Myocarditis and Cardiomyopathies

LECTURE IN INTERNAL MEDICINE FOR V COURSE STUDENTS

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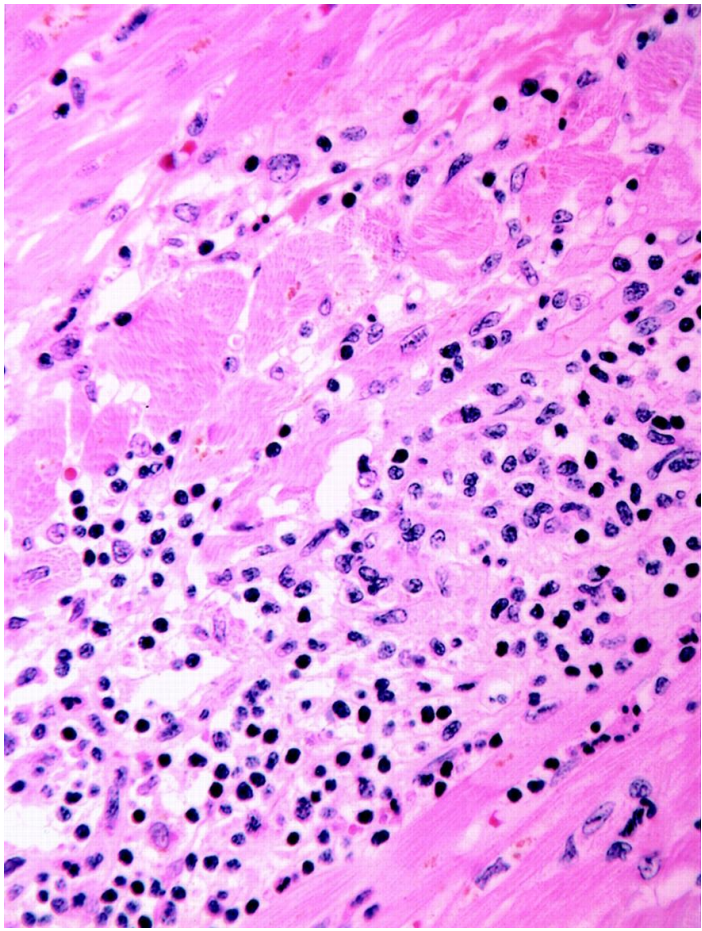
Myocarditis

Plan of the Lecture

- Definition
- Epidemiology
- Risk factors
- Etiology
- Mechanisms
- Classification
- Clinical investigation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic and treatment guidelines



http://circ.ahajournals.org/content/circulationaha/113/6/876/F1.large.jpg

Definition

Myocarditis is an inflammatory disease of the myocardium with a wide range of clinical presentations, from subtle to devastating, diagnosed by established histological, immunological and immunohistochemical criteria.

http://eurheartj.oxfordjournals.org/content/34/33/2636 http://emedicine.medscape.com/article/156330-overview

US MLE TEST

A 10-year-old male presents with multiple complaints. A few weeks ago, he had a sore throat that improved without specific therapy. Over the past several days he has experienced pain in his ankles and wrists and, more recently, his left knee. His mother noted several bumps on both of his elbows. He thinks the pain is better when he leans forward. On physical examination, he is noted to be mildly febrile, and a pericardial friction rub is auscultated. Which of the histopathologic findings is most likely associated with this patient's condition?

1.Atypical lymphocytes noted on peripheral blood smear, 2.Plasmodium falciparum ring forms in red blood cells on peripheral blood smear, 3.Needle-shaped, negatively birefringent crystal deposits surrounded by palisading histiocytes in the synovial fluid of an affected joint, 4. Interstitial myocardial granulomas containing plump macrophages with nuclei incorporating central wavy ribbons of chromatin, 5. Sterile vegetations on both the ventricular and atrial aspects of the mitral valve.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

US MLE TEST

Correct Answer 2: This patient's presentation is consistent with a diagnosis of acute rheumatic fever and associated carditis. Histologic findings associated with this condition include Aschoff bodies, interstitial myocardial granulomas composed of surrounding Anitschkow or caterpillar cells, which are plump macrophages with abundant cytoplasm and central, ovoid nuclei with slender ribbons of chromatin.

Incorrect Answers: 1.Atypical lymphocytosis is consistent with a diagnosis of infectious mononucleosis caused by EBV. 2.This finding is consistent with a diagnosis of malaria. 3.The deposition of monosodium urate crystals in synovial fluid describes the histological findings associated with gout. 5. These findings are consistent with a diagnosis of systemic lupus erythematous (SLE).

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

Epidemiology

- Incidence is estimated at 1-10 cases per 100,000 persons.
- Incidence of positive right ventricular biopsy findings in patients with suspected myocarditis is highly variable (ranging from 0-80%).
- As many as 1-5% of patients with acute viral infections may have involvement of the myocardium.
- No particular race predilection is noted for myocarditis except for peripartum cardiomyopathy that appears to have a higher incidence in patients of African descent.
- The incidence of myocarditis is similar between males and females.
- Patients are usually fairly young.

http://emedicine.medscape.com/article/156330-overview#a6

Risk Factors and Etiology: 1

Infections

- Viral (adenovirus, parvovirus B19, coxsackie virus, human immunodeficiency virus (HIV), enterovirus, rubella virus, poliovirus, cytomegalovirus, human herpesvirus, and possibly hepatitis C).
- Protozoan (*Trypanosoma cruzi* causing *Chagas disease* and *Toxoplasma gondii*).
- Bacterial (*Brucella*, *Corynebacterium diphtheriae*, *gonococcus*, *Haemophilus influenzae*, *Actinomyces*, *Tropheryma whipplei*, *Vibrio cholerae*, *Borrelia burgdorferi*, leptospirosis, and Rickettsia, *Mycoplasma pneumoniae*).

https://en.wikipedia.org/wiki/Myocarditis#Causes

Risk Factors and Etiology: 2

- Fungal (*Aspergillus*).
- Parasitic (Ascaris, *Echinococcus granulosus*, *Paragonimus westermani*, schistosoma, *Taenia solium*,*Trichinella spiralis*, visceral larva migrans, and *Wuchereria bancrofti*).
- Toxins (arsenic, toxic shock syndrome toxin, carbon monoxide, heavy metals (copper, iron), drugs (alcohol, anthracyclines, chemotherapy, antipsychotics, etc.).
- Immunologic (allergic (acetazolamide, amitriptyline), rejection after a heart transplant, autoantigens (scleroderma, systemic lupus erythematosus, sarcoidosis, Kawasaki disease, etc.).
- Physical agents (electric shock, hyperpyrexia, radiation).

https://en.wikipedia.org/wiki/Myocarditis#Causes

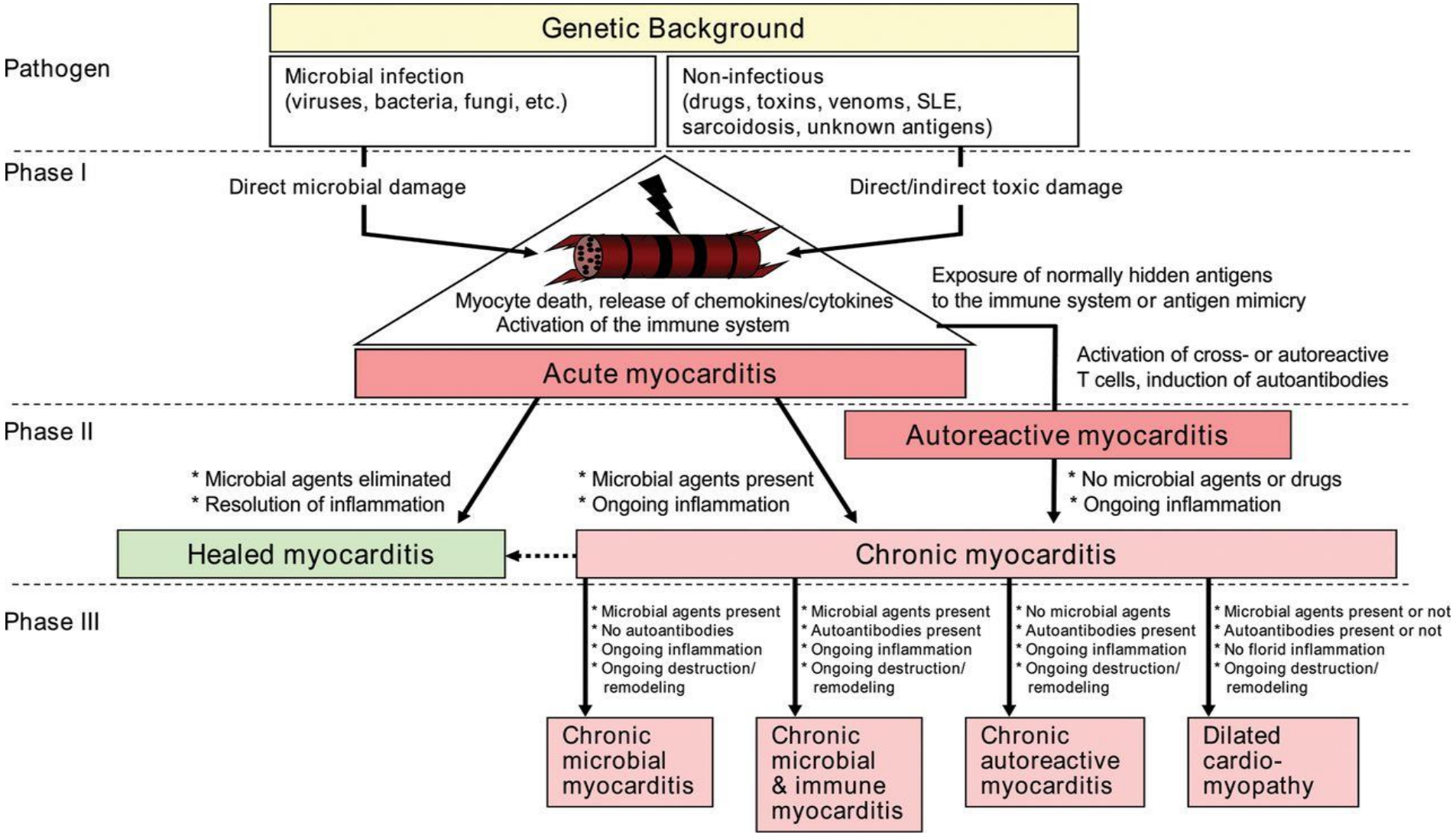
Mechanisms 1
(Viral and Autoimmune)

- There is evidence for viral and autoimmune mechanisms in individuals with or without a genetic predisposition.
- Enteroviruses that preferentially enter cardiomyocytes cause severe cytopathic effects due to virus replication in the first 2 weeks post-infection.
- The ongoing infection and inflammation trigger autoimmune reactions in the heart, most likely as a result of myocyte necrosis and subsequent release of self-antigens previously hidden to the immune system.

http://eurheartj.oxfordjournals.org/content/34/33/2636

Mechanisms

(From Myocarditis to Dilated Cardiomyopathy)



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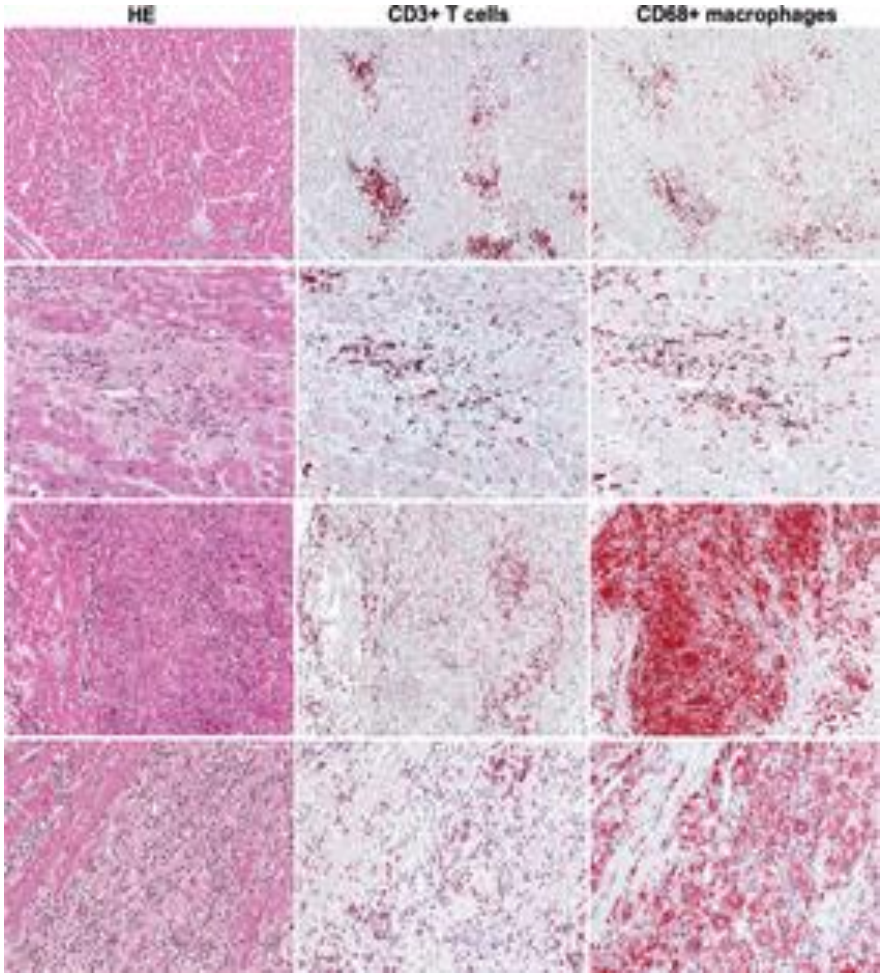
Mechanisms
(Histopathology and Immunopathology)

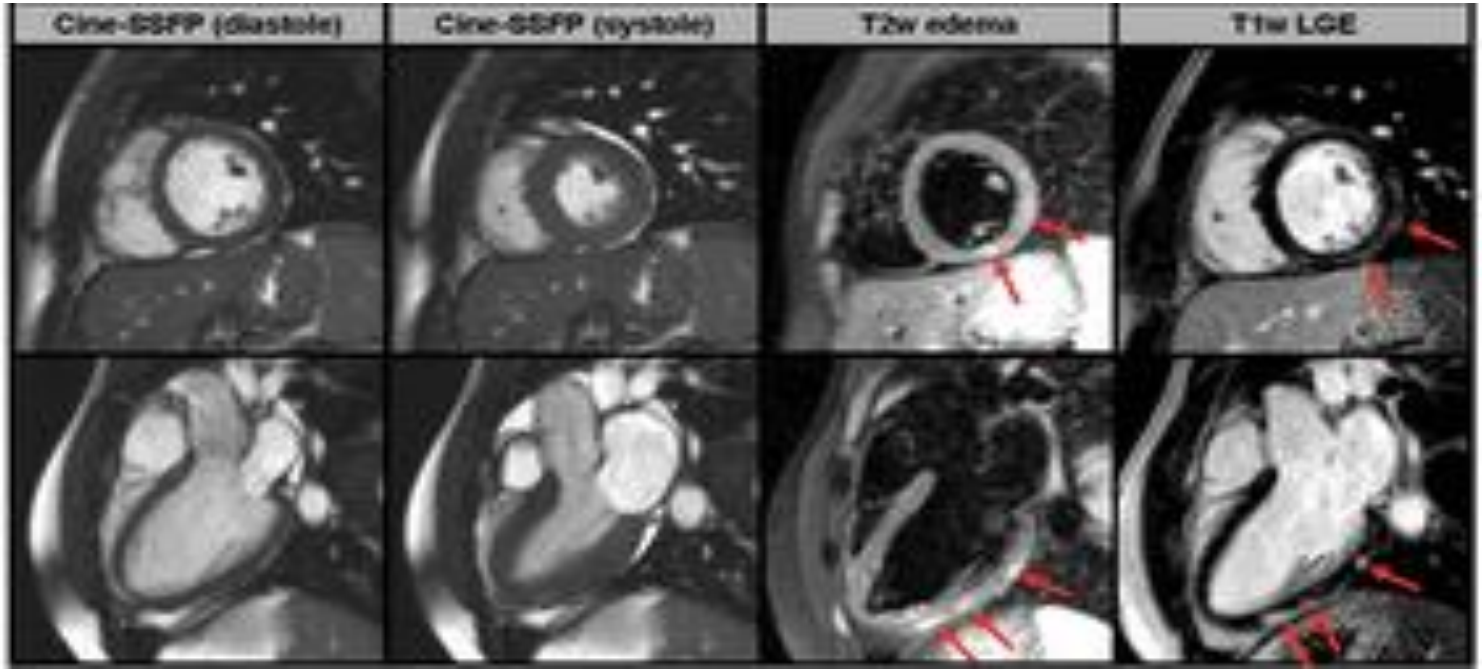


Acute lymphocytic myocarditis (first row), chronic lymphocytic myocarditis (second row), sarcoidosis (third row), and giant cell myocarditis (fourth row). Left column = haematoxylin-eosin; middle column = staining with anti-CD3 antibody (pan T lymphocyte marker); right column = staining with anti-CD68 antibody (macrophage marker).

http://eurheartj.oxfordjournals.org/content/34/33/2636

Mechanisms

(Histopathology and Immunopathology)



Short-axis (upper line) and long-axis (lower line) images of a patient with acute myocarditis. The presence of patchy focal edema in the subepicardium of the inferolateral wall (red arrows). Presence of subepicardially distributed LGE (red arrows) which is typical for acute myocarditis.

http://eurheartj.oxfordjournals.org/content/34/33/2636

Classification
(International Classification of Diseases (ICD)

I01.2 Acute rheumatic myocarditis.

