Myocardial and pericardial diseases

Sergio Caravita, MD, PhD

Department of Management, Information and Production Engineering, University of Bergamo
Cardiology Unit, IRCCS Istituto Auxologico Italiano San Luca Hospital, Milano

sergio.caravita@unibg.it
Myocardium and pericardium

Myocardium = heart muscle
Pericardium = double-walled sac containing the heart and the roots of the great vessels
Primary and secondary cardiomyopathies

Cardiomyopathies = diseases of the myocardium

**Primary Cardiomyopathies**
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Restrictive cardiomyopathy
- Arrhythmic cardiomyopathy
- ...

**Secondary cardiac diseases**
- Hypertension
- Ischemia
- Valvular disease
- Drugs or toxins (several antineoplastic agents, alcohol, recreational drugs)
- Radiation
- Metabolic cardiomyopathy
- Tako-tsubo cardiomyopathy (stress-induced cardiomyopathy)
- Peripartum cardiomyopathy
- Tachycardia
- Autoimmune diseases
- Infiltrative diseases
- ...
Agenda

Cardiomyopathies
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy

Myocarditis

Ischemic cardiomyopathy

Acute pericarditis

Pericardial effusion
Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by:

- **cardiac hypertrophy**, unexplained by the loading conditions;
- a **nondilated left ventricle**; and
- a **normal or increased ejection fraction**.

Cardiac hypertrophy is usually asymmetrical with greatest involvement most commonly of the basal interventricular septum subjacent to the aortic valve.

It is occasionally restricted to other myocardial regions, such as the apex, the midportion, and the posterior wall of the left ventricle.

At the cellular level, cardiac myocytes are hypertrophied, disorganized, and separated by areas of interstitial fibrosis.
Parenthesis
Left ventricular (LV) wall thickness and LV mass

LV thickness of the interventricular septum (IVS) and of the posterior wall (PW) are commonly measured by 2D or 3D echocardiography or by cardiac magnetic resonance imaging.

LV wall thickness is normally < 12 mm

LV mass can be calculated using wall thickness values

Normative values for LV mass (and LV mass index) exist for all of the above mentioned techniques.
Loading conditions

The heart is a muscle

If it has to cope with increased afterload or if it is chronically stressed (e.g. aortic stenosis, arterial hypertension, competitive sport) it can undergo morphological changes with cellular and macroscopic hypertrophy (↑ wall thickness, ↑ myocardial mass)
LV dimensions, i.e. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) are commonly measured by 2D or 3D echocardiography or by cardiac magnetic resonance imaging.

Normative values for LV volumes (indexed for BSA) exist for all of the above mentioned techniques.

Volumes are generally larger in males than in females.
Left ventricular ejection fraction (LVEF)

$$LVEF = \frac{LVEDV - LVESV}{LVEDV}$$

$$LVEF = \frac{SV}{LVEDV}$$

where $SV$ = stroke volume

$LVEF$ is normally $> 50-55\%$

It is a surrogate measure of systolic function
Parenthesis
Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by:

- cardiac hypertrophy, unexplained by the loading conditions;
- a nondilated left ventricle;
- a normal or increased ejection fraction.
Cardiac hypertrophy

Cardiac hypertrophy is usually **asymmetrical** with greatest involvement most commonly of the **basal interventricular septum** subjacent to the aortic valve.

It is occasionally restricted to other myocardial regions, such as the **apex**, the midportion, and the posterior wall of the left ventricle.

At the **cellular level**, cardiac myocytes are hypertrophied, disorganized, and separated by areas of interstitial fibrosis.

Marian AJ and Braunwald E Circ Res 2017
A patient with diffuse LV hypertrophy
HCM epidemiology

Prevalence of HCM is believed to be as high as 0.2% (or 1 in 500) in the general population.

HCM is a disorder without a distinct geographic, ethnic, or sex pattern of distribution.

Cardiac hypertrophy may be of late onset, and <13 mm, the diagnostic cut point for the diagnosis of HCM. Hence, HCM may be underdiagnosed in such individuals.

Moreover, the presence of concomitant conditions that may cause myocardial hypertrophy, such as arterial hypertension or aortic stenosis, may make the differentiation of primary (HCM) from secondary hypertrophy challenging.
HCM and genetics

HCM is a heritable disorder that is transmitted as an **autosomal dominant trait**, i.e. affected individuals are heterozygous: that is, they have one normal and one mutant copy of the gene.

