Review Article

Cardiogenic Causes of Fever

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Summary

Background: Persistent fever of unknown cause is only rarely of cardiac origin, but heart disease must be considered in the differential diagnosis. Aside from endocarditis, pericarditis and various other conditions may be responsible.

Methods: This review is based on pertinent articles retrieved by a selective search in PubMed and Google Scholar employing the term “fever” in combination with “myocardial infarction,” “pericarditis,” “endocarditis,” and “postcardiac injury,” with additional consideration of current cardiological guidelines.

Results: Endocarditis is associated with fever in 90% of cases, but 25–50% of patients also develop high body temperatures after acute myocardial infarction. In pericarditis, a temperature above 38°C indicates a poorer prognosis; if accompanied by other warning signs, it is an indication for hospitalization and pericardiocentesis. Fever can arise after cardiac surgical procedures as a manifestation of post-cardiotomy syndrome, a special type of perimyocarditis. There may be a latency period of up to 3 months.

Conclusion: Fever can have both infectious and non-infectious cardiac causes. Its interpretation depends on the clinical context. The evidence base for treatment is sparse, and controlled trials are needed.

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While any body temperature above 37.5 °C is considered abnormally high, the term “fever” is reserved for temperatures of at least 38.3 °C. This usage developed over the course of time and hints at different degrees of severity of a disease. Particularly in the elderly, however, the increase in temperature accompanying infection is less pronounced, with the result that infection can be present at normothermia or even in hypothermia (2).

Fever arises due to alteration of the temperature set-point in the hypothalamus. This leads to systemic reactions that serve to raise the body temperature, e.g., peripheral vasoconstriction. Other mechanisms are muscle tremors (shivering) to produce heat by mechanical means and an unclear amount of thermogenesis in brown adipose tissue (3).

Fever has to be distinguished from hyperthermia, in which the body temperature is elevated although no alteration of the temperature set-point has taken place. Hyperthermia is defined as a core body temperature ≥ 40 °C accompanied by neurological symptoms (4). Hyperthermia can arise owing to physical exercise in unfavorable conditions (e.g., sports on a hot day) or also in other circumstances that lead to disturbance of the body’s thermoregulation (e.g., too little fluid intake and subsequent reduced perspiration in the elderly).

The set-point is altered by the action of exogenous or endogenous pyrogens.

Exogenous pyrogens are substances that enter the body from outside, predominantly bacteria and their products (e.g., toxins such as endotoxin). These microbial structures are detected by receptors on the body’s own macrophages (toll-like receptors, TLR), leading to production of pyrogens (5).

Endogenous pyrogens are substances produced within the body that trigger the alteration in set-point. Among others, these include cytokines such as tumor necrosis factor, interleukin 2, and interleukin 6.

These endogenous pyrogens arise in the course of inflammatory processes and act via multiple signal transduction pathways to alter the set-point for core body temperature in the hypothalamus. A crucial part is played by the concentration of prostaglandin E2 (PGE2), the highest levels of which are found in the circumventricular organ. This structure, consisting of fenestrated endothelium and located in the regulatory center of the hypothalamus, plays a decisive part in the origin of fever (6). A rise in PGE2 level is triggered both by the binding of endogenous pyrogens

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FIGURE 1

Distribution of cardiological causes in patients with pyrexia of unknown origin according to the study by Vanderschueren et al. (e9), the largest and most detailed prospective investigation into the causes of persistent fever. With regard to our study, high numbers of cases of "cardiac" fever are found mainly in connection with endocarditis; pericarditis can occur in association with several of the disease groups (tuberculosis, neoplasia, noninfectious inflammatory diseases [NIID]). Due to the required disease duration of at least 3 weeks, it is unlikely that these statistics include any cases of post-myocardial infarction fever.

BOX 1

Key findings in endocarditis

- Clinical signs (fever, newly occurring heart sound, skin changes, elevated parameters of inflammation)
- Endocarditis-compatible changes on transesophageal echocardiography
- Positive blood cultures

and by direct activation of the TLR in the circumventricular organ, inducing the set-point change (7).

Our aim in publishing this article is to provide a review of the cardiogenic causes of fever (*Figure 1*). To this end, we searched the literature in PubMed and Google Scholar for the term "fever" in combination with "myocardial infarction," "pericarditis," "endocarditis," and "postcardiac injury". We also consulted the current guidelines of the European Society of Cardiology (8–10) and the German Cardiac Society (11, 12). Altogether the evidence is sparse, so that older publications often have to be consulted.

