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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

# Idiopathic Pericarditis—an Autoinflammatory Disease?

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## Abstract

**Purpose of the Review** Idiopathic acute and recurrent pericarditis are rare diseases of unknown origin. Here, we review trigger factors, pathomechanism, and treatment options for acute and recurrent pericarditis.

**Recent Findings** Acute pericarditis can be triggered by viral infections, myocardial ischemia, heart catheter interventions, cardiac surgery or seem to occur without any trigger. Earlier reports about viral nucleic acids in the effusion or myocardial autoantibodies in serum were detected only in a minority of patients. The current pathomechanistic concept focuses on the innate immune system. Clinical trials revealed that colchicine and anti-IL1β-targeted medication were effective to control acute and recurrent attacks.

**Summary** Activation of the innate immune system in pericarditis suggests that autoinflammation contributes to acute and recurrent pericarditis. The efficacy of colchicine and anti-IL1β-targeted medication in clinical trials indicates that acute and recurrent pericarditis should be regarded as an autoinflammatory disease. Therefore, idiopathic pericarditis should be considered as an autoinflammatory disease.

**Keywords** Acute pericarditis · Recurrent pericarditis · Autoinflammation · Inflammasome · Interleukin-1β · Colchicine

## Introduction

Pericarditis accounts for 5% of emergency department visits in the absence of myocardial ischemia [1]. Pericarditis is clinically classified as non-exudative, exsudative, exsudative-constrictive, or constrictive pericarditis [2•]. Acute pericarditis is active up to 6 weeks. Chronic pericarditis is active longer than 6 weeks [2•]. Recalcitrant pericarditis is a chronic pericarditis refractory to treatment. Recurrent pericarditis after 6 months is classified as chronic remittent pericarditis [2•]. Risk factors for an admission to the hospital are fever above 38 °C, subacute onset, therapeutic anticoagulation, immuno-suppressive therapy, arterial hypotension, jugular venous distension, and large volume effusions [3]. In developed countries, about 80% of cases with pericarditis are considered to be of postviral or idiopathic origin. Both conditions share an identical clinical presentation and are often referred as idiopathic pericarditis [4, 5]. Cardiotropic viruses like parvovirus-B19, herpes viruses (CMV; EBV; HHV6), influenza, hepatitis-C virus, human immunodeficiency virus, enterovirus, and adenovirus species have been described [6]. However, it remains controversial whether the presence of viral nucleic acids (RNA or DNA) in pericardial fluid is sufficient to indicate a significant contribution to the pathogenesis of pericarditis [4, 6]. Bacterial and parasitic infections are rare in developed countries [6]. Several drugs can induce a lupus-like syndrome which can present with pericardial effusion [7]. Furthermore, several types of post-cardiac injury syndromes can trigger an acute pericarditis [8]. Since patients are getting older, the number of cardiac ischemia and interventions will increase, indicating that post-infarction pericarditis will become more prevalent in the future.

This review focuses on recent advances in the recognition of autoimmune and autoinflammatory pathways which contribute to acute and recurrent pericarditis.

## Pericardial Effusion: Exsudate or Transsudate

Pleural and pericardial effusions are frequent in patients presenting with shortness of breath in chest pain units. The expanding opportunity to quantify biochemical parameters

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in body fluids leads to attempts to identify the cause of pleural and pericardial effusions. The first report providing diagnostic parameters for identification of a pleural exudate has been published in the 1970s by Light and colleagues [9]. These parameters were later referred as the Light criteria and were used simultaneously for pleural and pericardial effusions (Table 1) [10]. The original criteria by Light et al. have been revised recently and N-terminal pro-brain natriuretic peptide (NT-Pro-BNP) was added to identify transudate effusions due to heart failure [10–12]. More recently, a Spanish group reported the characteristic parameters for pleural and pericardial effusions in patients with acute idiopathic pericarditis and post cardiac injury syndromes [13•]. All these investigations conclude that exudates due to viral pleuritis, viral pericarditis, acute idiopathic pericarditis, and post cardiac injury syndromes can be differentiated by considering the clinical context but not by biochemical parameters derived from fluid analysis (Fig. 1) [10–12, 13•].