Offspring of affected individuals will therefore have a one in two risk of inheriting the mutation.

HCM is a genetically heterogenous disease with > 10 causative genes now identified.

**All these genes encode sarcomere or sarcomere-associated proteins**, and include the cardiac β-myosin heavy chain, cardiac troponin T gene, α-tropomyosin, myosin-binding protein C, cardiac troponin I, essential and regulatory myosin light chain, and more recently, the cardiac α-myosin heavy chain, titin and actin genes.
HCM and genetics

A single mutation is usually sufficient to cause the disease, albeit with variable penetrance and expression.

The variability of the phenotype is due, at least in part, to the causal mutation acting in concert with many other genetic and of nongenetic influences.

Approximately 60% of patients with HCM have a clearly recognizable familial disease.

A subset of HCM patients, ≈5%, exhibits 2 (digenic) or more (oligogenic) causal mutations in the same gene or causal mutations in different genes.

Variability in the phenotypic expression of hypertrophic cardiomyopathy (HCM).
HCM and genetics

The mechanistic events in HCM might be categorized into 4 sets of interlocking mechanisms.

The **primary defect is the mutation**. Initial or proximal phenotypes are defined as those resulting from the direct **effects of the mutations on the structure and function of the sarcomere proteins**.

The intermediary (or secondary) phenotypes include the **molecular changes that occur in response to the changes in the sarcomere protein structure and function**. Examples of the latter include altered gene expression and activation of the signaling pathways.

The tertiary effects are the ensuing **histological and pathological phenotypes**, which are the consequence of perturbation of a myriad of secondary molecular events in the myocardium, such as activation of the hypertrophic signaling pathways.

These molecular and histological changes lead to the clinical phenotypes of HCM (quaternary).

Marian AJ and Braunwald E Circ Res 2017
Determinants of the HCM phenotype

- **Primary defect (the causal mutation):**
  - mRNA transcription
  - Protein expression
  - Sarcomere assembly
  - Calcium sensitivity
  - ATPase activity
  - Force generation

- **Initial (proximal) defect(s):**
  - Signaling pathways
  - Gene expression
  - Post-translational modifications
  - Mitochondrial dysfunction
  - Trophic and mitotic factors

- **Secondary (intermediary) molecular changes:**
  - Myocyte hypertrophy
  - Myocyte disarray
  - Interstitial fibrosis
  - Cardiac hypertrophy

- **Tertiary (histological) phenotypes:**
  - Cardiac arrhythmias
  - Sudden cardiac death
  - Left ventricular outflow tract obstruction
  - Heart failure

- **Quaternary (clinical) phenotypes:**
  - Cardiac arrhythmias
  - Sudden cardiac death
  - Left ventricular outflow tract obstruction
  - Heart failure
The morphological, histological, and clinical phenotypes of HCM are the consequence of complex interactions among a large number of determinants, ranging from the causal genetic mutation to environmental factors.

The causal mutation is the prerequisite and a major determinant of the phenotype.

In addition, the histological and clinical phenotypes is also influenced by genetic backgrounds, which include the presence of additional pathogenic variants in pathways implicated in cardiac hypertrophy, epigenetic factors including noncoding RNAs, post-translational protein modifications, and environmental factors.

Thus, the tertiary and quaternary phenotypes of HCM are complex traits, influenced by a large number of determinants, each exerting a small effect, with the causal mutations imparting the largest effects.
HCM, pathophysiology and symptoms

Despite the presence of cardiac hypertrophy, patients with HCM are commonly asymptomatic or minimally symptomatic.

The most frequent symptoms result from 4 major pathophysiologic conditions:
- diastolic ventricular dysfunction,
- obstruction to left ventricular outflow tract (LVOT),
- imbalance between myocardial oxygen supply and demand,
- cardiac arrhythmias.
HCM pathophysiology

LV hypertrophy, fibrosis

LV diastolic dysfunction

Abnormal subvavular mitral apparatus

Hypertrophy of the basal septum

LVOT narrowing

Turbulent flow

SAM

SAM-mediated mitral regurgitation

LV=left ventricle
LVOT=left ventricular outflow tract
LVOTO= left ventricular outflow tract obstruction
SAM=systolic anterior movement of the mitral valve apparatus
HCM pathophysiology

