The Cardio-VASCULAR System

- ○ Anatomy
- ○ Histology
- ○ Pathology
- ○ Pharmacology
- ○ Physiology
- ● Microbiology

Lec #1-Viral Endocarditis
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- ○ Handout
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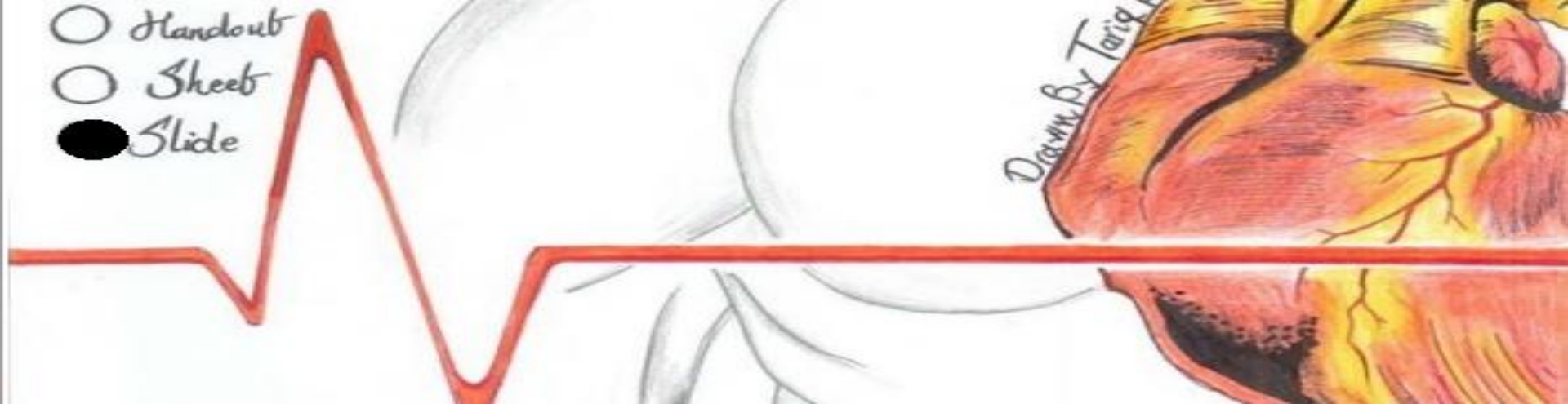

Medical Virology
Viral Carditis

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Myocarditis – Introduction

- Myocarditis is an inflammatory disorder of the myocardium with necrosis of the myocytes and associated inflammatory infiltrate.
- There are multiple etiologies including viral, bacterial, parasitic, fungal, allergic, eosinophilic, granulomatous, toxic, and post-viral immune-mediated response.
- It can be acute, subacute, or chronic, and there may be either focal or diffuse involvement of the myocardium.
- suspected myocarditis can be classified into the following 3 types based on pathologic findings as defined in the Dallas Criteria (1987).

Dallas criteria:

- **Active myocarditis:** the presence of an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease (CAD).
- **Borderline myocarditis:** the presence of an inflammatory infiltrate of the myocardium without necrosis or degeneration of adjacent myocytes.
- **Nonmyocarditis**

If an active or borderline inflammatory process is found, follow-up biopsies can be subclassified into **ongoing**, **resolving**, or **resolved myocarditi**s.

