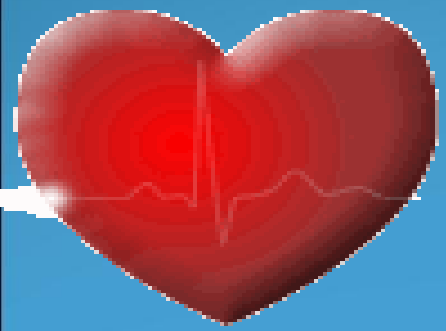
MYOCARDITIS



MYOCARDITIS

- Myocarditis is collection of diseases of infectious, toxic, and autoimmune etiologies characterized by inflammation of the heart.
- Subsequent myocardial destruction can lead to dilated cardiomyopathy.

Dallas Classification (1987)

Initial Biopsy

- Myocarditis: Myocardial necrosis, degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrate with or without fibrosis.
- Borderline myocarditis: Inflammatory infiltrate too sparse or myocyte damage not apparent.
- No myocarditis
- **Subsequent Biopsies**
- Ongoing (persistent) myocarditis with or without fibrosis.
- Resolving (healing) myocarditis with or without fibrosis.
- Resolved (healed) myocarditis with or without fibrosis.

CAUSES

- Amongst the infectious causes, viral acute myocarditis is by far the most common.
  - Identification of the coxsackie-adenovirus
  - Other viruses implicated in myocarditis include influenza virus, echovirus, herpes simplex virus, varicella-zoster virus, hepatitis, Epstein-Barr virus, and cytomegalovirus.
  - Human immunodeficiency virus (HIV)

CAUSES

- Nonviral infectious causes are numerous and varied.
- Bacteria: chlamydia (*C. pneumonia*/psittacosis) haemophilus influence, legionella, pneumophilia, brucella clostridium, francisella tularensis, neisseria meningitis, mycobacterium (tuberculosis), salmonella, staphylococcus, streptococcus A, S. pneumonia, tularemia, tetanus, syphilis, *Vibrio cholera*
- Spirocheta: *Borrelia recurrentis*, leptospira, *Treponema pallidum*
- Reckettsia: *Coxiella burnetii*, *R. rickettsii*/*prowazekii*
- Protozoa: *Entamoeba histolytica*, leishmania, *Plasmodium falciparum*,*Trypanosoma cruzi*, *Trypanosoma brucei*, *Toxoplasma gondii*
- Helmintic: ascaris, *Echinococcus granulosus*, Schistosoma, *Trichinella spiralis*,*Wuchereria bancrofti*

CAUSES

- Toxic myocarditis has a number of etiologies including both medical agents and environmental agents.
  - Numerous medications (eg, lithium, doxorubicin, cocaine, numerous catecholamines, acetaminophen)
  - Among the most common drugs that cause hypersensitivity reactions are penicillin, ampicillin, hydrochlorothiazide, methyldopa, and sulfonamide drugs.

CAUSES

- Environmental toxins include lead, arsenic, and carbon monoxide.
- Wasp, scorpion, and spider stings
- Radiation therapy may cause a myocarditis with the development of a dilated cardiomyopathy.

CAUSES

- Immunologic etiologies of myocarditis encompass a number of clinical syndromes and include the following:
  - Connective tissue disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and dermatomyositis.
- Rejection of the post-transplant heart may present as inflammatory myocarditis.

PATHOPHYSIOLOGY

Several mechanisms of myocardial damage

(1) Direct injury of myocytes by the infectious agent

(2) Myocyte injury caused by a toxin such as that from *Corynebacterium diphtheriae*

(3) Myocyte injury as a result of infection-induced immune reaction or autoimmunity

Pathophysiology

Triphasic disease process

- Acute Phase: Characterized by direct infiltration of cardiotropic virus into myocytes. There is no histological evidence of myocarditis at this point.
- Subacute Phase: Host attempts to clear the virus. Natural Killer cells, Macrophages, and Lymphoctes infiltrate infected heart tissue. Thee is subsequent proginflammatory cytokine release, NO production, antibody secretion, and upregulation of MHC
- Chronic Myocarditis: Dilated heart with evidence of fibrrosis

Phase I: Viral Infection and Replication

Phase 2: Autoimmunity and injury

Phase 3: Dilated Cardiomyopathy

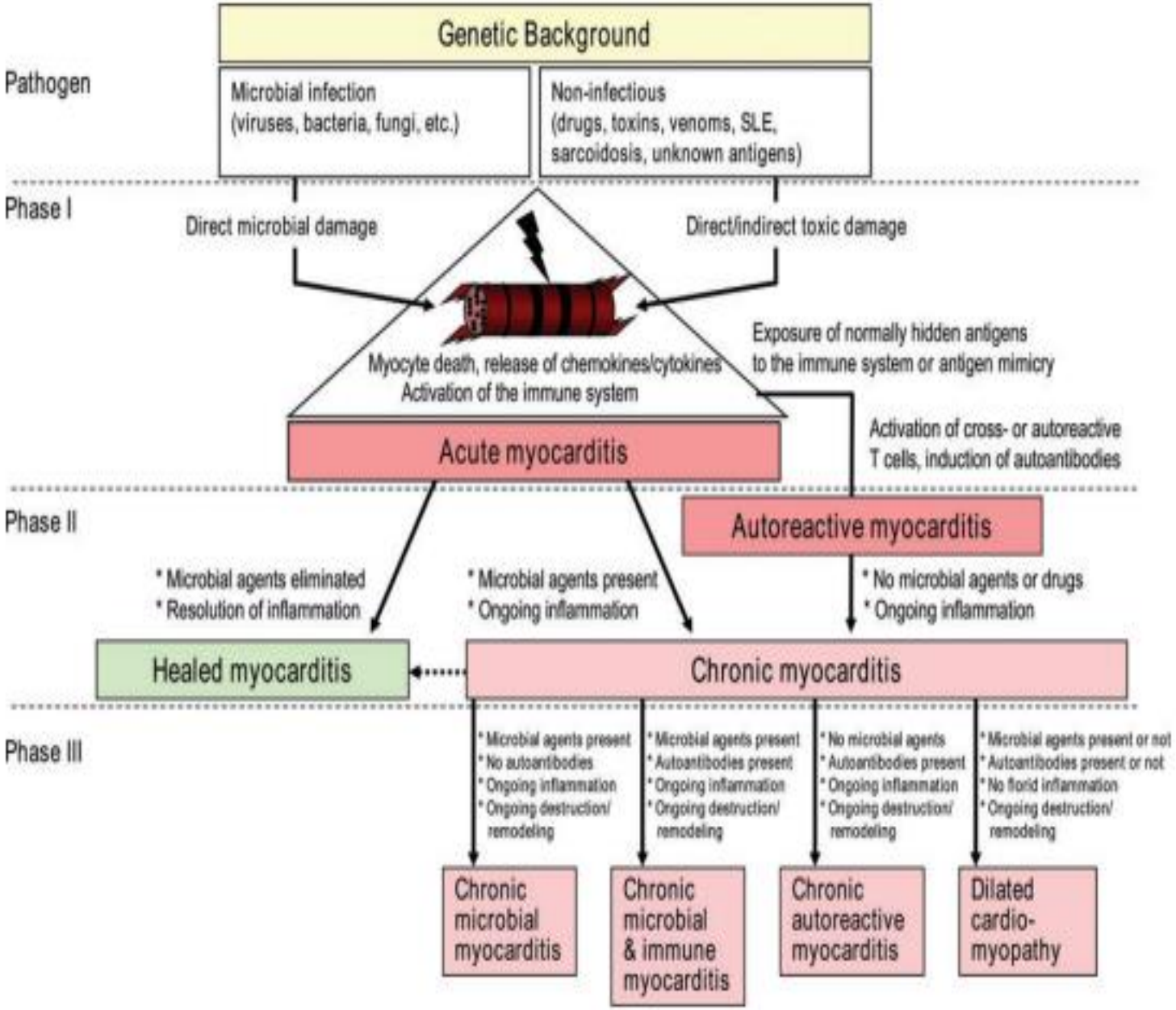
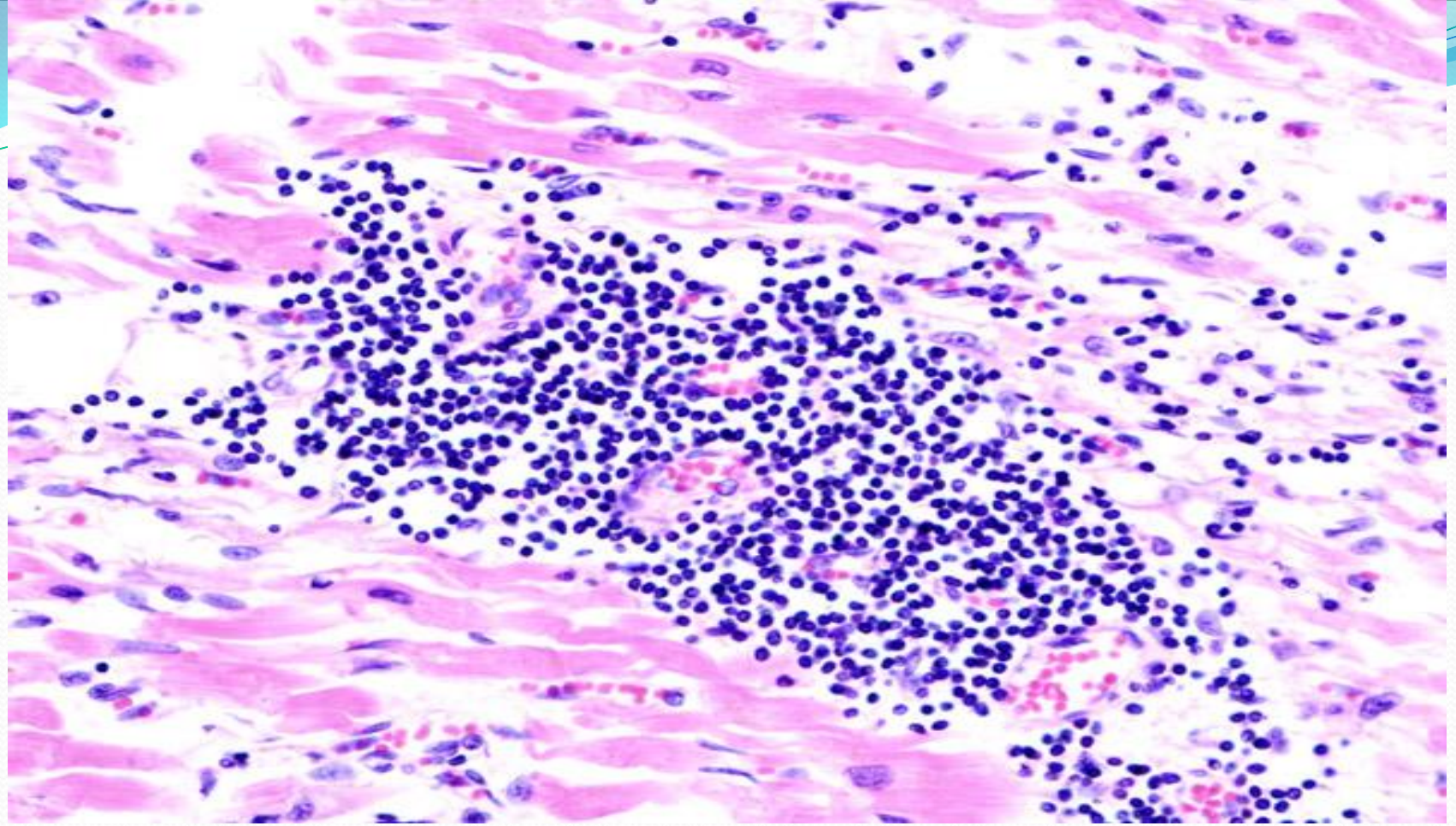


