

Hypertrophic Cardiomyopathy

Genetic pathogenesis • structural pathology • clinical consequences

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Objectives: Explain the HCM phenotype

- Recognize myocardial hypertrophy that is not explained by loading conditions
- Connect sarcomeric protein variants to ventricular thickening and abnormal function
- Identify characteristic gross and microscopic pathology
- Explain obstruction, clinical complications and treatment principles

Cardiomyopathies: Primary myocardial disease

- Cardiomyopathy denotes intrinsic myocardial dysfunction
- Primary disorders principally affect myocardium; Systemic disorders may involve it secondarily
- Coronary, hypertensive, valvular and congenital disorders must be considered separately

Pattern	Chamber	Principal defect
Dilated	Enlarged	Contractility
Hypertrophic	Thick-walled	Relaxation
Restrictive	Usually not dilated	Compliance

Three major morphofunctional patterns

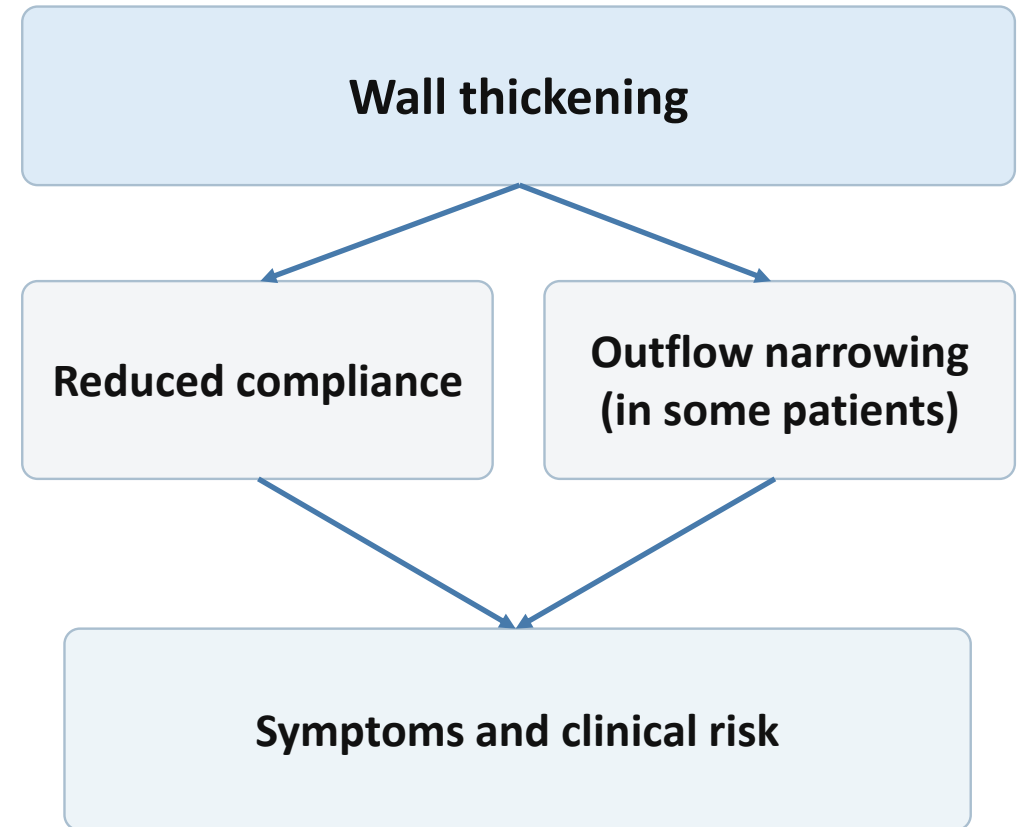
- Dilated cardiomyopathy: Chamber enlargement and reduced contraction
- Hypertrophic cardiomyopathy: Myocardial thickening with poor compliance
- Restrictive cardiomyopathy: Limited ventricular filling from stiffness

HCM	DCM
Marked wall thickening	Chamber dilatation
Usually nondilated	Poor contraction
Diastolic defect	Systolic defect

Schematic

Hypertrophic cardiomyopathy: Defining phenotype

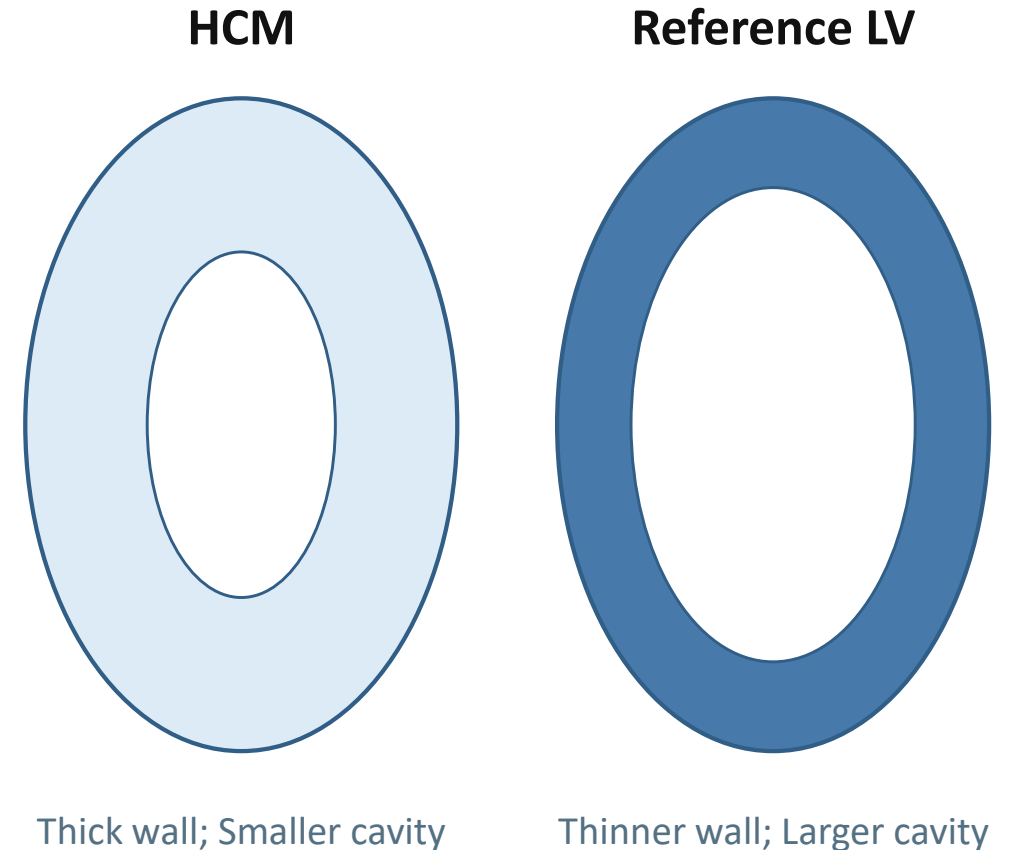
- Common, clinically heterogeneous genetic myocardial disorder
- Myocardial hypertrophy is disproportionate to other causes of ventricular thickening
- The ventricle is heavy, thick-walled and often hypercontractile
- The fundamental physiologic defect is impaired diastolic filling