I40.0 Infective myocarditis.

I40. 1 Isolated myocarditis.

I40.8 Other acute myocarditis.

I40.9 Acute myocarditis, unspecified.

I41 Myocarditis in diseases classified elsewhere (diphtheritic, gonococcal, meningococcal, syphilitic, tuberculous, influenzal, parasitic, rheumatoid, sarcoid, myocardial fibrosis).

apps.who.int/classifications/icd10/browse/2016/en#/I46

Classification

(Etiology, Cell Type, Clinical Type)

Etiology	Cell type	Clinical type
Virus	Lymphocytic type	Acute
Bacteria	Giant cell type	Fulminant
Fungi	Eosinophilic type	Chronic
Rickettsia	Granulomatous type	(prolonged)
Spirochetes		(latent)
Protozoa, parasites		
Other causes of infection		
Drugs, chemical substances		
Allergy, autoimmune		
Collagen disease, Kawasaki disease		
Sarcoidosis		
Radiation, heat stroke		
Unknown cause, idiopathic		

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Classification
(Lieberman' Classification)

- Fulminant myocarditis: follows a viral prodrome; distinct onset of illness consisting of severe cardiovascular compromise with ventricular dysfunction and multiple foci of active myocarditis.
- Acute myocarditis: less distinct onset of illness, with ventricular dysfunction.
- Chronic active myocarditis : less distinct onset of illness, with clinical and histologic relapses, with ventricular dysfunction.
- Chronic persistent myocarditis: less distinct onset of illness; persistent histologic infiltrate with foci of myocyte necrosis without ventricular dysfunction.

http://emedicine.medscape.com/article/156330-overview#a4

Classification
(The Dallas Classification (1987))

Initial biopsy:

- Myocarditis: 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 biopsy:

- Ongoing (persistent) myocarditis with or without fibrosis.
- Resolving (healing) myocarditis with or without fibrosis.
- Resolved (healed) myocarditis with or without fibrosis.

http://emedicine.medscape.com/article/156330-workup#c12

Classification
(WHO Marburg Criteria (1996))

First biopsy:

1. Acute myocarditis: a clear-cut infiltrate of $\geq$14 leukocytes/mm² (preferably activated T-cells).
2. Chronic myocarditis : an infiltrate of $\geq$14 leukocytes/mm² (preferably activated T-cells).
3. No myocarditis: No infiltrating cells, <14 leukocytes/mm².

Subsequent biopsies:

1. Ongoing (persistent) myocarditis. Criteria as in 1 or 2.
2. Resolving (healing) myocarditis. Criteria as in 1 or 2 but the immunological process is sparser than in the first biopsy.
3. Resolved (healed) myocarditis (the Dallas classification).

http://carditis.net/whfmyoca.htm

Clinical Investigation
(Signs and Symptoms)

- Fever, cardiac rhythm disturbance, hypotension, gallop rhythm, rales, jugular venous dilatation, and cardiac tamponade.
- Flu-like symptoms (chills, fever, headache, muscle aches, general malaise).
- Cardiac symptoms (a few hours to a few days after the initial signs and symptoms): heart failure, chest pain due to pericardial irritation, heart block and arrhythmia.
- Gastrointestinal symptoms: decreased appetite, nausea, vomiting, and diarrhea.

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Clinical Investigation
(Course of the Disease)

- The primary signs and symptoms and disease progression of myocarditis are relatively easy to grasp.
- The inflammatory phase lasts one to two weeks, and is followed by a recovery phase.
- Myocarditis causes myocardial necrosis and inflammation, which result in cardiac dysfunction and failure.
- Myocarditis usually manifests in an otherwise healthy person and can result in rapidly progressive (and often fatal) heart failure and arrhythmia.

http://emedicine.medscape.com/article/156330-overview https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Clinical Investigation
(Specific Findings in Special Cases)

- Sarcoid myocarditis: lymphadenopathy, sarcoid involvement in other organs (up to 70%).
- Acute rheumatic fever (affects heart in 50-90%; associated signs: erythema marginatum, polyarthralgia, chorea, subcutaneous nodules (Jones criteria).
- Hypersensitive/eosinophilic myocarditis (pruritic maculopapular rash and history of using offending drug).
- Giant cell myocarditis (ventricular tachycardia in rapidly progressive heart failure).
- Peripartum cardiomyopathy (heart failure in the last month of pregnancy or within 5 months following delivery).

http://emedicine.medscape.com/article/156330-overview

US MLE TEST

A 45-year-old African American woman presents to her family physician for a routine examination. Past medical history is positive for amyloidosis and non-rhythm-based cardiac abnormalities secondary to the amyloidosis. Which of the following cardiac parameters would be expected in this patient?

1. Preserved ejection fraction and increased compliance.
2. Preserved ejection fraction and decreased compliance.
3. Decreased ejection fraction and increased compliance.
4. Decreased ejection fraction and decreased compliance.
5. Increased ejection fraction and decreased compliance.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

US MLE TEST

Correct Answer 2: This patient has diastolic heart failure secondary to amyloidosis. Diastolic heart failure is characterized by a decrease in ventricular compliance with normal contractility (preserved ejection fraction).

Incorrect Answers: 1,3-5: These cardiac parameters are not generally seen in a patient with diastolic heart failure.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

Diagnosis
(Instrumental)

- Chest X-Ray: hear enlargement and pulmonary congestion.
- Electrocardiography (ECG): abnormal ST-T waves, conduction block, increase in the width of the QRS complex, potentially fatal arrhythmias.
- Echocardiography: transient wall thickening, reduced wall motion, reduced cardiac chamber size, pericardial effusion.
- Cardiac magnetic (CMR) and magnetic resonance imaging (MRI): the regions of the heart affected by inflammation.
- Cardiac catheterization including endomyocardial biopsy: myocardial degeneration, myocyte necrosis, inflammatory infiltrates, and/or interstitial edema of the myocardium.

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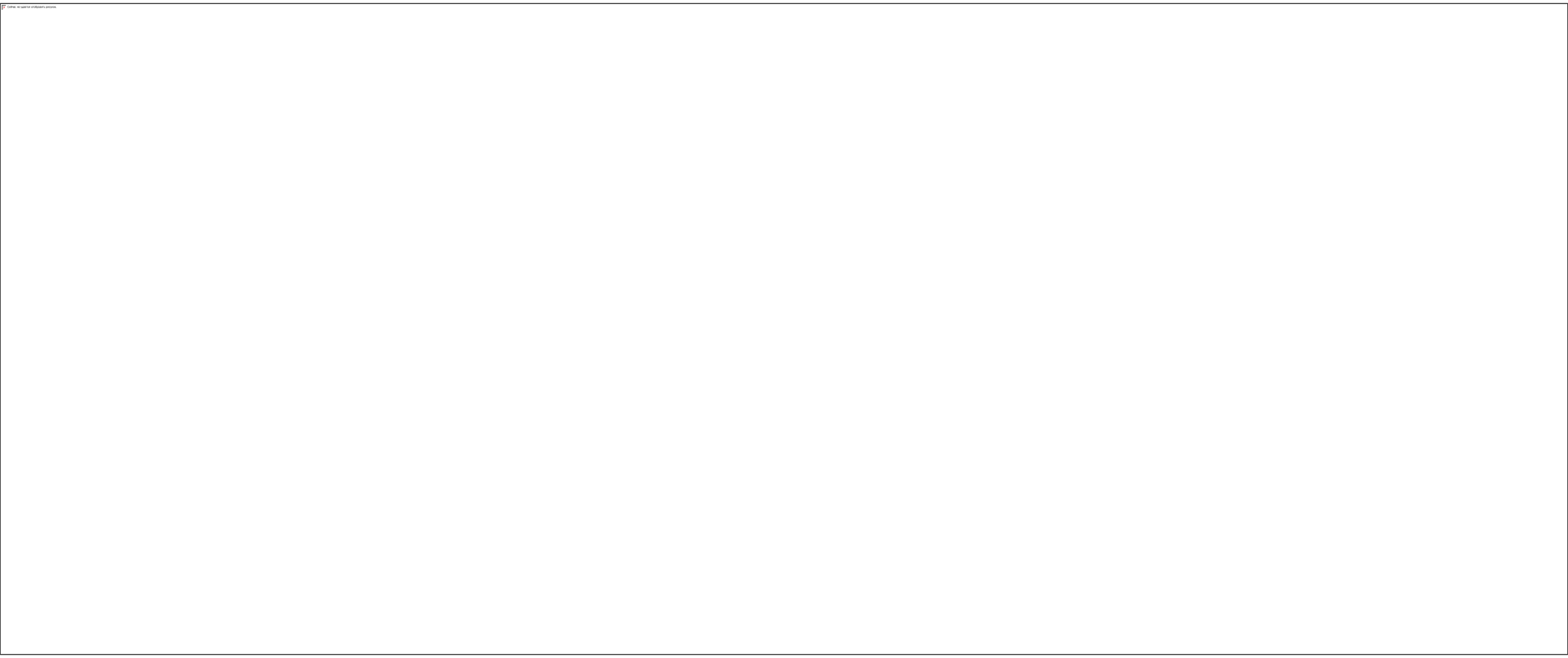
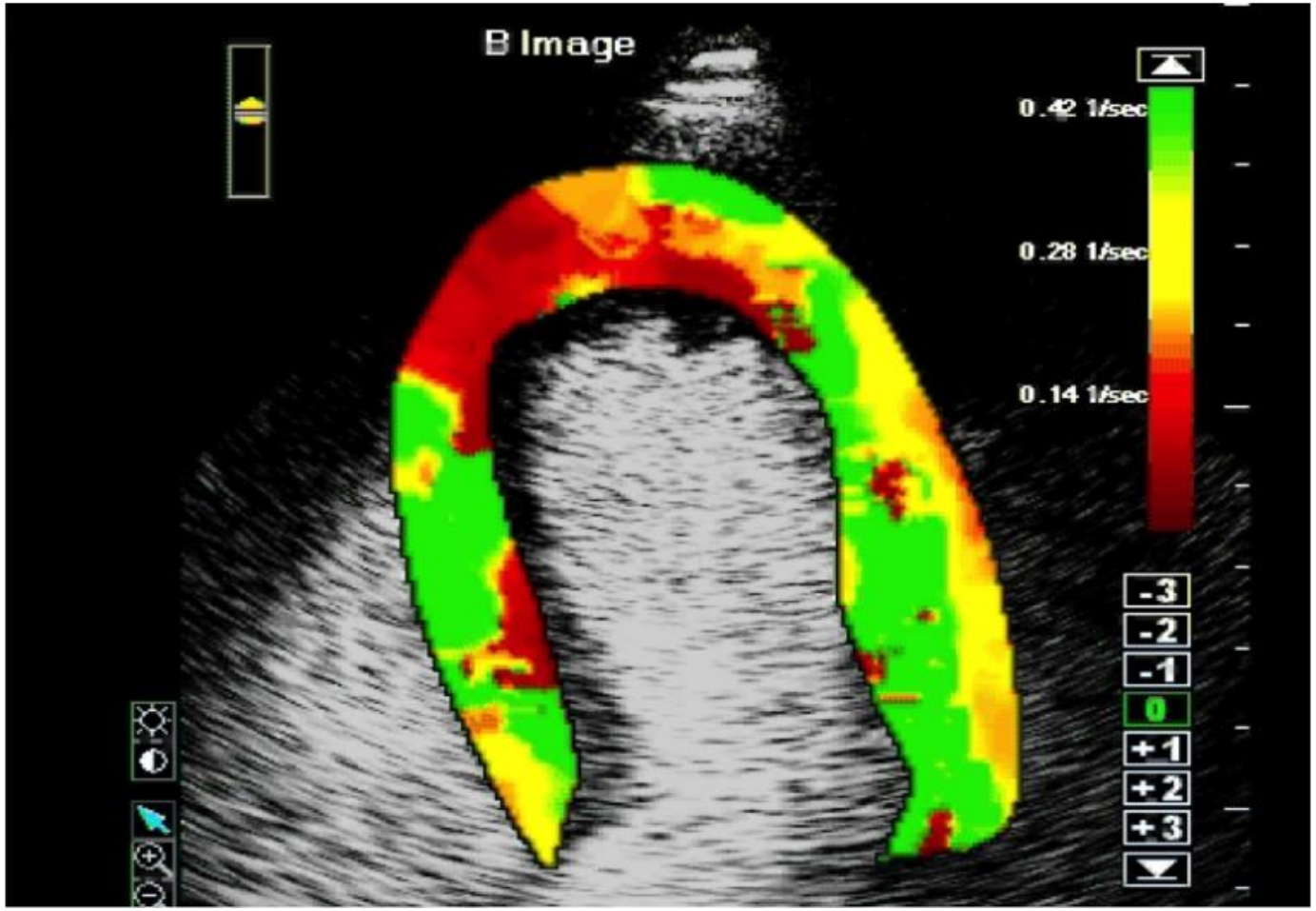
Diagnosis
(ECG)



Ventricular tachycardia (rapid ventricular rhythm disorder) in myocarditis.

http://www.isarherzzentrum.de/en/myocarditis

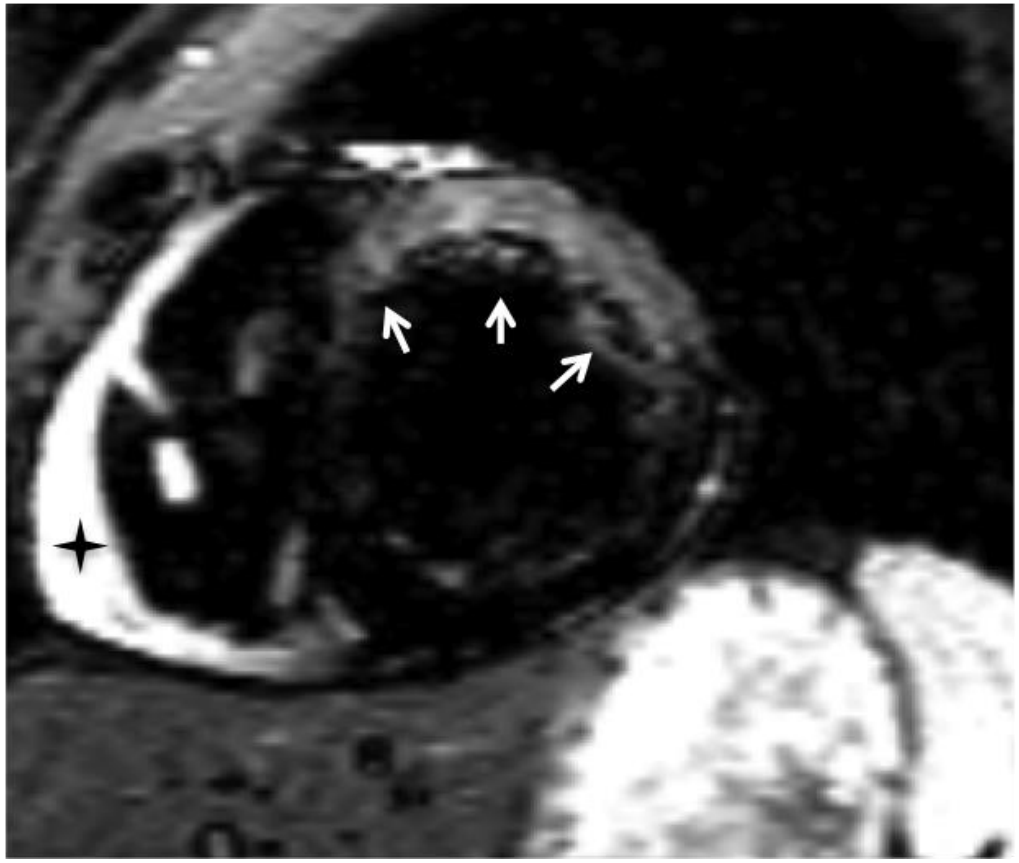
Diagnosis
(Echocardiography)