Post-myocardial infarction fever

Acute coronary syndrome is myocardial ischemia associated with the corresponding symptoms, the typical ECG signs, and/or elevation of troponin T or troponin I. Around 20% of myocardial infarctions do not display typical symptoms. Patients with diabetes mellitus and female patients are often oligosymptomatic (13).

A prolonged period of myocardial ischemia results in myocardial necrosis, the extent of which depends on the size of the coronary artery affected. The degeneration of such necroses is accompanied by activation of inflammatory processes. Central to this is the influx of macrophages, which phagocytize the dead tissue and help to induce formation of scar tissue.

Data from the era before coronary intervention show increased temperature in around 25 to 50% of patients (14). This can be prevented by early administration of a beta-blocker (15). It remains unclear, however, whether body temperature is correlated with infarct size (16). In fact, temperature reflects the activity of inflammatory processes. Higher levels of both inflammatory cytokines (e.g., interleukin-6, leukocytes, and hs-CRP) and neurohormones (e.g., brain natriuretic peptide, BNP) can be detected in patients with increased temperature. This seems to be clinically relevant: In the study by Naito et al., body temperature $\geq 38^\circ\text{C}$ was correlated with reduced left ventricular pump function, aneurysm formation, and rehospitalization due to heart failure (16).

It is unclear, however, whether increased body temperature after myocardial infarction can be classed as the pathophysiological expression of inflammatory restructuring processes or whether the elevated temperature in itself in fact has a negative impact on these processes. The findings of animal experiments indicate that the increase in temperature during myocardial infarction has a negative influence on infarct volume (17, 18).

It also remains uncertain whether fever following myocardial infarction requires treatment. There have been no systematic studies on the administration of antipyretics to patients who have suffered myocardial infarction. In contrast, several studies have investigated the induction of therapeutic hypothermia before or during a percutaneous coronary intervention with the aim of limiting infarct size (16, 19, 20). However, none of these studies has yet demonstrated convincingly that induction of mild hypothermia during a myocardial infarction is of any benefit to the patient (21, 22). This intervention thus has no current clinical relevance.

In summary, it can be stated that elevated body temperature following myocardial infarction is a marker for increased risk. However, there are currently no therapeutic strategies for this scenario. Symptomatic treatment of fever after a myocardial infarction may be indicated, but one must bear in mind that a very high temperature, or appearance of fever late after the infarction, may also be due to an infection.

Endocarditis

Endocarditis is a cardiac disease that is typically (in up to 90% of cases) accompanied by fever (23). A characteristic heart sound is another typical finding (in ca. 85% of cases). The patients complain of shivering, reduced appetite and weight loss, muscle pain, and arthropathy, together with a general feeling of malaise.

BOX 2

Infectious endocarditis can be considered definitely present if (a) both major criteria, (b) one major criterion and three minor criteria, or (c) all minor criteria are met*

Major criteria

- Blood cultures positive for infectious endocarditis
 - Endocarditis-typical micro-organisms from two independent blood cultures:
 - Viridans streptococci, *Streptococcus gallolyticus* (*S. bovis*), HACEK group, *Staphylococcus aureus* or
 - community-acquired enterococci without detection of a primary focus or
 - Micro-organisms compatible with infectious endocarditis in persistently positive blood cultures:
 - At least two positive cultures from blood samples at an interval of at least 12 h or
 - All of three or a majority of 4+ independent blood cultures (first and last samples taken at an interval of at least 1 h) or
 - One positive blood culture with *Coxiella burnetii* or phase-I IgG antibodies >1 : 800
- Imaging positive for infectious endocarditis
 - Echocardiogram positive for endocarditis
 - Vegetation
 - Abscess, pseudoaneurysms, intracardiac fistula
 - Valve perforation or aneurysms
 - Newly occurring partial dehiscence of a prosthetic valve
 - Demonstration of abnormal activity in the area of the implanted prosthetic valve on 18F-FDG-PET/CT (positron-emission tomography/computed tomography) (only if the prosthesis was inserted more than 3 months previously) or on SPECT/computed tomography with radioactively marked leukocytes
 - Definitive demonstration of paravalvular lesions on computed tomography

