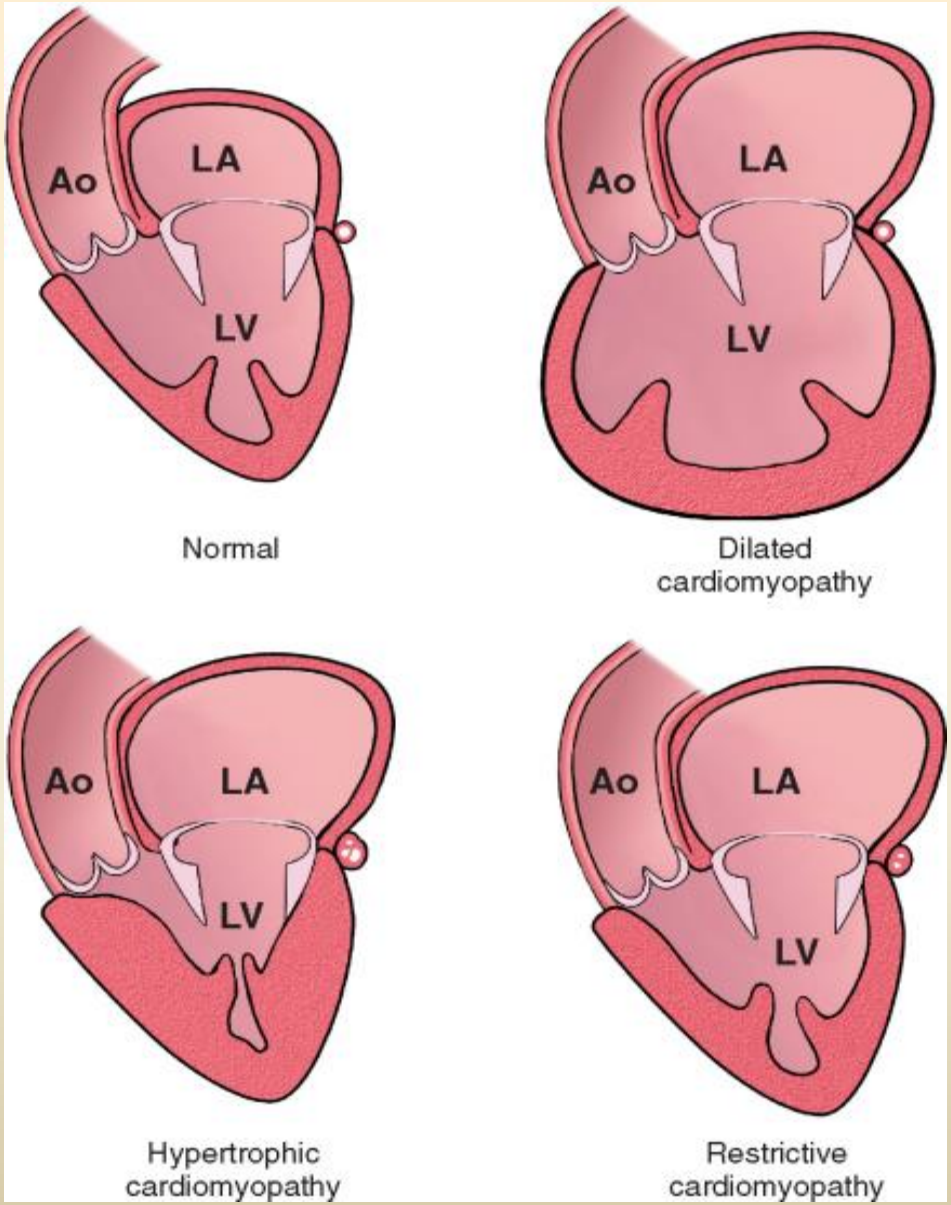
Cardiomyopathies

Cardiomyopathy

- "heart muscle diseases of unknown cause"
- Diseases of the myocardium associated with cardiac dysfunction

Classification

- Dilated cardiomyopathy (DCM)
- Hypertrophic cardiomyopathy (HCM)
- Restrictive cardiomyopathy (RCM)
- Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
- Unclassified cardiomyopathies


Ao
LA
LV
Normal
Ao
LA
LV
Dilated cardiomyopathy
Ao
LA
LV
Hypertrophic cardiomyopathy
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LA
LV
Restrictive cardiomyopathy

Dilated Cardiomyopathy

- Dilated cardiomyopathy is characterized by ventricular dilation and impaired contractile performance, which may involve the left or both ventricles

- May develop as a consequence of prior myocarditis or as a result of a recognized toxin, infection, predisposing cardiovascular disease (e.g., hypertension, ischemic or valvular heart disease
- When no cause or associated disease is identified, dilated cardiomyopathy has been termed **idiopathic**
- 50 to 60% of such patients have familial disease, and disease-causing mutations currently can be identified in 10 to 20% of such families.