Schematic

Thick wall does not imply poor systolic function

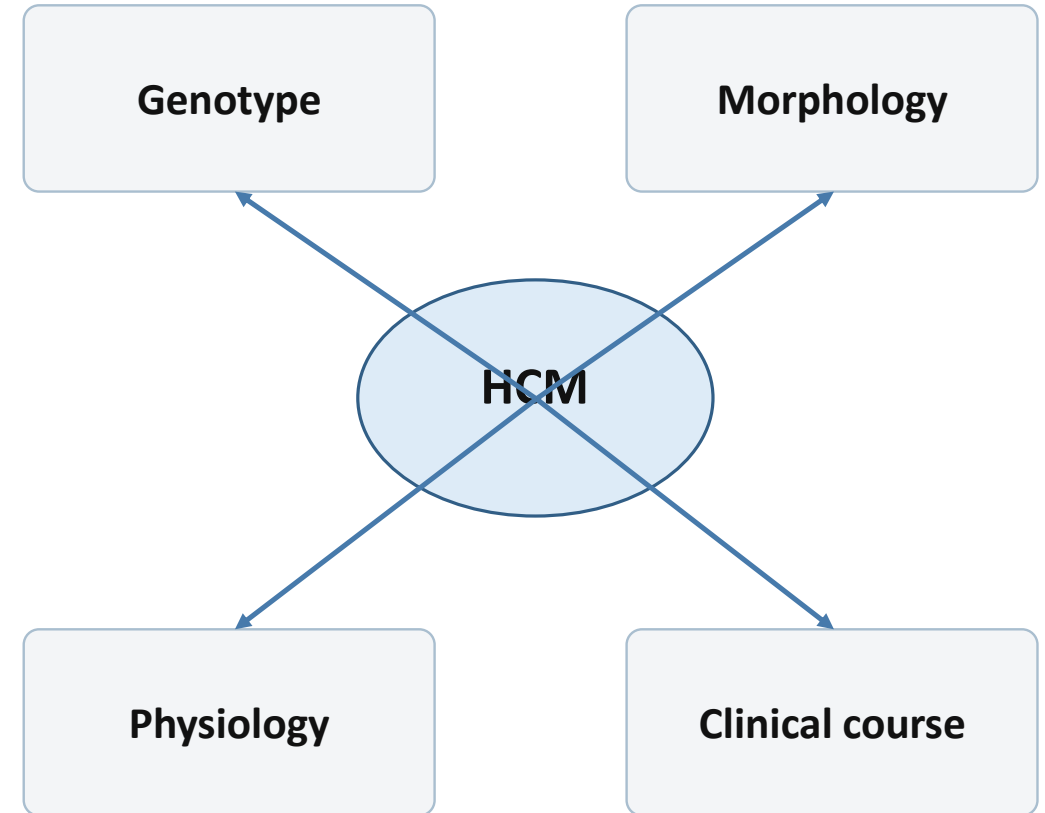
- A hypertrophied ventricle can contract vigorously yet fill inadequately
- Systolic function in typical HCM is usually preserved
- A reduced ventricular chamber and poor compliance lower stroke volume
- Contrast with DCM, where ineffective contraction is dominant



Schematic

Prevalence and clinical heterogeneity

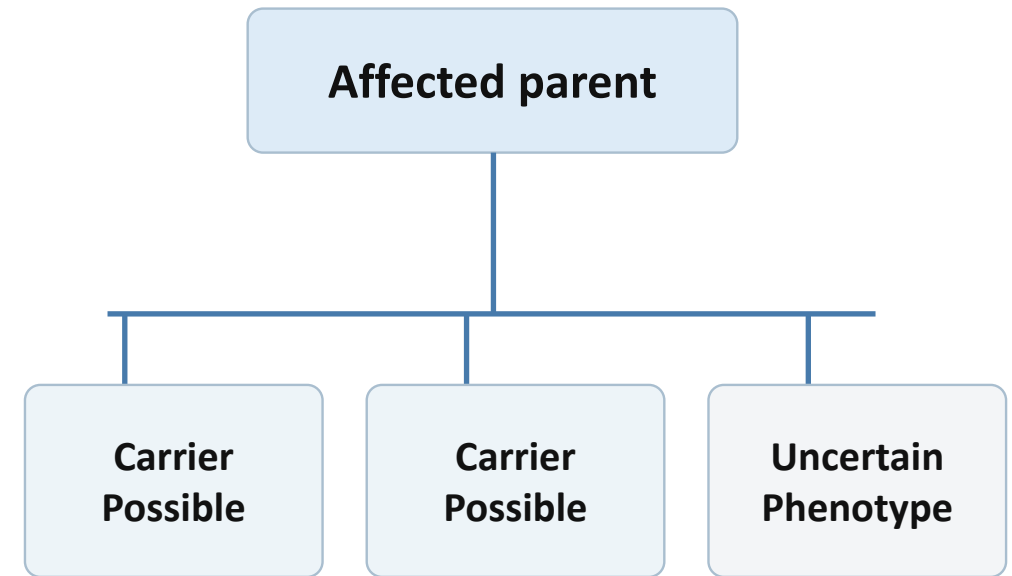
- An HCM prevalence of approximately 1 in 500
- Expression varies between families and among affected relatives
- Severity of hypertrophy, obstruction and clinical events is heterogeneous
- A single structural pattern does not determine an individual prognosis



Schematic

Autosomal dominant transmission

- Most familial cases show autosomal dominant inheritance
- An affected family can contain relatives with different degrees of expression
- A family history supports suspicion but is not a morphology substitute
- Variable penetrance complicates interpretation of screening results

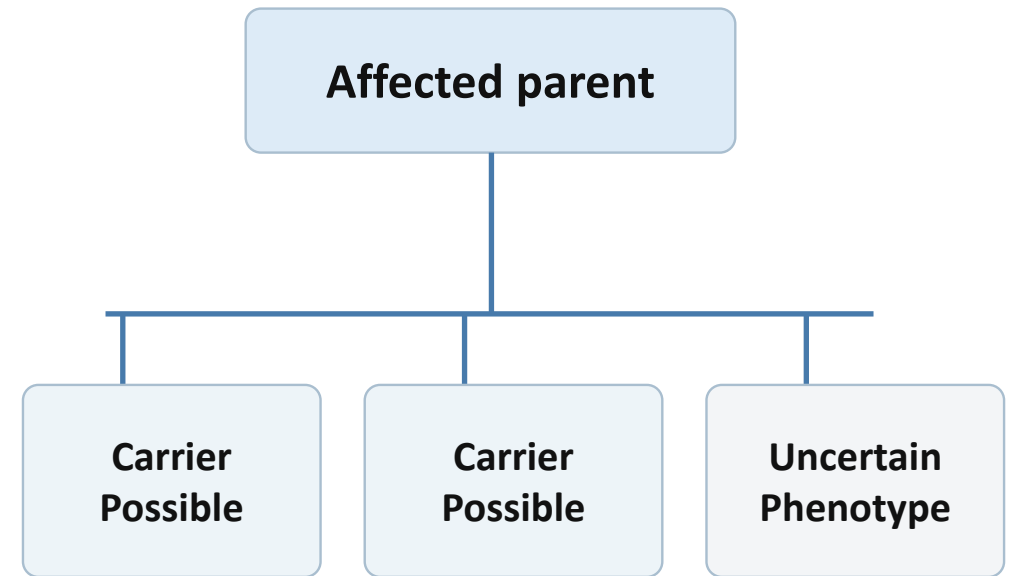


Illustrates dominant transmission and variable expression; Not a pedigree prediction

Schematic

Variable penetrance: A diagnostic limitation

- Not all individuals carrying a disease-associated variant manifest the same phenotype
- Age and family context can influence recognition of disease
- Genotype and visible hypertrophy do not map one-to-one
- Negative phenotype assessment at one time point does not resolve every inherited risk

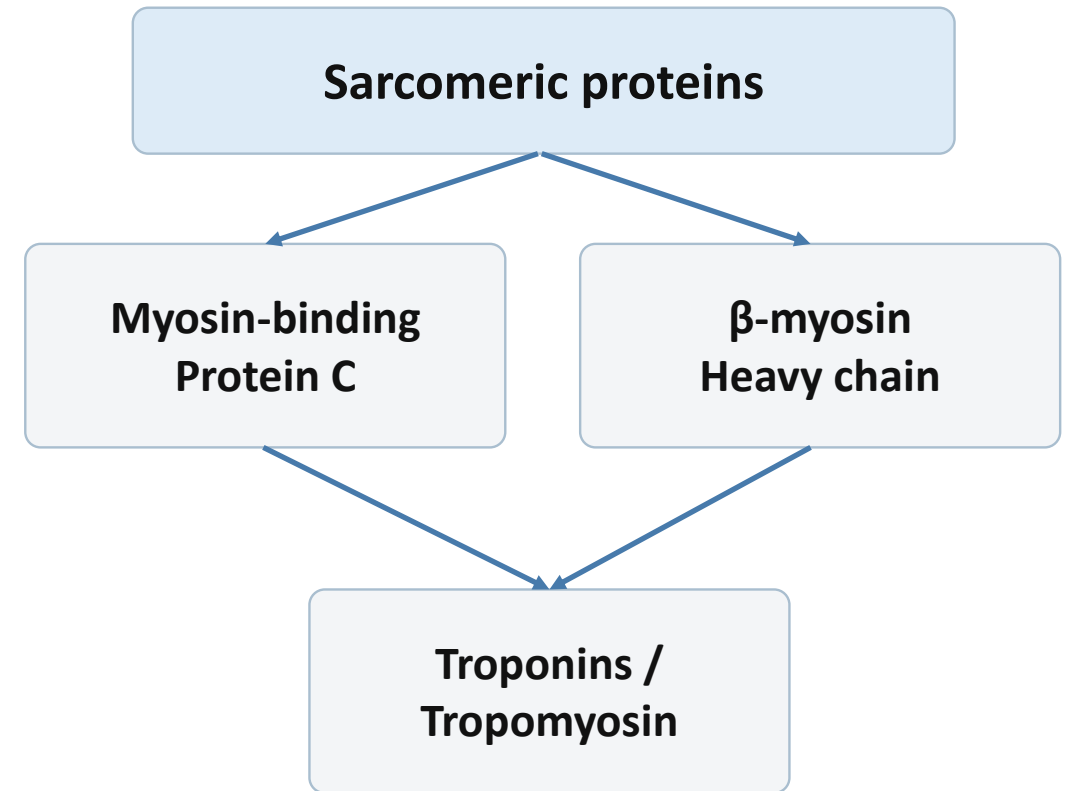


Illustrates dominant transmission and variable expression; Not a pedigree prediction

