are normalized (1,73). A minimal restriction of 3 months has been defined (1). The detrimental effects of exercise-induced tachycardia and shear stress on the pericardium are thought to worsen inflammation, and the inflammation-related increased blood flow to the pericardium may favor oxidative stress (74). Genetic variations may also account for worsening

TABLE 3 Randomized Clinical Trials in Acute and Recurrent Idiopathic Pericarditis With Colchicine Added to Aspirin

Trial (Year)	Indication	Blinding	Patients	Treatment Duration	Primary Endpoint	Results
COPE trial (2005)	Acute pericarditis	No	120 patients	3–4 weeks (A), 3 months (A + C)	Recurrence	33.3% in A vs. 11.7% in A + C (P = 0.009)
CORE trial (2005)	Recurrent pericarditis	No	84 patients	3–4 weeks (A), 6 months (A + C)	Recurrence	50.6% in A vs. 24% in A + C (P = 0.02)
CORP trial (2011)	Recurrent pericarditis	Yes	120 patients	A/Ib: 3–4 weeks; Pl or C: 6 months	Recurrence	55% in A vs. 24% in A + C (P < 0.001)
ICAP trial (2013)	Acute pericarditis	Yes	240 patients	A/Ib: 3–4 weeks; Pl or C: 3 months	Incessant or recurrent pericarditis	37.5% in A vs. 16.7% A + C (P < 0.001)
CORP-2 trial (2014)	Recurrent pericarditis (2 or more events)	Yes	240 patients	A/Ib/In: 3–4 weeks; Pl or C: 6 months	Recurrence	42.5% in A vs. 21.6% in A + C (P = 0.0009)
CAFE-AIP trial (2019)	First episode of acute pericarditis (not secondary to cardiac injury or connective tissue disease)	No	110 patients	Group 1: A/Ib/In: 3–4 weeks; group 2: A/Ib/In: 3–4 weeks + C: 3 months	Recurrence	13.5% in A/Ib/In vs. 7.8% in A/Ib/In + C (P = 0.34)

A = aspirin; C = colchicine; CAFE-AIP = Colchicine Administered in the First Episode of Acute Idiopathic Pericarditis; COPE = COlchicine for acute PEricarditis; CORE = COlchicine for RECurrent pericarditis; CORP = Colchicine for Recurrent Pericarditis; CORP-2 = Efficacy and Safety of Colchicine for Treatment of Multiple Recurrences of Pericarditis; Ib = ibuprofen; ICAP = Investigation on Colchicine for Acute Pericarditis; In = indomethacin; Pl = placebo.

inflammation from exercise in predisposed individuals (75). Expert opinions recommend that patients with pericardial LGE and/or elevated inflammatory markers be restricted for intense exercise. A heart rate below 100 beats/min with exertion is also recommended (76).

Management of patients with myocardial involvement. Hospitalization is recommended in patients with myocardial involvement (1). In animal models of myocarditis, NSAIDs were shown to increase mortality (77,78). Accordingly, a lower dose of NSAIDs is suggested in these cases by the European Society of Cardiology guidelines (1), and NSAID safety was recently confirmed (79). Patients should avoid physical activity for at least 6 months.

PROGNOSIS. The prognosis of pericarditis is essentially driven by the etiology. Idiopathic and viral pericarditis have an overall beneficial prognosis, but they can also be associated with a significant risk of recurrences (7). Purulent and neoplastic pericarditis often present with a different clinical course and reported mortality rates between 20% and 30% (67,80). Pericarditis with myocardial involvement has an overall favorable prognosis, with LV function normalization in about 90% of patients within 12 months and without an increased risk of death (27). Recurrent pericarditis is the most common and troublesome complication of acute pericarditis in clinical practice along with constrictive pericarditis and tamponade.

RECURRENT PERICARDITIS

EPIDEMIOLOGY. Up to 30% of patients with an acute pericarditis experience a recurrence after an initial symptom-free period of 4 to 6 weeks (4), especially if not treated with colchicine (7).