Figure 2 The picture shows the pathogenetic mechanisms involved in myocarditis and progression to dilated cardiomyopathy.



Histopathological image of viral myocarditis at autopsy in a patient with acute onset of congestive heart failure. Viral etiology, however, failed to be determined in postmortem serological study.

Symptoms and Signs

- Patients(59%) frequently present days to weeks after an acute febrile illness, particularly a flu-like syndrome

- Myocarditis is most commonly asymptomatic, with no evidence of left ventricular dysfunction
  - fever, malaise, fatigue, arthralgias, myalgias, and skin rash.

  -Cardiac symptoms may result from systolic or diastolic left ventricular dysfunction or from tachyarrhythmias or bradyarrhythmias (dyspnea, fatigue, decreased exercise tolerance, palpitations)

Table 3 **Clinical presentations of patients with biopsy-proven inflammatory heart muscle disease**

(1) Acute coronary syndrome-like
- (a) Acute chest pain
  - Frequently starting within 1–4 weeks of a respiratory or gastrointestinal infection
  - Frequently associated with severe and recurrent symptoms
  - In the absence of angiographic evidence of CAD
- (b) ST/T wave changes
  - ST-segment elevation or depression
  - T-wave inversions
- (c) With or without normal global or regional LV and/or RV dysfunction on echocardiography or CMR
- (d) With or without increased TnT/TnI that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months

(2) New onset or worsening heart failure in the absence of CAD and known causes of heart failure
- (a) New onset or progressive heart failure over 2 weeks to 3 months
  - Dyspnoea
  - Peripheral oedema
  - Chest discomfort
  - Fatigue
- (b) Impaired systolic LV and/or RV function, with or without an increase in wall thickness, with or without dilated LV and/or RV on echocardiography or CMR
- (c) Symptoms possibly started after a respiratory or gastrointestinal infection, or in the peri-partum period
- (d) Non-specific ECG signs, bundle branch block, AV-block, and/or ventricular arrhythmias

(3) Chronic heart failure in the absence of CAD and known causes of heart failure (see point 2 above)
- (a) Heart failure symptoms (with recurrent exacerbations) of >3 months duration
- (b) Fatigue, palpitation, dyspnoea, atypical chest pain, arrhythmia in an ambulant patient
- (c) Impaired systolic LV and/or RV function on echocardiography or CMR suggestive of DCM or non-ischaemic cardiomyopathy
- (d) Non-specific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block

(4) 'life-threatening condition', in the absence of CAD and known causes of heart failure comprising
- (a) Life-threatening arrhythmias and aborted sudden death
- (b) Cardiogenic shock
- (c) Severely impaired LV function

Symptoms and Signs

- In cases where a dilated cardiomyopathy has developed, signs of peripheral or pulmonary thromboembolism may be found.
- Diffuse inflammation may develop leading to pericardial effusion, without tamponade, and pericardial and pleural friction rub as the inflammatory process involves surrounding structures.

Clinical Findings

- Physical Examination
  -Tachycardia, hypotension, fever and tachycardia may be disproportionate to the degree of fever

- -Bradycardia is seen rarely, and a narrow pulse pressure is occasionally detected

- -Murmurs of mitral or tricuspid regurgitation are common , S3 and S4 gallops may also be heard.

- -Distended neck veins, pulmonary rales, wheezes, gallops, and peripheral edema may be detected