LV hypertrophy ▹ interstitial fibrosis

Impaired LV filling (LV diastolic dysfunction) ▹ LVEDP ▹ LA pressure ▹ pulmonary venous and pulmonary capillary pressure ▹ Pulmonary edema

LA=left atrium
LV=left ventricle
LVEDP=left ventricular end-diastolic pressure
HCM pathophysiology

LV hypertrophy → ↑ interstitial fibrosis → ↑ wall thickness of intramural coronary arteries

Myocardial oxygen supply/demand imbalance → Myocardial ischemia
HCM pathophysiology

↑ interstitial fibrosis

Myocardial ischemia

Ventricular arrhythmias
SAM-associated LVOT obstruction (LVOTO)

https://www.youtube.com/watch?v=ICZmnCw0E5E

https://www.youtube.com/watch?v=Kplt9wqS5b0

Approximately one third of patients with HCM have LVOT obstruction at rest, which is intensified with exercise.

One third have provokable obstruction, and the remaining third have LV hypertrophy without obstruction at rest and is not provokable.
HCM pathophysiology

LV hypertrophy, fibrosis

Hypertrophy of the basal septum

Abnormal subvalvular mitral apparatus

LVOT narrowing

Turbulent flow

SAM

SAM-mediated mitral regurgitation

LVOTO

Pulmonary edema

↑ pulmonary venous and pulmonary capillary pressure

↑ LA pressure

↑ LA pressure

↓ stroke volume

LA=left atrium
LV=left ventricle
LVOT=left ventricular outflow tract
LVOTO=left ventricular outflow tract obstruction
SAM=systolic anterior movement of the mitral valve apparatus
Dinamicity of LVOT obstruction (LVOTO)

- Preload
- Contractility
- LVOTO
- Afterload

Circadian rhythm
Body position
Physical activity, stress
Post-prandial
Drugs (sedation, anesthesia, …)

Beat-to-beat variability

Intra-exam variability
HCM pathophysiology and symptoms

LV hypertrophy, fibrosis

- Septal hypertrophy
- Abnormal subvavular mitral apparatus

LV diastolic dysfunction

- Myocardial O\textsubscript{2} supply/demand imbalance
- Ventricular arrhythmias
- Chronotropic incompetence

LVOT narrowing

- Turbulent flow
- SAM
- SAM-mediated mitral regurgitation

LVOTO

Dyspnea, syncope, sudden cardiac death

Dyspnea, fatigue

Chest pain

Dyspnea, fatigue

Dyspnea, fatigue, syncope
HCM - diagnosis

EKG (at rest or during prolonged 1-2-7 days monitoring)
- Signs of LV hypertrophy, arrhythmias

Echocardiography
- LV volume, LV wall thickness, LV mass, LV systolic function
- Mitral valve apparatus, presence/absence of SAM, mitral regurgitation
- LVOTO
- LA volume, pulmonary pressure

Echocardiography + provocative maneuvers (Valsalva maneuver, exercise)
- To evoke LVOTO

Cardiac catheterization (rarely needed)
- To assess LVOTO

Cardiac MRI
- LV volume, LV wall thickness, LV mass, LV systolic function
- Extent of LV fibrosis (late gadolinium enhancement)
HCM - diagnosis

Genetic testing

- **if positive, will support the diagnosis in a proband**, but if it is negative will not exclude it

- If a proband with a positive test is identified, cascade screening, that is, **testing for the presence of the variant in family members**, should be undertaken

- A positive screen, that is, mutation carrier relative of a patient with HCM, should lead to a detailed examination for the presence of the HCM phenotype

- **Relatives who are mutation carriers but phenotype negative** should be followed with clinical evaluation (history, physical examination, ECG, and echocardiogram) at yearly intervals or more frequently if symptoms develop
Sudden cardiac death (SCD) risk calculator

HCM Risk-SCD Calculator

Age
Maximum LV wall thickness
Left atrial size
Max LVOT gradient
Family History of SCD
Non-sustained VT
Unexplained syncope

Age at evaluation
Trans-thoracic echocardiographic measurement
Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation
The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous waveform Doppler from the apical three and five-chamber views. Peak outflow tract gradients should be determined using the modified Bernoulli equation: Gradient= 4V^2, where V is the peak aortic outflow velocity
History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-natal diagnosis)
3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation
History of unexplained syncope at or prior to evaluation

Risk of SCD at 5 years (%):__

ESC recommendation:

Reset

O’Mahony C et al Eur Heart J (2014) 35 (33) 2010-2020

HCM Risk-SCD should not be used in:
- Pediatric patients (<16 years)
- Elite/competitive athletes
- HCM associated with metabolic diseases (e.g. Anderson-Fabry disease), and syndromes (e.g. Noonan syndrome)
- Patients with a previous history of aborted SCD or sustained ventricular arrhythmia who should be treated with an ICD for secondary prevention

Caution should be exercised when assessing the SCD in patients following invasive reduction in left ventricular outflow tract obstruction with myectomy or alcohol septal ablation.
Pending further studies, HCM-RISK should be used cautiously in patients with a maximum left ventricular wall thickness ≥35 mm.

HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVOT = left ventricular outflow tract; NSVT = non-sustained ventricular tachycardia; SCD = sudden cardiac death; VT = ventricular tachycardia

https://doc2do.com/hcm/webHCM.html
HCM – treatment

Drugs: negative inotropes (in patients with LVOTO)

Septal reduction therapies (in patients with LVOTO)

Implantable cardioverter defibrillator, ICD (in patients at high risk of SCD)
Septal reduction therapies

- Septal myectomy
- Alcohol septal ablation

ICD (transvenous vs subcutaneous)


J Am Coll Cardiol 2013;61. DOI: 10.1016/j.jacc.2012.07.069
Agenda

Cardiomyopathies
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
Ischemic cardiomyopathy
Myocarditis

Acute pericarditis
Pericardial effusion
Dilated cardiomyopathy (DCM) is defined as **left ventricular (LV) dilation and systolic dysfunction in the absence of** coronary artery disease or abnormal loading conditions proportionate to the degree of LV impairment.

One of the leading causes of heart failure (HF), DCM predominantly affects younger adults and is the most frequent indication for cardiac transplantation.

The condition is best regarded not as a single disease entity, but rather as a nonspecific phenotype, the final common response of myocardium to a number of genetic and environmental insults.
Differentiation of DCM From Conditions With Phenotypic Overlap

Ischemic cardiomyopathy (relevant coronary artery stenosis)
Hypertensive heart disease (long standing, poorly controlled hypertension)
Advanced HCM
Arrhythmogenic cardiomyopathy
Myocardial non-compaction
Athlete’s heart
Cirrothic cardiomyopathy
Causes of DCM

Idiopathic

Genetic

Toxins: recreational drugs (alcohol, amphetamines, cocaine), chemotherapeutic agents (anthracyclines, trastuzumab), ...

Infectious: viral, bacterial, fungal, protozoal, rickettsial

Metabolic/endocrine: electrolyte disturbances, endocrine abnormalities, nutritional deficiencies

Inflammatory/infiltrative/autoimmune

Neuromuscular disease

Pregnancy

Tachyarrythmia

Japp AG et al. J Am Coll Cardiol 2016;67:2996-3010
Dilated cardiomyopathy - diagnosis

Clinical history

**Echocardiography** → dilated and dysfunctional LV; prediction of pre-dilated phenotype

**Cardiac magnetic resonance imaging** (provide clues in myocardial structure that can be of help to discriminate between etiologies; prediction of pre-dilated phenotype)

**Endomyocardial biopsy** (invasive; not routinely done: may reveal typical histological alterations suggesting a specific etiology)

**Genetics** (Molecular genetic analysis has uncovered “causal” mutations for DCM in over 60 genes. At present, routine genetic testing is only recommended in familial disease with ≥2 affected family members. Some genetic mutations predispose to cardiac arrhythmias and sudden cardiac death)
Stages of LV remodeling in DCM

**Latent**
- Early LV phenotype (e.g., ↓ strain, LV enlargement, diffuse fibrosis)
- +/- Pathogenic gene mutation
- Altered biomarkers

**Established**
- ↑ LV volume and ↓ LVEF
- Limited or no replacement fibrosis
- +/- Functional mitral regurgitation
- LV dyssynchrony
- Active myocarditis

**Advanced**
- Severely ↑ LV volume and ↓ LVEF
- Extensive replacement fibrosis
- Wall thinning
- +/- Right ventricular remodeling
- Refractory to conventional therapies

Japp AG et al. J Am Coll Cardiol 2016;67:2996-3010
The extent of **LV dilation and contractile impairment** in DCM is a major determinant of adverse outcomes.