Circulatory disorder (red) in an acute myocarditis.

http://www.isarherzzentrum.de/en/myocarditis

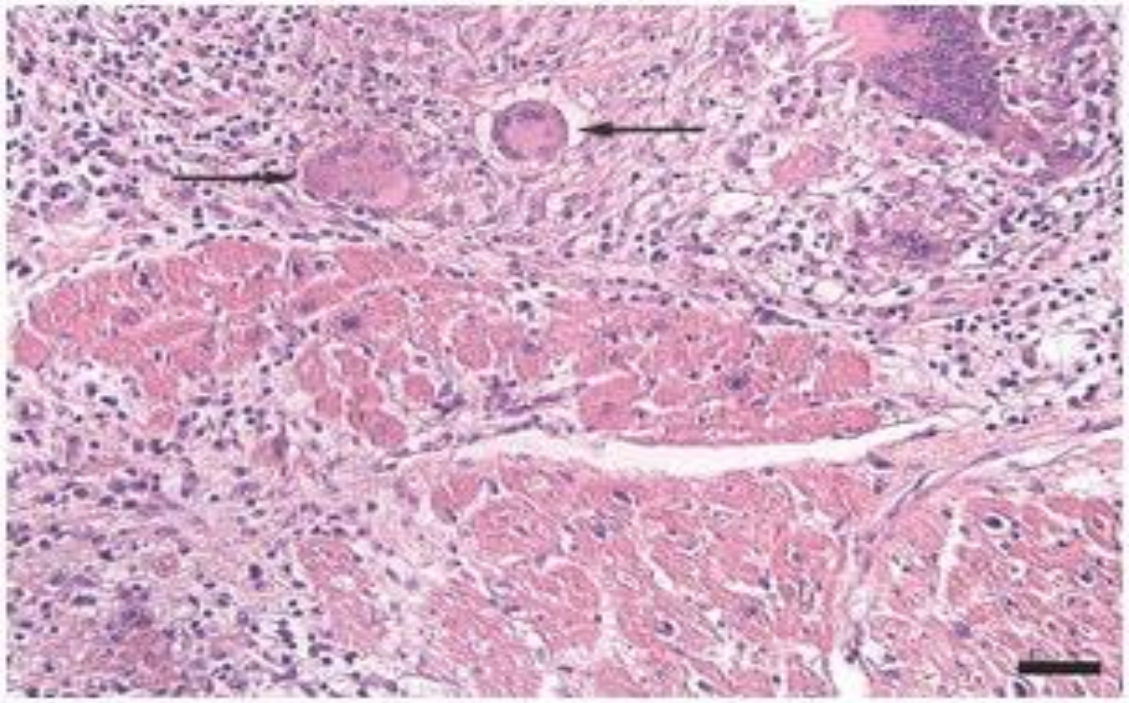
Diagnosis
(Magnetic Resonance Imaging)



Representation of edema in acute myocarditis (arrow indicators).
A pericardial effusion, aka fluid around the heart (star).

http://www.isarherzzentrum.de/en/myocarditis

Diagnosis
(Endomyocardial Biopsy)



Hematoxylin and eosin staining of the biopsy sample reveals extensive myocyte necrosis, cellular inflammation and the formation of multinucleated giant cells (arrows).

http://www.isarherzzentrum.de/en/myocarditis

Diagnosis
(Diagnostic Criteria for Acute Myocarditis in Endomyocardial Biopsy)

- Infiltration of many large or small mononuclear cells* (occasionally, a few polymorphonuclear leukocytes and multinucleated giant cells appear).
- Rupture, fusion and disappearance of cardiomyocytes.
- Interstitial edema (occasionally with fibril formation).

*Cell infiltrates are often observed adjacent to cardiomyocytes.

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Diagnosis
(Laboratory Studies)

- Complete blood count (CBC): leukocytosis (may demonstrate eosinophilia).
- Elevated erythrocyte sedimentation rate (other acute phase reactants, such as C-reactive protein).
- Rheumatologic screening : to rule out systemic inflammatory diseases,
- Elevated cardiac enzymes: transient elevation of C-reactive protein (CRP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), the MB form creatine kinase (CK-MB), and cardiac troponin T in blood.
- Serum viral antibody titers: for viral myocarditis.

http://emedicine.medscape.com/article/156330-overview

Diagnosis
(Viral Infection)

- Viral infection is confirmed if the viral antibody titer is at least four times higher in an acute phase serum sample than in a sample obtained in remission phase collected at least two weeks apart.
- Only approximately 10% of patients with viral infection exhibit a positive antibody titer.
- Polymerase chain reaction (PCR) is more useful for identifying the genomes of viruses causing myocarditis, but is not commonly performed.

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Diagnosis
(Differential Diagnoses)

- Alcoholic Cardiomyopathy.
- Cardiac Tamponade.
- Cardiogenic Shock.
- Chagas Disease (American Trypanosomiasis).
- Cocaine-Related Cardiomyopathy.
- Coronary Artery Atherosclerosis.
- Dilated Cardiomyopathy.
- Hypertrophic Cardiomyopathy.
- Peripartum Cardiomyopathy.
- Restrictive Cardiomyopathy.

http://emedicine.medscape.com/article/156330-differential

Treatment
(Diet and Physical Activity)

- Patients should consume a low-sodium diet similar to that for heart failure management.
- Physical activity should be restricted to reduce the work of the heart during the acute phase of myocarditis.
- Terms of physical activity limitation:
  - 10 – 14 days – mild myocarditis (up to ECG normalization),
  - 4 – 6 weeks – moderate myocarditis (up to normalization of heart size),
  - individually – severe myocarditis (up to decreasing of HF severity and disappearance of rhythm disorders).

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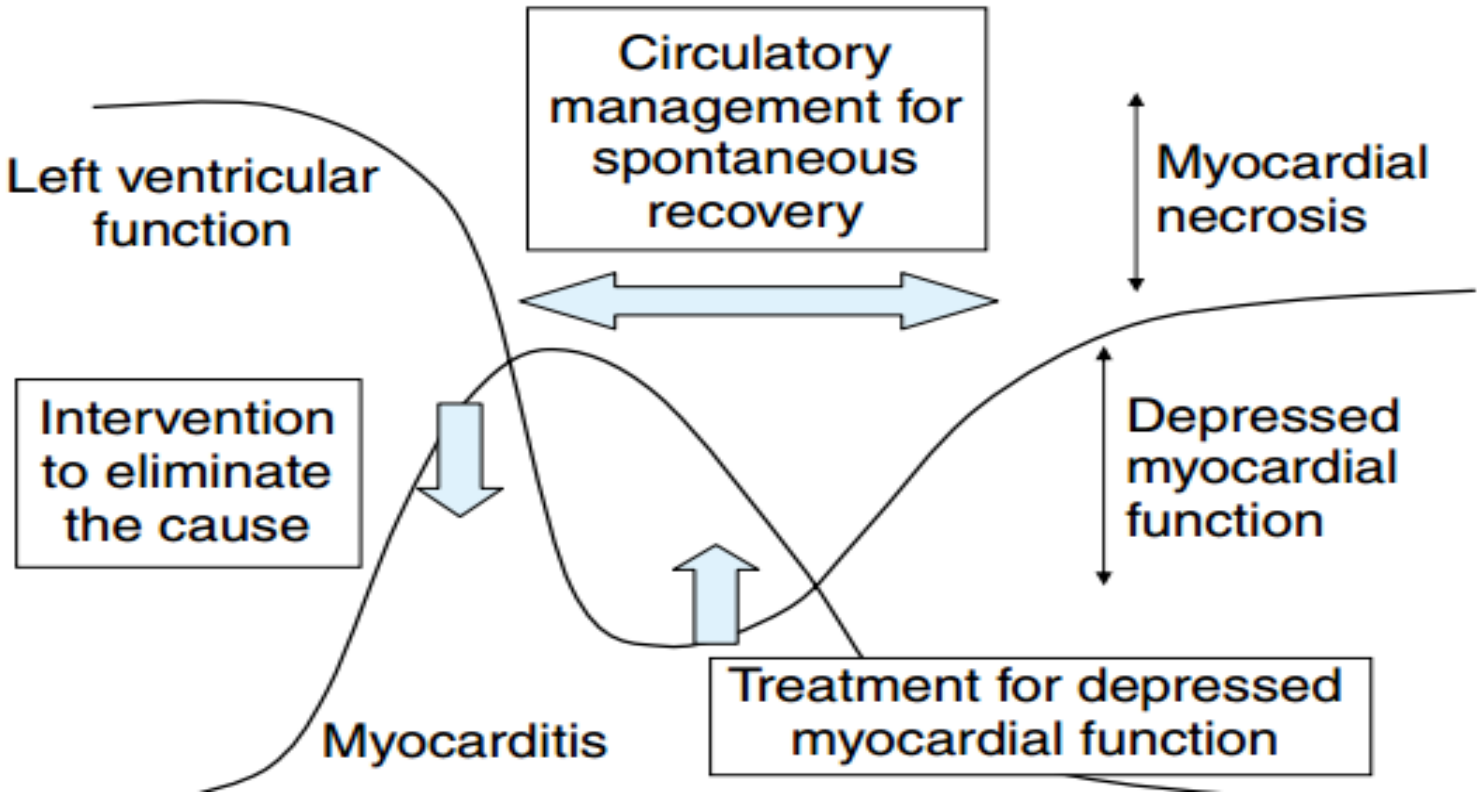
Treatment

(Tasks)



Myocarditis is treated in three ways: (1) intervention to eliminate the cause, (2) intervention to improve hemodynamic compromise, and (3) intervention in cardiac dysfunction.

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Treatment
(Etiotropic)

- Antibiotic therapy only after the confirmation of the etiological factor (diphtheria).
- Antiviral drugs only for proven viral myocarditis (etiologic agent is known AND sensitive to antiviral drug), however, beneficial effects are seen only if therapy is started prior to inoculation or soon thereafter.
- Nevertheless, antiviral therapy may be considered in acute, fulminant myocarditis, in institutional outbreaks and in laboratory-acquired cases.

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Treatment
(Intensive Immunosuppressive Therapy)

- Intensive immunosuppressive therapy (e.g., corticosteroids, azathioprine, cyclosporine, muromonab-CD3/OKT3) has been shown to have some benefit only in small-scale clinical studies in the treatment of giant cell myocarditis and has not been validated in large clinical trials.
- At this time, immunosuppressive therapy is not recommended for myocarditis until clear evidence is available from the results of multicenter trials.

http://emedicine.medscape.com/article/156330-overview

Treatment
(Pathogenetic Pharmacotherapy)

- Vasodilators (e.g., nitroglycerin, sodium nitroprusside).
- Angiotensin-converting enzyme inhibitors.
- Diuretics (e.g., furosemide).
- Anticoagulation may be advisable as a preventive measure.
- Antiarrhythmics can be used cautiously, although most antiarrhythmic drugs have negative inotropic effects that may aggravate heart failure; supraventricular arrhythmias should be converted electrically.
- Inotropic drugs (e.g., dobutamine, milrinone) may be necessary for severe decompensation, although they are highly arrhythmogenic.

http://emedicine.medscape.com/article/156330-overview

Treatment
(Supportive Care and Surgical Intervention)

- Hemodynamic and cardiac monitoring,
- Administration of supplemental oxygen,
- Fluid management,
- Temporary transvenous pacing for complete heart block,
- Cardiac transplantation,
- Extreme cases: ventricular assist device or percutaneous circulatory support; left ventricular assistive devices (LVADs) and extracorporeal membrane oxygenation.

http://emedicine.medscape.com/article/156330-overview

Consultations

- Cardiothoracic surgery.
- Infectious disease and/or rheumatology consultations.

Rheumatic heart disease

http://emedicine.medscape.com/article/156330-treatment

Prognosis

- In the acute phase, myocarditis management of cardiac pump failure and potentially fatal arrhythmias is the main clinical challenge.
- The prognosis of myocarditis varies depending on the pathogenesis and type of disease.
- Patients who survive fulminant myocarditis have a good prognosis.
- Predictors of death or need for heart transplantation include syncope, low ejection fraction, and left bundle-branch block, all indicators of advanced cardiomyopathy.

https://www.jstage.jst.go.jp/article/circj/75/3/75_CJ-88-0008/_pdf

Prophylaxis

- Vaccination should reduce the incidence of myocarditis caused by measles, rubella, mumps, poliomyelitis, and influenza.
- The development of vaccines for other cardiotropic viruses may prevent viral myocarditis in the future.

http://emedicine.medscape.com/article/156330-treatment

Abbreviations

ACE - angiotensin converting enzyme

CMR - cardiac magnetic resonance

ECG - electrocardiogram

MRI - magnetic resonance imaging

HIV - human immunodeficiency virus

LVADs - left ventricular assistive devices

Diagnostic and treatment guidelines

Current state of knowledge on etiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Guidelines for Diagnosis and Treatment of Myocarditis

2015 ESC Guidelines for the management of infective endocarditis

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

Update on Myocarditis

Cardiomyopathies

Plan of the Lecture

- Definition
- Epidemiology
- Risk factors
- Etiology
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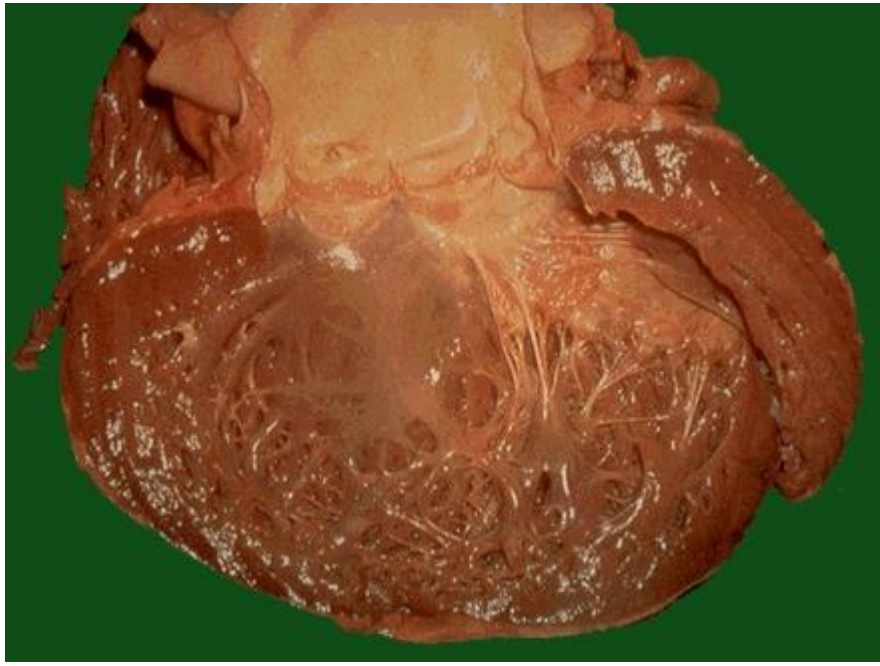


A large, dilated left ventricle typical of a dilated, or congestive, cardiomyopathy

http://library.med.utah.edu/WebPath/CVHTML/CV093.html

Definition

Cardiomyopathies (CM) are defined by structural and functional abnormalities of the ventricular myocardium that are unexplained by flow-limiting coronary artery disease or abnormal loading conditions and historically have been subdivided into primary disease, in which the heart is the only involved organ, and secondary forms where the cardiomyopathy is a manifestation of a systemic disorder.

http://eurheartj.oxfordjournals.org/content/early/2014/08/28/eurheartj.ehu284

US MLE TEST

A 20-year-old male presents to his primary care physician for a sports physical. If the physician is worried about hypertrophic cardiomyopathy in this patient, what physical examination finding and hereditary pattern would be expected for this disease process?