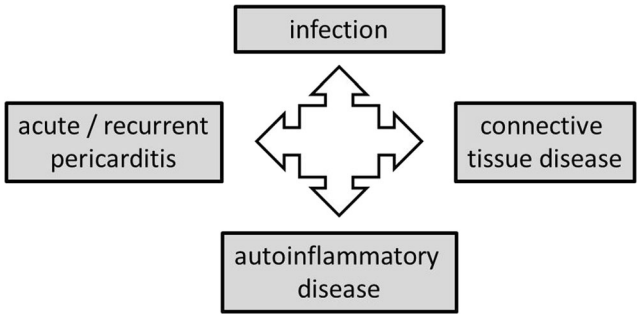


**Fig. 1** The clinical spectrum of infection-triggered pericarditis, autoimmune disease, and autoinflammatory syndromes as differential diagnoses in patients with idiopathic acute or recurrent pericarditis

## Viral or Idiopathic Pericarditis?

Other approaches to differentiate between viral and idiopathic pericarditis compared cytokine concentrations in sera and exudates [14]. This study suggested that the pericardial fluid in viral pericarditis exhibits high TNFα and low TGFβ1 concentrations in contrast to autoreactive pericarditis which showed low IL6 concentrations when compared to pericardial fluid from patients with stable coronary artery disease and bypass surgery [14]. However, these findings should be confirmed in a larger cohort before conclusions can be drawn.

Another study of the same group detected viral genomes in 51 of 259 pericardial exudates (19.7%) [6]. The most frequent viral genomes were parvovirus B19 ($n = 25$) and Epstein-Barr virus (EBV; $n = 19$) [6]. Single patients were positive for CMV, influenza, hepatitis C, or HHV6 [6]. Viral genomes were detected in patients with infectious disease ($n = 34/34$), malignant pericarditis ($n = 12/73$), and iatrogenic and traumatic pericarditis ($n = 5/39$) [6]. Investigators from Israel analyzed the seasonal pattern of pericarditis [15]. This group observed a peak incidence of acute pericarditis in late winter (January to March) [15] which seems to support the hypothesis of a viral infection. In contrast, patients with recurrent pericarditis did not show a seasonal pattern and were evenly distributed throughout the year [15]. It is tempting to speculate that genetic variants contribute to recurrent pericarditis and viral triggers might be not essential for triggering flares [15].

Taken together, these studies would be consistent with viral infections triggering acute pericarditis. However, since parvovirus B19, EBV, and other herpes viruses can be detected ubiquitously in adults, a passive transport to the pericardium via mononuclear cells could be an alternative explanation for viral genomes in patients with traumatic pericardial effusions [16, 17].

## Tissue Damage and Danger Signals

Innate immune responses are activated by pathogen recognition receptors (PRR). Infectious agents can bind and activate toll-like receptors (TLR) which recognize a pathogen-associated molecular pattern (PAMP) (Fig. 2). Bacterial lipopolysaccharide binds to TLR4, viral and bacterial RNA binds to TLR3,7,8, and DNA oligonucleotides bind and activate endosomal TLR9 [19]. TLR ligation activates the adaptor molecules MyD88 and TRIF which both activate the transcription factors NFκB and interferon-regulatory-factor-1

**Table 1** Laboratory parameters in serum and pericardial effusion differentiate between exsudate and transudate pericarditis. The parameters follow the criteria suggested by Light [9–12] with the exception of LDH higher than the originally suggested 2/3 of upper normal limit of serum LDH to avoid false positive exsudates

| | Exsudate | Transsudate |
|---|---|---|
| Absolute protein in effusion | > 30 g/l | < 30 g/l |
| Protein ratio (effusion/serum) | > 0.5 | < 0.5 |
| Absolute LDH in effusion | > 300 U/l | < 300 U/l |
| LDH ratio (effusion/serum) | > 0.6 | < 0.6 |
| White cell count in effusion | > 1000/μl | < 1000/μl |
| NT-pro-BNP in serum | < 1500 pg/ml | > 1500 pg/ml |
| predominant neutrophils (> 50%) | pneumonia, pulmonary embolism, pancreatitis | |
| predominat lymphocytes (> 50%) | viral pleuritis, post-cardiac injury, tuberculosis | |
| eosinophilic effusion (> 10%) | post-traumatic, hypersensitivity or allergic reactions, parasite infection | |