ETIOLOGY. The etiology of recurrent pericarditis is presumed to be an immune-mediated phenomenon (10) related to an incomplete treatment of the disease rather than to a recurrent viral infection (81). This is supported by the time to event, the evidence of nonorgan-specific antibodies, and the good response to corticosteroid therapy (82). Factors associated with an increased risk of recurrences are female sex, previous corticosteroid use, and frequent prior recurrences (8,51,52).

DIAGNOSIS. There are no clear differences regarding clinical presentation between acute and recurrent pericarditis. However, a symptom-free interval of 4 to 6 weeks and evidence of new pericardial inflammation are needed for the diagnosis.

TREATMENT. Colchicine. A meta-analysis of 5 controlled clinical trials studies in patients with recurrent pericarditis showed a remarkable reduction in recurrences with colchicine (51,83,84). In Table 3, 3 studies are shown supporting the efficacy of colchicine in recurrences.

Corticosteroids. Corticosteroids at low doses (0.2 to 0.5 mg/kg) are often used and associate with a high treatment success rate, although a significant number of patients becomes corticosteroid-dependent (51,62,85).

IL-1 blockers. IL-1 blockade with anakinra is beneficial for the treatment of recurrent pericarditis (63,86,87), as shown by several case series and the randomized controlled AIRTRIP (Anakinra-Treatment of Recurrent Idiopathic Pericarditis) trial (63,87). The AIRTRIP trial included patients with recurrent

pericarditis resistant to colchicine and dependent on corticosteroid therapy, who received anakinra for 60 days followed by randomization to either anakinra 100 mg daily or placebo for an additional 6 months. A statistical difference in benefit in the anakinra group compared with placebo was found without any increase in the risk of serious infections (88). The main advantages of the drug are a rapid onset of effect and the capability of a quick withdrawal of corticosteroids. The potential disadvantages include a long duration of therapy and higher costs. A 24-week follow-up phase 2 study with rilonacept, a recombinant chimeric fusion protein acting as a trap for IL-1α and IL-1β in 16 patients with recurrent pericarditis and full medical therapy showed a decrease in both chest pain and CRP levels after the first injection (89).

Additional immunosuppressive drugs. Immunosuppressive drugs were used as corticosteroid-sparing agents. Azathioprine has shown its efficacy in long-term treatment requiring high doses of corticosteroids (90). Methotrexate and mycophenolate mofetil are effective and well tolerated in patients with idiopathic recurrent pericarditis not responsive to corticosteroids, who were corticosteroid-dependent, or who had unacceptable corticosteroid-related side effects (91). Limited evidence suggests efficacy of intravenous immunoglobulins (92).

Pericardiectomy. Pericardiectomy should be considered as a last option for refractory cases and should be performed only in tertiary, high-volume centers (93). The identification of the best candidates, the timing of the procedure, and potential complications still represent challenges, with clinical data accumulating only in recent years (94–96). The timing of pericardiectomy is recommended in those patients with a poor quality of life or refractory chest pain despite optimal duration of best medical therapy (97). Operative mortality remains not negligible, especially in older patients and in those with congestive heart failure, diabetes, chronic obstructive pulmonary disease, pre-operative renal impairment, chest irradiation, and prior cardiac surgery (94–96). Finally, although pain is usually significantly improved, residual chest pain after surgery may persist.

COMPLICATIONS OF ACUTE AND RECURRENT PERICARDITIS

EFFUSIVE PERICARDITIS AND TAMPONADE.

Epidemiology. Pericardial effusion is present in 50% to 65% of patients (8) and can lead to cardiac tamponade. Acute idiopathic pericarditis is most often associated with minimal or small effusions compared with a higher risk of tamponade in neoplastic, tuberculous, or hypothyroidism-related pericarditis (98,99).