1. No change in murmur intensity with valsalva; X-linked recessive, 2. Decreased murmur intensity with valsalva; X-linked recessive, 3. Decreased murmur intensity with valsalva; autosomal dominant, 4. Increased murmur intensity with valsalva; autosomal dominant, 5. Increased murmur intensity with valsalva; X-linked recessive.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

US MLE TEST

Correct Answer 4: Hypertrophic cardiomyopathy (HCM) will present with a systolic murmur that increases in intensity with the valsalva maneuver. HCM is inherited in an autosomal dominant fashion.

Incorrect Answers: 1-3 & 5: None of these combinations of murmur alterations and inheritance patterns are correct for the specific pathology of hypertrophic cardiomyopathy.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

Epidemiology
(Dilated Cardiomyopathy)

- The estimated prevalence of dilated cardiomyopathy (DCM) is 1:2500.
- The incidence of DCM discovered at autopsy is estimated to be 4.5 cases per 100,000 population per year, whereas the clinical incidence is 2.45 cases per 100,000 population per year.
- DCM is the most common type, occurring mostly in adults 20 to 60.
- Men are more likely in men than in women.

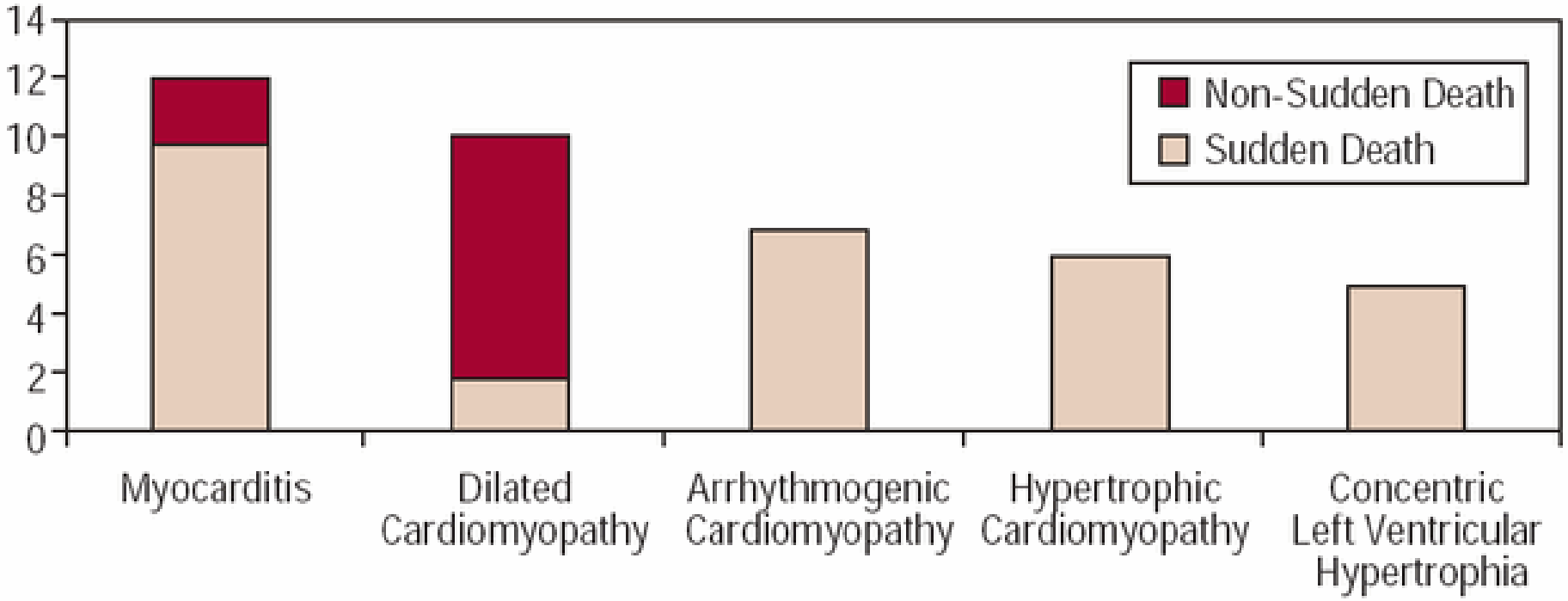
emedicine.medscape.com/article/2017823-overview#a3 heart.org/HEARTORG/Conditions/More/Cardiomyopathy/Dilated-Cardiomyopathy_UCM_444187_Article.jsp#.V34FCLiLQhc

Epidemiology
(Hypertrophic Cardiomyopathy)

- Hypertrophic cardiomyopathy (HCM) occurs with an incidence of 1 in 500 people in the general population and is the most common cause of sudden death in children and adults under 35 years.
- The mean age is 57 (16 to 87) years.
- HCM is autosomal dominant with no known sex predilection.
- Sudden death is most common in young patients, and death from heart failure or stroke occurs more frequently in middle age and beyond.
- Apical HCM is seen much more commonly in Asian people.

http://bestpractice.bmj.com/best-practice/monograph/409/basics/epidemiology.html

Epidemiology
(Distribution of Myocardial Diseases According to the Manner of Death)



http://www.revespcardiol.org/en/myocardial-disease-mortality-in-children/articulo/13086406/

Risk Factors and Etiology
(Dilated Cardiomyopathy)

- DCM can be familial, primary without family history, or secondary (associated with or caused by other conditions).
- Familial DCM (>25% of cases of DCM), is usually autosomal dominant.
- 2 of 3 patients have sporadic DCM and about 15% of them arise from chronic myocarditis.
- Noninflammatory etiologies and associations include alcoholism; anthracycline drugs; ingestion of metals; autoimmune, systemic and mitochondrial disorders.
- The distinction between the cause and risk factor(s) DCM is sometimes blurred.

http://emedicine.medscape.com/article/2017823-overview#a2

Risk Factors and Etiology

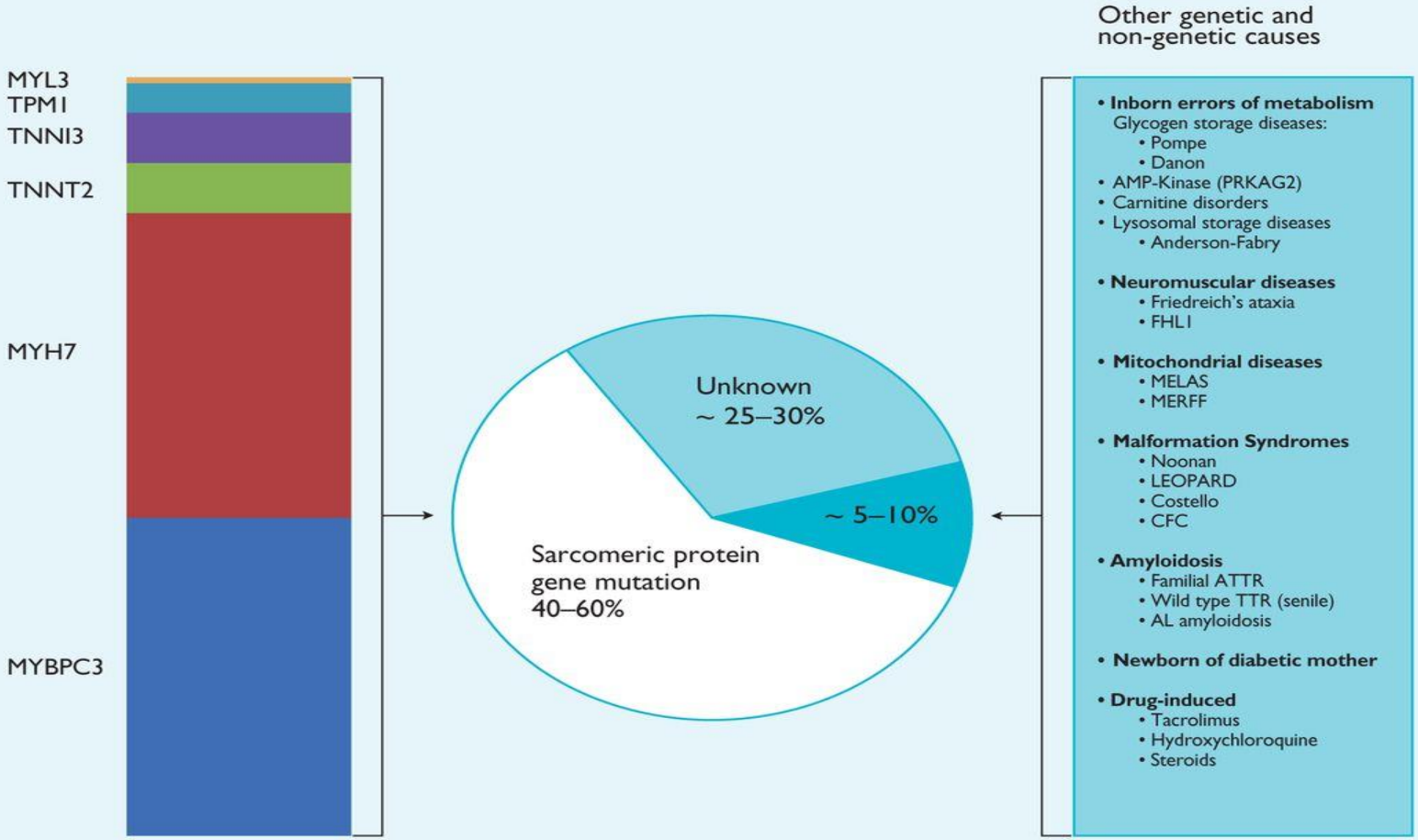
(Hypertrophic Cardiomyopathy)

- Abnormal calcium kinetics leads to the inappropriate myocardial hypertrophy and specific features of HCM, particularly in patients with diastolic functional abnormalities.
- Genetic causes (an autosomal dominant Mendelian-inherited disease in approximately 50% of cases (at least 6 different genes on at least 4 chromosomes are associated with HCM, with more than 50 different mutations discovered thus far)).
- Other causes: abnormal sympathetic stimulation; abnormally thickened intramural coronary arteries; subendocardial ischemia; cardiac structural abnormalities.

http://emedicine.medscape.com/article/152913-overview

Risk Factors and Etiology

(Diverse Etiology of Hypertrophic Cardiomyopathy)



The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

http://eurheartj.oxfordjournals.org/content/early/2014/08/28/eurheartj.ehu284

US MLE TEST

A 17-year-old previously healthy, athletic male suddenly falls unconscious while playing soccer. His athletic trainer comes to his aid and notes that he is pulseless. He begins performing CPR on the patient until the ambulance arrives and pronounces the teenager dead. What is the mechanism behind the most likely cause of death?

1. Myocardial infarction.
2. Heart failure due to diastolic dysfunction.
3. Arrhythmia.
4. Outflow obstruction.
5. Rapid volume loss.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

US MLE TEST

Correct Answer 3: This case of sudden death is most likely caused by a ventricular arrhythmia that arises from hypertrophic cardiomyopathy.
Incorrect Answers: 1: It is unlikely that an athletic 17-year-old with no past medical history would have a myocardial infarction, 2: Diastolic dysfunction occurs when there is not enough filling space in the heart resulting in a low stroke volume; although this can be seen in hypertrophic cardiomyopathy, it is not the primary cause of death, 4: Outflow obstruction occurs in hypertrophic cardiomyopathy but it is not the main cause of death, 5: Rapid volume loss, such as in bleeding, is unlikely in the patient scenario.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

Mechanisms

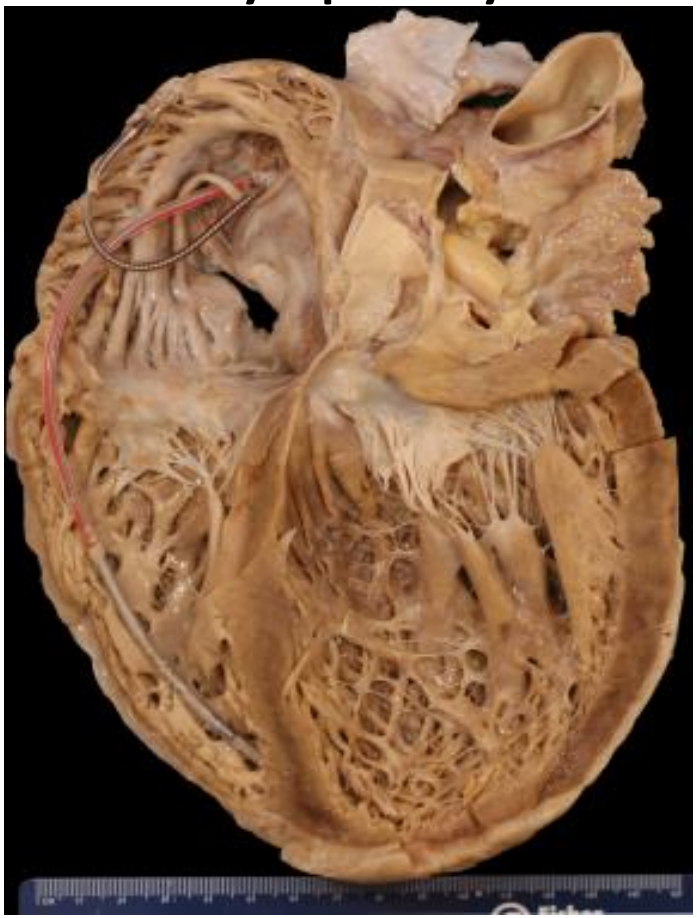
(Dilated Cardiomyopathy: Gross Findings)

- Cardiomegaly is a requisite for the diagnosis of DCM (the mean heart weight is about 600 g).
- Typically, 4-chamber dilatation that is greater in the ventricles than the atria is found.
- LV wall thickness is often normal, in contrast to hypertensive cardiomyopathy with failure.
- Mitral insufficiency may result from papillary muscle dysfunction secondary to LV and changes in LV wall shape, and tricuspid regurgitation results from annular dilatation.
- Mural thrombi are common in patients who do not receive anticoagulation.
- Diffuse or patchy endocardial fibrosis is frequent.

http://emedicine.medscape.com/article/2017823-overview#a9

Mechanisms

(Dilated Cardiomyopathy: Gross Findings)



Gross heart specimen from a patient with DCM who died in end-stage heart failure. Defibrillator leads are in the right heart. The ventricles are dilated more than the atria.