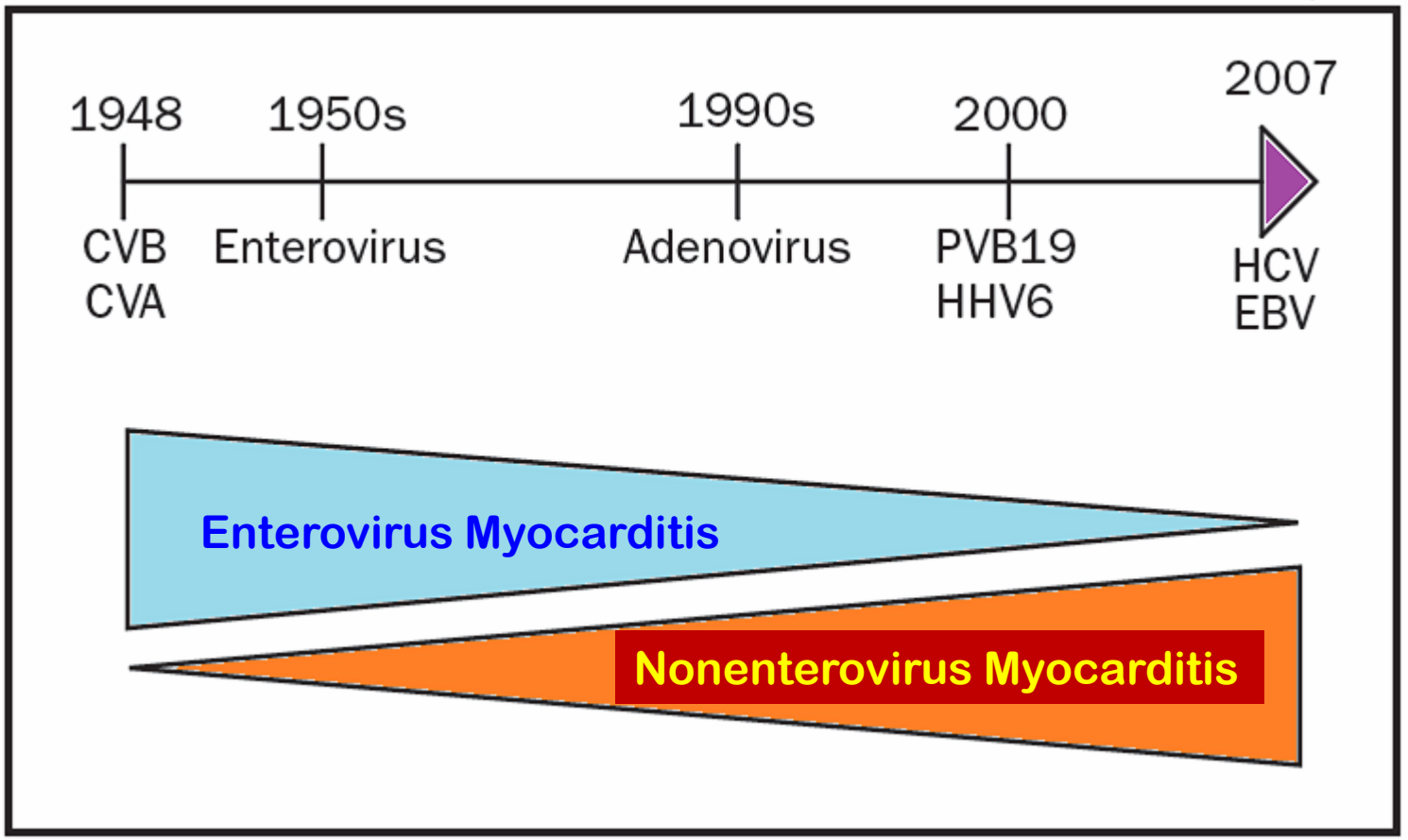
Historical Background

- Recognized as early as 1806 as a persistent inflammatory process of the myocardium following infections, such as diphtheria, that led to progressive cardiac damage and dysfunction

- In 1837, the term *myocarditis* was first introduced to describe inflammation or degeneration of the heart detected by postmortem examination.

- In 1980, Endomyocardial biopsy allowed the sampling of human myocardial tissue during life and consequently enabled antemortem diagnosis of myocarditis.

Evolution of viral causes of myocarditis over time



CVA = coxsackievirus A; CVB = coxsackievirus B; EBV = Epstein-Barr virus;
HCV = hepatitis C virus; HHV6 = human herpesvirus 6; PV-B19 = parvovirus B19.