Minor criteria

- Predisposition: predisposing heart disease or intravenous drug abuse
- Fever: body temperature >38 °C
- Vascular phenomena (including those only detected on imaging): severe arterial embolisms, septic pulmonary infarctions, mycotic aneurysms, intracranial hemorrhage, conjunctival bleeding, Janeway lesions
- Immunological phenomena: glomerulonephritis, Osler nodes, Roth lesions, rheumatoid factors
- Microbiological demonstration: positive blood cultures that do not correspond to either of the major criteria or serological detection of an active infection by an organism compatible with endocarditis

*Duke criteria as modified according to (11)

Furthermore, swift progression of infection symptoms or newly occurring signs of heart failure in connection with a history typical of infection should prompt consideration of endocarditis (8).

Cutaneous manifestations are also classically used as diagnostic criteria. While petechiae may occur (in around 20 to 40% of patients) and be helpful in clinical diagnosis, other skin signs such as Osler nodes and Janeway lesions have become rarer since the introduction of antibiotics, as have ocular signs (Roth spots) (24).

Suspicion of endocarditis should be expressed whenever the corresponding symptoms (pyrexia of unknown origin and the characteristic heart sound) occur in a patient exhibiting the risk factors for endocarditis. These factors are as follows:

- Previous infectious endocarditis
- Presence of an artificial heart valve or cardiac implant
- Congenital or acquired cardiac abnormalities

Long-term intravenous access ports and intravenous drug abuse also predispose to endocarditis. In some cases questioning may reveal a recent dental intervention (25) (Box 1).

There are no specific laboratory tests for endocarditis. The parameters of inflammation usually show pathological values. The retention parameters may also be elevated. Involvement of the kidneys is not uncommon (6 to 30%) and may, for example, take the form of acute renal failure with elevated creatinine or glomerulonephritis (Löhlein focal nephritis), which can be detected by urinalysis (26–29).

Infectious endocarditis is diagnosed on the basis of the modified Duke system, which distinguishes major and minor criteria. While echocardiographic demonstration of a vegetation (Figure 2) and microbiological detection of typical pathogens are major criteria, predisposition, immunological and vascular phenomena, body temperature, and the demonstration of atypical pathogens play a role as minor criteria (8) (Box 2).

TABLE

Initial antibiotic treatment of endocarditis without detection of pathogen

Preparation	Dosage	Duration
In patients with community-acquired endocarditis of natural valves or endocarditis after valve replacement >12 months; no penicillin allergy		
Ampicillin + (flu)cloxacillin + gentamicin	12 g/d i.v. divided into 4–6 doses 12 g/d i.v. divided into 4–6 doses 3 mg/kg BW/d i.v. or i.m. 1 × daily	Until detection of pathogen Optimization of antibiotic regimen in culture-negative endocarditis
Alternative for patients with penicillin allergy*		
Vancomycin + gentamicin	30–60 mg/kg BW/d i.v. divided into 2 doses 3 mg/kg BW/d i.v. or i.m. 1 × daily	Until detection of pathogen Optimization of antibiotic regimen in culture-negative endocarditis
In patients with treatment-associated endocarditis (e.g., hospital or care facility) of natural valves or endocarditis after valve replacement > 12 months		
Vancomycin + gentamicin + rifampicin	30 mg/kg BW/d i.v. divided into 2 doses 3 mg/kg BW/d i.v. or i.m. 1 × daily 900–1200 mg i.v. or p.o. in 2–3 doses	Until detection of pathogen Optimization of antibiotic regimen in culture-negative endocarditis

*The dosages of vancomycin and gentamicin are adapted to therapeutic drug monitoring. Also with other antibiotics, measurement of blood concentrations is feasible and particularly useful in the event of treatment failure (adapted from [8]).
BW = Body weight, d = day, i.m. intramuscular, i.v. = intravenous, p.o. = per os

Pathogens that can cause infectious endocarditis include (30):

- *Staphylococcus aureus*/coagulase-negative staphylococci: ca. 41%
- Streptococci: ca. 31%
- Enterococci: ca. 9%
- Others (HACEK, fungal infection, demonstration of several species): ca. 9%
- No pathogens cultured: 10%

The selection of antibiotics and the duration of treatment depend on the pathogen detected, the patient's allergy profile, the pathogen's resistance pattern, and the part of the heart affected (right heart or left heart, natural or artificial valve, infection of an implanted device) (Table).