(IRF1) [20]. NFκB induces the transcription and release of pro-interleukin-1 (pro-IL-1) to the cytoplasm. IRF1 induces the mitochondrial deoxyribonucleotide kinase CMPK2 and the subsequent release of reactive oxygen species and oxidized mitochondrial DNA (ox-mt-DNA) to the cytoplasm where ox-mt-DNA activates the NLRP3 inflammasome [21]. NLRP3 is a cytosolic pattern recognition receptor that is activated in response to various pathogen-derived and endogenous agents [22]. Activated NLRP3 binds the adaptor molecule ASC and procaspase-1 to orchestrate the assembly of the NLRP3 inflammasome. The protein complex activates caspase-1 which subsequently releases bioactive IL-1β due to limited proteolysis of pro-IL1 [22]. Activated NLRP3 also induces gasdermin-D-dependent cell lysis, a process called pyroptosis [23]. Cell death is associated with the release of intracellular debris including LDH, ATP, RNA, and DNA which is collectively called as the damage-associated molecular pattern (DAMP) (Fig. 2). The recognition of DAMP by innate immune cells activates several pathways including lectin-, IL1-, TNF-, and interferon pathways which finally activate NFκB and NLRP3 inflammasomes in neutrophils and monocytes [23, 24]. The removal of cellular debris by phagocytosis stimulates antigen presenting cells, T- and B-lymphocytes which might induce the expression of autoantibodies (Fig. 2).

## Adaptive Immunity and Autoantibodies

Antigen-presenting cells phagocytose cell debris and present nuclear antigens to T- and B-lymphocytes which induces antinuclear-antibodies (ANA) (Fig. 2). ANA can be detected in the serum of patients and healthy controls at low titers without specificity for extracted nuclear antigens. Myocardial damage releases myocardial autoantigens which might stimulate tissue-specific T- and B-lymphocytes to produce anti-heart antibodies (AHA) and anti-intercalated disk antibodies (AIDA) [25]. A study of patients with recurrent pericarditis detected AHA in 25/40 patients (62.5%), AIDA in 10/40 patients (25%), and ANA ≥ 1:160 in 2/40 patients (5%) [25]. AHA and/or AIDA were detected in 27/40 (67.5%) of patients with recurrent pericarditis [25]. Usually, low titer AHA and low titer AIDA predominate and one third of patients remained completely negative for heart-specific antibodies [25]. The possibility remains that AHA and AIDA could be