Pathobiology

- Systolic dysfunction may result from a variety of causes
- Altered hemodynamic parameters of decreased stroke volume and increased chamber pressures trigger the recognized neurohumoral changes of heart failure

- The insult to myocyte integrity may be relatively acute and may trigger programmed cell death (apoptosis);
- Insidious progression is the rule in inherited dilated cardiomyopathy and is also seen with viral persistence, anthracycline toxicity, and autoimmune dilated cardiomyopathy

- A trigger with immune-mediated pathogenesis in genetically predisposed individuals
- Mutations in genes encoding important structural proteins in 20 to 30% of families with dilated cardiomyopathy
- Sarcomeric genes (10%) and lamin A/C (5%)
- One third of probands and family members develop low-titer, organ-specific autoantibodies to cardiac α-myosin
- Viral persistence has also been implicated as an ongoing trigger of immune-mediated damage

Clinical Manifestations

- Gradual decrease in exercise capacity may be appreciated only in retrospect.

- The initial presentation is often with acute decompensation triggered by an unrelated problem, such as anemia, thyrotoxicosis, or infection

- Symptoms relating to raised filling pressures:

orthopnea, nocturnal cough, paroxysmal nocturnal dyspnea, peripheral edema

- Precede symptoms of low cardiac output:

Fatigue, dyspnea on exertion

Diagnosis

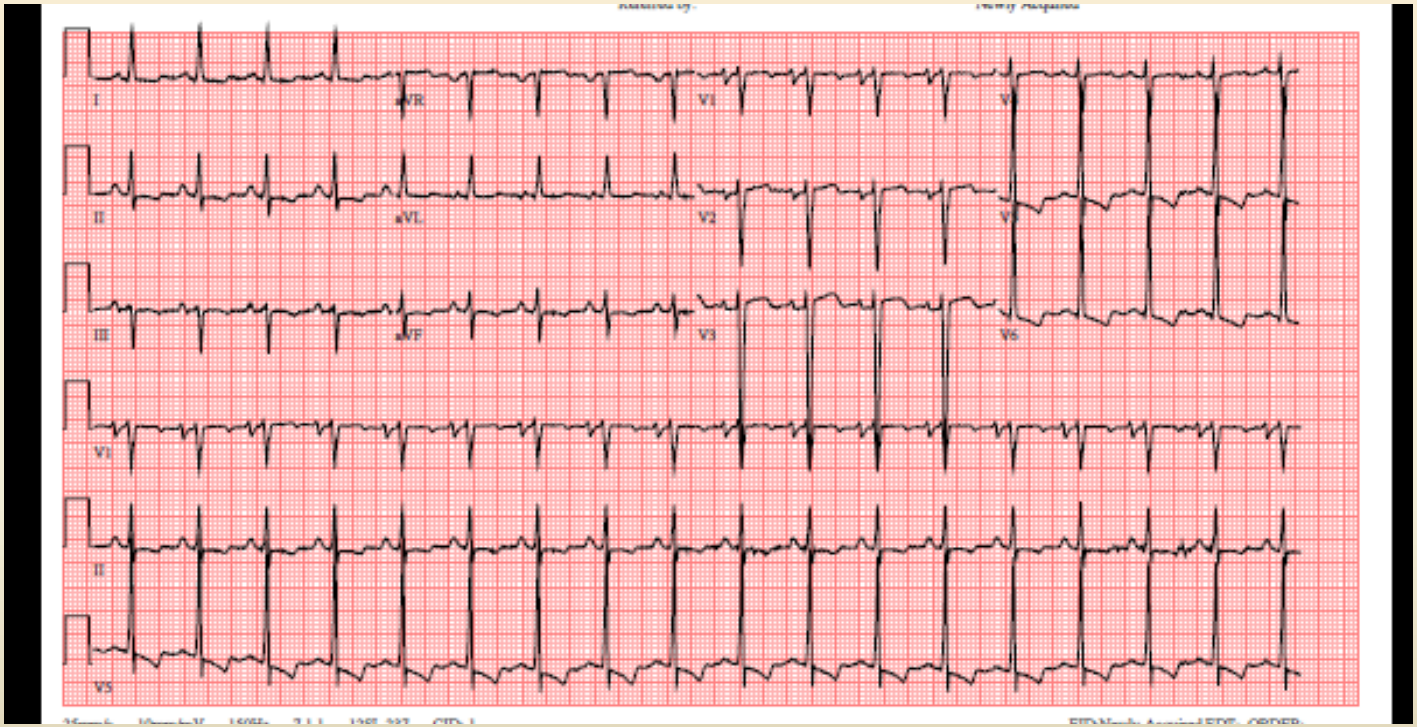
- Signs or symptoms of heart failure accompanied by indices of advanced left ventricular impairment and dilation
- An early diagnosis of dilated cardiomyopathy requires consideration of the common recognized causes:
- systemic hypertension, valvular heart disease, associated systemic disorders, high-output states, and the muscular dystrophies