Alongside conservative treatment with antibiotics, in specific risk constellations (acute heart failure owing to abnormalities, uncontrollable infection, prevention of thromboembolic events [8]) early surgical intervention is justified, with the aim of resection of the infected tissue and restoration of the cardiac structures including reconstruction or replacement of the affected valves (8). Around 50% of patients with left heart endocarditis undergo surgery at some point in the course of disease (31). A cardiac surgeon should therefore be consulted at an early stage in every case of endocarditis. The currently prevailing guidelines recommend the formation of an "endocarditis team" of cardiologists, cardiac surgeons, neurologists, neurosurgeons, infectiologists, and microbiologists.

Operative treatment is indicated whenever conservative measures prove insufficient to cure a case of endocarditis. Early surgery is also indicated for

prevention of complications (e.g. neurological complications). The following situations are potentially critical enough to justify early surgical intervention:

- New or progressive heart failure. Surgery is particularly urgent in the event of acutely occurring insufficiency of the aortic or mitral valve.
- Signs of uncontrollable local or systemic infection, e.g., persistently positive blood cultures despite adequate antibiotic treatment.
- For prevention of thromboembolic events, if the vegetations exceed a certain size.

The data on which the timing and performance of surgical or surgical reconstruction are based derive from a small number of observational studies (32–36). The sole randomized trial on this topic seems to confirm a benefit of early surgical intervention with regard to embolic events in patients with left heart endocarditis, severe valve defects, and large vegetations (37). This underlines the importance of interdisciplinary decision-making based on the risk constellation in each individual patient.

Pericarditis

The clinical signs of acute pericarditis are a combination of fever, sharp pleuritic chest pain, and the pericardial friction rub (a "squeaky leather" sound) on auscultation.

In 80% of cases the ECG is characterized by ubiquitous ST-segment elevations that cannot be localized. PR depressions are also typical (38). In contrast to acute myocardial infarction, Q peaks and R loss are rare and the ST elevation is concave. In two thirds of cases ECG shows a usually small (<10 mm) pericardial effusion. In

the laboratory, the inflammation markers (leukocytes, C-reactive protein [CRP], erythrocyte sedimentation rate) are elevated.

The diagnosis of pericarditis can be made if two of the following four diagnostic criteria are fulfilled (9):

- Typical chest pain
- Pericardial friction rub
- Concave, ubiquitous ST elevations and PR depressions on ECG
- Newly occurring or enlarging pericardial effusion

In many cases the pericardial inflammation extends to parts of the myocardium. In fact, the above-mentioned ECG changes already imply myocardial involvement, because the pericardium is electrically inert. Other findings that point to involvement of the myocardium are (40):

- Heart rhythm disorders, including ventricular rhythm disorders right up to ventricular fibrillation (e1)
- Reduced left ventricular ejection fraction
- Raised troponin levels
- Demonstration of myocardial involvement on cardiac magnetic resonance imaging

In the industrialized nations the vast majority (80 to 90%) of cases of acute pericarditis are idiopathic or viral in origin. Other causes (ca. 15%) are autoimmune disease (7.3%), neoplasia (5.1%), tuberculous pericarditis (3.8%), and suppurating pericarditis (0.7%). These nonviral forms of pericarditis have a poor prognosis (e2). The following risk factors determine whether the prognosis is favorable or unfavorable:

- Fever ($>38^{\circ}\text{C}$)
- Subacute disease course
- Pericardial effusion >20 mm or its hemodynamic effects
- Treatment failure after 7 days' administration of non-steroidal antiinflammatories (NSAR)

In the presence of one or more of these risk factors the patient should be admitted to the hospital and further diagnostic procedures (e.g., pericardiocentesis) considered (9, e2).

The first-line treatment of acute pericarditis comprises administration of NSAR, if possible in combination with low-dose colchicine (39). Prednisolone should be reserved for cases in which the first-line treatment fails or is contraindicated. The prognosis of acute viral pericarditis is good.

If pericarditis recurs after a symptom-free interval of 4 to 6 weeks, the recommended treatment comprises NSAR plus colchicine. If the symptoms persist, corticosteroids are administered. Should further escalation be necessary, intravenous immunoglobulins, anakinra (an interleukin-1 receptor antagonist), and azathioprine can be given.