Clinical features and imaging. Physical examination may show signs of hemodynamic impairment known as Beck's triad: hypotension, jugular vein distention, and muffled heart sounds. Tachycardia is the most sensitive sign, whereas pulsus paradoxus is the most specific. A pericardial rub is usually not detectable due to the presence of a large amount of fluid (100). A decrease in the amplitude of QRS complexes on the ECG may be found. As well, electrical alternans in QRS complexes can develop for the fluctuation of the heart within the pericardial effusion.

An echo-free space between the epicardium and the pericardial layers may allow for a semi-quantitative assessment of effusion severity (32). Nevertheless, there are some pitfalls regarding echocardiographic assessment. Because the descending aorta is extrapericardial, the accumulation of fluid between the descending aorta and the heart in the parasternal long axis establishes the fluid as pericardial rather than pleural (32). Another issue is the distinction between effusion and epicardial fat, the latter being brighter than the myocardium and moving in concordance with the heart differently from the pericardial effusion. Although the echocardiography can estimate the characteristics of the fluid (presence of clots, adhesions, fibrin, and so on), CMR and CT scan allow for a better definition.

Cardiac tamponade markedly alters cardiac filling dynamics. The most important echocardiographic signs are the presence of effusion, dilation of inferior vena cava and supra-hepatic veins, and a low end-diastolic and -systolic volume of the left ventricle. A biphasic inspiratory bounce of the interventricular septum is seen. Right chamber collapse during diastole is a specific sign for cardiac tamponade. Duration of right atrium collapse that exceeds one-third of the ventricular systole is rather sensitive and highly specific for cardiac tamponade (32). In the context of markedly elevated right atrial and ventricular diastolic pressures, diastolic collapse of the right atrium and ventricle may be however missing. Changes in mitral and tricuspid inflow velocities at pulsed wave Doppler are used to measure interventricular dependence, another sign of tamponade. Changes with respiration that exceed 30% and 40%, respectively, are considered highly suggestive of tamponade (101).

Prognosis. The prognosis varies largely depending on the etiology and the degree of hemodynamic impairment. Bacterial, tuberculous, cancer-related, and connective tissue disease-related effusions have worse prognosis than effusions complicating

idiopathic pericarditis. Cardiac tamponade is life-threatening and immediate treatment is needed.

Management. The treatment of cardiac tamponade is the drainage of the pericardial content under imaging guidance (102). Surgical drainage is desirable in patients with intrapericardial bleeding and in those with clotted hemopericardium or thoracic conditions making the needle drainage difficult or ineffective or where a large effusion and tamponade are expected to recur. In this case, a pericardial window creating a communication with the pleural space is often employed (103). Mechanical ventilation with positive airway pressure should be avoided in patients with tamponade (102).

CONSTRICTIVE PERICARDITIS. Epidemiology. Constrictive pericarditis may develop without effusion or through the organization of a previous effusion. Men have a higher risk of developing constrictive pericarditis than women (104). Tuberculosis is the leading cause of constrictive pericarditis in developing countries, whereas in the rest of the world idiopathic or viral remains the most common etiology, followed by post-cardiac injury, post-radiation therapy, rheumatologic diseases, malignancies, and traumas (96,104-106). The risk of this complication is 20% to 30% following a tuberculous pericarditis (70) and decreases when coinfection with the human immunodeficiency virus occurs (107). The risk is lower in post-cardiac injury syndrome compared with bacterial or tuberculous pericarditis (108). Despite similar findings with imaging techniques, differences may be observed in the operating room when the macroscopic anatomy of constrictive pericarditis is observed (109).

Diagnosis. The diagnosis is usually made by Doppler echocardiography in patients with history and physical findings suggesting a high clinical suspicion of constrictive pericarditis. The clinical symptoms are not specific and include fatigue, exercise intolerance, dyspnea, anorexia, and weight loss. Physical examination may show signs of right heart failure. Jugular venous pressure is elevated with rapid x- and y-descent waves without decrease or even with an increase during inspiration (Kussmaul's sign) (105,110). Upon auscultation, the presence of a pericardial knock has been reported in up to 47% of patients (105). Pulsus paradoxus has also been reported (105,111). There is no pathognomonic ECG pattern.