ECG

- The changes of early disease are not specific and may include:

left axis deviation and T wave abnormalities.

- With progressive and advanced disease, conduction abnormalities develop: PR prolongation, QRS widening, and left bundle branch block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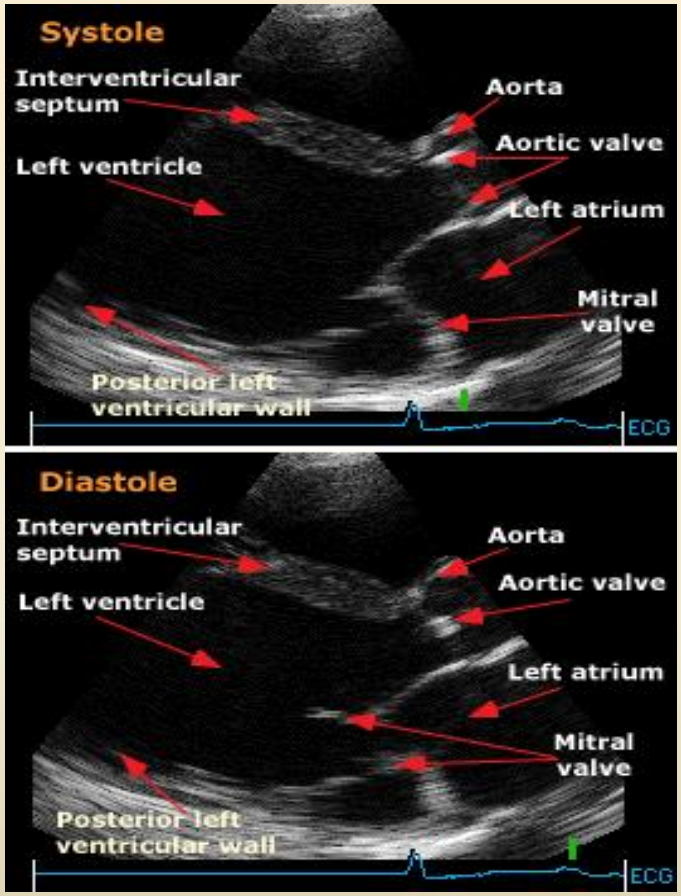
Echocardiogram

- As a baseline and for serial assessment to monitor disease progression and the effect of treatment


Systole
Interventricular septum
Aorta
Aortic valve
Left ventricle
Left atrium
Mitral valve
Posterior left ventricular wall
ECG
Diastole
Interventricular septum
Aorta
Aortic valve
Left ventricle
Left atrium
Mitral valve
Posterior left ventricular wall
ECG

MRI

- Gadolinium-enhanced magnetic resonance imaging may be very helpful in differentiating segmental wall motion abnormalities in dilated cardiomyopathy from previous myocardial infarction

Biopsy

- Occasionally should be considered in patients with potential unexplained myocarditis.