http://emedicine.medscape.com/article/2017823-overview#a9

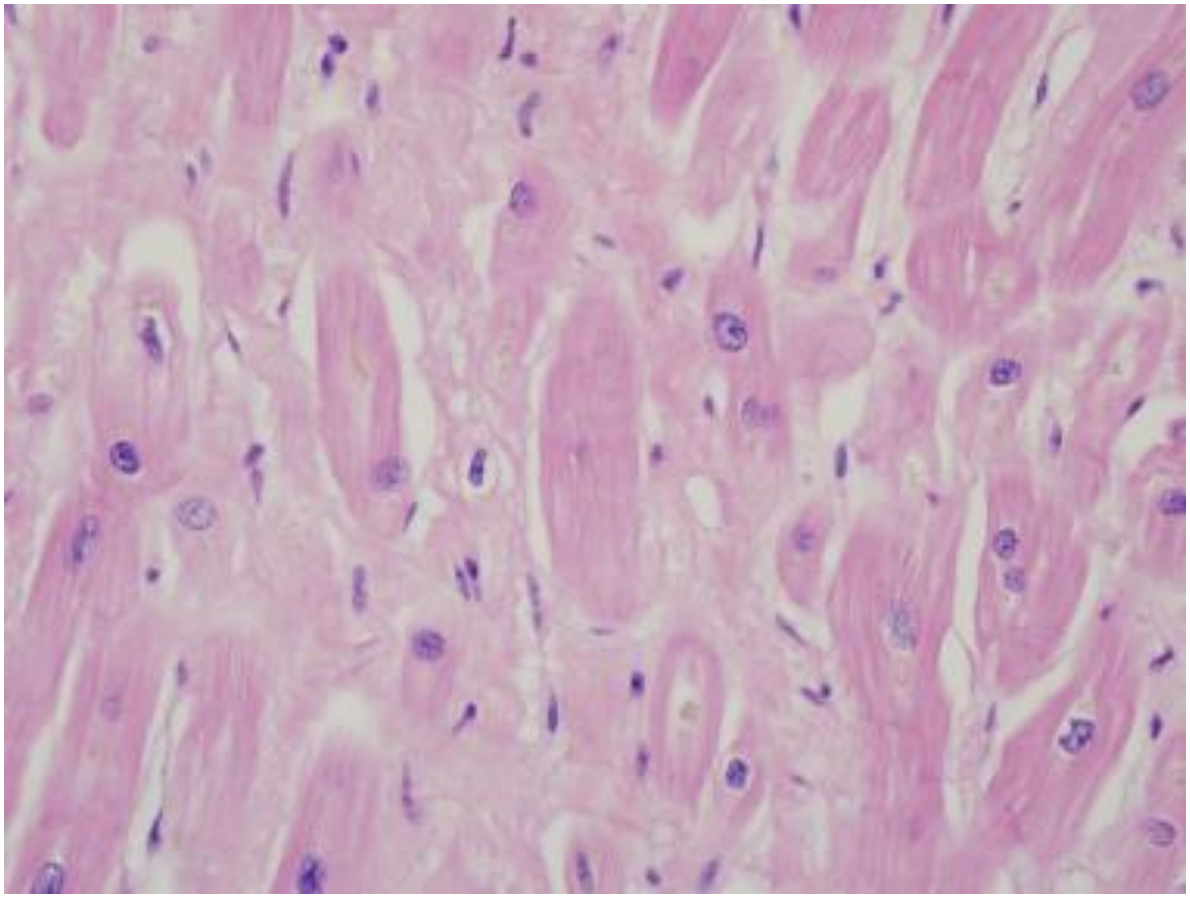
Mechanisms
(Dilated Cardiomyopathy: Microscopic Findings)

- The histologic features of DCM are nonspecific.
- In biopsies, the findings range from minimal variation in myocyte size to typical features of myofiber loss, interstitial fibrosis, and marked variation in myofiber size.
- Transmural scars may also occur in dilated cardiomyopathy.
- Quantitation of collagen has shown up to 4 times the normal collagen concentration, with a decrease in mature cross-linked collagen, correlating with an increase in neutrophil-type collagenase activity.
- The volume density of myofibrils is reduced, and mitochondrial density is normal, but the mitochondria are more numerous and small.

http://emedicine.medscape.com/article/2017823-overview#a9

Mechanisms

(Dilated Cardiomyopathy: Microscopic Findings)



Heart section from a cardiac explant in a patient with end-stage DCM. There is focal interstitial fibrosis. The change is nonspecific and can be seen in heart failure from any cause.

http://emedicine.medscape.com/article/2017823-overview#a9

Mechanisms

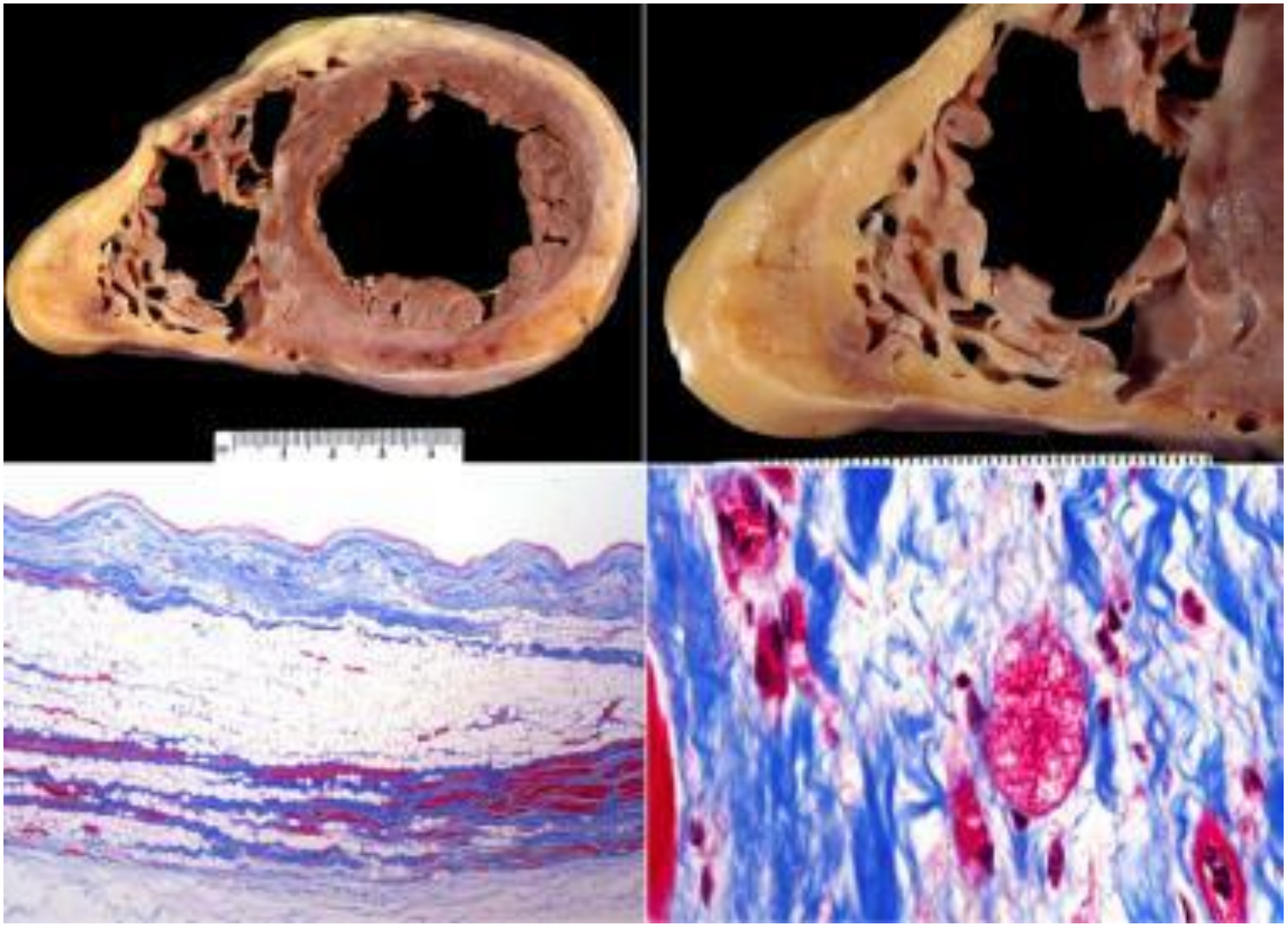
(Dilated Cardiomyopathy: Immunohistochemistry)

- Immunolocalization of sarcomeric and cytoskeletal proteins have demonstrated abnormal distribution in explanted hearts from patients with DCM.
- Tubulin and desmin are increased in amount and irregularly distributed.
- Titin, a member of the sarcomeric skeleton family, is reduced, in areas where contractile material is lacking.
- Connexin-43 is also decreased.
- Increased myocyte cell death and apoptosis is found.
- In cases of dystrophin-related dilated cardiomyopathy, immunohistochemical and molecular studies are essential to identify protein and gene defects.

http://emedicine.medscape.com/article/2017823-overview#a9

Mechanisms

(Dilated Cardiomyopathy: Immunohistochemistry)



Arrhythmogenic right ventricular cardiomyopathy (ARVC).

http://emedicine.medscape.com/article/2017949-overview

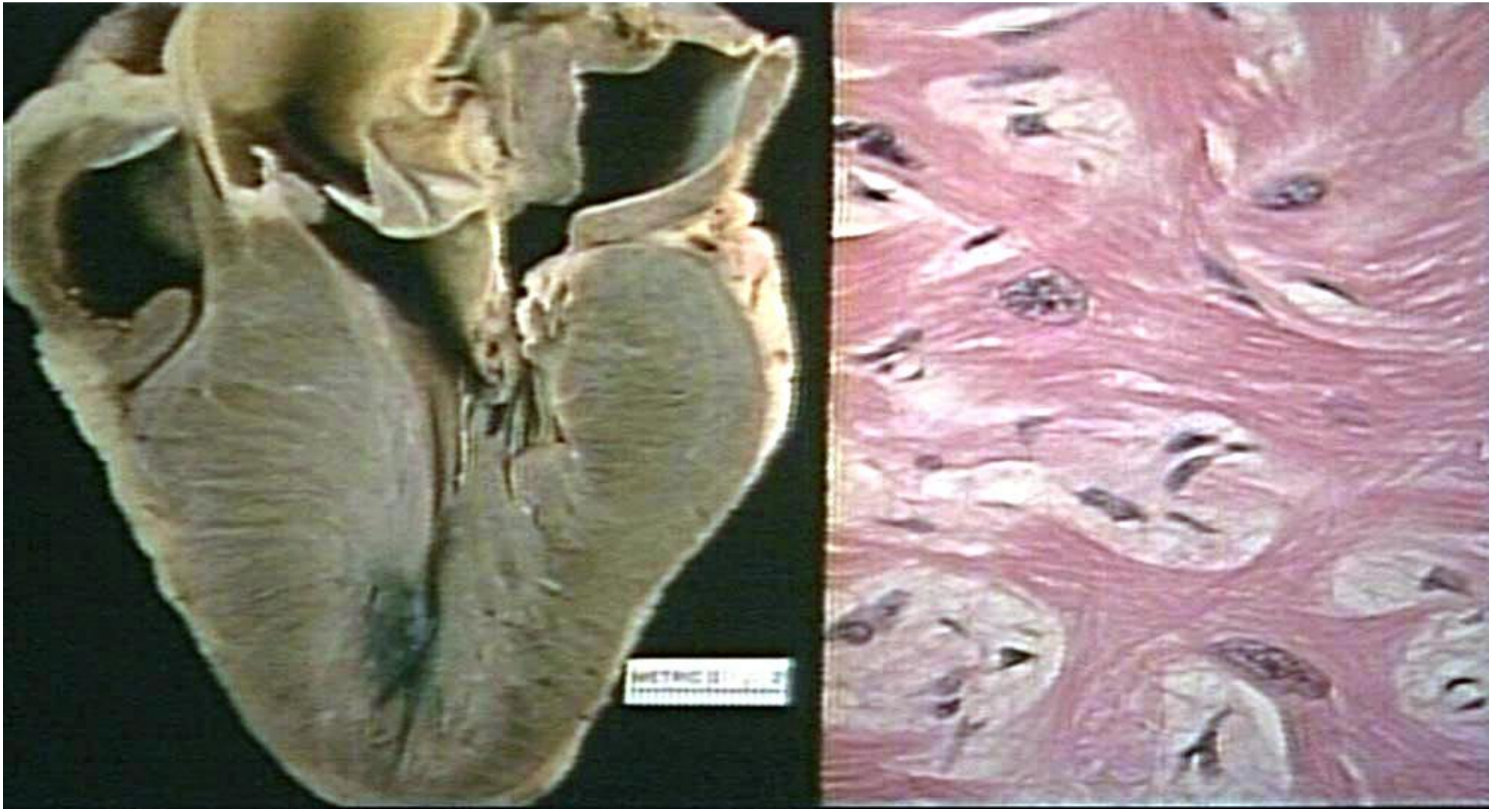
Mechanisms

(Hypertrophic Cardiomyopathy (HCM): Gross Findings)

- About 1/4 individuals demonstrate an obstruction to the outflow of blood from the LV during rest and in 70% of patients, obstruction can be provoked under certain conditions (dynamic outflow obstruction).
- Myocardial hypertrophy and extracellular fibrosis predispose to increased LV stiffness which in concert with compromised cellular energetics and abnormal calcium handling lead to diastolic dysfunction.
- The altered structure of the coronary vessels and increased diastolic pressure, with the hypertrophy and outflow tract obstruction, may cause myocardial ischemia, and may trigger ventricular arrhythmias.

http://pathologyoutlines.com/topic/hearthypertrophic.html

Mechanisms
(Hypertrophic Cardiomyopathy: Gross Findings)



http://www.pathguy.com/sol/07811.jpg

Mechanisms

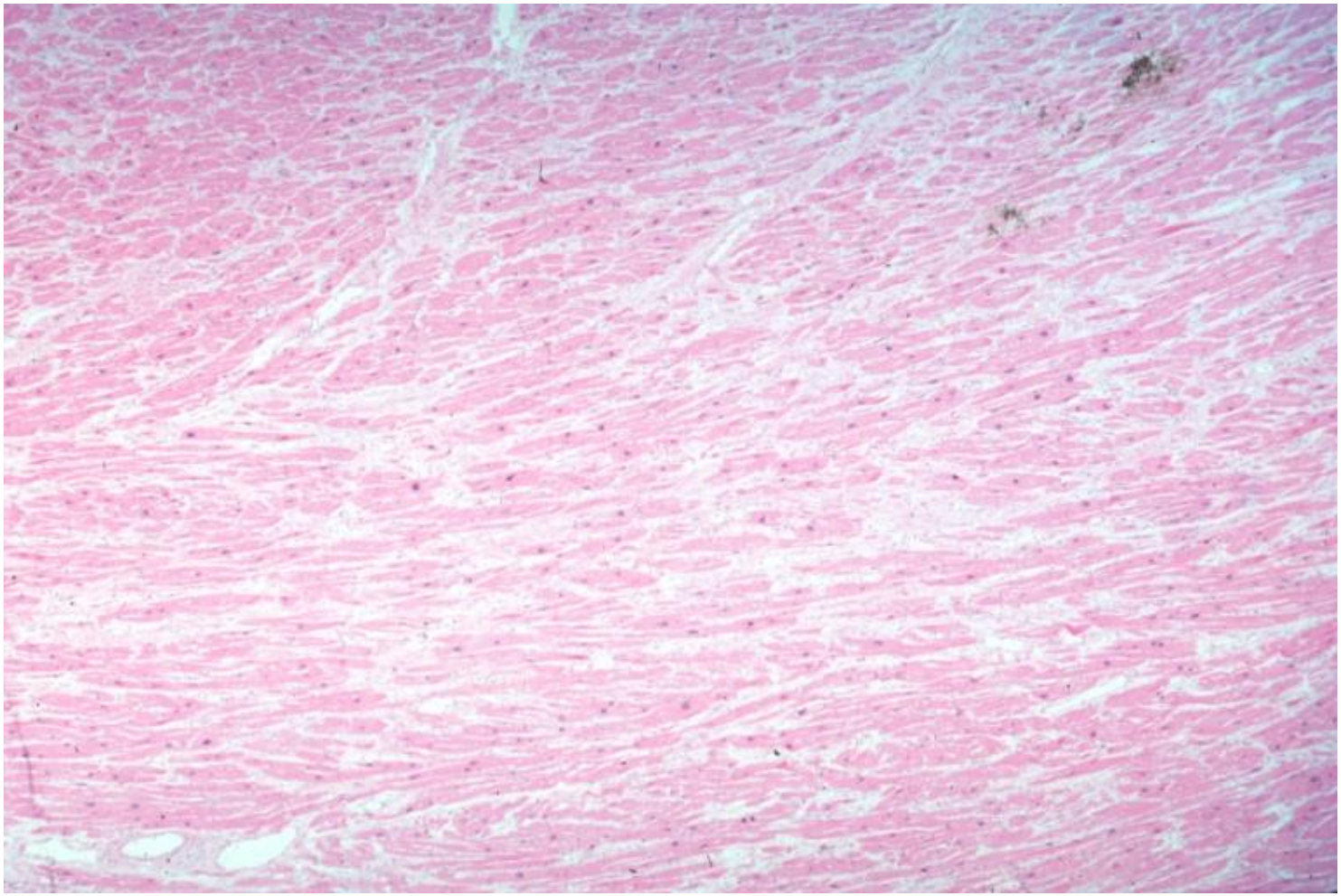
(Hypertrophic Cardiomyopathy: Microscopic Findings)