**Left ventricular enlargement without systolic dysfunction** represents a well-defined precursor of inherited DCM.

Myocardial deformation imaging (strain analysis) may provide phenotypic markers of latent DCM earlier than left ventricular enlargement.

In **patients receiving cardiotoxic cancer therapy**, reductions in global longitudinal strain ≥10% consistently precede and predict the development of overt LV dysfunction. Subclinical detection in these patients is crucial because timely intervention (e.g., change in chemotherapy regimen) may prevent disease progression, whereas systolic dysfunction is often irreversible once LVEF declines.

Japp AG et al. J Am Coll Cardiol 2016;67:2996-3010
CENTRAL ILLUSTRATION: Potential for Detailed DCM Assessment to Guide Therapy

Stage of left ventricular (LV) remodeling

Latent
- Early LV phenotype (e.g., ↓ strain, LV enlargement, diffuse fibrosis)
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Established
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- Severely ↑ LV volume and ↓ LVEF
- Extensive replacement fibrosis
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- +/- Right ventricular remodeling
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Treatment strategies
- Retard remodeling:
  - Neurohormonal blockade
  - Molecular / gene therapy
  - Imaging & biomarker surveillance
- Reverse remodeling:
  - Neurohormonal blockade
  - Cardiac resynchronization
  - Mitral valve interventions
  - Molecular / gene therapy
  - Immunosuppressive / antiviral treatment
- Regenerate:
  - Stem cell therapy
  - ‘Bridge to recovery’ LV assist device
- Replace:
  - HEART TRANSPLANT
  - LV ASSIST DEVICE

DRUGS
INTERVENTIONS

CENTRAL ILLUSTRATION: Precision Medicine for Dilated Cardiomyopathy

Who To Treat

Environment Risk
- Very Low
- Low
- Medium
- High
- Very High

Genetic Risk
- Very Low
- Low
- Medium
- High
- Very High

Identification of High-Risk Individuals

How To Treat

Treatment Specificity
- Genotype
- Modifiers
- Phenotype

Treatment Scalability

Treatment Targets

When to Treat

Deep Phenotyping
- ECHO
- MRI
- ECG
- Biomarkers

Timing of Intervention

Normal Heart
- Prevention of Onset

Early Disease
- Prevention of Progression

Overt DCM
- Treatment of Symptoms

Agenda

Cardiomyopathies
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy

Ischemic cardiomyopathy

Myocarditis

Acute pericarditis

Pericardial effusion
Ischemic cardiomyopathy

LV systolic dysfunction with one or more of the following: a history of prior myocardial revascularisation or myocardial infarction, more than 75% stenosis in the left main stem or left anterior descending artery, or two vessels or more with a greater than 75% stenosis.
LV remodeling after myocardial infarction

Postinfarction remodeling has been arbitrarily divided into
- an early phase (within 72 hours)
- a late phase (beyond 72 hours).

The **early phase** involves expansion of the infarct zone, which may result in early ventricular rupture or aneurysm formation.

**Late remodeling** involves the left ventricle globally and is associated with time-dependent dilatation, the distortion of ventricular shape, and mural hypertrophy.

The failure to normalize increased wall stresses results in progressive dilatation, recruitment of border zone myocardium into the scar, and deterioration in contractile function.

Sutton MG, Sharpe N. Circulation 2000;101:2981-2988
Ischemic cardiomyopathy

Jessup M, Brozena S. N Eng J Med 2003
LV remodeling after myocardial infarction

Left ventricular remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors.

The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote noninfarcted myocardium.

Myocyte necrosis and the resultant increase in load trigger a cascade of biochemical intracellular signaling processes that initiates and subsequently modulates reparative changes, which include dilatation, hypertrophy, and the formation of a discrete collagen scar.

Ventricular remodeling may continue for weeks or months until the distending forces are counterbalanced by the tensile strength of the collagen scar.

This balance is determined by the size, location, and transmurality of the infarct, the extent of myocardial stunning, the patency of the infarct-related artery, and local tropic factors.