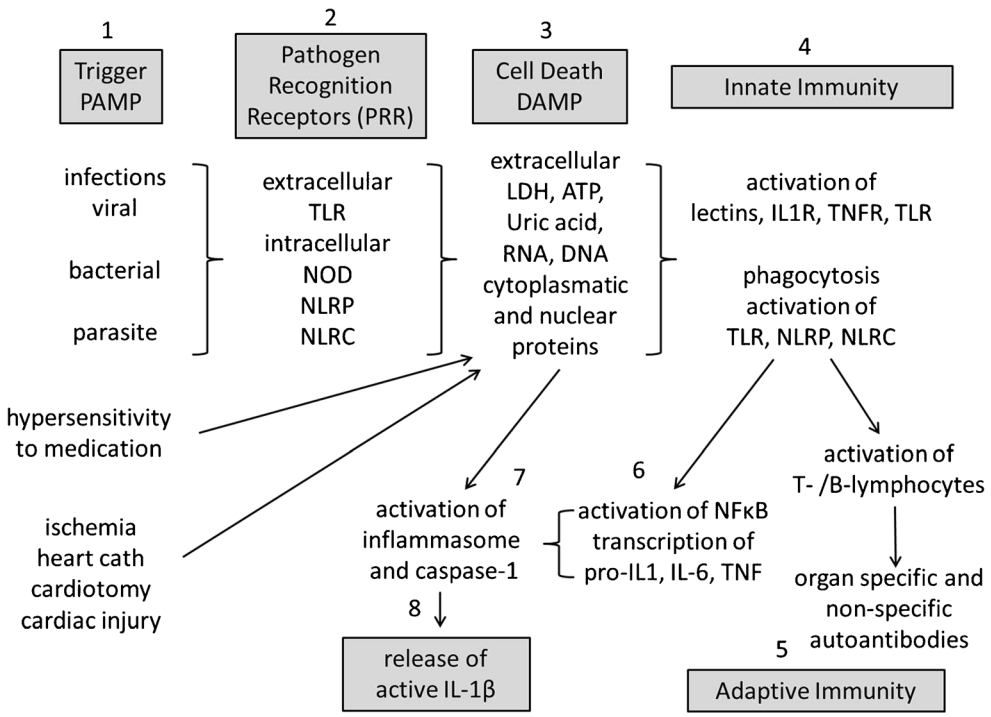


**Fig. 2** The currently proposed pathomechanism of pericarditis. The pathogen-associated molecular pattern (PAMP) of infectious agents (1) triggers pathogen recognition receptors (PRR) on the surface of immune cells or within the cytoplasm of phagocytes (2). PRR are toll-like receptors (TLR), NOD1 and NOD2, NOD-like receptors with pyrin (NLRP) or caspase recruitment domains (NLRC) (2). Activation of immune cells and tissue cells will lead to cell death and the release of intracellular components like ATP, uric acid, RNA, and DNA into the extracellular space (3). The release of these molecules during cell death confers a danger-associated molecular pattern (DAMP) with further activation of cell surface receptors and intracellular receptors (4). Activation of B- and T-lymphocytes might induce autoantibodies (5). Activation of NFκB, transcription of pro-inflammatory cytokines (6) and activation of purine receptors by extracellular ATP (7) activate the inflammasome and caspase-1 (7) which release IL1β (8). Adapted from [18]

an epiphenomenon which is not linked to the pathogenesis of acute and recurrent pericarditis.

## Pericarditis and Autoinflammatory Diseases

Familial Mediterranean Fever (FMF) is characterized by recurrent attacks of shivering followed by fever on the first day and abdominal pain for 2 days. Patients with severe disease also report thoracic pain due to pleuro-pericarditis without effusion [26]. In 75% of patients, two mutations in the *MEditerranean Fever Gene (MEFV)* can be detected [27–29]. However, in some cases, *MEFV* variants seem to follow an autosomal dominant trait [30]. Frequency and severity of FMF attacks can be reduced significantly by colchicine. About 5 to 10% of patients are non-responders to colchicine or cannot tolerate colchicine due to nausea, vomiting, or feeling drugged [31]. Blocking IL1β with anakinra or canakinumab is a safe and efficient alternative for these patients [30]. Although an Italian group was unable to detect *MEFV* variants in 23 patients with recurrent pericarditis [32], other reports describe a clinical overlap between FMF and recurrent pericarditis [33].

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is an autosomal dominant inherited autoinflammatory disease characterized by fever, abdominal pain due to peritonitis, myalgia, and erysipel-like erythema [34•]. Genetic variants are detected in the *TNFRSF1A* gene [34•]. Colchicine is not effective in TRAPS. Pulses of glucocorticoids are partially effective in TRAPS but high doses are required. A recent trial has shown that canakinumab is safe and efficient for reducing inflammatory attacks in patients with TRAPS [35]. A *TNFRSF1A* variant was detected in a patient with recurrent pericarditis who was refractory to colchicine [36]. Analysis of an Italian cohort of 131 patients with recurrent pericarditis revealed 8 patients (6%) with a *TNFRSF1A* variant [37]. Furthermore, in patients with an apparently normal *TNFRSF1A* genotype in Sanger sequencing, the possibility of a genetic mosaicism cannot be excluded [38].

Cryopyrin-associated periodic syndrome (CAPS) comprises familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neuro-cutaneous arthritis or newborn onset of multi-systemic inflammatory disease. These diseases are characterized by cold-induced urticarial rashes, conjunctivitis, arthritis, headaches, and hearing loss [39]. Multiple variants in the *NLRP3* gene were described in the autosomal dominant trait of the CAPS disease spectrum with a range from mild urticaria, moderate hearing loss to severe systemic disease with organ failure [39]. The clinical symptoms of CAPS and systemic inflammation are effectively suppressed by blocking IL-1β [40]. A recent analysis of 14 French patients with CAPS but no *NLRP3* variant in Sanger sequencing detected a somatic *NLRP3* mosaicism in 4 patients with a clinical CAPS phenotype [41]. Another group from Italy reported a patient with pericarditis during CAPS attacks [42]. These reports show that variants of *MEFV*, *TNFRSF1A*, and *NLRP3* are associated with autoinflammatory syndromes and can be detected also in a proportion of patients with recurrent pericarditis. These findings expand the initial concept of a hereditary fever syndrome to a broader clinical spectrum with variable age at onset of inflammatory attacks including recurrent pericarditis [43].

## Medical Treatment for Acute and Recurrent Pericarditis

Non-steroidal anti-inflammatory drugs have been used first to relieve thoracic pain, dyspnea, and fever [4, 5]. Various NSAID were used in small trials and none was more effective than any other. Current recommendations suggest the use of, e.g., Ibuprofen 400–800 mg tid with or without colchicine [4, 5]. It needs to be kept in mind that Ibuprofen (not most of the other NSAIDs) interferes with the binding of Acetylsalicylates to thrombocytes so that Acetylsalicylates should be taken 2 h before Ibuprofen.