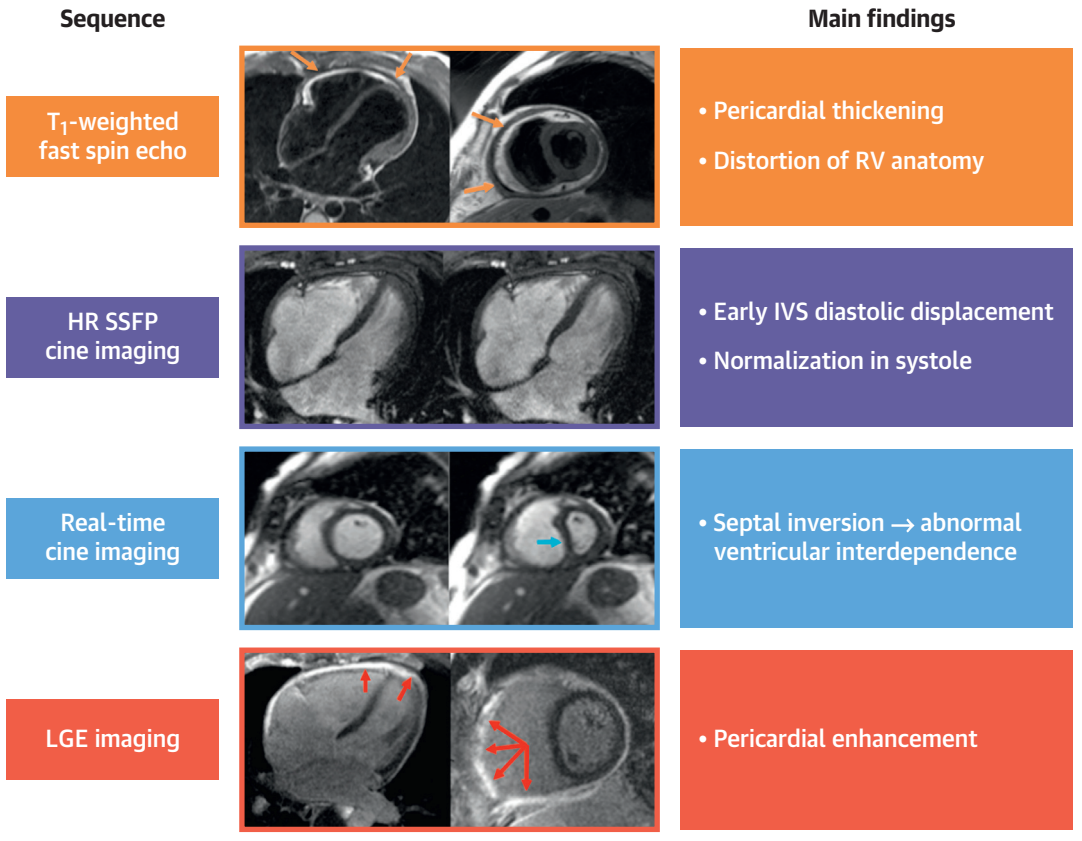
Biomarkers and imaging. High levels of CRP and ESR predict a more favorable response to anti-inflammatory treatment (112). Levels of N-terminal pro-B-type natriuretic peptide tend to be lower compared with patients with other causes of heart failure. It is not uncommon to have an association between constrictive pericarditis and an underlying myocardial disease presenting with high B-type natriuretic peptide levels (113).