Schematic

The sarcomere is the primary genetic target

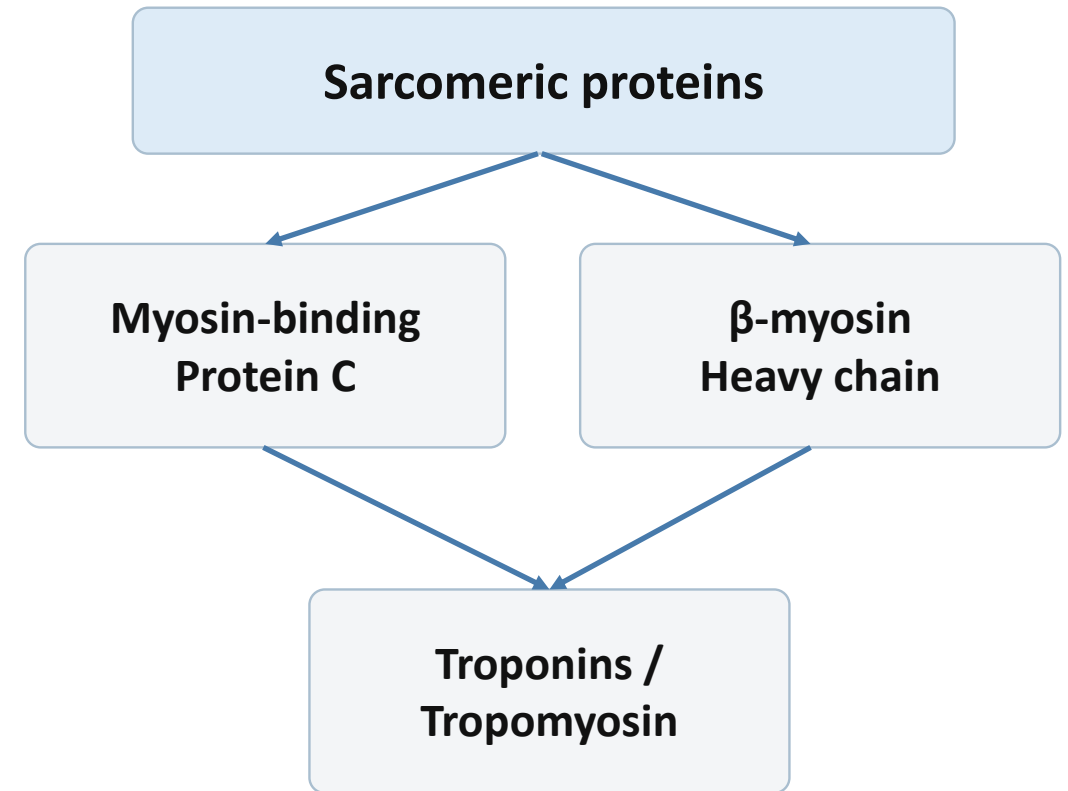
- HCM commonly arises from variants in genes encoding sarcomeric proteins
- The involved machinery regulates myocardial force generation
- Myosin-associated and thin-filament proteins are repeatedly implicated
- Many genetic variants can converge on similar thick-walled morphology



Schematic

Myosin-binding protein C and β -myosin

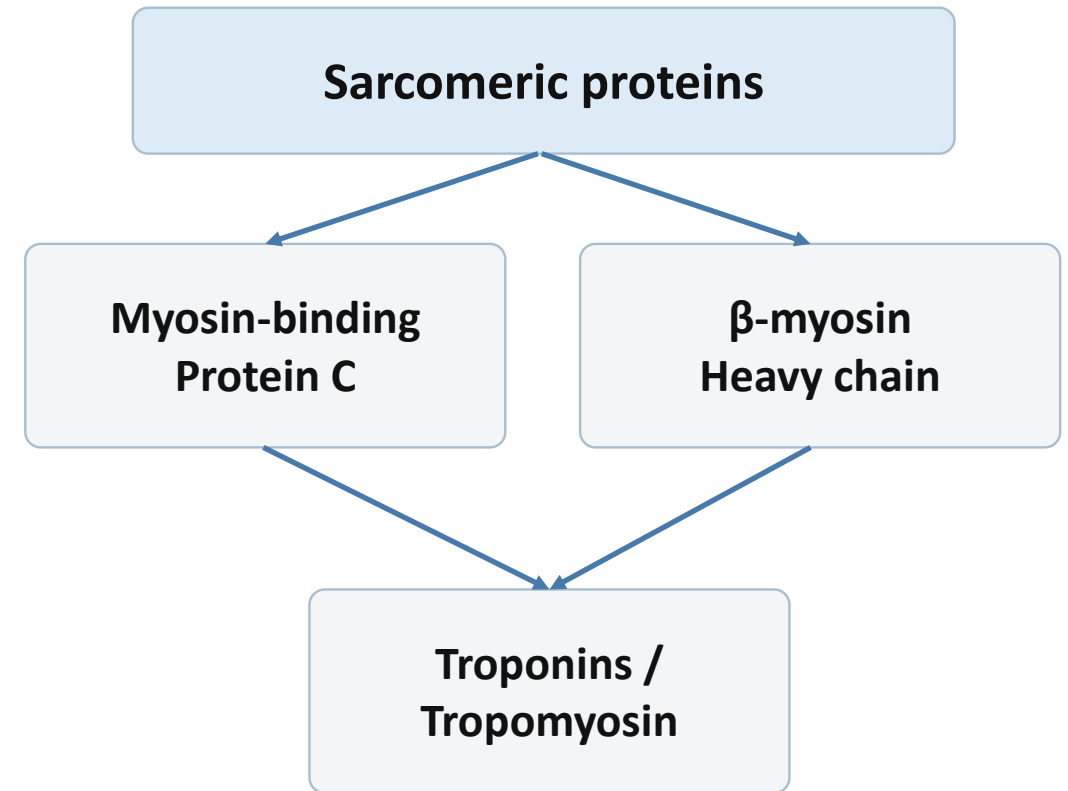
- Alterations involving myosin-binding protein C are prominent
- β -myosin heavy chain, encoded by MYH7, is another major affected protein
- Distinct mutations in one protein can produce the HCM phenotype
- Clinical behavior cannot be deduced simply from the name of the protein