- The earliest histological changes are myocyte disorganization which is widespread throughout the ventricles.
- The interventricular septum demonstrates myocyte disarray, the hallmark of HCM.
- The abnormal arrangement of large hypertrophied muscle bundles crossing each other.
- The most sensitive and specific change is circular arrays of myocytes around central foci of connective tissue .
- Cross sections of the sarcomere show a highly organized orthohexagonal array.
- The abnormal myosin interferes with the normal spatial arrangement of the myofibril.

http://pathologyoutlines.com/topic/hearthypertrophic.html

Mechanisms

(Hypertrophic Cardiomyopathy: Microscopic Findings)



Interstitial fibrosis with many fibroblastic cells.

http://www.wikidoc.org/index.php/File:3480.jpg

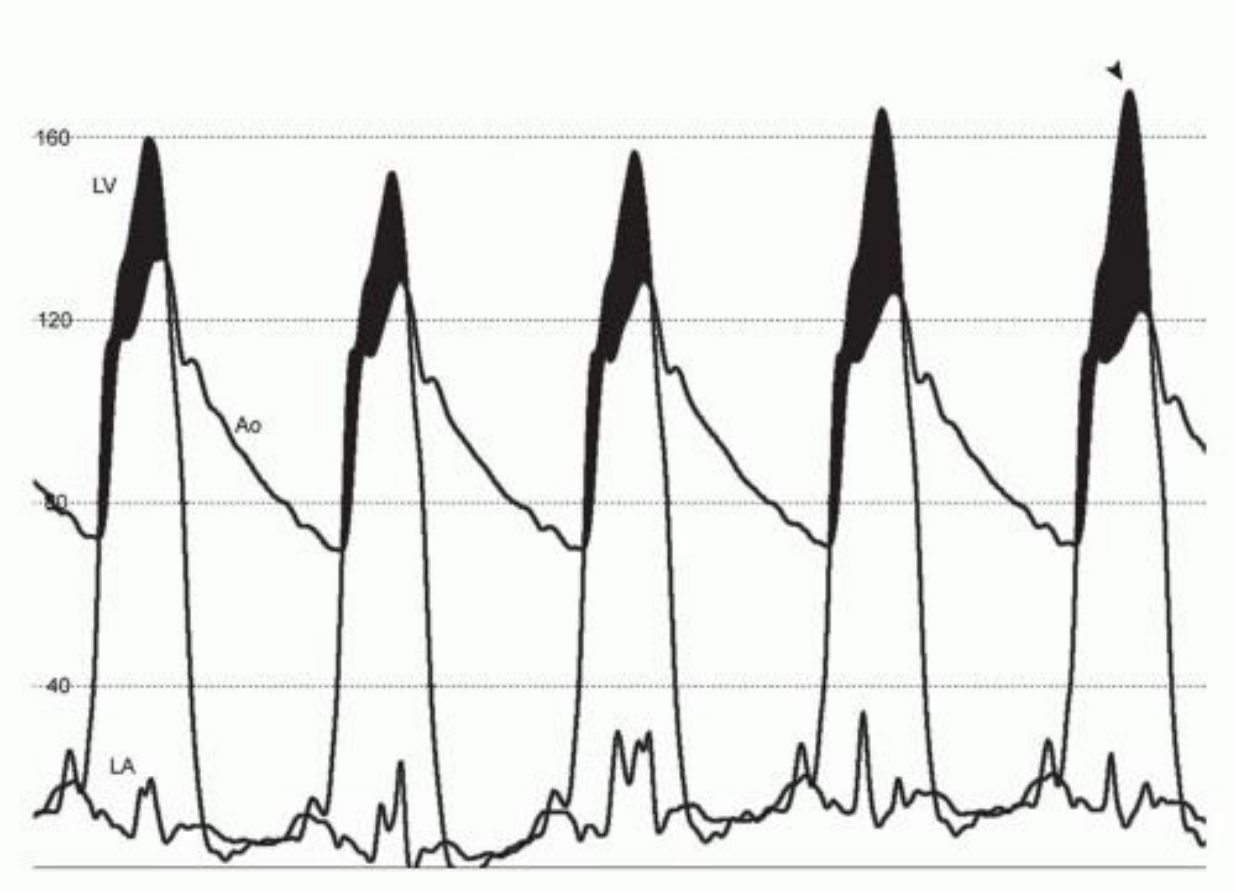
Mechanisms
(Hypertrophic Cardiomyopathy: Pathophysiology)

- The greatest factor is the dynamic pressure gradient across the LV outflow tract.
- The explanations for the systolic anterior motion of the mitral valve (MV): (1) the MV is pulled against the septum by contraction of the papillary muscles; (2) the MV is pushed against the septum; (3) the MV is drawn toward the septum (Venturi effect).
- Most patients have abnormal diastolic function, which impairs ventricular filling and increases filling pressure, despite a normal or small ventricular cavity.

http:// http://emedicine.medscape.com/article/152913-overview#a3

Mechanisms

(Hypertrophic Cardiomyopathy: Pathophysiology)



Changes in left ventricular outflow tract obstruction. Ao, ascending aorta; LA, left atrium; LV, left ventricle.

http://thoracickey.com/hypertrophic-cardiomyopathy-2/

US MLE TEST

A 28-year-old female presents to her primary care physician complaining of a one-week history of fatigue, progressively worsening shortness of breath, and swelling of her feet and ankles. Her past medical history is unremarkable. Her temperature is 37 C (98.6 F), blood pressure is 120/70 mmHg, pulse is 84/min, and respiratory rate is 20/min. Her physical exam is also notable for bibasilar crackles, jugular venous distension, an S3 gallop, and 2+ pitting edema up to the ankles bilaterally. Her electrolytes and complete blood count are within normal limits. Transthoracic echocardiogram of her heart will likely show which of the following?

1. Mitral stenosis, 2. Aortic valve vegetations, 3. Idiopathic pulmonary arterial hypertension, 4. Dilated ventricles with diffuse hypokinesia, 5. Eccentric cardiac hypertrophy.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

US MLE TEST

Correct Answer 4: This patient has acute onset of congestive heart failure (CHF) following a recent upper respiratory tract infection, suggesting dilated cardiomyopathy secondary to acute viral myocarditis. Echocardiography would reveal dilated ventricles with diffuse hypokinesia.

Incorrect Answers: 1: Mitral stenosis is characterized by a mid-diastolic murmur and opening snap, with EKG evidence of left atrial hypertrophy, 2: Aortic valve vegetations would result from infective endocarditis, resulting in fevers, chills, and aortic regurgitation, 3: Idiopathic pulmonary arterial hypertension would typically present with dyspnea on exertion and isolated right-sided heart failure in more advanced cases. 5: Eccentric hypertrophy is seen in chronic volume overload and would not be present in acute CHF.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

Classification
(International Classification of Diseases (ICD): 1)

142 Cardiomyopathy

I42.0 Dilated (congestive) CM

I42.1 Obstructive hypertrophic CM = hypertrophic subaortic stenosis

I42.2 Other (nonobstructive) hypertrophic CM

I42.3 Endomyocardial (eosinophilic) disease

I42.4 Endocardial fibroelastosis (congenital CM)

I42.5 Other restrictive cardiomyopathy

I42.6 Alcoholic CM

I42.7 CM due to drugs and other external agents

I42.8 Other CM

I42.9 CM , unspecified

I43* CM in diseases classified elsewhere

I43.0* CM in infectious and parasitic diseases classified elsewhere

CM in metabolic diseases

CM in nutritional diseases

CM in other diseases classified elsewhere

apps.who.int/classifications/icd10/browse/2016/en#/I46

Classification
(Primary and Secondary)

- Primary/intrinsic cardiomyopathies:
  - Genetic (HCM, arrhythmogenic right ventricular CM (ARVC), left ventricle (LV) non-compaction, Ion Channelopathies, DCM, restrictive CM (RCM).
  - Acquired (stress CM, myocarditis, ischemic CM).
- Secondary/extrinsic CM: metabolic/storage (Fabry's disease, hemochromatosis), endomyocardial (endomyocardial fibrosis, hypereosinophilic syndrome), endocrine (diabetes mellitus, hyperthyroidism, acromegaly), cardiofacial (noonan syndrome), neuromuscular (muscular dystrophy, Friedreich's ataxia), other (obesity-associated cardiomyopathy).

https://en.wikipedia.org/wiki/Cardiomyopathy

Classification
(World Health Organization Classification)

Type	Features	Causative Factors
Dilated	Dilated left or both ventricle(s), with impaired contraction	Ischemic, idiopathic, familial-genetic, immune, alcoholic, toxic, valvular
Hypertrophic	Left or right ventricular hypertrophy, or both	Familial, with autosomal dominant inheritance
Restrictive	Restrictive filling and reduced diastolic filling of one or both ventricles	Idiopathic, amyloidosis, endomyocardial fibrosis
Arrhythmoge-nic right ventricular	Fibrofatty replacement of right ventricular myocardium, Uhl's anomaly (parchment heart)	Unknown; familial, with incomplete penetrance; possible autosomal recessive inheritance; rare forms (eg, Naxos disease)
Unclassified	Not typical for previous four groups	Fibroelastosis, noncompacted myocardium, systolic dysfunction with minimal dilation, mitochondrial disease

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/dilated-restrictive-cardiomyopathy/

Clinical Investigation
(Signs and Symptoms)

Dilated Cardiomyopathy

- Some patients remain asymptomatic throughout life.
- Some patients have severe symptoms of heart failure; arrhythmias; systemic embolism; angina, but only in the presence of ischemic heart disease.

Hypertrophic Cardiomyopathy

- Some patients remain asymptomatic throughout life.
- Some patients have severe symptoms of heart failure, arrhythmias, systemic embolism.
- Some patients die suddenly, often in the absence of previous symptoms.

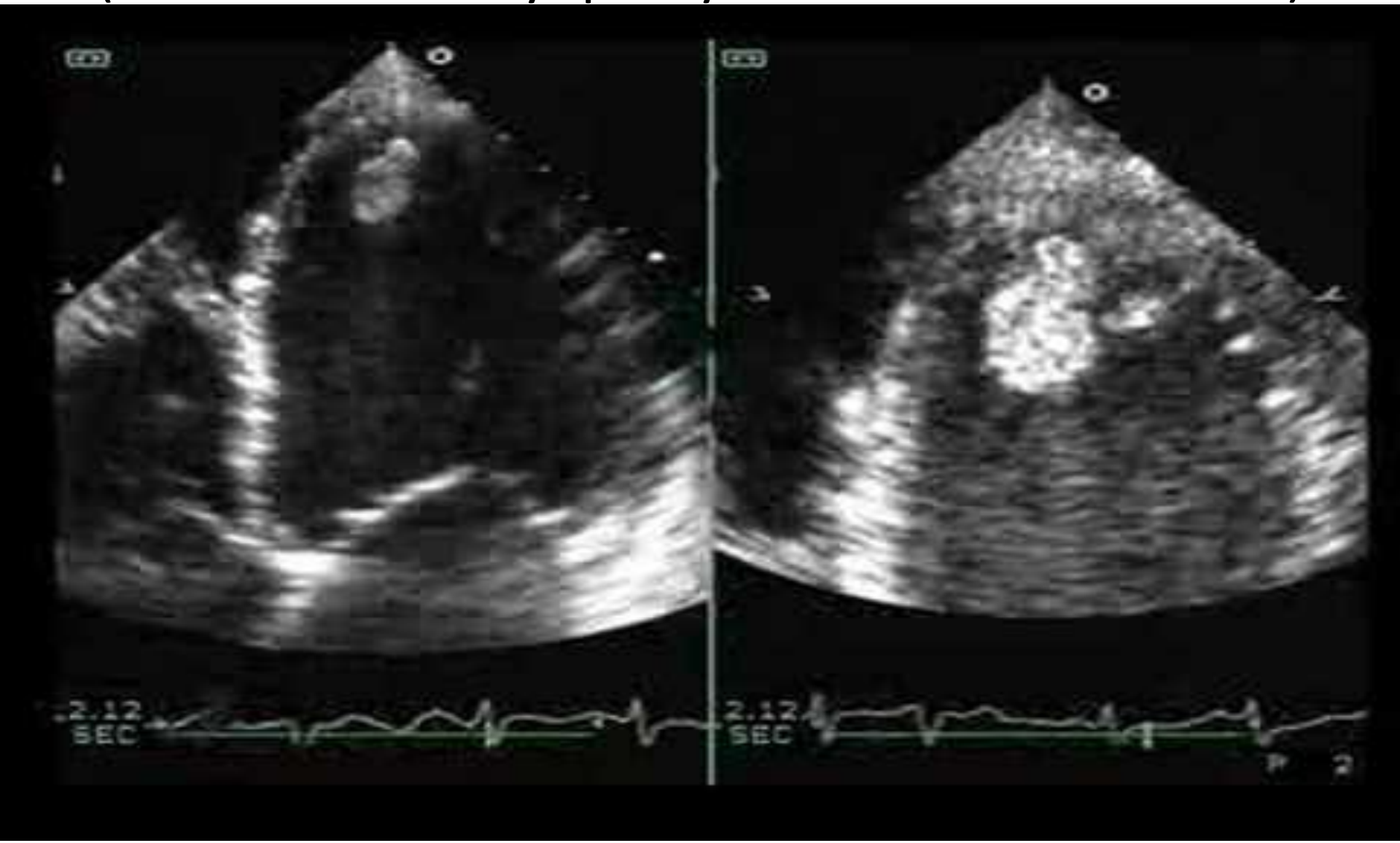
en.wikipedia.org/wiki/Dilated_cardiomyopathy#Signs_and_symptoms pathologyoutlines.com/topic/heartdilated.html pathologyoutlines.com/topic/hearthypertrophic.html

Diagnosis
(Dilated Cardiomyopathy)

- DCM is characterized by enlargement of the heart with a decreased shortening fraction (usually less than 25%), sinus tachycardia or atrial fibrillation, left bundle-branch block (LBBB).
- Genetic testing can help understand the underlying cause of the DCM.
- DCM is usually identified when limiting symptoms are severe, but arrhythmias or sudden death are uncommonly early manifestations.
- Arrhythmias in DCM are typically prominent only after the onset of significant heart failure.
- A family history of DCM is present in over 50% of patients.