Postpericardiotomy syndrome: a special form of pericarditis

Pericarditis after heart surgery involving opening of the pericardium, with or without accompanying pericardial effusion, is referred to as postpericardiotomy syndrome.

Figure 2: A mitral valve imaged by transesophageal echocardiography: intercommissural slice with typical vegetations (arrows) as major criterion for infectious endocarditis

Therefore all routine cardiac operations, such as coronary bypass surgery, correction of heart valve abnormalities, and aortic arch surgery, bear the risk of postpericardiotomy syndrome. This also applies to operations performed without a heart–lung machine (so-called off-pump techniques) and to minimally invasive valve surgery via anterolateral routes without median sternotomy (e3). The incidence of postpericardiotomy syndrome after heart surgery is 10 to 15%. The etiology has not yet been completely elucidated. On the basis of the demonstration of antimyocardial antibodies, it is assumed that an autoimmune reaction represents the underlying pathophysiological process, possibly in association with a previous latent viral infection. The combination of the presence of antibodies and trauma to the mesothelial pericardial cells seems to bring about the release of cardiac antigens, which in turn set the immune reaction in motion. The resulting immune complexes are deposited in the pericardium, and also partly in the pleura or the lungs themselves, and trigger the continued immune response (e4–e6). The hypothesis that these processes underlie postpericardiotomy syndrome is supported by studies in which a correlation was observed between the pre- and post-operative ratio of anti-actin and anti-myosin antibodies and the incidence of clinically significant postpericardiotomy syndrome (e7).

The clinical presentation of postpericardiotomy syndrome corresponds to that of acute pericarditis, so the same diagnostic criteria can be applied. Postpericardiotomy syndrome typically appears not immediately subsequent to the pericardial trauma but after a latency period of up to a few weeks, by which time the patient is no longer in the hospital but in the care of his/her primary care physician or cardiologist. The most commonly occurring symptoms are fever and pleuritic chest pain. Further investigation reveals pericardial effusions in 55 to 90% and elevated

Key messages

- Fever arises as the result of a centrally regulated process triggered by exogenous or endogenous pyrogens. These lead to alteration of the temperature set-point in the hypothalamus, which regulates mechanisms of heat production and release throughout the body; an increase in temperature ensues.
- Fever sometimes accompanies acute myocardial infarction and may be a pointer to the extent of infarction and the prognosis.
- The infectious cardiologic disease classically associated with fever is endocarditis. The Duke criteria are used to establish the diagnosis.
- Most cases of pericarditis are idiopathic or of viral origin. A body temperature > 38 °C is a warning sign that should prompt an extended diagnostic work-up and hospital admission.
- Postpericardiotomy syndrome is an antibody-triggered inflammation of the pericardium that may occur after heart surgery. Alongside secondary infections, it is a differential diagnosis when fever is observed following a cardiac operation.

inflammation parameters in 40 to 74% of patients. Pericardial friction rub and ECG changes are found in fewer cases. Despite the high frequency of pericardial effusions, hemodynamically relevant tamponades occur in only 2% of patients (e5).

Postpericardiotomy syndrome is diagnosed on the basis of the clinical presentation in a patient who has undergone pericardial manipulation. It should be noted, however, that postpericardiotomy syndrome occasionally occurs following noncardiac interventions that involve pericardial irritation (e.g., extensive pulmonary tumor resection). Moreover, the syndrome may emerge only after a latency period of up to 3 months. Repeated ECG is the best means of detecting a pericardial effusion and tracking its expansion. The ECG findings must always be correlated with the clinical situation. Pericardial effusions occur in 50 to 85% of patients after heart surgery and typically reach their greatest extent on postoperative day 10, before the resorption phase begins (e6).

The treatment of choice for suspected postpericardiotomy syndrome is nonsteroidal anti-inflammatory drugs (NSAID). Two alternative currently recommended treatment strategies are (a) administration of acetylsalicylic acid in an initial dose of 750 to 1000 mg 3 times daily and (b) administration of 600 to 800 mg ibuprofen 3 times daily, in each case with weekly dose reduction and treatment for a total of 3 to 4 weeks. In the rare cases where this is not successful, schemes involving treatment with colchicine and glucocorticoids can be considered (e8).

Postpericardiotomy syndrome has a favorable prognosis. Annual ECG is advisable because of the occasional occurrence of constrictive pericarditis.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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► **Supplementary material:**
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