Schematic

Thin-filament genes contribute to HCM

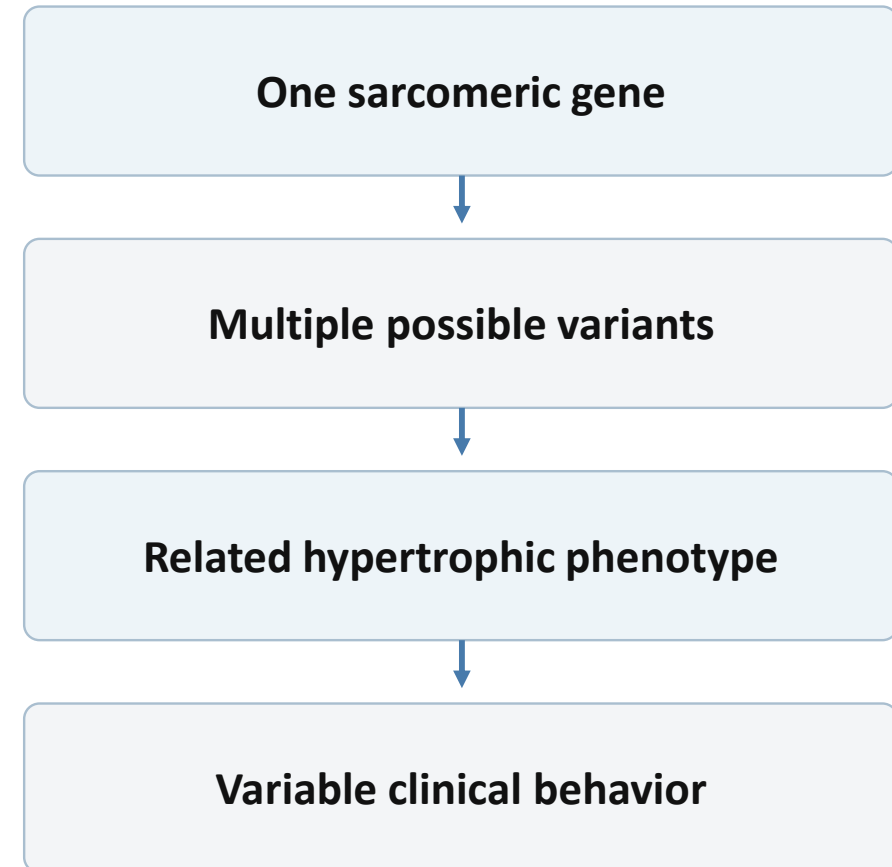
- Cardiac troponin I and troponin T are implicated in HCM
- α -tropomyosin is another sarcomeric target account
- These proteins participate in regulating contraction
- The diversity of affected proteins explains genetic heterogeneity



Schematic

Allelic heterogeneity within a single gene

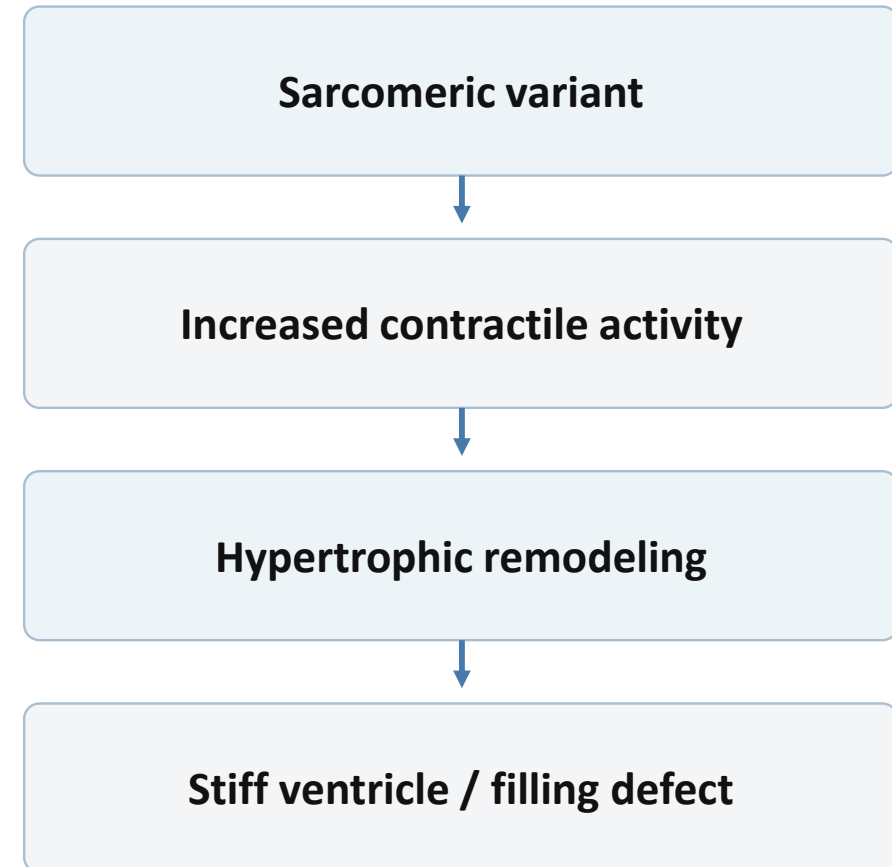
- Different pathogenic variants in the same sarcomeric gene may cause HCM
- Numerous distinct β -myosin heavy-chain variants
- Morphologic similarity does not imply identical molecular etiology
- Variant-level interpretation requires more than an abnormal gene label



Schematic

Functional consequence: Hypercontractility

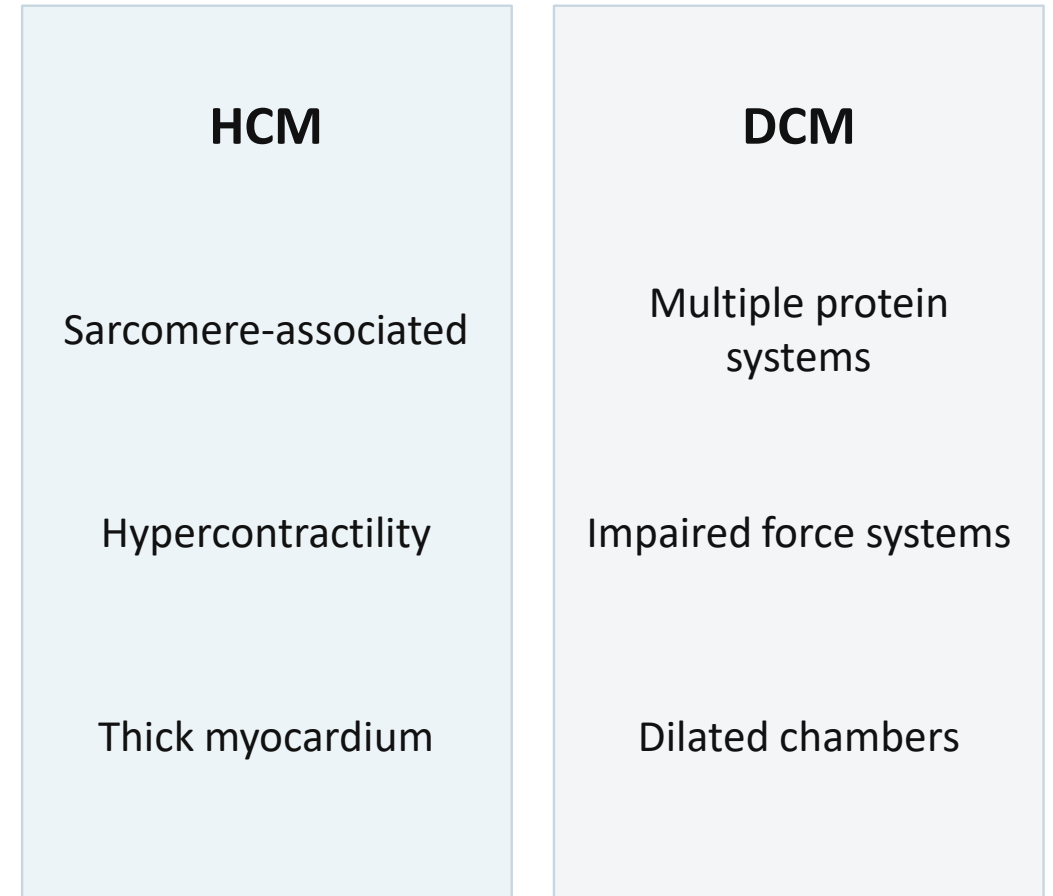
- A unifying gain-of-function effect for the HCM-associated sarcomeric variants it discusses
- Sarcomeric hypercontractility distinguishes typical HCM mechanisms from DCM
- Increased force generation does not ensure effective ventricular filling
- This mechanism informs myosin-directed therapeutic approaches