Pathphysiology

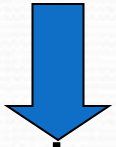
- Myocarditis generally results in a decrease in myocardial function, with concomitant enlargement of the heart and an increase in the end-diastolic volume caused by increased preload.
- Normally, the heart compensates for dilation with an increase in contractility (Starling law), but because of inflammation and muscle damage, a heart affected with myocarditis is unable to respond to the increase in volume.
- In addition, inflammatory mediators, such as cytokines and adhesion molecules, as well as apoptotic mechanisms are activated.
- The progressive increase in left ventricular end-diastolic volume increases left atrial, pulmonary venous, and arterial pressures, resulting in increasing hydrostatic forces.
- These increased forces lead to both pulmonary edema and congestive heart failure.
- Without treatment, this process may progress to end-stage cardiac failure and death.

Pathogenesis

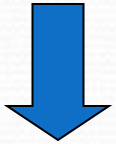
- Both direct viral-induced myocyte damage and post-viral immune inflammatory reactions contribute to myocyte damage and necrosis
- Inflammatory lesions and the necrotic process may persist for months, although the viruses only replicate in the heart for at most two or three weeks after infection
- Evidence from experimental models has incriminated cytokines such as interleukin-1 and TNF, oxygen free radicals and microvascular changes as contributory pathogenic factors

- Three phases:

Viral Infection and Replication



Autoimmunity and injury



Dilated cardiomyopathy

Phase I: Viral Infection and Replication

- Viruses like coxsackievirus B cause an infectious phase, which lasts 7-10 days, and is characterized by active viral replication

- Virus infection directly contributes to cardiac tissue destruction by cleaving the cytoskeleton protein dystrophin, leading to a disruption of the dystrophin-glycoprotein complex causing the release of antigenic intracellular components such as myosin into the bloodstream