Sutton MG, Sharpe N. Circulation 2000;101:2981-2988
LV remodeling after myocardial infarction

Myocyte Death

- Neutrophil infiltration
- Activation of MMPs in ECM
- Degradation of inter-myocyte collagen struts
- Myocyte slippage

Increased plasma NE

- Enhanced NE release
- From adrenal medulla
- And sympathetic nerve terminals

Increased ANP, BNP

- Juxtaglomerular Apparatus
- Activation of RAAS

Increased Na+, Water excretion

- ET-1 release

Decreased Volume SVR

Transient Improvement LV function

Macrophage & fibroblast chemotaxis

Fibroblast proliferation

Macrophage transformation

ACE expression

TGF-β1 release from macrophages

Local AIII & Aldosterone production

Fibroblast transformation into myofibroblast

TGF-β1 expression

- Activation of TIMPs
- Type I & III collagen synthesis

Fibrosis

Myocyte Hypertrophy

Wall thinning

Ventricular Dilatation

Early Remodeling (<72 hours)

- Increased wall stress
- Mechanical stretch

Local AIII release

Activation of fetal gene program

Increased contractile proteins

Late Remodeling

Sutton MG, Sharpe N. Circulation 2000;101:2981-2988
Myocardial stunning and hibernation

**Myocardial stunning** is a state of reversible hypocontractility that persists despite restoration of blood flow following transient or recurrent ischaemia.

**Myocardial hibernation** is an adaptive process to repetitive ischaemia secondary to chronically reduced myocardial blood flow and reduced coronary flow reserve, whereby a loss in contractile apparatus results in reduced demand, which has been coined the ‘smart heart’.

Myocardial hibernation can occur also in remote areas from true ischemic areas. These areas may behave ‘smartly’, with a downregulation of contractile function in order to preserve energy.

Hibernation is also accompanied by several structural changes. Chronic hibernation can lead to irreversible structural changes, with development of fibrosis and expansion of the extracellular space leading to myocardial scar.
LV remodeling after myocardial infarction

LV Remodeling Post Anteroseptal MI

1 week
EDV 137ml ESV 80ml
EF 41%

3 months
EDV 189ml ESV 146ml
EF 23%

Apical 4 Chamber View
End-diastole

Sutton MG, Sharpe N. Circulation 2000;101:2981-2988
Ischemic cardiomyopathy - treatment

Coronary artery revascularization (see treatment of ischemic heart disease)
Heart failure treatment (see treatment of heart failure)
Agenda

Cardiomyopathies
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
Ischemic cardiomyopathy

Myocarditis

Acute pericarditis
Pericardial effusion
Myocarditis

Inflammatory disease of the heart muscle cells
It is pathologically identified by conventional histology and immunohistochemical techniques as an infiltration of mononuclear cells to the myocardium.

Myocarditis can be acute, subacute, or chronic and may either involve focal or diffuse areas of the myocardium

Fulminant lymphocytic myocarditis → left ventricle (LV) systolic dysfunction with cardiogenic shock

Nonfulminant myocarditis may be acute or chronic myocarditis that often progresses in an insidious manner.
- Acute myocarditis may lead to complete resolution or stable dilated cardiomyopathy (DCM)
- Chronic active myocarditis is defined as an ongoing myocarditis with visible fibrosis

The clinical manifestations of myocarditis are heterogeneous, ranging from virtually asymptomatic states with vague signs and symptoms to severe myocardial destruction by virus and immune cells yielding cardiogenic shock and arrhythmias.

Myocarditis can be caused by
- a broad range of infectious agents (viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa),
- noninfectious triggers (toxins and hypersensitive reactions).
Pathogenesis of viral myocarditis

At the cellular and tissue levels, the pathological progression of viral myocarditis consists of 3 stages:

the acute stage triggered by viral entry and replication,
the subacute stage characterized by inflammatory cell infiltration,
the chronic stage featuring cardiac remodeling.

The pathogenesis of viral myocarditis is caused by both direct injury mediated by viral infection and indirect damage secondary to the immune responses of the host.

Viral infection of the heart triggers the activation of the host antiviral immune response, which is characterized by the infiltration of natural killer cells and macrophages, followed by virus-specific T lymphocytes. The immune response functions as a double-edged sword: initial activation is beneficial to the host by limiting viral spread; however, a persistent and excessive immune response conveys harmful consequences contributing to the progression of myocarditis and DCM.

The balance between the antiviral influences and the deleterious effects on cardiac function is an important determinant of the severity of myocarditis and the ultimate progression to DCM.
Myocarditis - diagnosis

**EKG** (low sensitivity, may exhibit nonspecific T waves and ST-segment changes including ST-segment elevation)
Myocarditis - diagnosis

Echocardiography

rule out other causes of HF

investigates cardiac chamber sizes, wall thicknesses, and systolic and diastolic functions, and thus does not provide direct evidence of myocarditis.