Schematic

One gene can contribute to contrasting cardiomyopathies

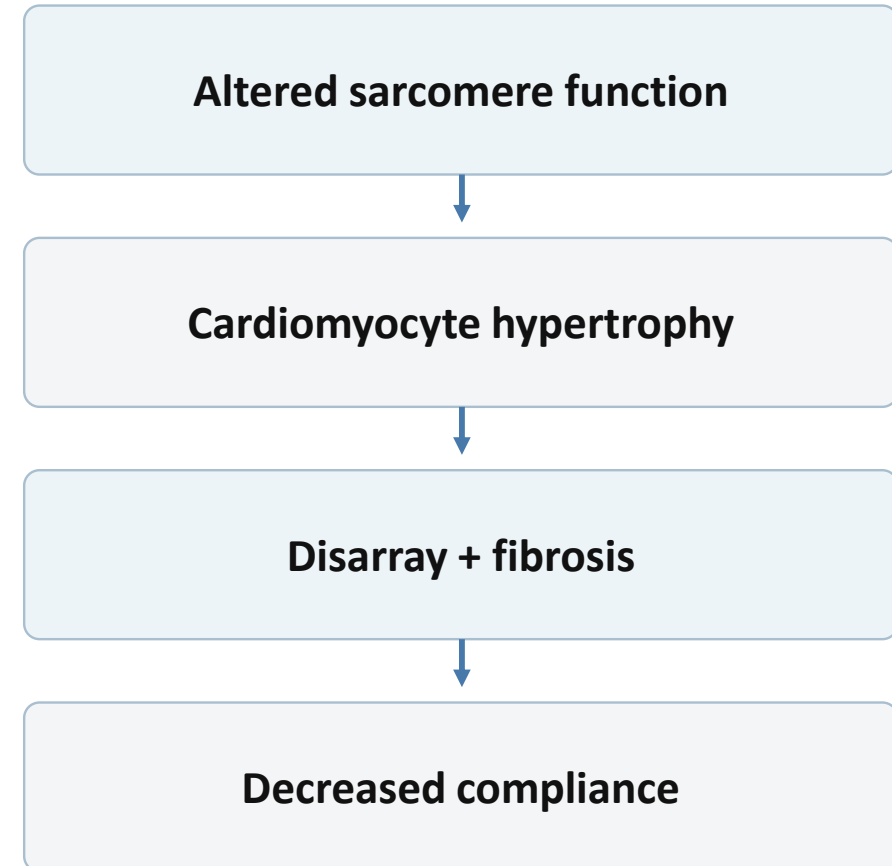
- MYH7 variants are discussed in both HCM and DCM
- The nature of functional disturbance, not merely the gene name, matters
- HCM-associated hypercontractility with DCM-associated impaired function
- Avoid assuming all variants in one gene lead to the same morphology



Schematic

From sarcomeric dysfunction to morphology

- Abnormal force regulation is linked to hypertrophic remodeling
- The ventricular wall increases in mass without proportionate chamber dilatation
- Cellular disorganization and fibrosis compound functional impairment
- The morphologic phenotype creates the substrate for impaired filling



Schematic

Genotype alone cannot establish prognosis

- Many reported variants have uncertain significance
- Clinical implications vary substantially across pathogenic variants
- A variant must be interpreted alongside the phenotype and family history
- Uncertain variants should not be equated with proven disease causation

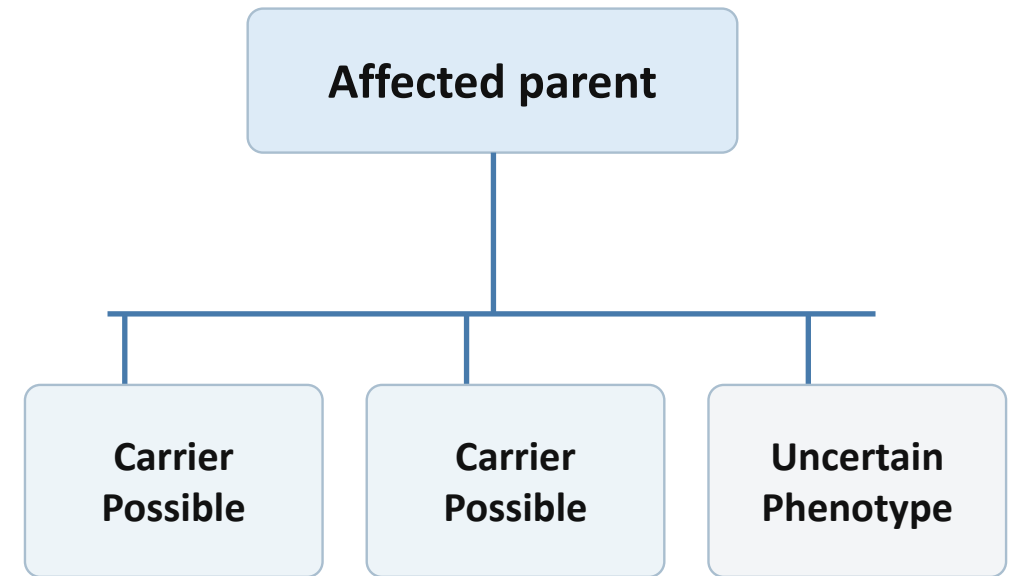
Genetic finding

Phenotype and pedigree

Clinically contextualized interpretation

Family evaluation requires context

- A genetic diagnosis can inform assessment of relatives
- Variable penetrance limits predictions based on one family member
- A variant of uncertain significance is not equivalent to a pathogenic mutation
- Phenotypic assessment remains important within affected families

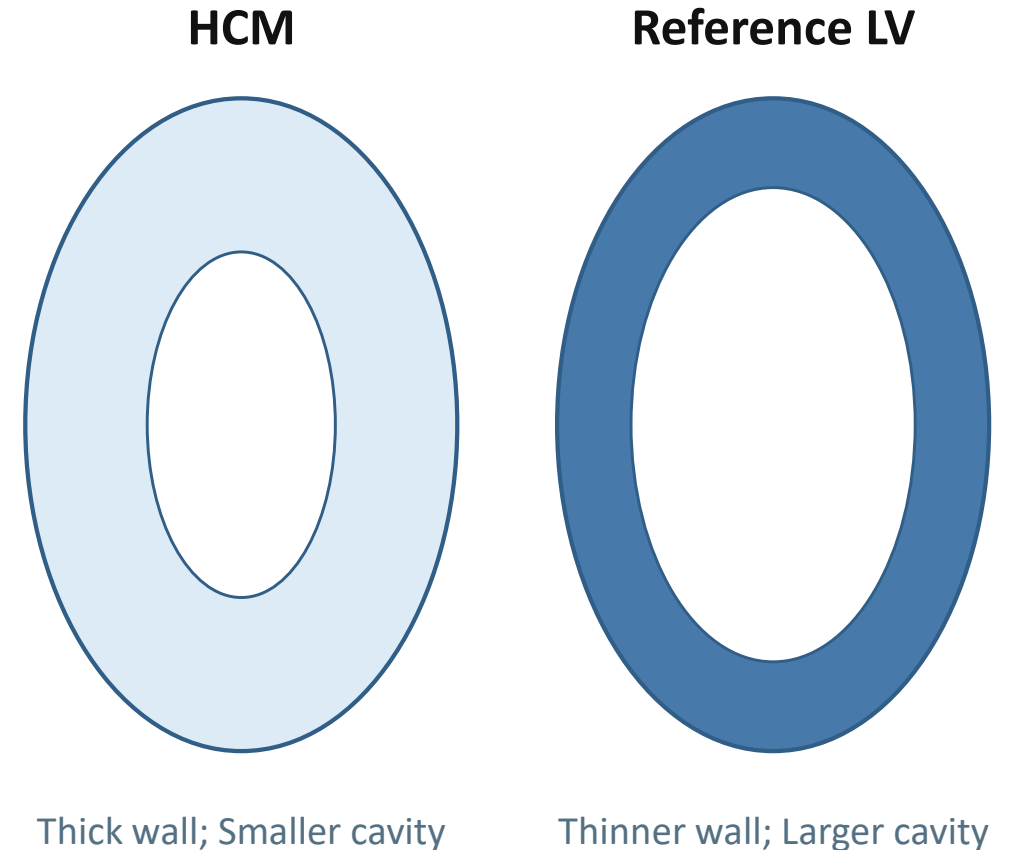


Illustrates dominant transmission and variable expression; Not a pedigree prediction

Schematic

Massive hypertrophy with little dilatation

- A large cardiac mass accompanies marked myocardial wall thickening
- The ventricular cavities are usually not dilated
- These gross findings contrast with the flabby dilated heart in DCM
- Thickness and stiffness together constrain effective filling