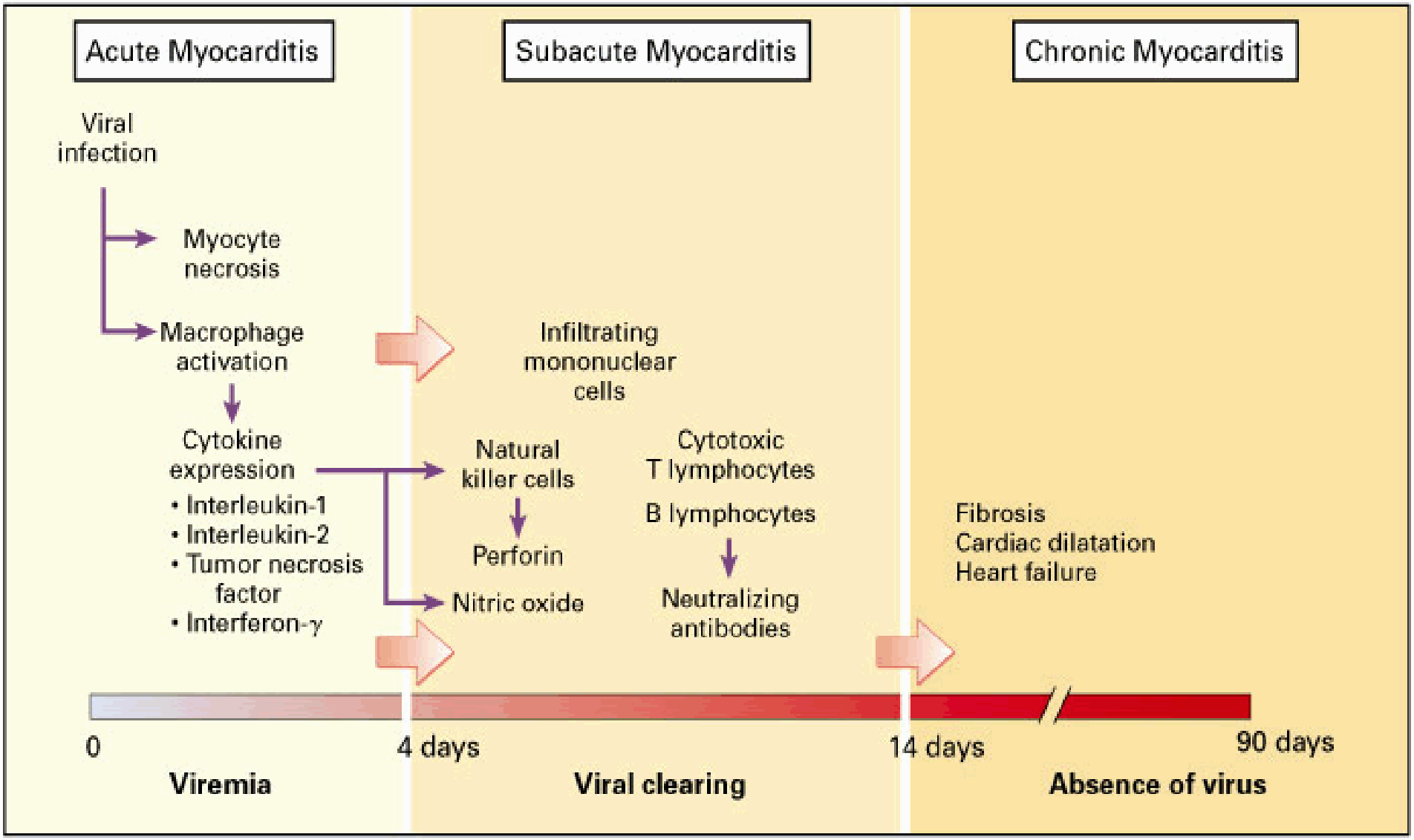
Phase II: Autoimmunity and injury

- The local release of cytokines, such as interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor (TNF), and nitric oxide may play a role in determining the T-cell reaction and the subsequent degree of autoimmune perpetuation
- These cytokines may also cause reversible depression of myocardial contractility without causing cell death.
- Immune-mediated by CD8 lymphocytes and autoantibodies against various myocyte components
- Antigenic mimicry, the cross reactivity of antibodies to both virus and myocardial proteins
- Myocyte injury may be a direct result of CD8 lymphocyte infiltration
- The cytotoxic activity against healthy cardiomyocytes was myocyte - specific, induced by $CD8^{+}$ lymphocytes and MHC restricted.

Phase III: Dilated Cardiomyopathy (DCM)

- Viruses may also directly cause myocyte apoptosis.
- During the autoimmune phase, cytokines activate the matrix metalloproteinase, such as gelatinase, collagenases, and elastases.
- In later stages of immune activation, cytokines play a leading role in adverse remodeling and progressive heart failure.
- Cardiomyopathy develops despite the absence of viral proliferation but is correlated with elevated levels of cytokines such as TNF.

Stages of Viral Myocardium Infection



Viral Causes

- Infecting organisms include the following:
  - Coxsackievirus types A and B, especially type B, are the most common viral causes of myocarditis.
  - Adenovirus (types 2 and 5 most common)
  - Cytomegalovirus
  - Echovirus
  - Epstein-Barr virus
  - Hepatitis C virus
  - Herpes Simplex virus
  - Human immunodeficiency virus
  - Influenza and parainfluenza viruses
  - Measles virus
  - Mumps, associated with endocardial fibroelastosis (EFE)
  - Parvovirus B19
  - Poliomyelitis virus
  - Rubella virus
  - Varicella -Zoster virus

Coxsackieviruses

- Coxsackie B viruses are estimated to be responsible for at least 50% of the cases of infection-caused heart diseases.
- For reasons yet unknown, the cardiac disease caused by this virus mainly occurs in middle-aged men, with onset occurring, on average, around age 42 years.
- The cardiac disease becomes apparent about two weeks after exposure to the virus.

Coxsackie Virus Clinical Manifestations

- The early symptoms of the coxsackie -induced cardiac myopathy include some generalized viral symptoms-fever, fatigue, malaise-with the addition of chest pain.
- As the virus enters the heart cells, the immune system attacks and damages both infected and normal heart cells; the affected individual feels severe fatigue when there is significant impairment of heart function.
- In most cases, the disease is resolved spontaneously without any treatment, though some permanent heart damage may have occurred
- In about 20% of the cases, there can be progressive disease or recurrence of symptoms; the heart damage can be extensive, causing arrhythmias, weakened left ventricular functions, and, in the worst cases, heart failure requiring heart transplantation.