Treatment

- Supportive therapy includes:
- Sodium and fluid restriction,
- Avoidance of alcohol and other toxins,
- Use of established heart failure medications

Alcoholic Cardiomyopathy

- Alcohol and its metabolite, acetaldehyde, are cardiotoxins acutely and chronically.
- Myocardial depression is initially reversible but, if sustained, can lead to irreversible vacuolization, mitochondrial abnormalities, and fibrosis
- The amount of alcohol necessary to produce symptomatic cardiomyopathy in susceptible individuals is not known
- Abstinence leads to improvement in at least 50% of patients with severe symptoms, some of whom normalize their left ventricular ejection fractions

Chemotherapy

- Doxorubicin (Adriamycin) cardiotoxicity causes characteristic histologic changes on endomyocardial biopsy, with overt heart failure in 5 to 10% of patients who receive doses greater than or equal to 450 mg/m2 of body surface area
- Cyclophosphamide and ifosfamide can cause acute severe heart failure and malignant ventricular arrhythmias
- 5-Fluorouracil can cause coronary artery spasm and depressed left ventricular contractility.
- Trastuzumab has been associated with an increased incidence of heart failure

Metabolic Causes

- Excess catecholamines, as in *pheochromocytoma*
- *Cocaine* increases synaptic concentrations of catecholamines by inhibiting reuptake at nerve terminals; the result may be an acute coronary syndrome or chronic cardiomyopathy.

- *Thiamine deficiency* can cause beriberi heart disease, with vasodilation and high cardiac output followed by low output.
- *Calcium deficiency* resulting from hypoparathyroidism, gastrointestinal abnormalities, or chelation directly compromises myocardial contractility.
- *Hypophosphatemia* which may occur in alcoholism, during recovery from malnutrition, and in hyperalimentation, also reduces myocardial contractility.
- Patients with *magnesium depletion* owing to impaired absorption or increased renal excretion also may present with left ventricular dysfunction.

Skeletal Myopathies

- Duchenne's muscular dystrophy and Becker's X-linked skeletal muscle dystrophy typically include cardiac dysfunction
- Maternally transmitted mitochondrial myopathies such as Kearns-Sayre syndrome frequently cause cardiac myopathic changes

Peripartum Cardiomyopathy

- Peripartum cardiomyopathy appears in the last month of pregnancy or in the first 5 months after delivery in the absence of preexisting cardiac disease
- Lymphocytic myocarditis, found in 30 to 50% of biopsy specimens, suggests an immune component
- The prognosis is improvement to normal or near-normal ejection fraction during the next 6 months in more than 50% of patients.

Hypertrophic Cardiomyopathy

- Genetically determined myocardial disease
- Defined clinically by the presence of unexplained left ventricular hypertrophy
- Pathologically by the presence of myocyte disarray surrounding increased areas of loose connective tissue

- Usually familial, with autosomal dominant inheritance.
- Abnormalities in sarcomeric contractile protein genes account for approximately 50 to 60% of cases

Gene	Protein	Frequency
MYH7	β-Myosin heavy chain	25–35%
MYBPC3	Cardiac myosin binding protein C	20–30%
TNNT2	Cardiac troponin T	3–5%
TNNI3	Cardiac troponin I	<5%
TPM1	α-Tropomyosin	<5%
MYL2	Regulatory myosin light chain	<5%
MYL3	Essential myosin light chain	Rare
ACTC	α-Cardiac actin	Rare
TTN	Titin	Rare
TNNC1	Cardiac troponin C	Rare
MYH6	α-Myosin heavy chain	Single study
CRP3	Muscle LIM protein	Rare

Pathology

- Typically, heart weight is increased and the interventricular septum is hypertrophic,
- Any pattern of thickening may occur
- Histologically, the hallmark of hypertrophic cardiomyopathy is myocyte disarray.
- Results from the loss of the normal parallel arrangement of myocytes, with cells forming in whorls around foci of connective tissue