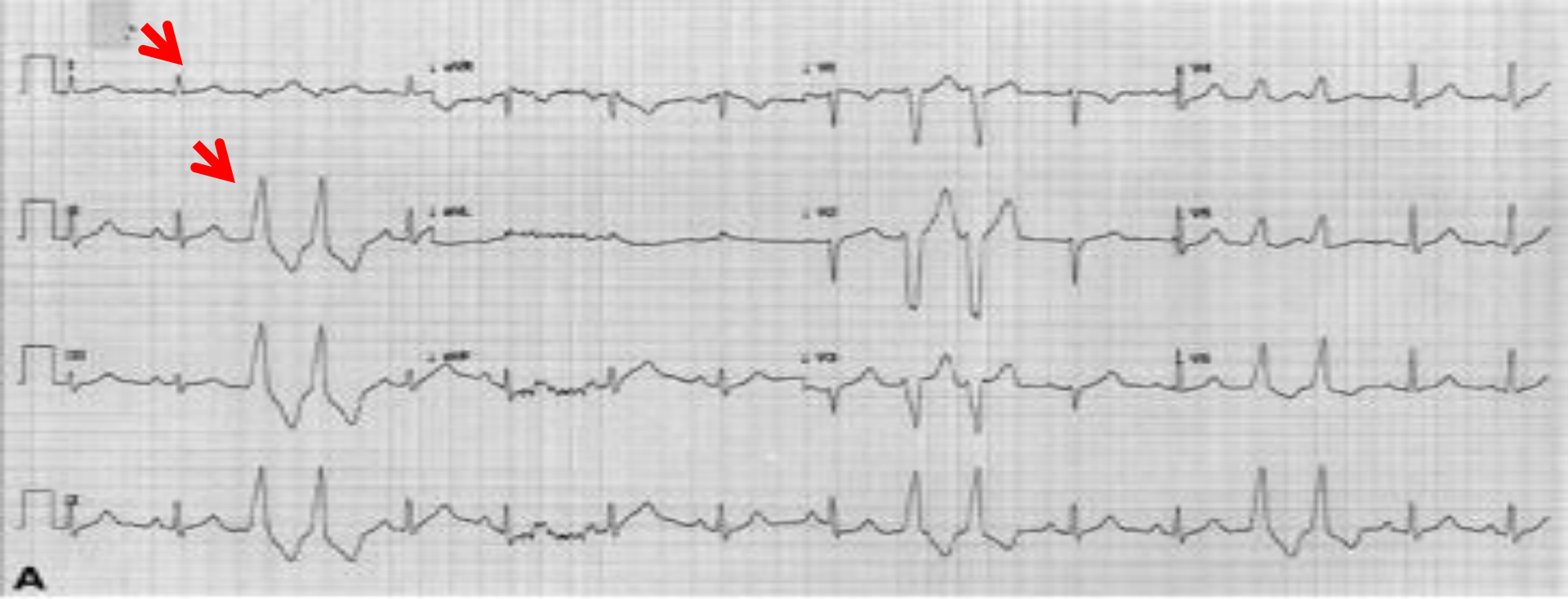
Diagnostic Studies

Electrocardiography

-The most common abnormality is sinus tachycardia.

- may show ventricular arrhythmias or heart block, or it may mimic the findings in acute myocardial infarction or pericarditis with ST segment elevation, ST segment depression, PR segment depression, and pathological Q-waves

-Relations between these clinical and laboratory findings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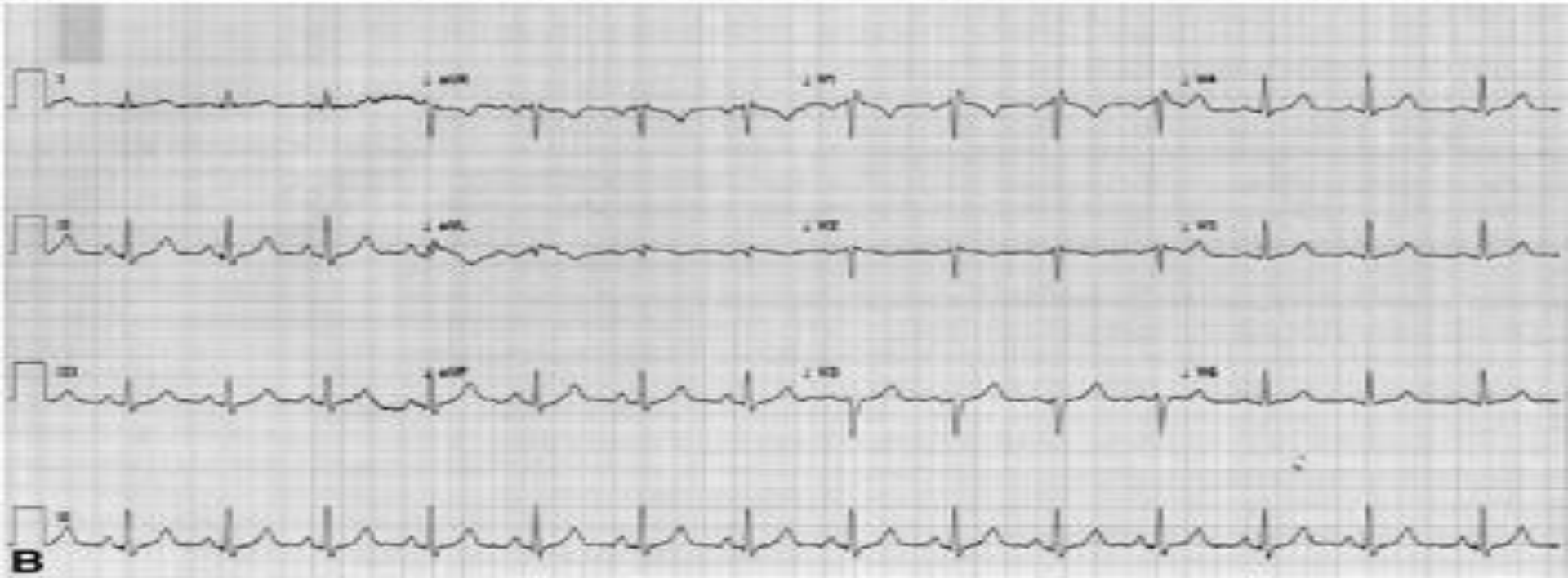
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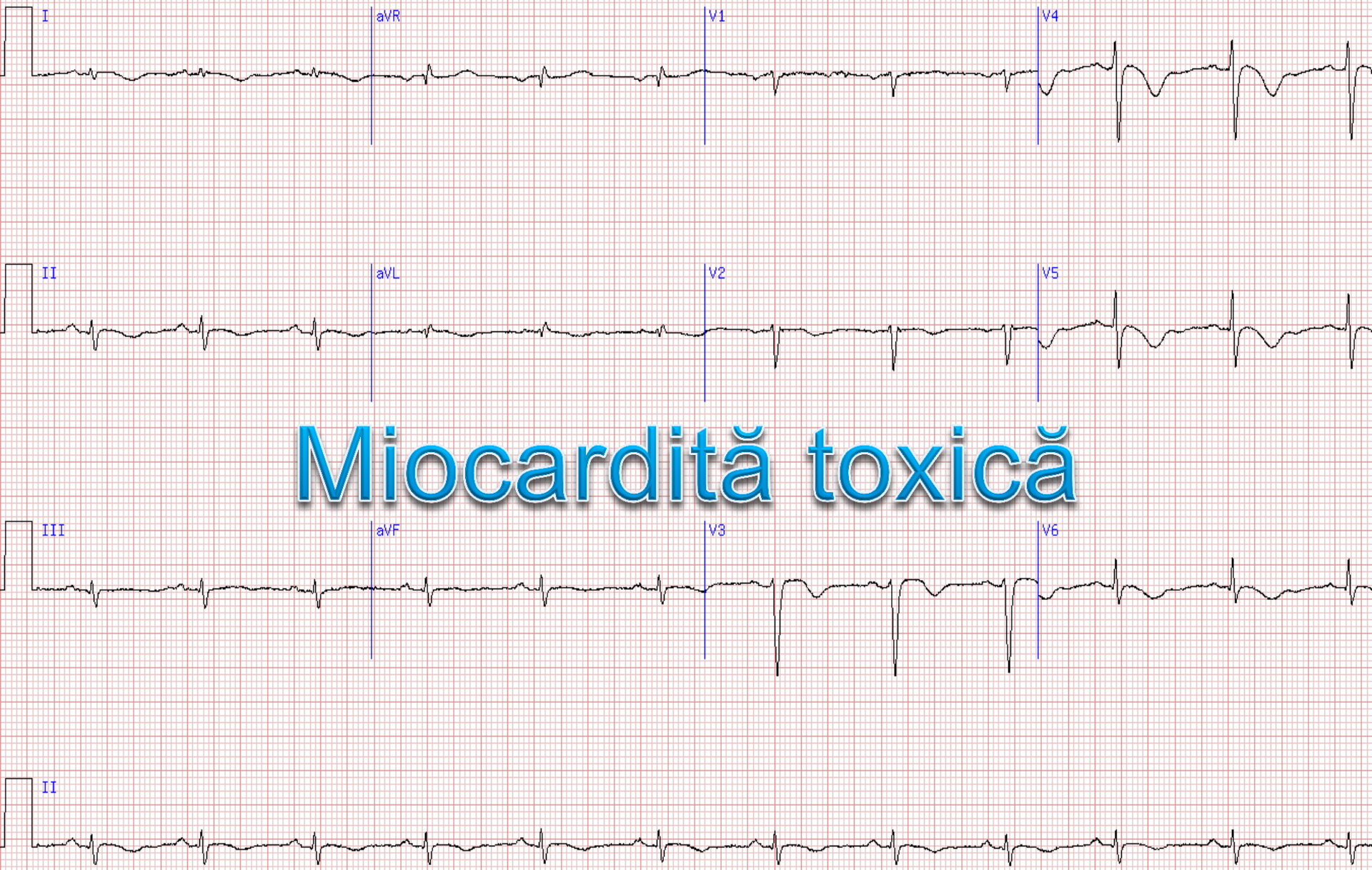
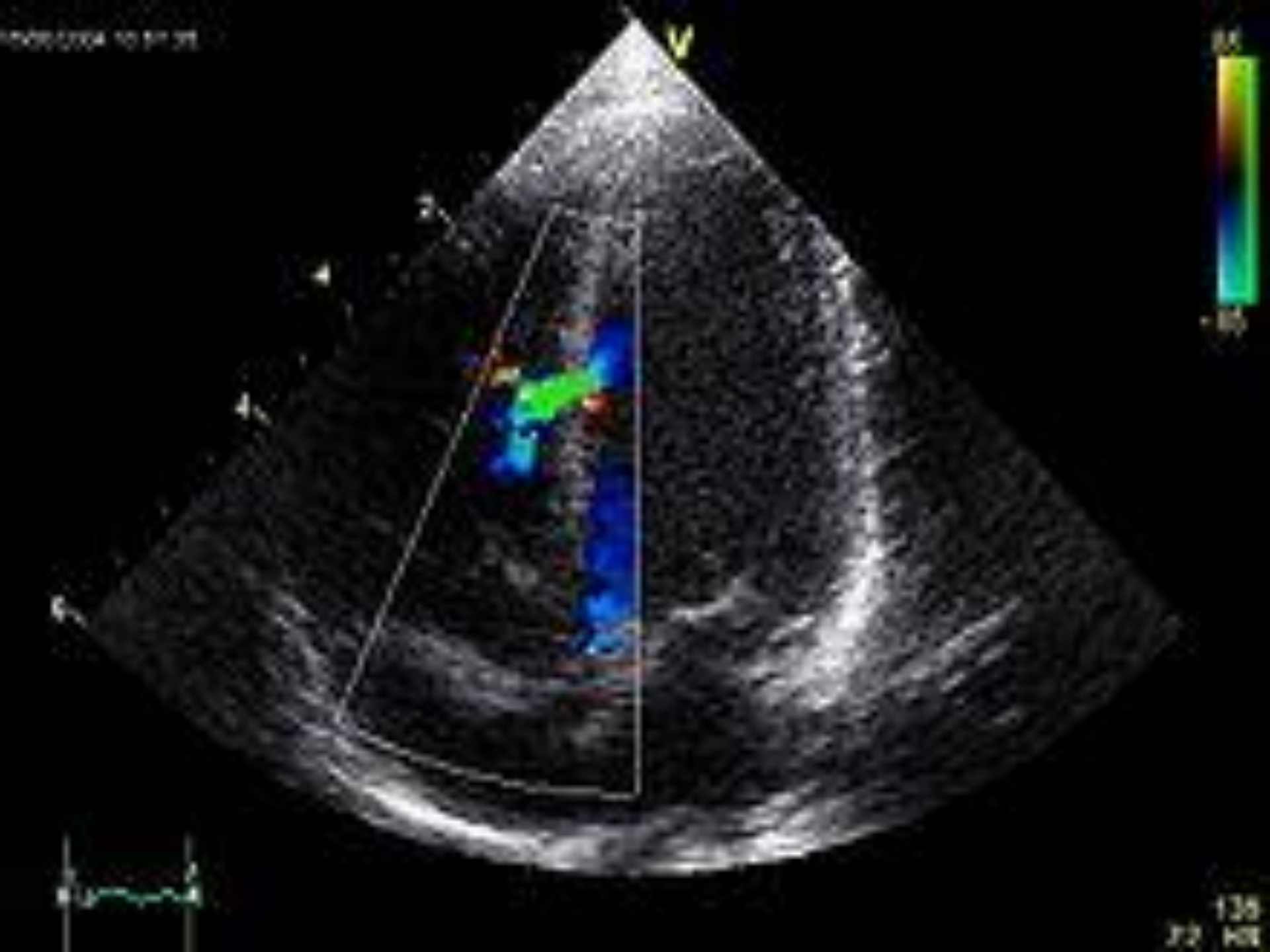