However, patients with fulminant myocarditis often lack cardiac dilation and exhibit increased septal thickness, whereas patients with acute myocarditis may exhibit a spherical-shaped ventricle that remodels to a more elliptical shape over the period of a few months with normal wall thickness.
Myocarditis - diagnosis

Cardiac MRI

c-contrast enhancement (CE) CMR is a more sensitive technique of cMRI and can detect areas of myocardial damage in patients with acute myocarditis.

cMRI sensitivity and specificity are as high as 100% and 90%, respectively, when compared with histology confirmed samples identified by CE-CMR.

This technique also rules out ischemic causes because CE in ischemic infarction will include subendocardial layers of the myocardium
Endomyocardial biopsy

EMB positivity in acute myocarditis patients is defined as lymphocytic infiltration in association with myocyte necrosis/death (Dallas Criteria). Patients exhibiting borderline myocarditis are defined as those with lymphocytic infiltration in the absence of myocyte necrosis.
Myocarditis - treatment

Pathogen Inhibition

Early application of antiviral agents is a potential therapeutic avenue to halt the development of viral myocarditis. Several antiviral agents have shown favorable effects in clinical trials but are not routine treatment.

Immune Modulation

After the acute phase, the further development of myocarditis in the subacute phase is thought to be predominantly a result of exaggerated autoimmune responses. Thus, the application of immunosuppressive drugs seems plausible for the treatment of myocarditis and could be used in some patients.

Heart Failure Therapy

Because antiviral therapy benefits little in the subacute stages of myocarditis and the effects of immunomodulatory drugs on infectious myocarditis are still controversial, therapy to relieve HF is still a major strategy used in the treatment of patients with myocarditis.

Mechanical circulatory supports for heart function also aids in the recovery of myocarditis. Although such supports cannot cure myocarditis itself, the devices allow avoidance of fatality and increase the survival longevity of patients, especially in those with cardiogenic shock.
Agenda

Cardiomyopathies
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
Ischemic cardiomyopathy
Myocarditis

Acute pericarditis
Pericardial effusion
The pericardium and pericardial diseases

The pericardium (from the Greek περί, ‘around’ and κάρδιον, ‘heart’) is a double-walled sac containing the heart and the roots of the great vessels. The pericardial sac has two layers, a serous visceral layer (also known as epicardium when it comes into contact with the myocardium) and a fibrous parietal layer. It encloses the pericardial cavity, which contains pericardial fluid. The pericardium fixes the heart to the mediastinum, gives protection against infection and provides lubrication for the heart.

Pericardial diseases may be either isolated disease or part of a systemic disease.

The main pericardial syndromes that are encountered in clinical practice include

- **pericarditis** (acute, subacute, chronic and recurrent),
- **pericardial effusion,**
- **cardiac tamponade,**
- **constrictive pericarditis**
- **pericardial masses.**
Pericarditis is the most common disease of the pericardium encountered in clinical practice. The incidence of acute pericarditis has been reported as 27.7 cases per 100,000 population per year in an Italian urban area.
Acute pericarditis

Acute pericarditis is an inflammatory pericardial syndrome with or without pericardial effusion.

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<thead>
<tr>
<th>Pericarditis</th>
<th>Definition and diagnostic criteria</th>
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<tr>
<td>Acute</td>
<td>Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria:</td>
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<tr>
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<td>(1) pericarditic chest pain</td>
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<td>(2) pericardial rubs</td>
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<td>(3) new widespread ST-elevation or PR depression on ECG</td>
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<td>(4) pericardial effusion (new or worsening)</td>
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<td>Additional supporting findings:</td>
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<td>- Elevation of markers of inflammation (i.e. C-reactive protein, erythrocyte sedimentation rate, and white blood cell count);</td>
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<td>- Evidence of pericardial inflammation by an imaging technique (CT, CMR).</td>
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Acute pericarditis

It may be asymptomatic or manifests with chest pain. Rarely, if associate with relevant pericardial effusion it can cause hemodynamic instability
**Acute pericarditis – etiology**

A simple aetiological classification for pericardial diseases is to consider **infectious and non-infectious causes**

In developed countries, **viruses** are usually the most common aetiological agents of pericarditis,