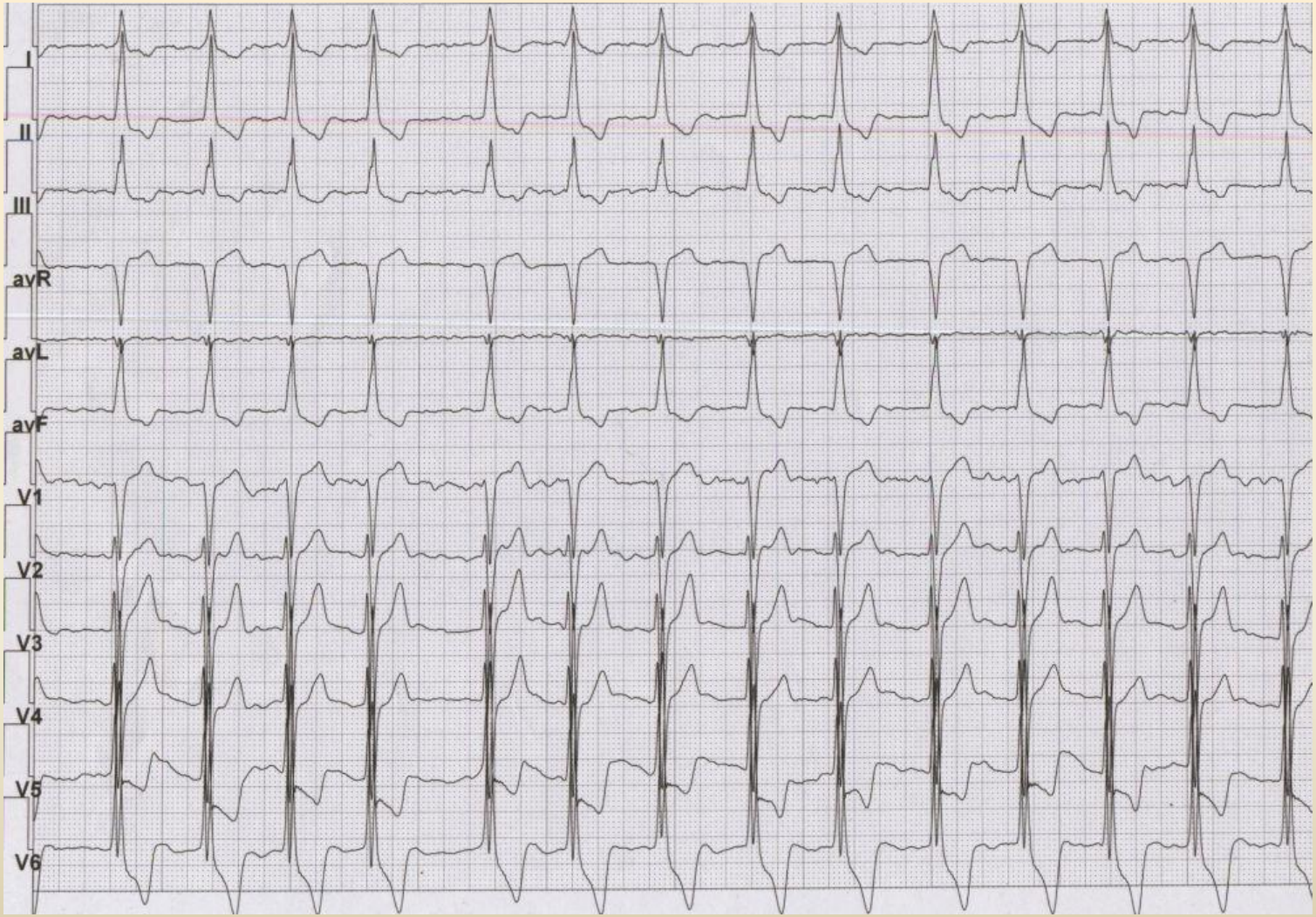
- Left ventricular hypertrophy is usually associated with:
- hyperdynamic indices of systolic performance,
- impaired diastolic function,
- clinical features suggestive of ischemia

- Clinical expression of left ventricular hypertrophy usually occurs during periods of rapid somatic growth,
- May be during the first year of life or childhood but more typically during adolescence and, occasionally, in the early 20s

- Most patients are asymptomatic or have only mild or intermittent symptoms.
- Symptomatic progression is usually slow, age related, and associated with a gradual deterioration in left ventricular function over decades

- Symptoms may develop at any age, even many years after the appearance of LVH
- Occasionally, sudden death may be the initial presentation