Chest radiography shows pericardial calcification in 25% to 30% of cases (114). Echocardiography can show concomitant effusion in 30% to 40% of patients. Additionally, a diastolic septal bounce and the respirophasic septal shift due to interventricular dependence can be seen (115). The mitral inflow velocities typically show a pseudo-normal or restrictive filling pattern (E/A >1 and a deceleration time <150 ms). The respiratory variation in filling velocities has the same thresholds as in cardiac tamponade. Due to tissue tethering, mitral lateral e′ velocity might be lower than medial e′ velocity, a finding called *anulus reversus*. Higher mitral annular e′ velocities in patients with symptoms and signs of heart failure are suggestive of constrictive pericarditis (i.e., >8 cm/s). Inferior vena cava plethora and a normal or increased propagation velocity of early diastolic transmitral flow on color M-mode are common signs (116), while expiratory hepatic vein diastolic reversal wave is the most specific echocardiographic sign (116). Global longitudinal strain and early diastolic tissue velocities are generally preserved, whereas circumferential strain, torsion, and early diastolic untwisting are reduced (117). Some studies have been conducted aimed at elucidating key elements to differentiate constriction from restriction (118). As a result, longitudinal strains have been found regionally reduced in the free wall of both ventricles, especially in the circumferential directions in constriction (32,119). Deeper insights into the pathophysiological mechanisms concerning strain analysis have been discussed elsewhere (120,121).

CMR has a role in the evaluation of patients with suspected constriction when echocardiography is inconclusive (35), such as in patients with prior radiation therapy (42). CMR findings in constrictive pericarditis are described in **Figure 4**. The presence of active pericardial inflammation is the best predictor of constriction reversibility with anti-inflammatory treatment. LGE assessment, therefore, can be very useful in the identification of patients who may better respond to therapy (122).

CT has greater sensitivity than chest radiography to detect pericardial calcifications and pericardial effusion. Also, it can detect other structural involvement in systemic diseases and is very helpful in the preoperative planning of pericardiectomy and to assess the remaining pericardium when incomplete resection is made. Other findings are increased pericardial thickness and calcification. Nonvisualization of the

FIGURE 4 Cardiac Magnetic Resonance Findings in Patients With Constrictive Pericarditis



In T_1-weighted fast spin echo images, 4-chamber **(left)** and short-axis **(right)** sequences demonstrate pericardial thickening **(arrows)** and distortion of right ventricular anatomy. In diastolic **(left)** and systolic **(right)** high-resolution steady-state-free-precession cine imaging, the early diastolic displacement of the interventricular septum is shown, which normalizes in systole **(right).** This results in the appearance of a septal "bounce," indicative of abnormal right ventricular filling dynamics. The real-time cine images at rest **(left)** and with the patient performing a deep inspiration **(right)** show a septal inversion **(right, arrow)** indicative of abnormal ventricular interdependence in a case of pericardial constriction. The 4-chamber **(left)** and short-axis **(right)** late gadolinium enhancement pictures show intense pericardial enhancement **(arrows)** in a patient with constrictive pericarditis. IVS = interventricular septum; other abbreviations as in Figure 2.

posterolateral LV wall on dynamic CT may indicate myocardial fibrosis or atrophy, which is associated with a poor surgical outcome (123). Of interest, positron emission tomography/CT using ^{18}F-fluorodeoxyglucose can identify pericardial inflammation, aiding in identifying those patients with active inflammation who may benefit from anti-inflammatory treatment (124).

Cardiac catheterization is currently reserved for patients in whom noninvasive diagnostic methods are inconclusive and the clinical suspicion remains high (125). The key elements for diagnosing constrictive pericarditis in invasive hemodynamics are: 1) elevation and equalization of cardiac diastolic pressures in the 2 ventricles (<5 mm Hg difference); 2) prominent rapid diastolic filling waves on both ventricles (≥5 mm Hg, referred to as a square root sign); 3) reduced cardiac output; and 4) an exaggerated inspiratory decrease in systolic blood pressure (>10 mm Hg) (126). These elements can be masked by the assessment at rest and by treatment with diuretic agents; therefore, an intravenous volume expansion challenge is reasonable in patients with high pre-test probability and nondiagnostic invasive hemodynamics.