**Tuberculosis** (TB) is the most frequent cause of pericardial diseases in the world and developing countries, where TB is endemic. In this setting, TB is often associated with human immunodeficiency virus (HIV) infection, especially in sub-Saharan Africa
Acute pericarditis - etiology

Infectious causes
Viral (common)
Bacterial: Mycobacterium tuberculosis (common), other bacteria (rare)
Fungal (very rare)

Non-infectious causes
Autoimmune (common): systemic autoimmune and auto-inflammatory diseases; systemic vasculitides; sarcoidosis…
Neoplastic: secondary metastatic tumors (common); primary tumors (rare)
Metabolic: uremia, myxedema, anorexia nervosa
Traumatic and iatrogenic: postmyocardial infarction syndrome; postpericardiotomy syndrome
Drug-related (rare)
Acute pericarditis – etiology

It is not mandatory to search for the aetiology in all patients, especially in countries with a low prevalence of TB, because of the relatively benign course associated with the common causes of pericarditis and the relatively low yield of diagnostic investigations.
Acute pericarditis – treatment

Viral pericarditis $\rightarrow$ high dose antiinflammatory drugs (e.g. aspirin, ibuprofen, steroids; colchicine)
Most patients with acute pericarditis (generally those with presumed viral or idiopathic pericarditis) have a good long-term prognosis.
Pericardial effusion

The normal pericardial sac contains 10–50 ml of pericardial fluid as a plasma ultrafiltrate that acts as a lubricant between the pericardial layers.

Any pathological process usually causes an inflammation with the possibility of increased production of pericardial fluid.

Pericardial effusion may be classified according to its onset (acute or subacute vs. chronic when lasting >3 months), distribution (circumferential or loculated), haemodynamic impact (none, cardiac tamponade, effusive-constrictive), composition.
Pericardial effusion

A significant proportion of patients with pericardial effusion are asymptomatic and pericardial effusion constitutes an incidental and unexpected finding on X-ray or echocardiogram performed for other reasons.
Pericardial effusion – clinical presentation

The clinical presentation of pericardial effusion varies according to the speed of pericardial fluid accumulation.

If pericardial fluid is rapidly accumulating, the evolution is dramatic and even small amounts of blood may cause an increase in intrapericardial pressure within minutes and overt cardiac tamponade. A slow accumulation of pericardial fluid allows the collection of a large effusion in days to weeks before a significant increase in pericardial pressure causes symptoms and signs.

The diagnosis of pericardial effusion is generally performed by echocardiography.
Cardiac tamponade is a life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots or gas.
Cardiac tamponade

The stiffness of the pericardium determines fluid increments precipitating tamponade, as illustrated by characteristic pericardial pressure–volume (strain–stress) curves:

there is an initial slow ascent, followed by an almost vertical rise. This steep rise makes tamponade a ‘last-drop’ phenomenon: the final increment produces critical cardiac compression and the first decrement during drainage produces the largest relative decompression.
Pericardial effusion - diagnosis

Echocardiography is the single most useful diagnostic tool to identify pericardial effusion and estimate its size, location and degree of haemodynamic impact.

**Signs of tamponade can be identified by echocardiography:** swinging of the heart, early diastolic collapse of the right ventricle, late diastolic collapse of the right atrium, abnormal ventricular septal motion, exaggerated respiratory variability (>25%) in mitral inflow velocity, inspiratory decrease and expiratory increase in pulmonary vein diastolic forward flow, respiratory variation in ventricular chamber size, aortic outflow velocity (echocardiographic pulsus paradoxus) and inferior vena cava plethora

[https://www.youtube.com/watch?v=tokryY1koxE](https://www.youtube.com/watch?v=tokryY1koxE)

Echocardiography is used to guide pericardiocentesis.
Pericardial effusion - diagnosis

CT and CMR are often less readily available and are generally unnecessary unless Doppler echocardiography is not feasible.

Cardiac catheterization is rarely used to diagnose cardiac tamponade.
Pericardial effusion / cardiac tamponade - treatment

The treatment of cardiac tamponade involves drainage of the pericardial fluid, preferably by needle pericardiocentesis, with the use of echocardiographic or fluoroscopic guidance, and should be performed without delay in unstable patients.

Alternatively, drainage is performed by a surgical approach, especially in some situations such as purulent pericarditis or in urgent situations with bleeding into the pericardium.