- 30% of adults develop exertional chest pain
- Atypical, prolonged, and noted at rest or nocturnally.
- Postprandial angina associated with mild exertion is typical.
- Mild to moderate dyspnea is common in adults
- 20% of patients experience syncope
- Palpitations are a frequent complaint
- Sustained palpitations are usually caused by supraventricular tachyarrhythmias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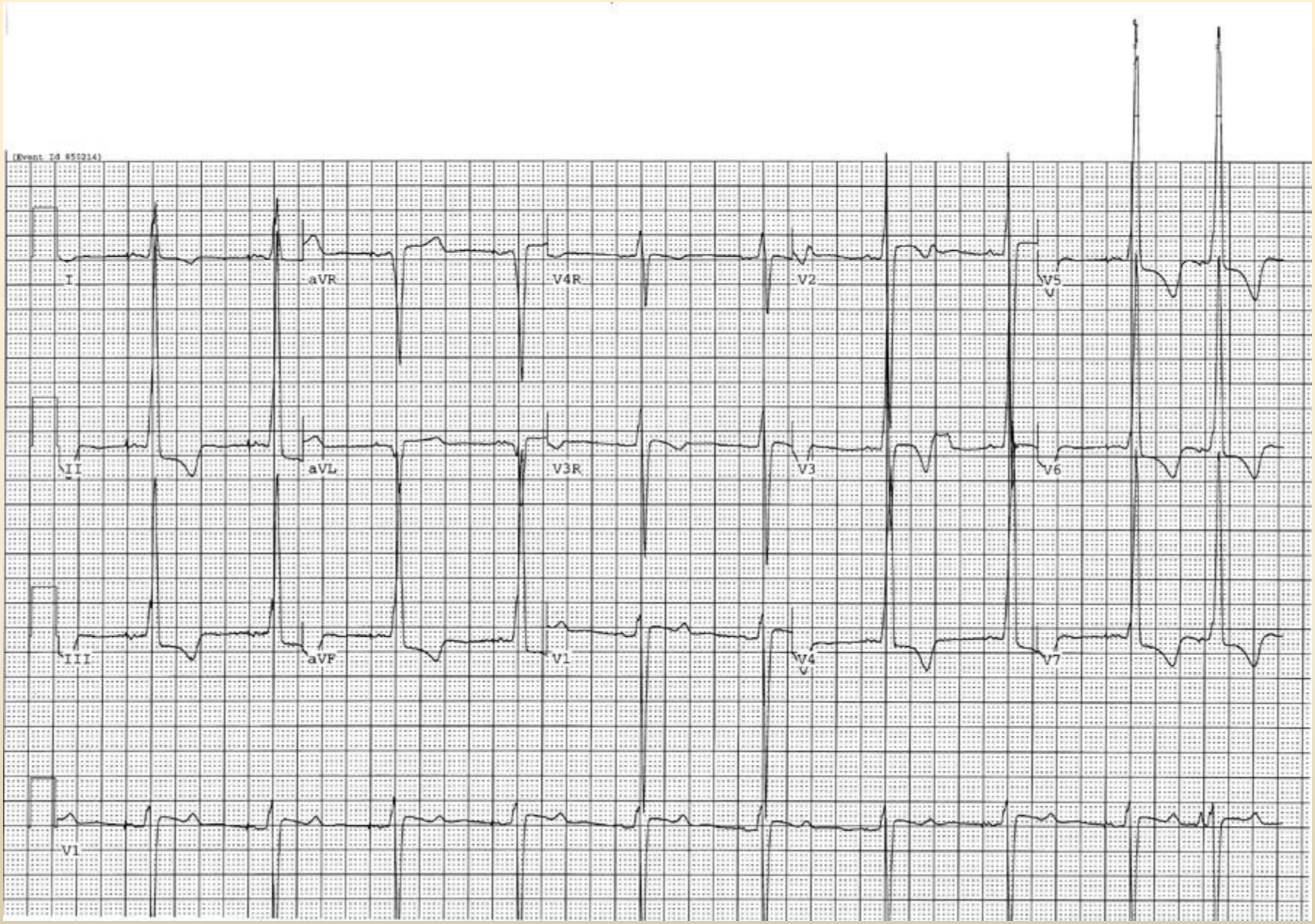
Diagnosis