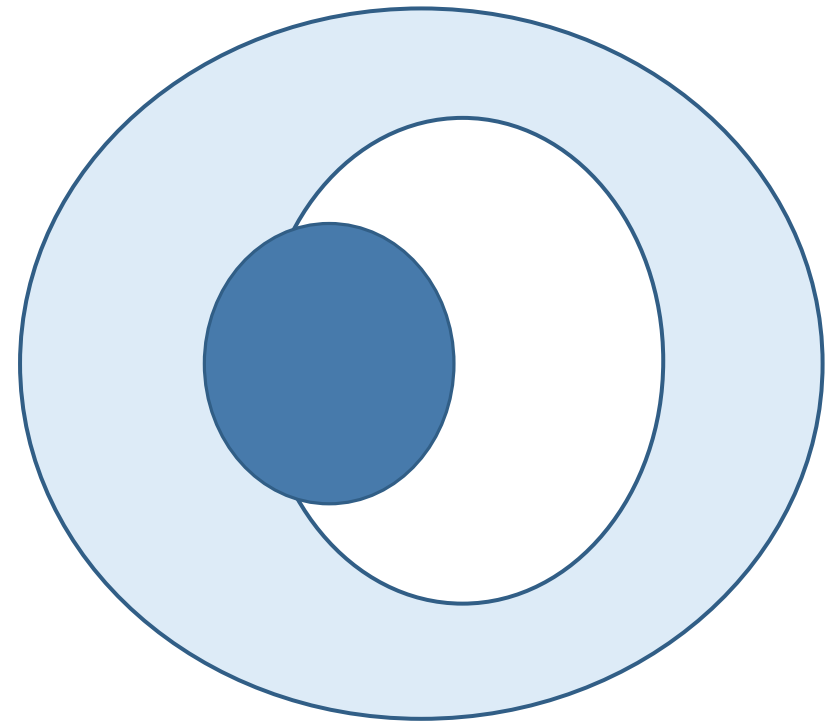


Schematic

Asymmetric septal hypertrophy

- The classic gross pattern disproportionately affects the ventricular septum
- The septum is thicker than the left ventricular free wall
- This pattern in roughly two-thirds of cases
- A concentric symmetric pattern occurs in other patients

Simplified LV cross-section

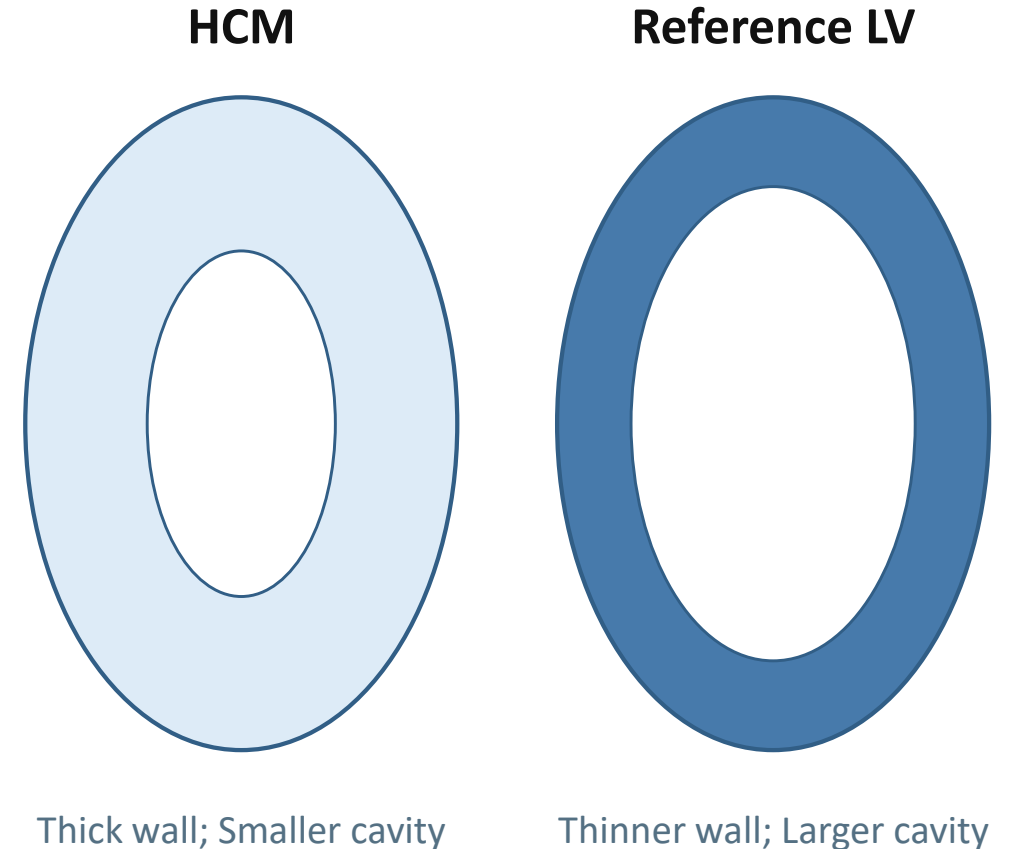


Dark blue: Septal projection White: Residual LV cavity

Schematic

HCM is not always asymmetric

- Concentric, relatively symmetrical hypertrophy can occur
- Do not require a bulging septum in every HCM specimen
- Gross distribution varies despite a related physiologic phenotype
- Consider other causes of concentric thickening in the differential

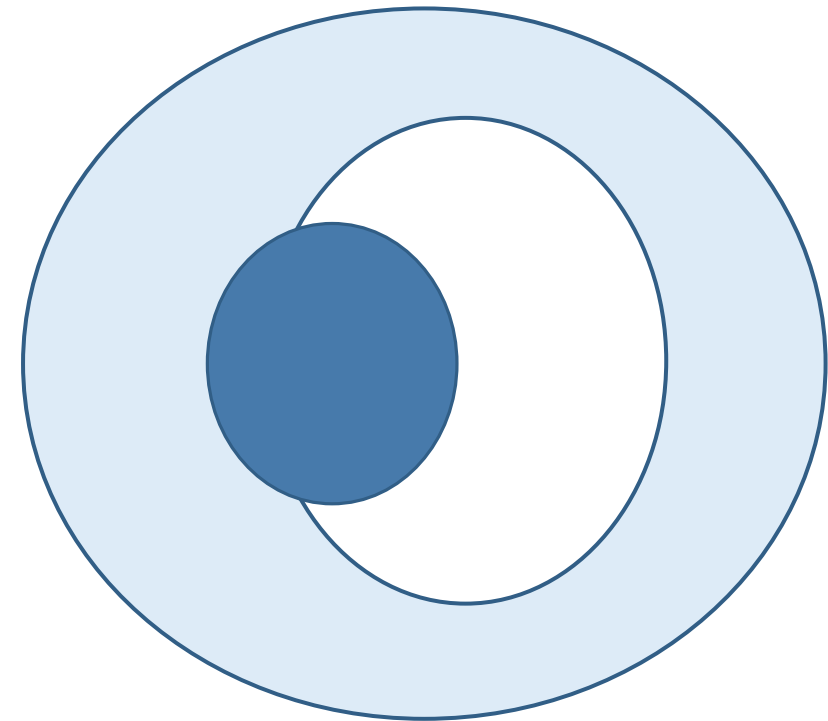


Schematic

The subaortic septum matters

- Septal hypertrophy is often most pronounced in the subaortic region
- The thickened septum projects toward the outflow channel
- Regional anatomy sets up potential mitral–septal interaction
- Septal geometry is central to obstructive HCM

Simplified LV cross-section



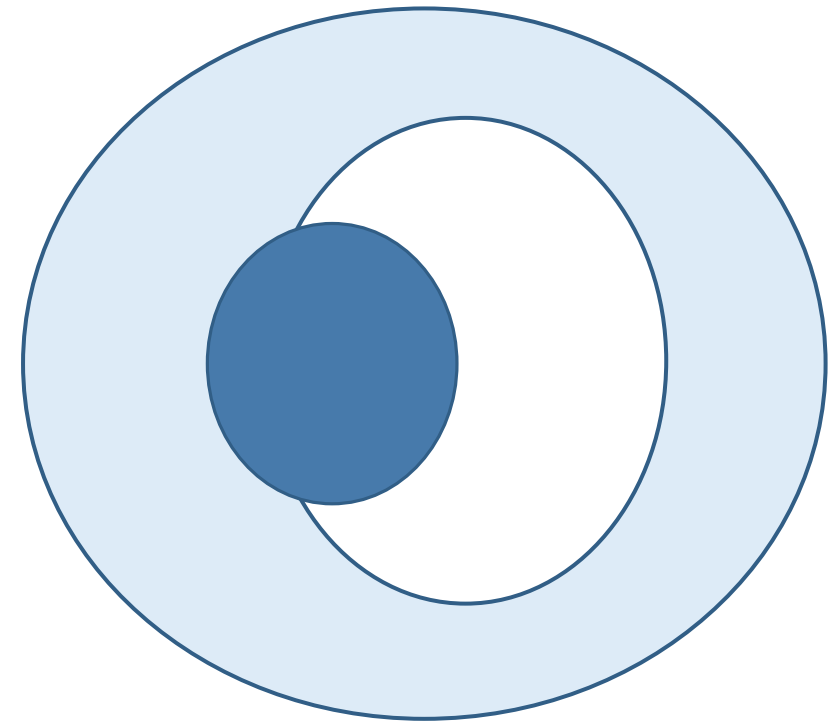
Dark blue: Septal projection White: Residual LV cavity