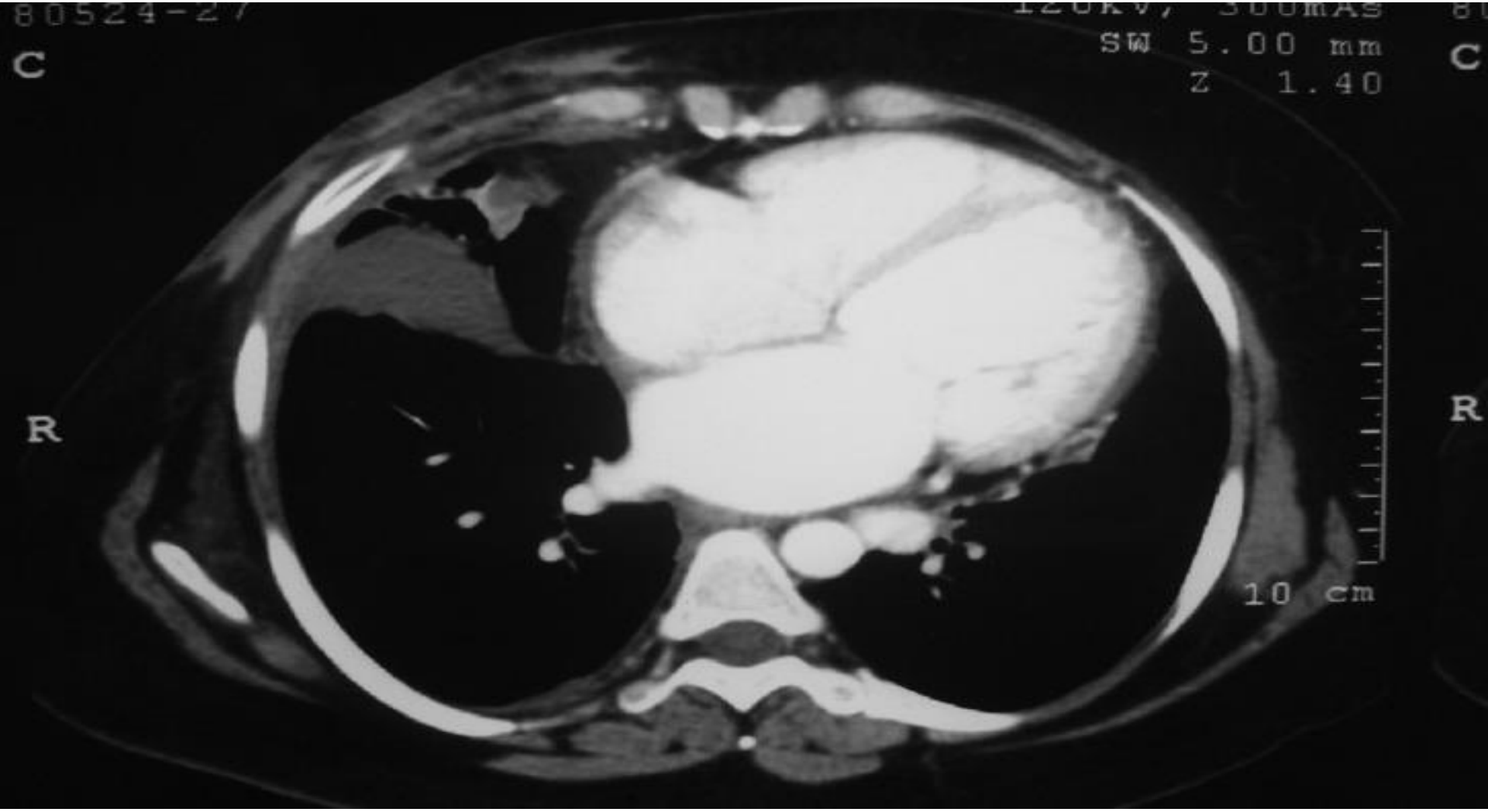
https://en.wikipedia.org/wiki/Dilated_cardiomyopathy#Signs_and_symptoms clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/cardiac-arrhythmias/

Diagnosis
(Dilated Cardiomyopathy with Mural Thrombus)



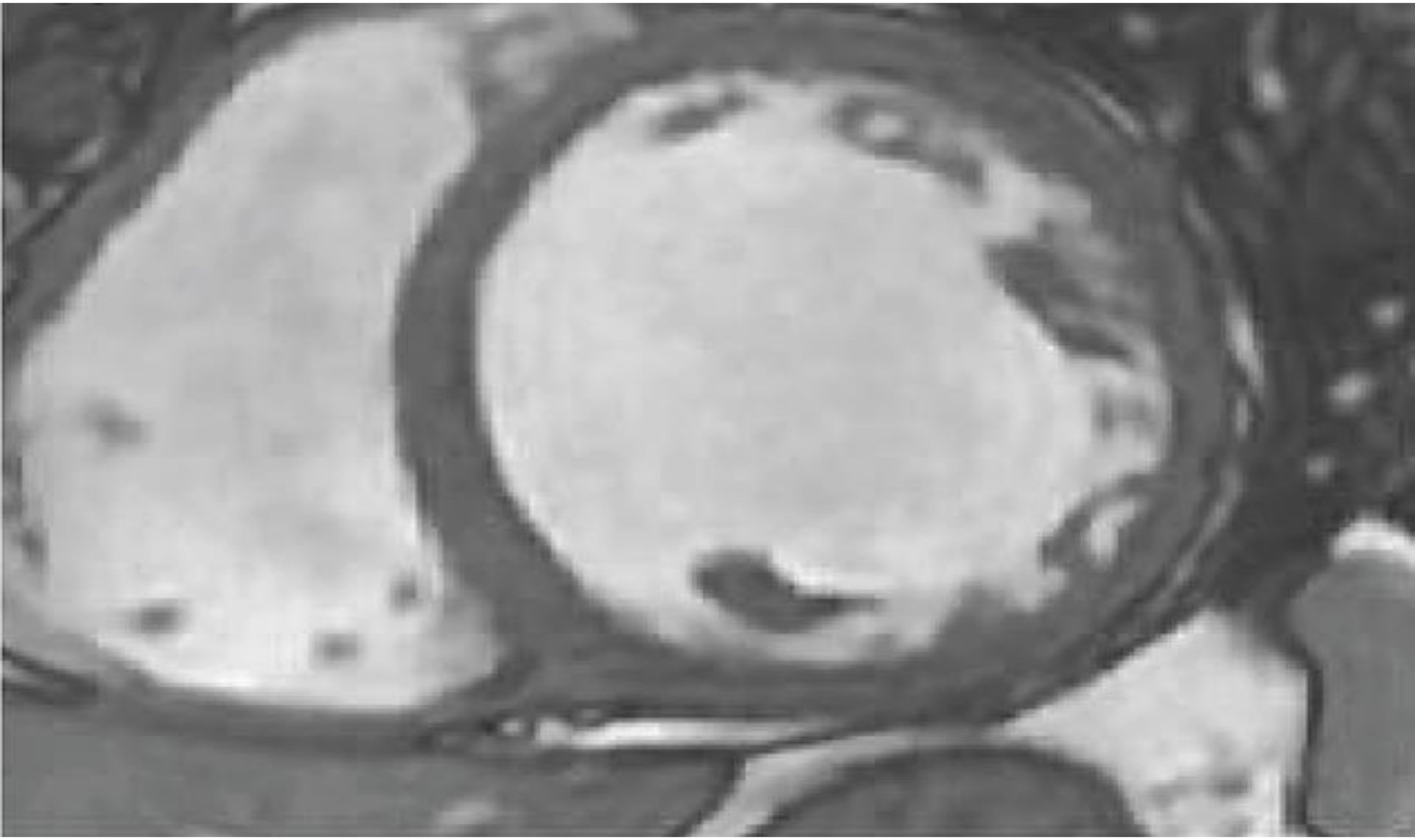
https://i.ytimg.com/vi/FtcDPkKE6to/hqdefault.jpg

Diagnosis
(Dilated Cardiomyopathy following Trastuzumab Chemotherapy)



http://medind.nic.in/ibi/t12/i1/ibit12i1p131.htm

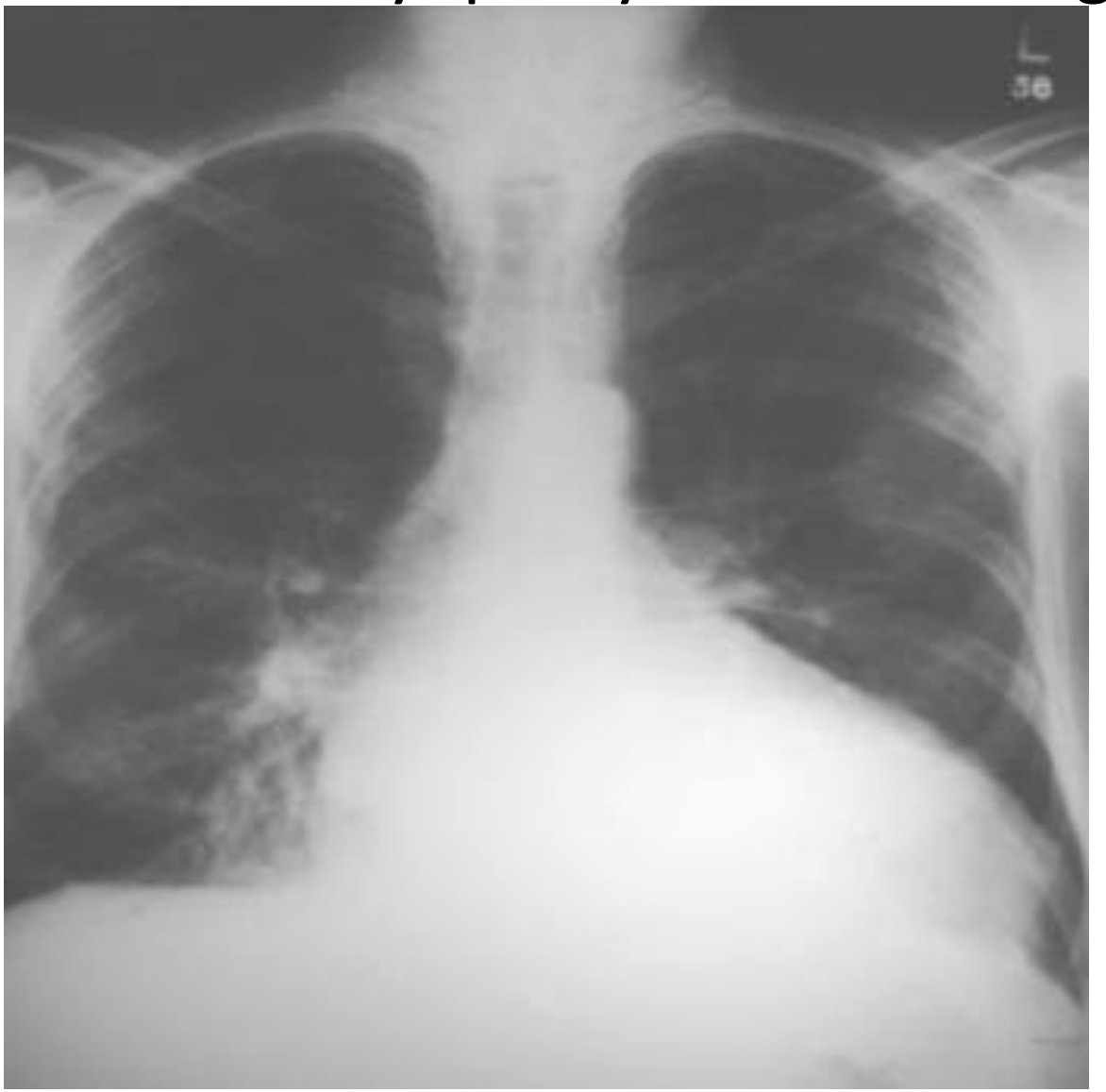
Diagnosis
(Dilated Cardiomyopathy: The Veteran Athlete's Heart)



http://www.aspetar.com/journal/viewarticle.aspx?id=33#.V39bWLiLQhc

Diagnosis

(Dilated Cardiomyopathy: Chest Radiograph)



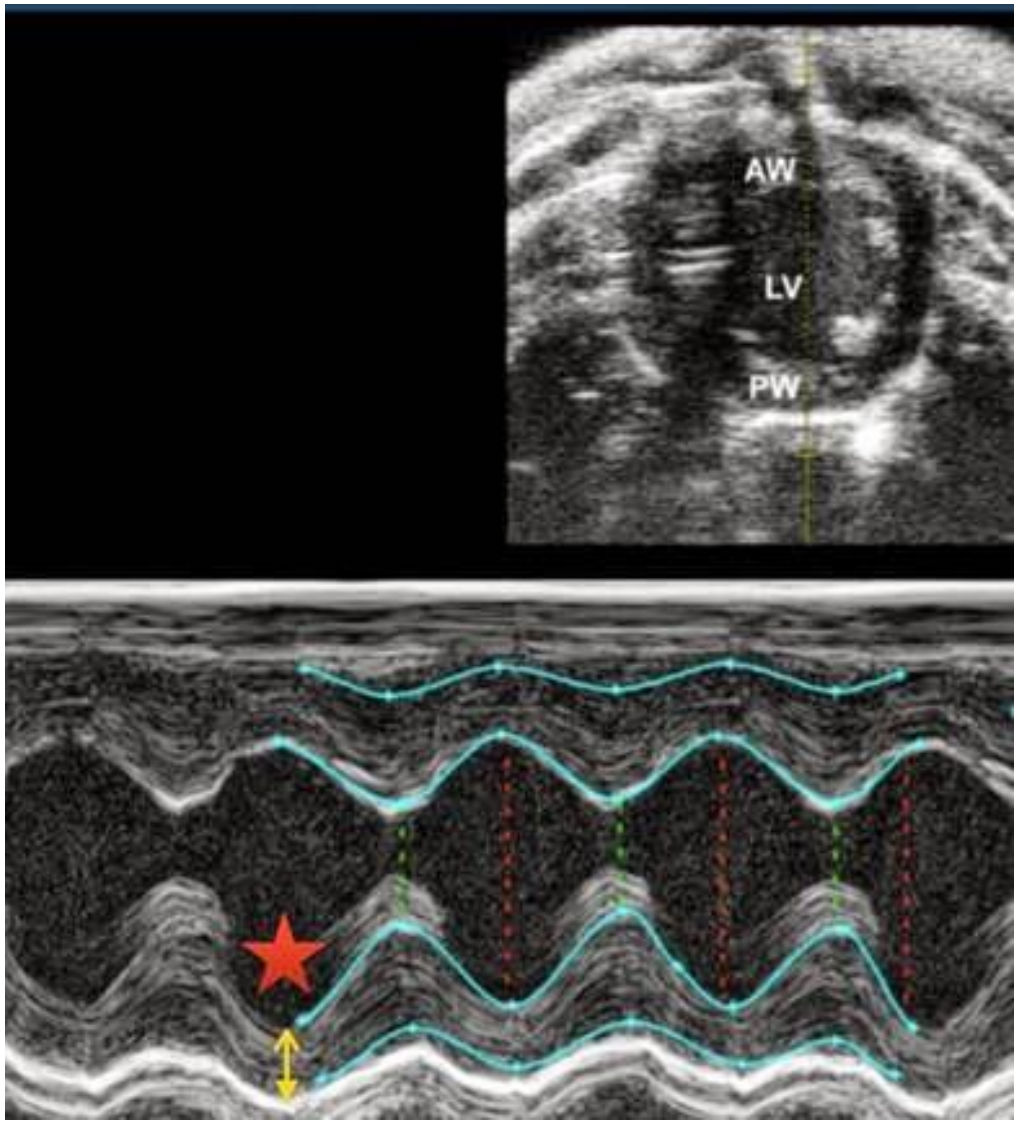
http://emedicine.medscape.com/article/348284-overview

Diagnosis
(Hypertrophic Cardiomyopathy)

- No specific laboratory blood tests are required.
- Genetic testing is not yet widely available.
- Imaging data: abnormal systolic anterior leaflet motion of the mitral valve, LVH, left atrial enlargement, small ventricular chamber size, septal hypertrophy with septal-to-free wall ratio greater than 1.4:1, mitral valve prolapse, mitral regurgitation, decreased midaortic flow, partial systolic closure of the aortic valve in midsystole.
- Electrocardiography (ECG): ST-T wave abnormalities and LVH, axis deviation, conduction abnormalities, sinus bradycardia, ectopic rhythm, atrial enlargement, abnormal and prominent Q wave in the anterior precordial and lateral limb leads, atrial fibrillation, etc.