Miocardită toxică

Diagnostic Studies

- Echocardiography - to exclude other causes of heart failure and identify ventricular thrombi.
- There are no specific echocardiographic features of myocarditis.
- Segmental or global wall motion abnormalities can mimic myocardial infarction.
- Patients with fulminant myocarditis tend to present with more normal cardiac chamber dimensions and thickened walls, compared with patients with less acute myocarditis who have greater left ventricular dilation and normal wall thickness.
- Right ventricular dysfunction is an uncommon but important predictor of death or cardiac transplantation.



IMAGING STUDIES

- Chest radiography
- MRI is capable of showing abnormal signal intensity in the affected myocardium.

Table 5 Diagnostic cardiac magnetic resonance criteria for myocarditis

In the setting of clinically suspected myocarditis (*Tables 3–4*), CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:

(1) Regional or global myocardial signal intensity increase in T2-weighted oedema images[a]
(2) Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images[b]
(3) There is at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement)[c]

A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present

A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if

- None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation
- One of the criteria is present

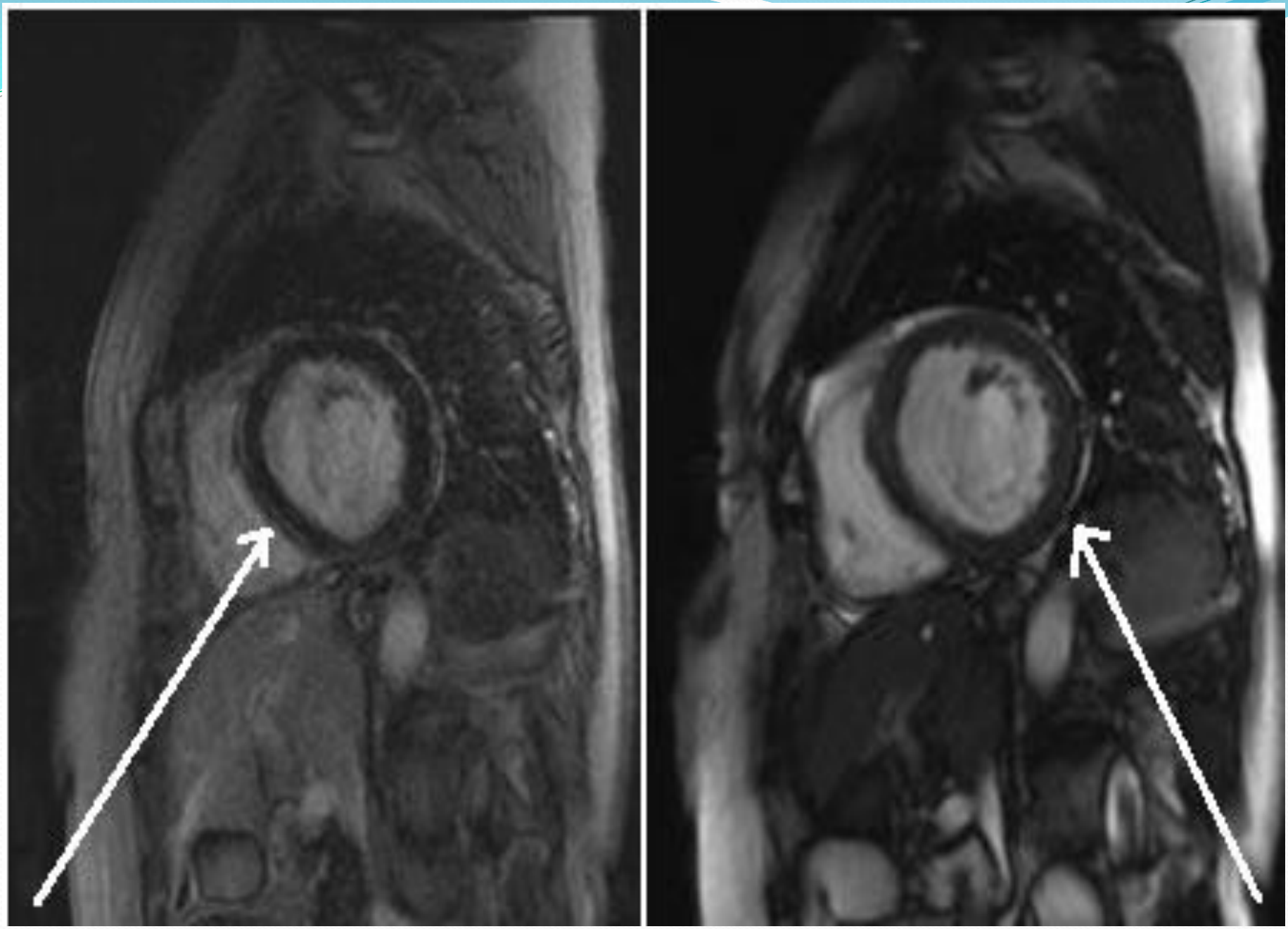
The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis

Table reprinted with permission from (20).