Management. When laboratory or imaging signs of active inflammation are present, a course of anti-inflammatory treatment is indicated (112). Cautious diuresis is indicated for patients with evidence of volume overload and right-sided heart failure symptoms (127). Reduction of heart rate with β-adrenergic receptor blockers, or possibly ivabradine, may

improve symptoms in patients with resting tachycardia (128).

In chronic cases with persistent New York Heart Association functional class III or IV symptoms refractory to treatment, radical pericardiectomy may be indicated, although burdened by a significant operative mortality (129). Of note, patients with mild symptoms derive little or no benefit from pericardiectomy. Similarly, long-lasting constrictive pericarditis in patients with low ejection fraction and heart failure may yield unacceptable surgical results, and symptomatic treatment should be recommended in these cases (1).

Pericardial effusion with or without constriction is the most commonly observed type of pericardial disease in patients with previous radiation therapy (130,131). They present concurrent cardiomyopathy with intractable congestive heart failure symptoms (132). Hence, the treatment of heart failure is usually recommended, whereas pericardiectomy is not recommended as it may not eliminate symptoms and the overall prognosis is unfavorable (105).

Prognosis. Predictors of poor overall survival are prior chest irradiation, chronic renal dysfunction, higher pulmonary arterial systolic pressure, abnormal left ventricular systolic function, lower serum sodium level, and older age. If untreated, the prognosis of symptomatic constrictive pericarditis is poor.

EFFUSIVE-CONSTRICTIVE PERICARDITIS. Effusive-constrictive pericarditis (ECP) is a clinical syndrome in which constrictive visceral pericarditis coexists with pericardial effusion. In some patients with scarred, rigid parietal and visceral pericardium, tamponade can occur with relatively little accumulation of fluid. ECP is revealed in patients for whom drainage of pericardial fluid does not restore normal intracardiac pressures. This presentation appears to be more common following tuberculous pericarditis or hemopericardium, and further management after removal of the fluid is warranted (133). Also, purulent pericarditis can cause ECP (7), commonly provoked by *Propionibacterium acnes*, Staphylococci, and Streptococci (68,134).

The diagnosis is confirmed by echocardiography (135), as removal of pericardial effusion does not improve diastolic dysfunction. A visceral pericardiectomy can be necessary, although curative surgery increases morbidity and mortality and should be reserved for patients who are not responding to anti-inflammatory drugs.

UNSOLVED ISSUES AND FUTURE DIRECTIONS

Acute and recurrent pericarditis remain challenging diseases, as patients generally suffer from multiple flares and may become corticosteroid-dependent, experiencing adverse systemic events. Although many clinical trials have addressed most of the questions regarding the diagnosis, some uncertainties remain. Subacute presentation represents a common event among patients with pericarditis, with worse clinical profile compared with those with acute symptoms (136). In this view, it is worth working on these patients to increase the pathophysiological variants in which a benign course may not be the case.

With regard to etiology, the viral cause is believed to account for a minority of cases. However, pericardial recurrences are often determined by an excessively quick tapering of the anti-inflammatory medications in the absence of a proven viral reinfection. Finally, current advances in the pathophysiology of this disease might suggest a role for autoinflammatory causes resulting from cardiotropic viruses or nonspecific agents in genetically predisposed individuals with an abnormal innate immunity response (137). Despite these hypotheses, a demonstration of a virus-induced disease and the central role of the NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome in the pathophysiology are still lacking, mainly because an animal model of acute pericarditis has been only recently introduced (58,138).

CONCLUSIONS

Acute pericarditis remains the most common presentation of pericardial diseases. Although generally benign, pericarditis can be fraught by a significant number of complications and recurrences. According to geographical differences, the etiology varies and so do its prognosis and treatments. The awareness of the diagnostic and etiologic features of pericarditis is key for a proper treatment and the prevention of complications. Imaging studies are essential in the diagnosis and guidance for tailored treatment. In patients with recurrent or constrictive pericarditis or in those dependent on corticosteroids, targeted therapies with IL-1 blockers or other immunomodulators represent promising therapies.

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