- The initial diagnostic evaluation includes a family history focusing on premature cardiac disease or death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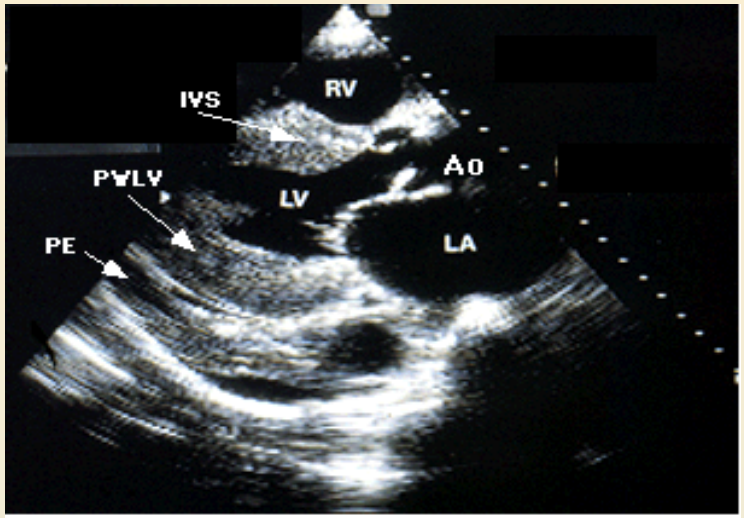
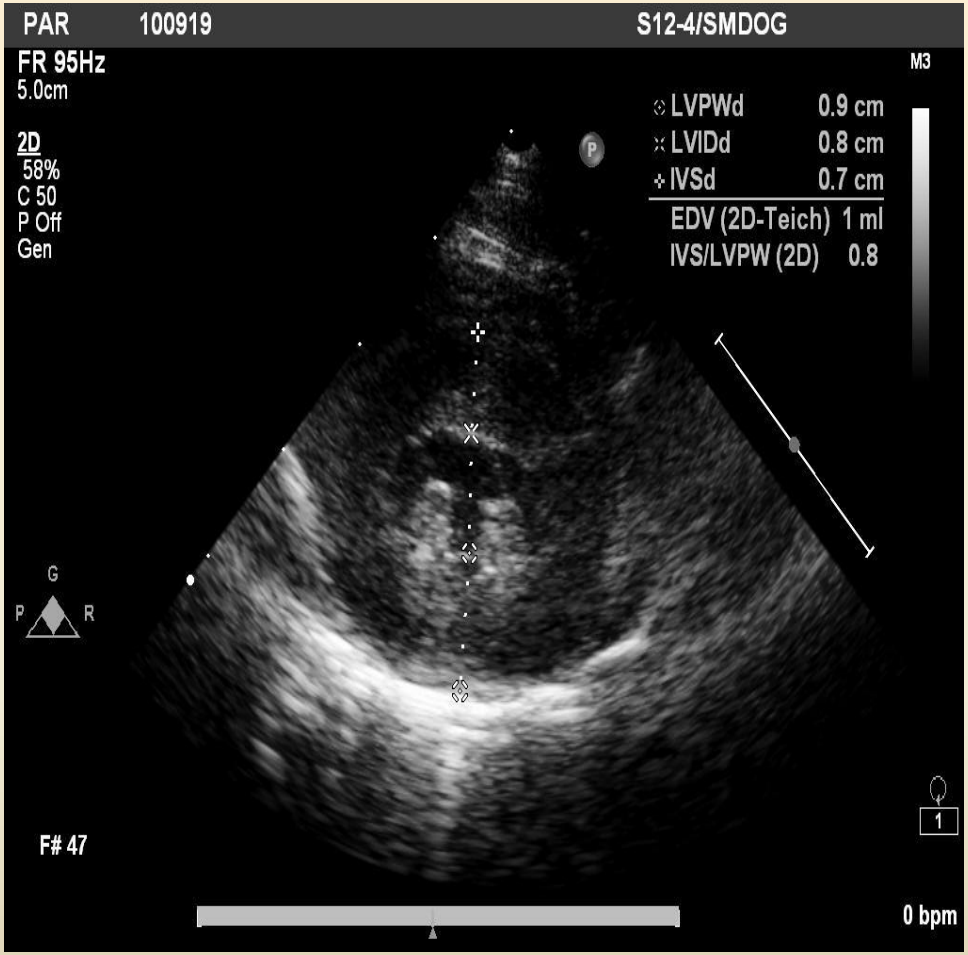


Hypertrophic cardiomyopathy The parasternal long axis view from a two dimensional echocardiogram in a patient with hypertrophic cardiomyopathy shows significant hypertrophy of the interventricular septum (IVS) as well as the posterior left ventricular wall (PWLV); the echo-free space behind the posterior wall is a pleural effusion (PE). RV, right ventricle; Ao, aorta,;LV, left ventricle; LA, left atrium



DIAGNOSTIC CRITERIA FOR HYPERTROPHIC CARDIOMYOPATHY

Major Criteria	Minor Criteria
ECHOCARDIOGRAPHY	
Left ventricular wall thickness ≥13 mm in the anterior septum or posterior wall or ≥15 mm in the posterior septum or free wall	Left ventricular wall thickness of 12 mm in the anterior septum or posterior wall or of 14 mm in the posterior septum or free wall
Severe SAM of the mitral valve (septal-leaflet contact)	Moderate SAM of the mitral valve (no mitral leaflet-septal contact)
	Redundant mitral valve leaflets
ELECTROCARDIOGRAPHY	
Left ventricular hypertrophy with repolarization changes (Romhilt and Estes)	Complete bundle branch block or (minor) interventricular conduction defects (in left ventricular leads)
T wave inversion in leads I and aVL (≥3 mm) (with QRS-T wave axis difference ≥30 degrees), V_3–V_6 (≥3 mm) or II and III and aVF (≥5 mm)	Minor repolarization changes in left ventricular leads
	Deep S wave in lead V_2 (>25 mm)
Abnormal Q waves (>40 msec or >25% R wave) in at least two leads from II, III, aVF (in absence of left anterior hemiblock), and V_1–V_4; or I, aVL, V_5–V_6	Unexplained chest pain, dyspnea, or syncope