[a]Global signal intensity (SI) increase has to be quantified by an SI ratio of myocardium over skeletal muscle of ≥ 2.0. If the edema is more subendocardial or transmural in combination with a colocalized ischaemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported.

[b]A global SI enhancement ratio of myocardium over skeletal muscle of ≥ 4.0 or an absolute myocardial enhancement of $\geq 45\%$ is consistent with myocarditis.

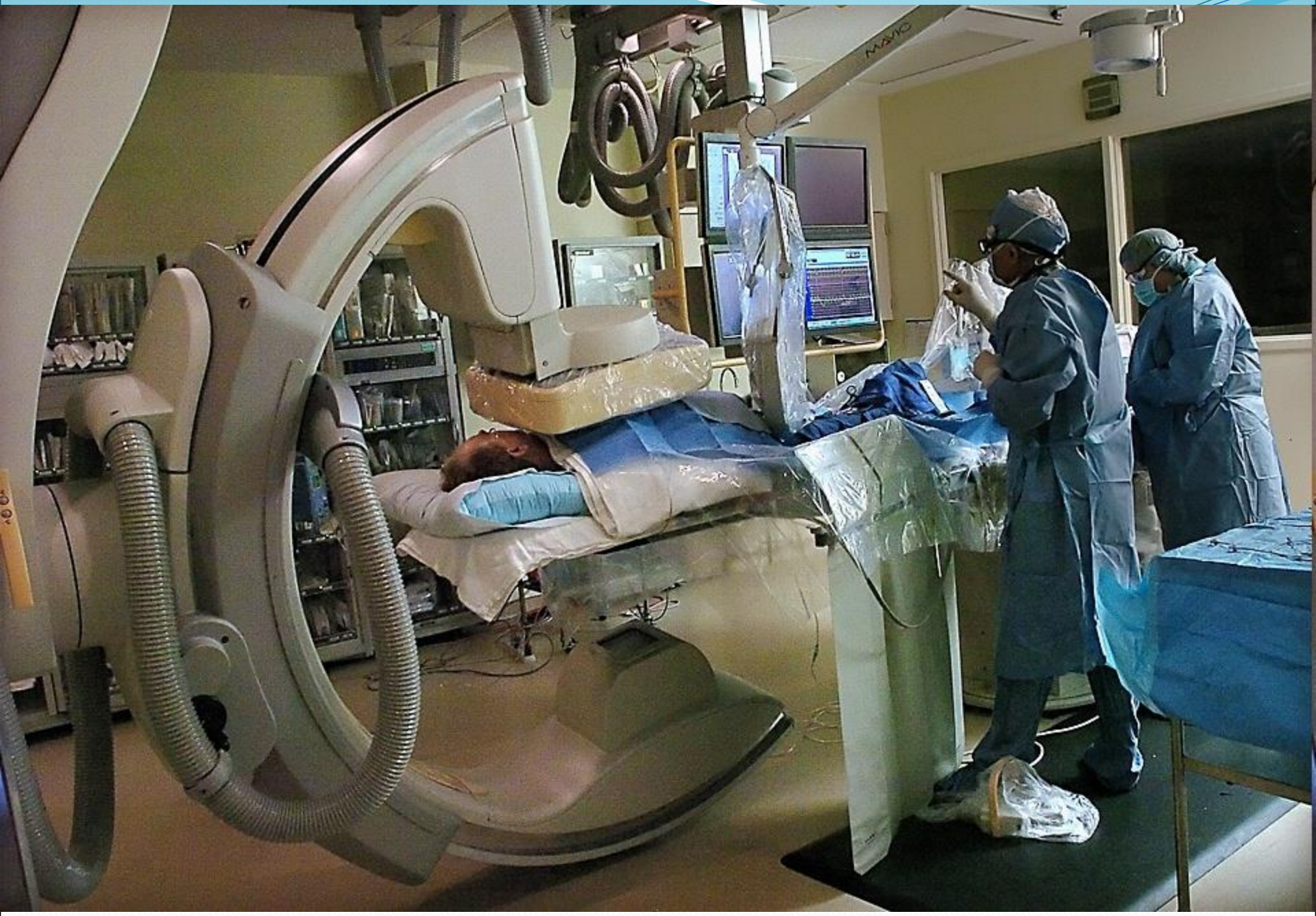
[c]Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is colocalized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.



Cardiac catheterization

-elevated left ventricular end-diastolic pressure, a depressed cardiac output, and increased ventricular volumes

-Coronary angiogram typically demonstrates normal coronary arteries.