Schematic

Why the left ventricular cavity becomes narrow

- Disproportionate myocardial growth encroaches on luminal space
- In classic asymmetric disease, the cavity may become banana-like
- A smaller chamber limits end-diastolic filling volume
- A hypercontractile wall cannot compensate fully for poor filling

Simplified LV cross-section

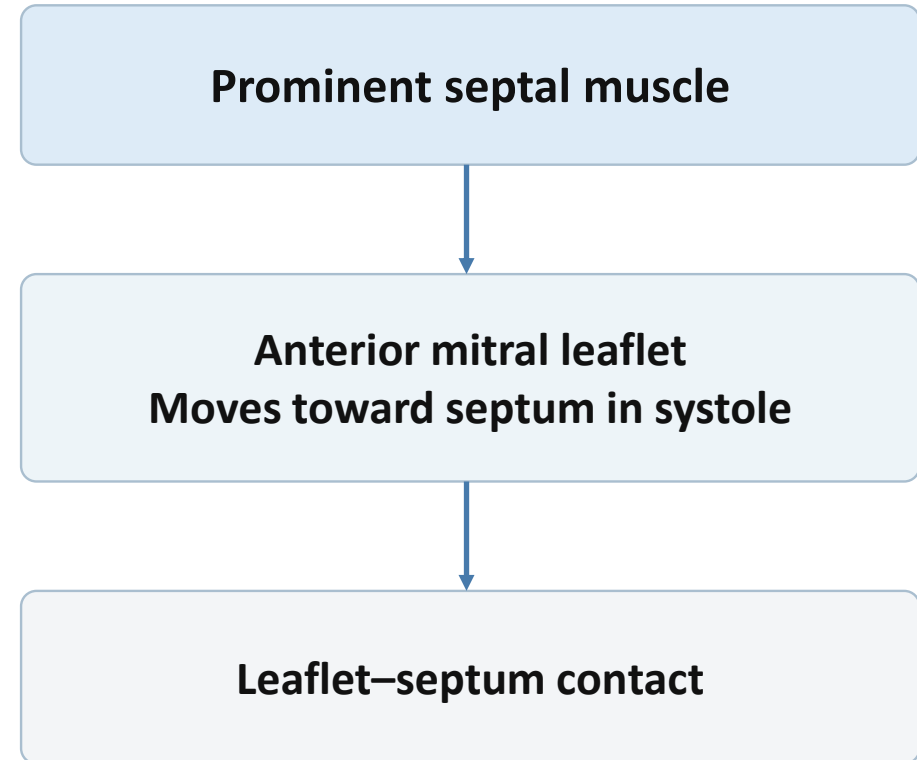


Dark blue: Septal projection White: Residual LV cavity

Schematic

Two components of the obstructive phenotype

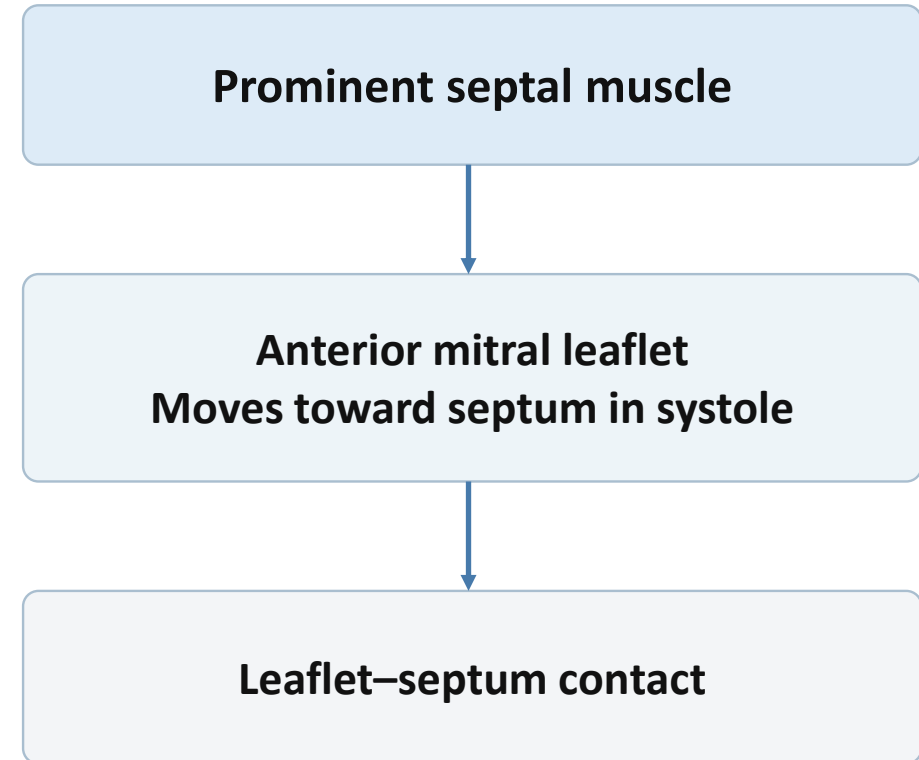
- A prominent septum creates a reduced outflow passage
- Systolic movement of the anterior mitral leaflet adds dynamic narrowing
- Obstruction is functional and varies with systolic geometry
- Not every patient has clinically important obstruction



Schematic

Systolic anterior motion (SAM)

- During systole, the anterior mitral leaflet can move toward the septum
- The echocardiographic term is systolic anterior motion
- Leaflet–septal contact can exacerbate outflow obstruction
- The mechanism is dynamic rather than a fixed stenotic valve lesion



Schematic

Why a fibrous endocardial plaque forms

- Repeated mitral leaflet contact with the septum may injure endocardium
- The contact region may develop a fibrous endocardial plaque
- Thickening of the anterior mitral leaflet can also accompany contact
- These findings anatomically corroborate the dynamic mechanism

Septal bulge

Geometric narrowing

Leaflet contact

Endocardial friction

Fibrous plaque

Repeated contact site

Schematic

Gross pathology: An integrated inspection

- Assess overall cardiac weight and ventricular wall thickness
- Compare septal thickness with the LV free wall
- Evaluate chamber size and the subaortic region
- Look for a fibrous endocardial contact plaque