Differential Diagnosis

- Causes of left ventricular hypertrophy:

-Long-standing systemic hypertension

-Aortic stenosis

-Highly trained athletes

Treatment

- In the absence of a specific underlying cause or aggravating factor, treatment is for the various stages of heart failure
- Supportive therapy includes sodium and fluid restriction, avoidance of alcohol and other toxins, and use of established heart failure medications

Restrictive Cardiomyopathy

- Characterized by impaired filling and reduced diastolic volume of the left and/or right ventricle despite normal or near-normal systolic function and wall thickness

- Primary forms are uncommon,
- Secondary forms, the heart is affected as part of a multisystem disorder,
- Usually present at the advanced stage of an infiltrative disease (e.g., amyloidosis or sarcoidosis) or a systemic storage disease (e.g., hemochromatosis).

- Restrictive cardiomyopathy may be familial
- Part of the genetic and phenotypic expression of hypertrophic cardiomyopathy caused by sarcomeric contractile protein gene abnormalities

- Secondary forms:

- amyloidosis, hemochromatosis, several of the glycogen storage diseases, and Fabry's disease

- Reported in association with skeletal myopathy and conduction system disease as part of the phenotypic spectrum caused by mutations in lamin A or C.

CAUSES OF RESTRICTIVE CARDIOMYOPATHIES

INFILTRATIVE DISORDERS
Amyloidosis Sarcoidosis
STORAGE DISORDERS
Hemochromatosis Fabry's disease Glycogen storage diseases
FIBROTIC DISORDERS
Radiation Scleroderma Drugs (e.g., doxorubicin, serotonin, ergotamine)
METABOLIC DISORDERS
Carnitine deficiency Defects in fatty acid metabolism
ENDOMYOCARDIAL DISORDERS
Endomyocardial fibrosis Hypereosinophilic syndrome (Lofler's endocarditis)
MISCELLANEOUS CAUSES
Carcinoid syndrome

Pathophysiology

- Increased stiffness of the endocardium or myocardium, induces ventricular pressures to rise disproportionately to small changes in volume until a maximum is reached.

- In infiltrative diseases such as amyloidosis or sarcoidosis, the increased stiffness results from infiltrates within the interstitium between myocardial cells.
- In the storage disorders, the deposits are within the cells

Clinical Manifestations

- Presenting clinical features develop as a consequence of raised ventricular filling pressures
- Not distinguishable from those of heart failure resulting from systolic impairment
- Atrial dilation and atrial fibrillation are common

Diagnosis

- Based on the demonstration of the abnormal filling pattern by Doppler echocardiography
- Magnetic resonance imaging is useful to delineate the distribution of disease

- Presence of abnormal amyloid protein in amyloidosis,
- Noncaseating granuloma in sarcoidosis,
- Abnormal iron studies in hemochromatosis,
- Reduced α_1-galactosidase levels in Fabry's disease

Arrhythmogenic Right Ventricular Cardiomyopathy

- A genetically determined heart muscle disorder characterized by fibrofatty replacement of right ventricular myocardium.
- Associated with arrhythmia, heart failure, and premature sudden death.

- Inherited as an autosomal dominant disease, usually with incomplete penetrance,
- Recessive forms with cutaneous manifestations have been recognized
- Recognized mutations account for approximately 40% of cases

Clinical Manifestations

- In the early phase, patients are usually asymptomatic
- Resuscitated cardiac arrest and sudden death may be the initial manifestations
- The overt arrhythmic phase most often first occurs in adolescents and young adults, when patients note palpitations or syncope

- The third phase, characterized by diffuse right ventricular disease, usually is recognized in the middle and later decades;
- Patients may present with right-sided heart failure despite relatively preserved left ventricular function
- In the advanced stage, obvious left ventricular involvement and biventricular heart failure are seen

Treatment

- Intracardiac defibrillator with supplemental antiarrhythmic agents