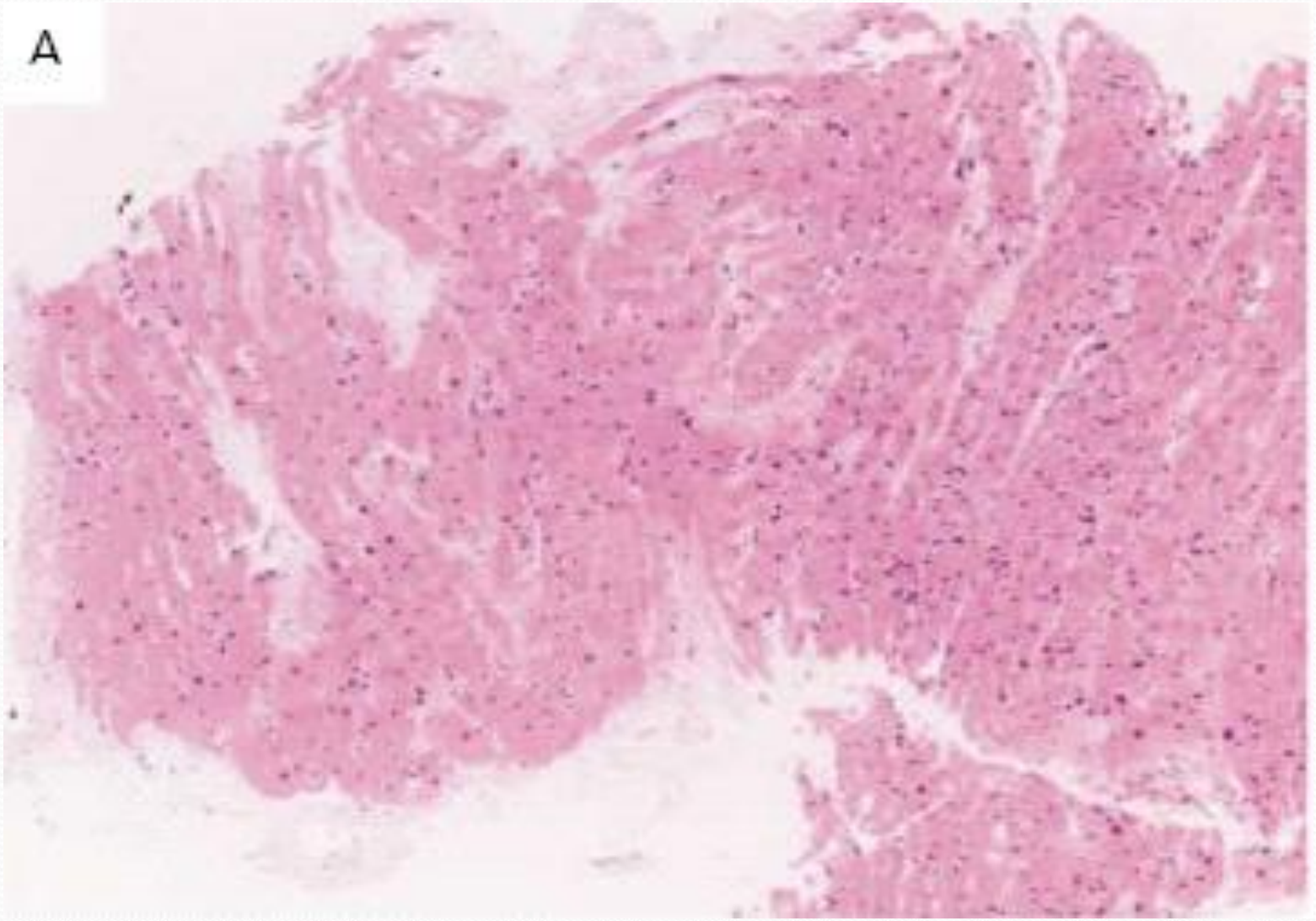
Endomyocardial biopsy

- gold standard for the diagnosis of myocarditis

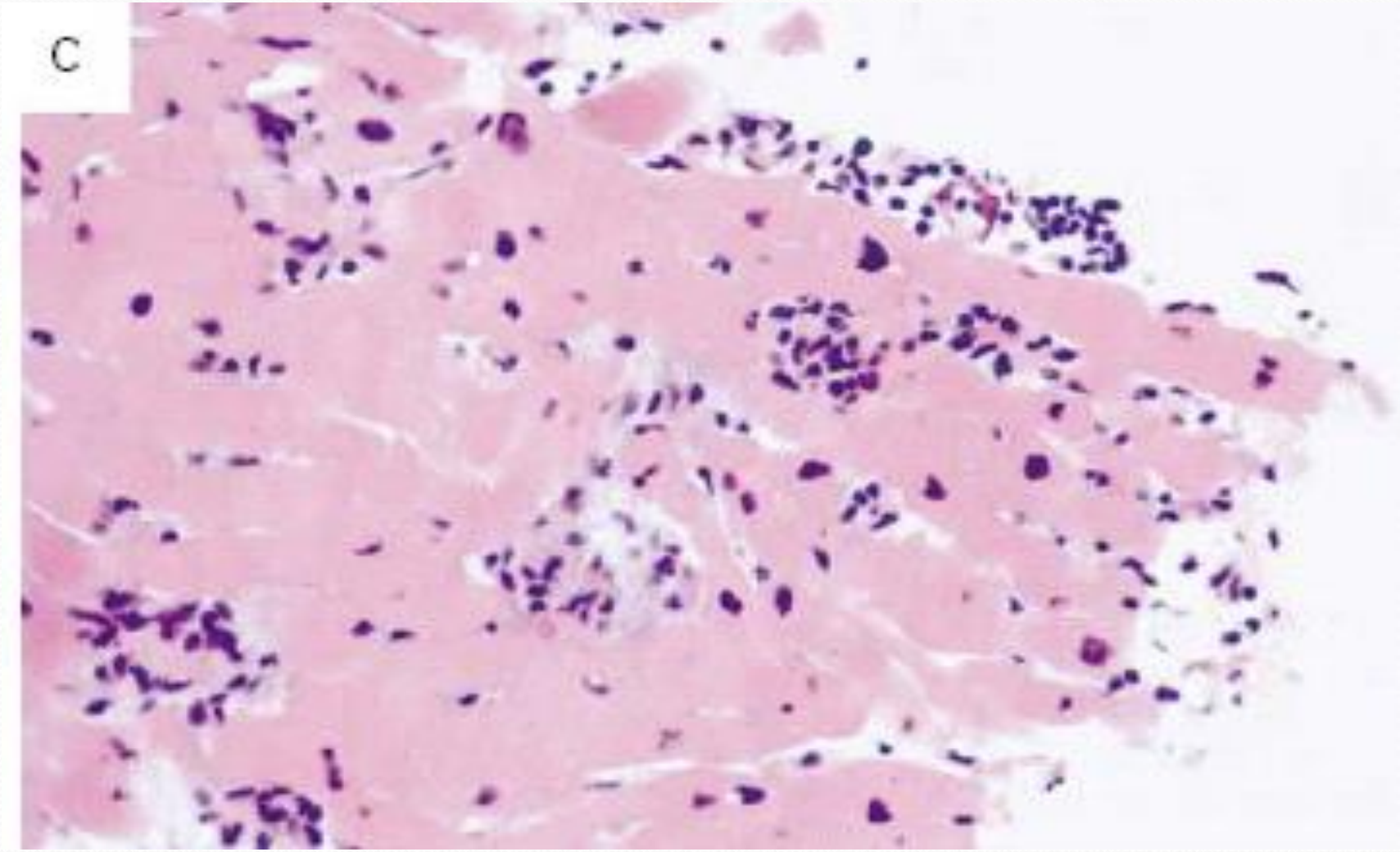
-Dallas criteria (an inflammatory infiltrate of the myocardium +injury to the adjacent myocytes)

-borderline myocarditis is made when the infiltrate is not accompanied by myocyte injury

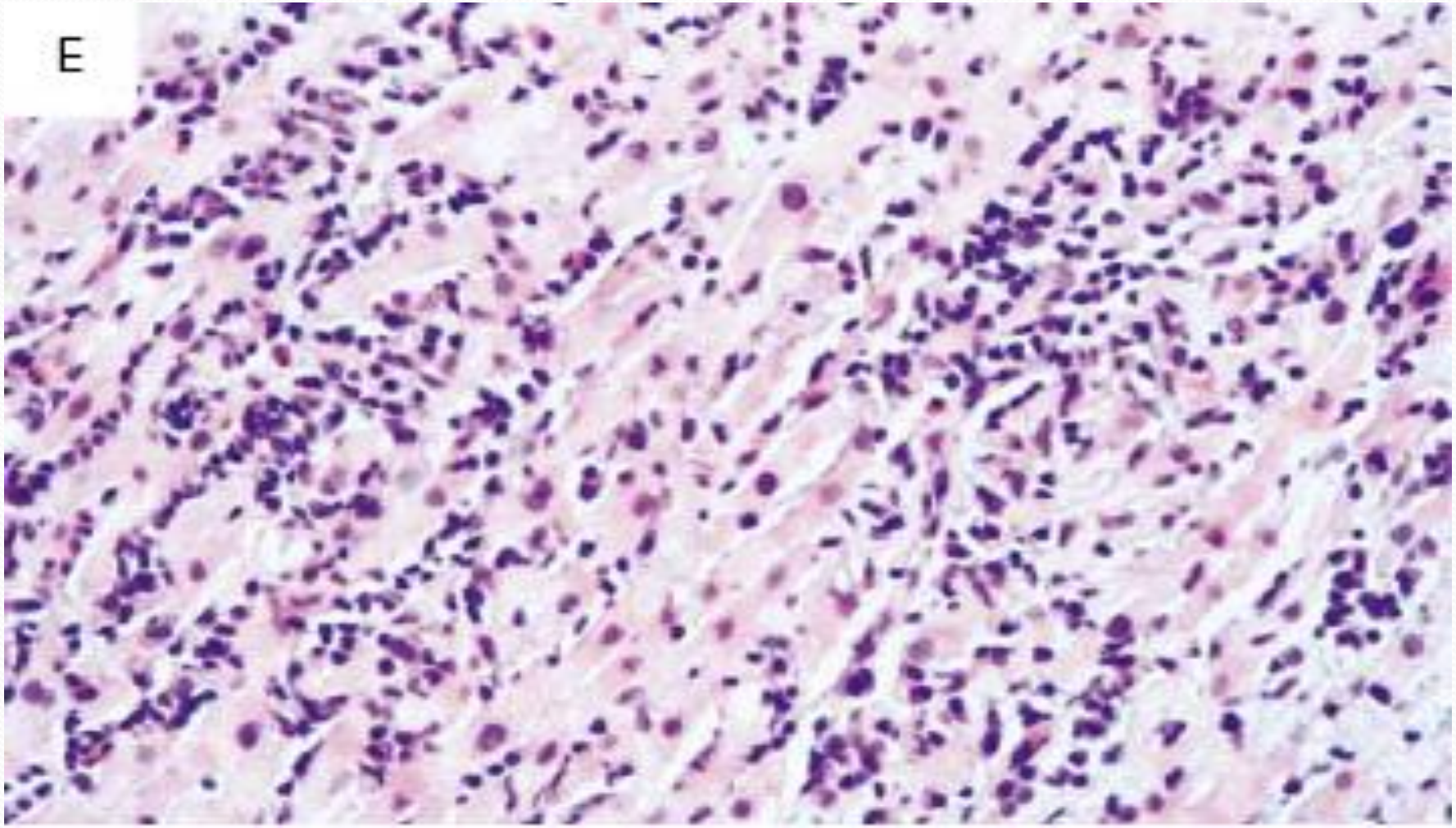
Normal Myocardium



Borderline Myocarditis



Active Myocarditis



LABORATORY STUDIES

- Cardiac troponin I may be more sensitive because it is present for longer periods after myocardial damage from any cause.
- Erythrocyte sedimentation rate (ESR) is elevated in 60% of patients with acute myocarditis.
- Leukocytosis is present in 25% of cases.