- In these severe cases, cardiac disease progression persists after the virus is long gone; the immune system continues to damage the heart.
- Heart failure: This is the most common presenting picture in all ages.
- Chest pain: Although rare in young children, this may be the initial presentation for older children, adolescents, and adults.
- Chest pain may be due to myocardial ischemia or concurrent pericarditis.
- Arrhythmia

Laboratory Diagnosis

- Complete blood count with differential
  - Acute anemia of any origin may cause heart failure, and chronic anemia exacerbates heart failure; both respond to blood transfusion.
  - The presence of lymphocytosis or neutropenia supports diagnosis of a viral infection.
- Blood culture: It is important to rule out any bacterial infection
- Viral culture: Nasopharyngeal and rectal swabs may help identify etiology.
- Viral Serology: A 4-fold increase in a specific titer from the acute to convalescent phase is strong evidence of infection.
- Molecular Tests:
  - In situ hybridization
  - Polymerase chain reaction (PCR)

Enzyme Biomarkers:

- Elevated secondary to myocardial damage from inflammatory cell infiltrates, cytokine activation and virus-mediated cell death.
- More useful when high sensitivity thresholds are used
- Troponin T threshold of >0.1ng/mL increases sensitivity from 34% to 53% and a specificity of 94%
- Cardiac biomarkers i.e. creatine kinase and troponin T and I (elvated in around 40%) are routinely measured
- CKMB is not useful - too insensitive (overall 8%).
- ESR found to have low sensitivity and specificity.

Treatments/Therapeutic Approaches

- Supportive therapy
- Immunosuppression
- Interferon
- Intravenous immunoglobulin
- Immune adsorption
- Immune modulation
- Vaccination

Prognosis

- Acute myocarditis and mild cardiac involvement generally will recover in the majority of cases without long-term sequelae, Granulomatous necrotizing myocarditis is lethal if overlooked and untreated.
- Nonfulminant active myocarditis has a mortality rate of 25% to56% within 3 to 10 years.
- Myocarditis Treatment Trial, still have a relatively poor prognosis. These patients all had the diagnosis of myocarditis based on the Dallas biopsy criteria and showed a mortality of 20% at 1 year and 56% at 4.3 years, with many cases of chronic heart failure despite OMT.

Epidemiology

- No racial predilection exists.
- No sex predilection exists in humans, but there is some indication in laboratory animals that the disease may be more aggressive in males than in females.
- Certain strains of female mice had a reduced inflammatory process when treated with estradiol.
- In other studies, testosterone appeared to increase cytolytic activity of T lymphocytes in male mice.
- No age predilection exists.
- Younger patients, especially newborns and infants, and immunocompromised patients may be more susceptible to myocarditis.

Mortality/Morbidity

- With suspected coxsackievirus B, the mortality rate is higher in newborns (75%) than in older infants and children (10-25%).
- Complete recovery of ventricular function has been reported in as many as 50% of patients.
- Some patients develop chronic myocarditis (ongoing or resolving) and/or dilated cardiomyopathy and may eventually require cardiac transplantation.

Prevention

- As a result of the widespread use of vaccination in developed countries, myocarditis secondary to measles, rubella, mumps, poliomyelitis, and influenza is now rare
- Similarly, the elimination of trichinosis by meat inspection has eliminated this infection
- It is possible that vaccines against other cardiotropic viruses may prevent viral myocarditis

Other Rare Causes of Heart Infection

- **Bacterial Causes**
  - **Diphtheria** - Myocarditis
  - **Psittacosis** (*Chlamydia psittaci)* - Endocarditis
  - **Q fever** (*Coxiella burnetii)* - Pericarditis, myocarditis, and endocarditis. Endocarditis is frequently associated with purpuric rash, renal insufficiency, stroke, and heart failure.
  - **Typhus** (*Rickettsia spp)* - Myocarditis
- **Parasitic Causes**
  - **Chagas' Disease** (*Trypanosoma cruzi*) - Myocarditis
  - **Trichinosis** (*Trichinella spiralis)* – Myocarditis
  - **Amebiasis** (*Entameba histolytica*) - Pericarditis
  - **Trypanosomiasis** (*Trypanosoma brucei rhodesiense* or *T b gambiense)* - Myocarditis