The COPE trial randomized 120 patients with acute pericarditis to treatment with colchicine in addition to conventional therapy or aspirin alone [44]. The addition of colchicine was associated with a significant reduction of inflammatory symptoms and reduction of recurrent attacks [44]. These results were confirmed by the ICAP trial where 240 patients with acute pericarditis were randomized to receive colchicine 0.5 mg to 1 mg daily or placebo for 3 months [45•]. In the ICAP trial symptom persistence, rate of remission after 1 week, recurrence, and time to recurrence of pericarditis were significantly improved by colchicine [45•]. Finally, a recent Cochrane data review confirmed the beneficial effects of colchicine for acute or recurrent pericarditis [46]. However, the review also mentioned that only a few trials with small number of patients were available and especially patients with multiple resistant recurrent pericarditis were not represented in these trials although these patients are in the most need for treatment [46].

In the COPE trial, patients with aspirin intolerance or contraindications were treated with glucocorticoids [44]. Patients who received glucocorticoids seemed to have more recurrent flares than others [44]. A retrospective study analyzed 100 patients with acute pericarditis treated with prednisone [47]. The study compared low-dose (0.2–0.5 mg/kg/day) with high-dose prednisone (1.0 mg/kg/day) for 4 weeks, followed by slow tapering of the prednisone dose every 1–2 weeks [47]. Eighty percent of patients in both arms were also treated with colchicine [47]. The study showed that prednisone side effects, recurrence of pericarditis, and hospitalization were significantly worse when patients received high-dose prednisone [47].

Azathioprine is often used to facilitate prednisone tapering in patients with autoimmune disease. A retrospective analysis of 46 patients with recurrent pericarditis showed that 29 patients (63%) significantly reduced their prednisone dose without recurrence of pericarditis during follow-up for years [48]. Finally, 27 patients discontinued azathioprine and remained in a stable drug-free remission [48]. Hepatotoxicity, leucopenia, and gastrointestinal symptoms were reported by a few patients and subsided either spontaneously or after reducing azathioprine [48]. However, not all patients responded to azathioprine and the need of monitoring for hepatotoxicity and myelosuppression, the use of comedication (no allopurinol or febuxostat allowed) and comorbidities in older patients might limit the use of azathioprine for recurrent pericarditis.

Intravenous immunoglobulins (IVIG) are used as a safe alternative for patients with refractory disease where immunosuppression is not wanted. Few anecdotal reports and small case series with a total of 30 patients were reported for pericarditis [49]. These patients were treated with 0.4–0.5 g/kg for 5 days and cycles were repeated according to the clinical response [49]. Recurrent pericarditis occurred in 27% of patients after the first cycle of IVIG and 17% of patients remained on corticosteroids at the end of follow-up [49].

Advances in the understanding of the role of IL-1β for the pathogenesis of myocardial infarction and heart failure led to trials of Anakinra and Canakinumab for several diseases of the heart [50, 51].

Anakinra is a recombinant IL1 receptor antagonist which blocks the binding site of IL1β at the IL1 receptor. A British group reported 2 patients with recurrent pericarditis and reviewed 16 patients from the literature treated with Anakinra [52]. All patients failed to respond to colchicine. Anakinra was effective in all patients and azathioprine was less effective in this small cohort [52]. A group from Greece reported a case series of 10 patients with recurrent pericarditis treated with Anakinra [53]. In this cohort, the pericarditis rapidly responded to Anakinra and glucocorticoids were tapered [53]. However, when seven patients discontinued Anakinra, the pericarditis reoccurred in five patients [53]. A recent trial from Italy reported 21 patients with recurrent pericarditis who were resistant to colchicine and dependent on glucocorticoids [54••]. All patients were treated and responded well to Anakinra. At baseline, patients were randomized to continue with Anakinra or placebo injections. Recurrent pericarditis occurred in 9 of 10 patients assigned to placebo and in 2 of 11 patients who continued with Anakinra [54••].