OTHER TESTS

- If a systemic disorder (eg, SLE) is suspected, antinuclear antibody (ANA) and other collagen vascular disorder laboratory investigations may be useful.

Table 4 Diagnostic criteria for clinically suspected myocarditis

Clinical presentations[a]
Acute chest pain, pericarditic, or pseudo-ischaemic
New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Subacute/chronic (>3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
Unexplained cardiogenic shock
Diagnostic criteria
I. ECG/Holter/stress test features
Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia
II. Myocardiocytolysis markers
Elevated TnT/TnI
III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)
New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
IV. Tissue characterization by CMR
Oedema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.

Differential diagnosis

- Dilative cardiomyopathy
- Secondary cardiomyopathy
- Electrolyte disturbance

Non-pharmacological treatment

- Bed rest
- Reducing salt and liquids intake
- No training for athletes – 6 months

Therapeutic options

- treatment of heart failure
- treatment of arrhythmias
- treatment of conduction abnormalities – heart blocks

Therapeutic options

- Intravenous gamma - globulin in children
- Antibiotics in bacterial myocarditis
- Anti-lymphocyte monoclonal antibodies
- Alfa and beta interferon (positive viral PCR reaction)
- Immunosupresion in giant cell myocarditis and autoimmune myocarditis
- Glucocorticoids and azathioprine – debatable (negative viral PCR reaction)
- NSAIDs are contraindicated in the ACUTE PHASE (increase cardiomyocyte lesion and necrosis).

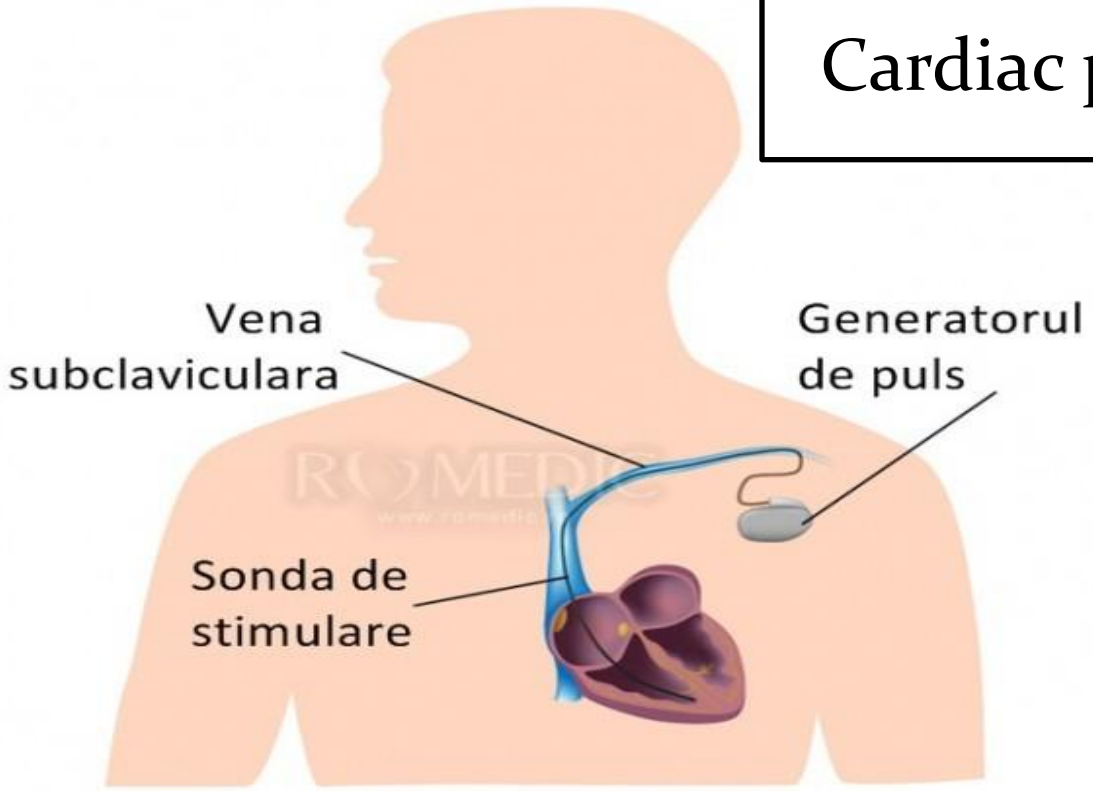
Treatment of heart failure

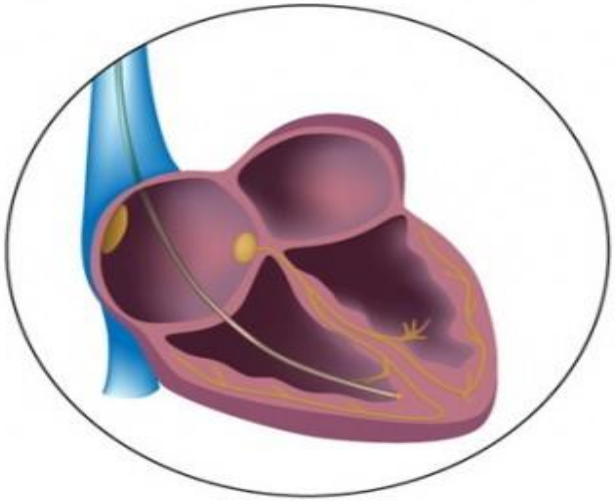
- Vasodilators (nitroglycerin, sodium nitroprusside)
- Angiotensin II converting enzyme inhibitors (enalapril, lisinopril, ramipril) or angiotensin II receptor blockers (valsartan, losartan, candesartan)
- Loop diuretics (furosemide, torasemide)
- Mineralocorticoid receptor antagonists (spironolactone, eplerenone)
- Beta-blockers (metoprolol succinate, bisoprolol, nebivolol, carvedilol)
- Drugs with positive inotropic effect (dobutamine, milrinone)

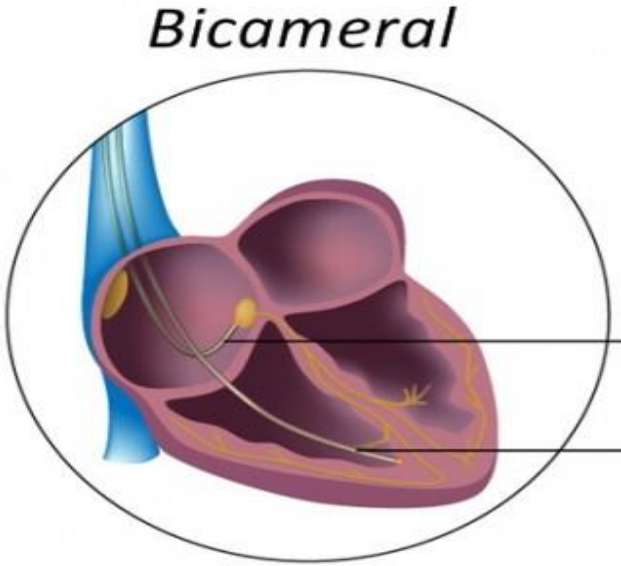
Surgical treatment in Myocarditis

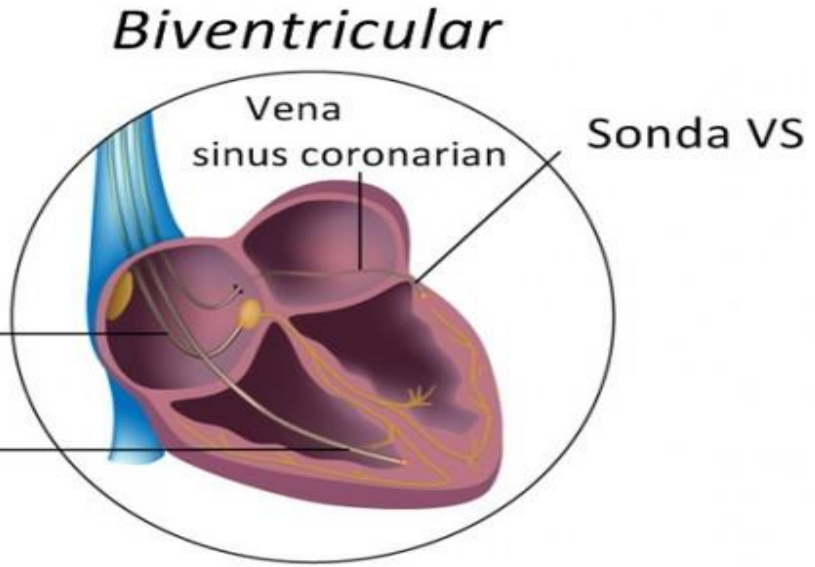
- Implantation of pacemaker in patients with complete heart block
- Cardiac transplantation
- Left ventricular assist devices