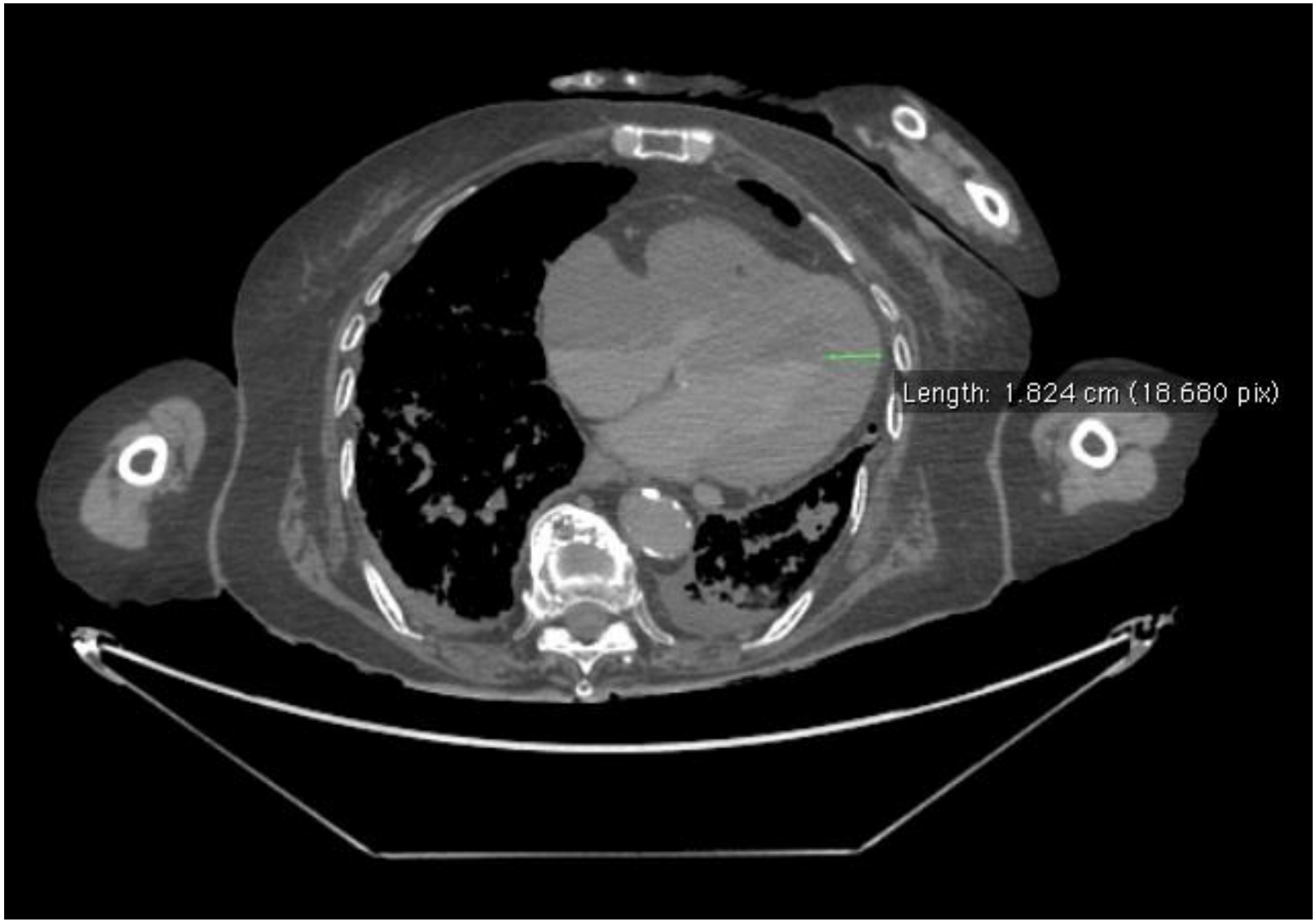
http://emedicine.medscape.com/article/152913-overview#showall

Diagnosis
(Hypertrophic Cardiomyopathy)



http://2.bp.blogspot.com/-FLBZEezZ9kg/VBSgVem1leI/AAAAAAAABx4/Ztwyi3saNtE/s1600/cardiaccompassmmodewithwithleftventricalcalc.jpeg

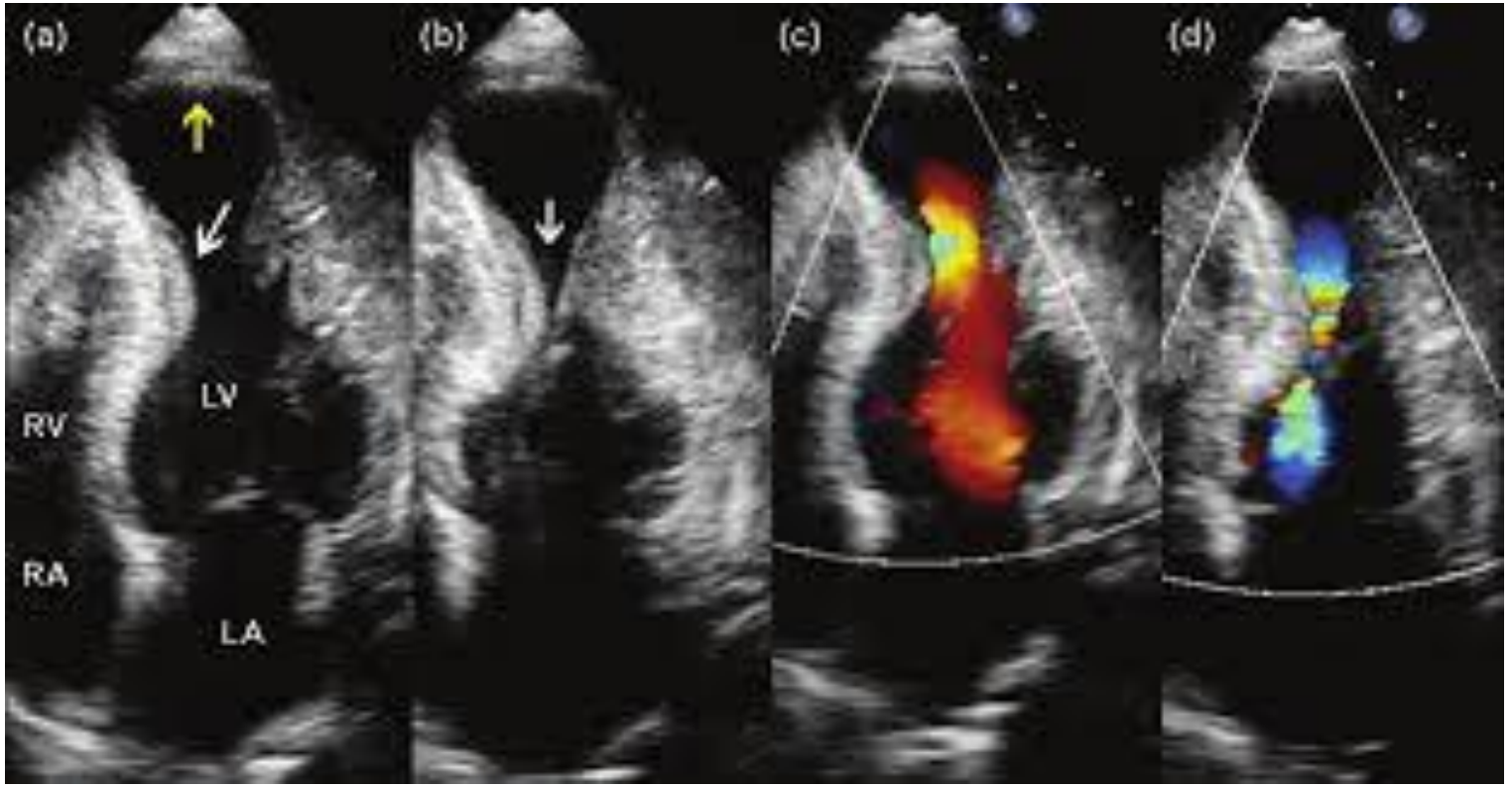
Diagnosis
(Hypertrophic Cardiomyopathy)



http://www.med.umich.edu/lrc/coursepages/m1/anatomy2010/html/clinicalcases/cardiomegaly/cardiomegaly.html

Diagnosis

(Hypertrophic Cardiomyopathy: Midventricular Obstructive)

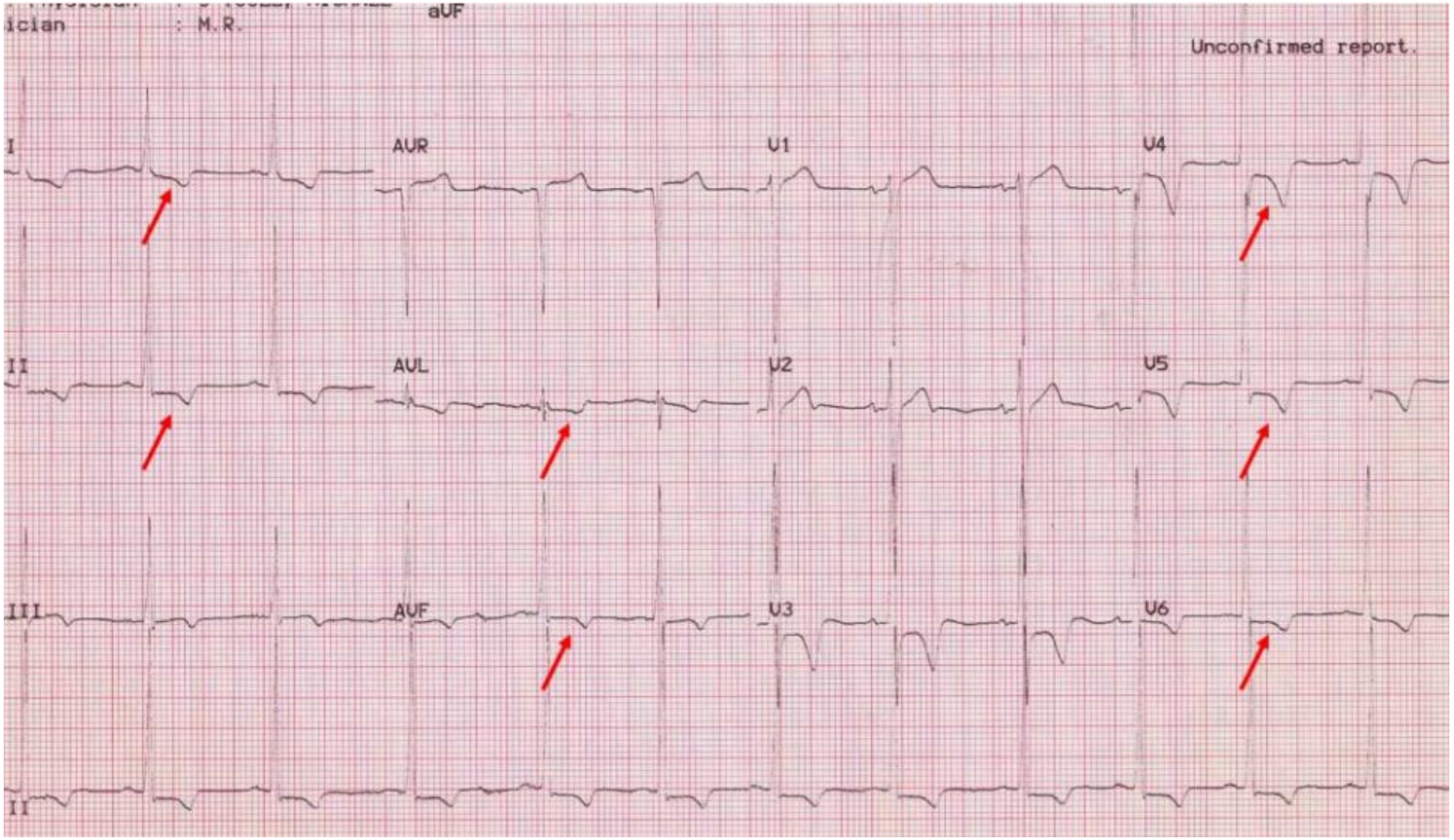


Abnormal ECG in a patient with hypertrophic cardiomyopathy. Note the T wave inversion and ST depression in the inferolateral leads (arrows)

http://journals.lww.com/jcardiovascularmedicine/Abstract/2015/11000/Clinical_characteristics_and_prognosis_of_60.4.aspx

Diagnosis

(Hypertrophic Cardiomyopathy in Athletes)



Abnormal ECG in a patient with hypertrophic cardiomyopathy. Note the T wave inversion and ST depression in the inferolateral leads (arrows)

http://emedicine.medscape.com/article/348284-overview

US MLE TEST

A 58-year-old man presents to his primary care doctor complaining of several months of worsening shortness of breath and ankle swelling. He has no significant past medical or surgical history. His temperature is 37 C (98.6 F), pulse is 78, blood pressure is 130/72 mm Hg, and respiratory rate is 16. He has elevated jugular venous pressure, diminished breath sounds at the lung bases, tender hepatomegaly, and bilateral pitting ankle edema. There are no murmurs, rubs, or gallops. His chest x-ray shows a normally sized heart and bilateral pleural effusions. Echocardiography shows symmetrical thickening of the left ventricle, normal left ventricular volume, and mildly reduced systolic function. Which of the following lab tests would help identify a reversible cause of this patient's illness?

1. Liver function tests, 2. Transferrin saturation, 3. Serum protein electrophoresis, 4. Antitopoisomerase antibodies , 5. Serum angiotensin converting enzyme (ACE) levels.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

US MLE TEST

Correct Answer 2: This patient has congestive heart failure secondary to restrictive cardiomyopathy. Hereditary hemochromatosis is a reversible cause of restrictive cardiomyopathy and is diagnosed by measuring serum transferrin saturation.
Incorrect Answers: 1: Although hemochromatosis does cause hepatocellular damage resulting in elevated LFTs, this test is nonspecific for diagnosing hemochromatosis, 3: Serum protein electrophoresis would aid in the diagnosis of systemic amyloidosis, which is generally considered irreversible, 4: Antitopoisomerase antibodies are measured to diagnose systemic sclerosis, which is also an irreversible condition, 5: ACE levels are sometimes used to help diagnose sarcoidosis, an irreversible cause of restrictive cardiomyopathy.

https://www.medbullets.com/step1-endocrine/9019/pheochromocytoma

Treatment
(Dilated Cardiomyopathy)

- Essentially the same as treatment of chronic heart failure (HF).
- Drug therapy can slow down progression and in some cases even improve the heart condition and may include salt restriction, angiotensin converting enzyme (ACE) inhibitors, diuretics, anticoagulants.
- Surgery: artificial pacemakers; implantable cardioverter-defibrillators; ventricular remodeling, heart transplantation may be considered.

https://en.wikipedia.org/wiki/Dilated_cardiomyopathy#Signs_and_symptoms

Treatment
(Hypertrophic Cardiomyopathy)

- A significant number of patients do not have any symptoms and will have normal life expectancies, though they should be counseled to avoid particularly strenuous activities or competitive athletics.
- In patients with resting or inducible outflow obstructions, situations that will cause dehydration or vasodilation should be avoided.
- The primary goal of medications is to relieve symptoms, and first-line agents include beta blockers and calcium channel blockers (verapamil).
- Surgery: septal myectomy, septal ablation, implantable pacemaker or defibrillator, cardiac transplantation.

https://en.wikipedia.org/wiki/Hypertrophic_cardiomyopathy#Treatment

Prognosis

- DCM: survival rate of less than 50% at 10 years; there is a negative association survival with frequent ventricular tachyarrhythmias that require antiarrhythmic treatment or automated implantable cardioverter-defibrillator (AICD) placement.
- HCM: annual mortality rates of up to 6% , important independent predictors of mortality are mutations in the b-MHC, occurrence of atrial fibrillation, stroke, presence of basal outflow obstruction of at least 30 mm Hg and marked left ventricular wall thickness of more than 25 mm.

http://emedicine.medscape.com/article/2017823-overview#a4 http://pathologyoutlines.com/topic/hearthypertrophic.html

Prophylaxis

- Cardiomyopathy may be due to an underlying diseases or conditions.
- Treating that conditions early enough may help prevent cardiomyopathy complications.
- Sudden cardiac arrest (SCA) may be prevented in patients at high risk if they are treated with an implantable cardioverter defibrillator.

en.wikipedia.org/wiki/Supraventricular_tachycardia#Medications

Abbreviations

ACE – angiotensin converting enzyme

Ao -ascending aorta

ARVC - arrhythmogenic right ventricular cardiomyopathy

DCM - dilated cardiomyopathy

ECG – electrocardiography

HCM - hypertrophic cardiomyopathy

HF - chronic heart failure

LA - left atrium

LBBB - left bundle-branch block

LV - left ventricle

MV - mitral valve

SCA - sudden cardiac arrest

Diagnostic and treatment guidelines

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

Hypertrophic Cardiomyopathy

Dilated Cardiomyopathy