Canakinumab is a humanized monoclonal antibody against IL-1β. Canakinumab is approved for CAPS [55], and other autoinflammatory syndromes like TRAPS, colchicine-resistant FMF, and mevalonatekinase deficiency [35]. A group from Athens, Greece, reported about the use of Canakinumab for colchicine resistant recurrent pericarditis in three patients [56]. Canakinumab was given every 4 to 8 weeks. Two patients were in complete remission with canakinumab glucocorticoids were discontinued [56]. A third patient responded only partially to Canakinumab 300 mg every 4 weeks and Canakinumab was discontinued [56]. In summary, anti-IL-1β targeted therapy is effective in patients with recurrent pericarditis who are resistant to colchicine and high doses of glucocorticoids are required (Table 2).

## Surgical Management of Pericardial Disease

Surgical treatment options for pericardial disease were reviewed recently [57]. Nataf et al. showed that subtotal pericardiectomy

**Table 2** A comprehensive analysis of epidemiologic and clinical parameters in patients with a pericardial exsudate. No single parameter differentiates causes of pericarditis

| Clinical feature | Viral infection | Idiopathic pericarditis | Autoinflammatory syndrome | Connective tissue disease |
|---|---|---|---|---|
| Gender female/male | 1:1 | 1:1 | 1:1 | 8:2 |
| Age at onset (years) | any | any | < 20 | any |
| Arthralgia or Myalgia | + | – | ± | ++ |
| Fever | + | + | + | + |
| Rash | + | – | + | + |
| Pleurisy | ± | ++ | + | + |
| Exsudate | + | ++ | ± | + |
| Episode duration > 4 weeks | – | + | ± | + |
| seasonal pattern | late winter | acute: Jan-March recurrent: no pattern | no pattern | summer |
| ANA > 1:320 (normal < 1:80) | – | – | – | ++ |
| Response to glucocorticoids | – | + | ± | ++ |
| Response to colchicine | – | + | FMF + CAPS/TRAPS - | – |
| Response to anti-IL1 | – | ++ | ++ | – |

had beneficial effects in 75 patients with constrictive pericarditis [58]. Another report showed that the long-term survival was improved further when radical pericardiectomy ($n = 414$) rather than subtotal pericardiectomy ($n = 71$) were combined with medical treatment [59]. The overall survival was 80% at 5 years and 60% at 10 years after pericardiectomy in this cohort [59]. The late survival was 90% at 10 years in patients with effusive pericarditis, 80% in patients with pericardial constriction, and < 30% in patients with pericardial tamponade [59]. The authors mention that pericardiectomy should be performed before the left ventricular ejection fraction has declined and renal failure evolved as these factors contributed to the overall mortality [59].

## Are Acute and Recurrent Pericarditis Autoinflammatory Syndromes?

Epidemiologic data suggest that acute pericarditis might be triggered by infections and recurrent pericarditis might be associated with genetic variants with an impact on inflammasome activity and a disposition to produce more IL-1β than healthy controls. The current concept of the pathogenesis of pericarditis comprises various triggers like infection, drugs, trauma, which are finally converging on a common pathway for IL-1β synthesis (Fig. 2). Clinical trials showed efficacy of colchicine and IL-1-blocking medication which suggests that acute and recurrent pericarditis have a strong autoinflammatory component. Genetic variants in the fever genes probably facilitate a prolonged, recurrent of refractory course of pericarditis (Table 2). The occurrence of organ specific autoantibodies in some patients cannot be confirmed in other patients with the same disease. In addition, autoantibodies are usually detected at low titers and low specificity. This suggests that the activation of antigen-specific B- and T-lymphocytes is probably an epiphenomenon and not central to the pathophysiology of pericarditis. The presence of viral nucleic acids can be demonstrated only in a minority of patients. When high sensitivity PCR methods are used to detect common herpes viruses in body fluids, a threshold for clinical significant amounts of nucleic acids should be considered. Therefore, the wealth of arguments favors an autoinflammatory mechanism rather than viral or autoimmune mechanisms in acute and recurrent pericarditis which is consistent with recent reviews on this topic [18, 50, 51, 60].

The pros and cons of the term "idiopathic" pericarditis have been discussed recently by Brucato and colleagues [50]. Idiopathic suggests that we do not know anything about the cause or the best treatment for pericarditis. However, based on the references discussed in this review, we suggest the term autoinflammatory acute and recurrent pericarditis at least for patients without clinical signs of infection. Furthermore, more trials about the use of anti-IL1-blocking medication for pericarditis are warranted.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Blank reports grants and personal fees from Novartis, grants and personal fees from SOBI, during the conduct of the study.

Hanns-Martin Lorenz declares no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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