Cardiac pacemaker implantation

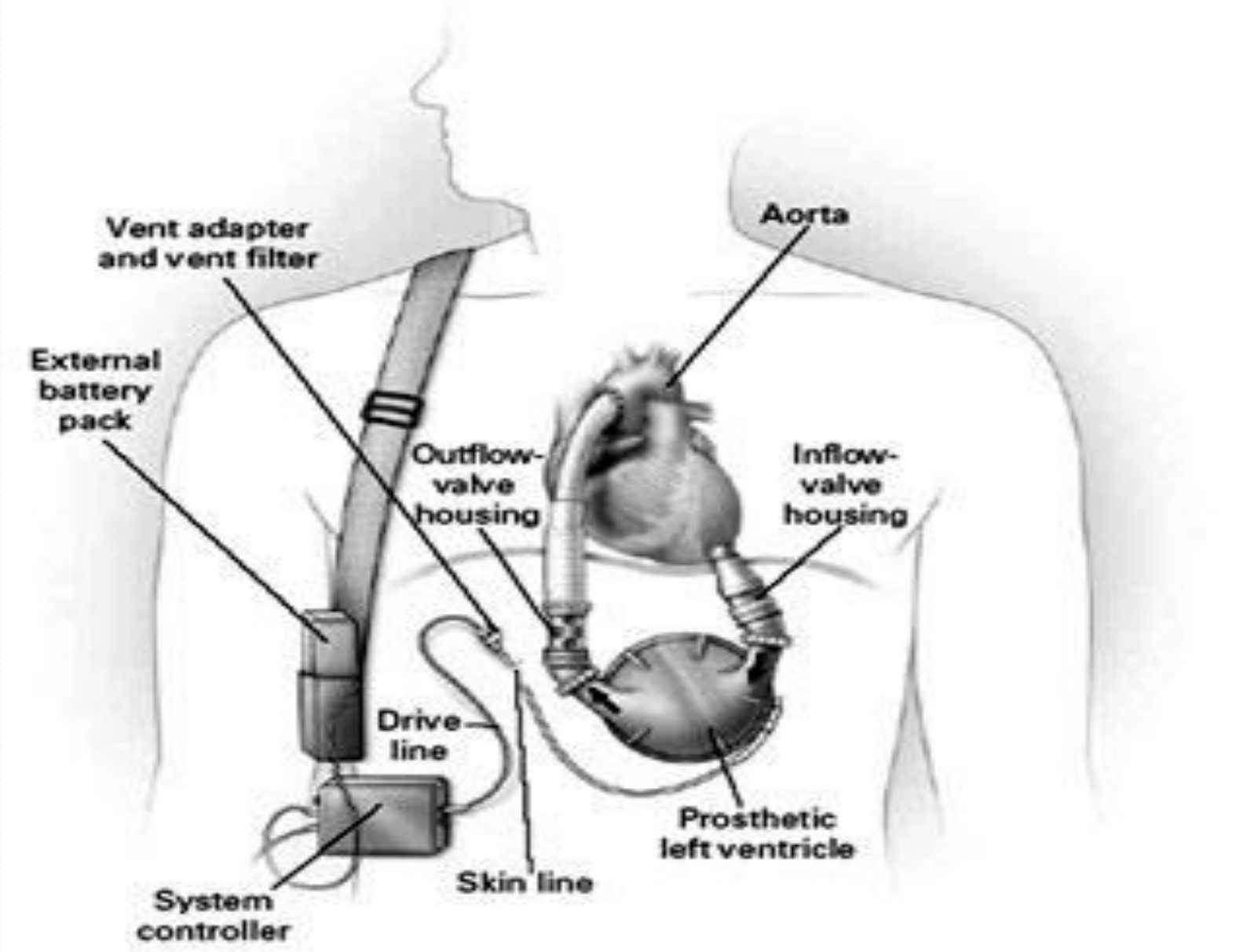








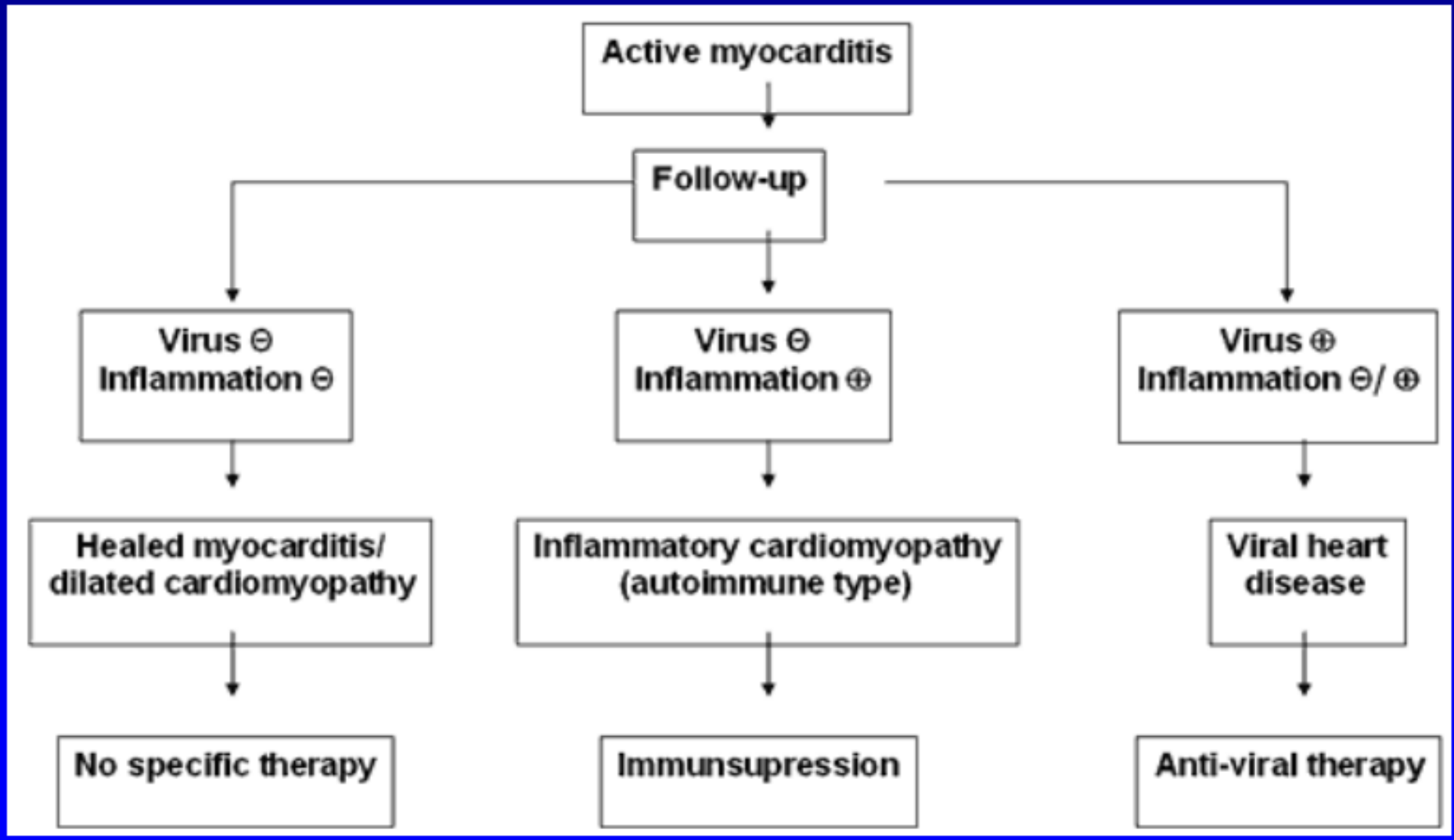
Left ventricular assist devices



Complications

- Sudden death
- Heart failure
- Arrhythmias
- Progression to dilative cardiomyopathy

MYOCARDITIS ALGORITHM



PROPHYLAXIS

- Prevention of infectious diseases by means of appropriate immunizations and early treatment appears to be important in decreasing the incidence of myocarditis.

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