Septal bulge

Geometric narrowing

Leaflet contact

Endocardial friction

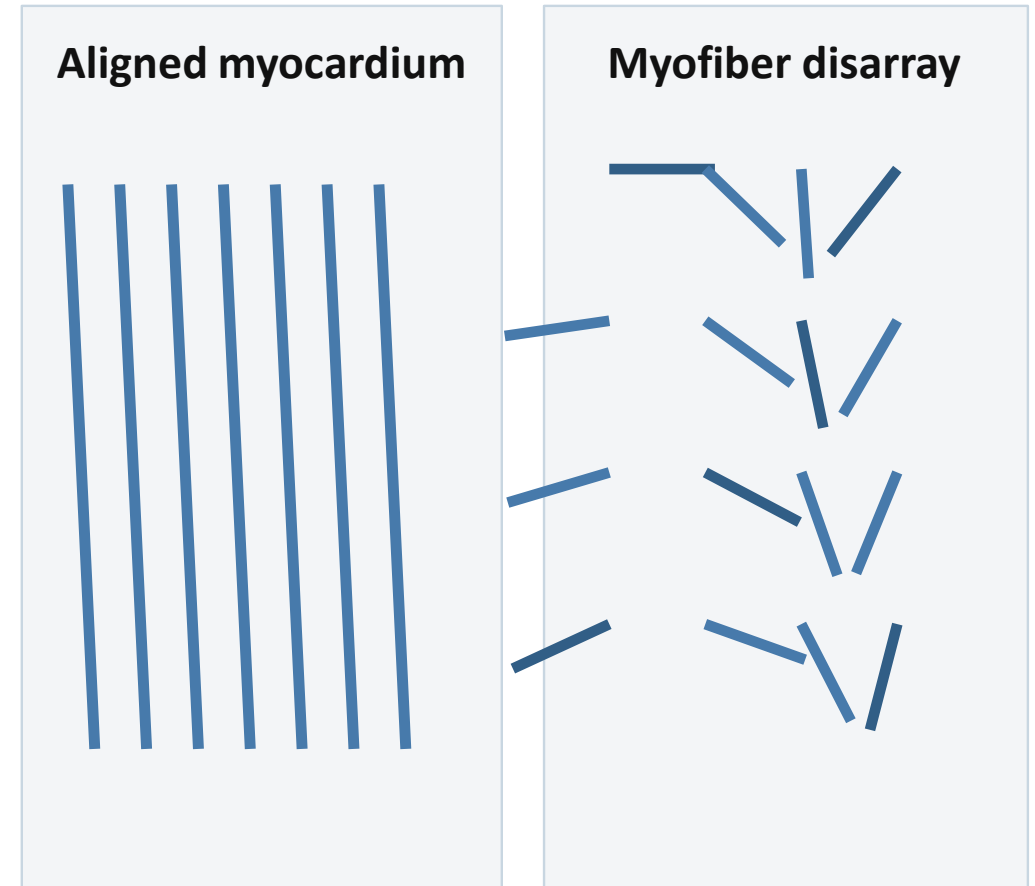
Fibrous plaque

Repeated contact site

Schematic

Cardiomyocyte hypertrophy

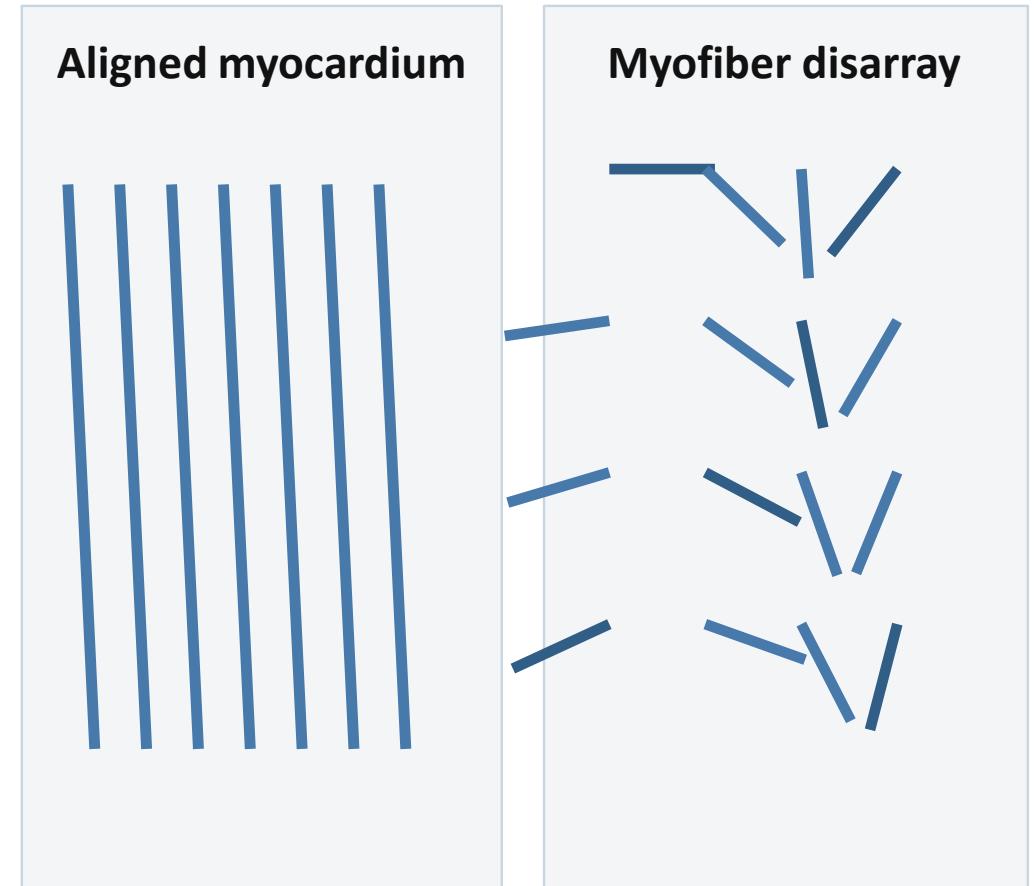
- Individual cardiomyocytes are conspicuously enlarged
- Hypertrophy is a hallmark at the microscopic level
- Large fibers alone do not define HCM without the broader phenotype
- Interpret size changes together with disarray, fibrosis and clinical context



Conceptual fiber organization — not histology
Schematic

Myofiber disarray

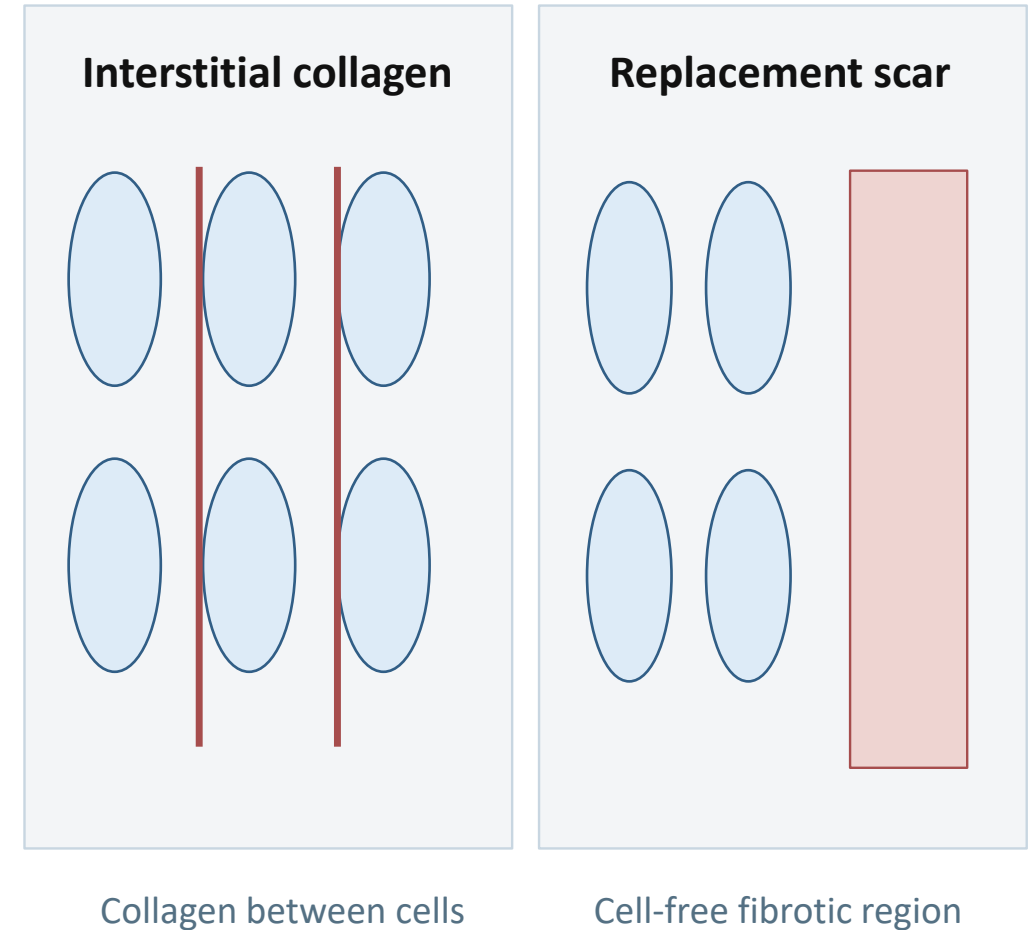
- Bundles of myocytes run in haphazard rather than parallel directions
- Disorganization may affect individual cells and intracellular myofibrils
- Architectural disarray is a classic histologic hallmark
- It should be interpreted alongside the full pattern of myocardial findings



Conceptual fiber organization — not histology
Schematic

Interstitial and replacement fibrosis

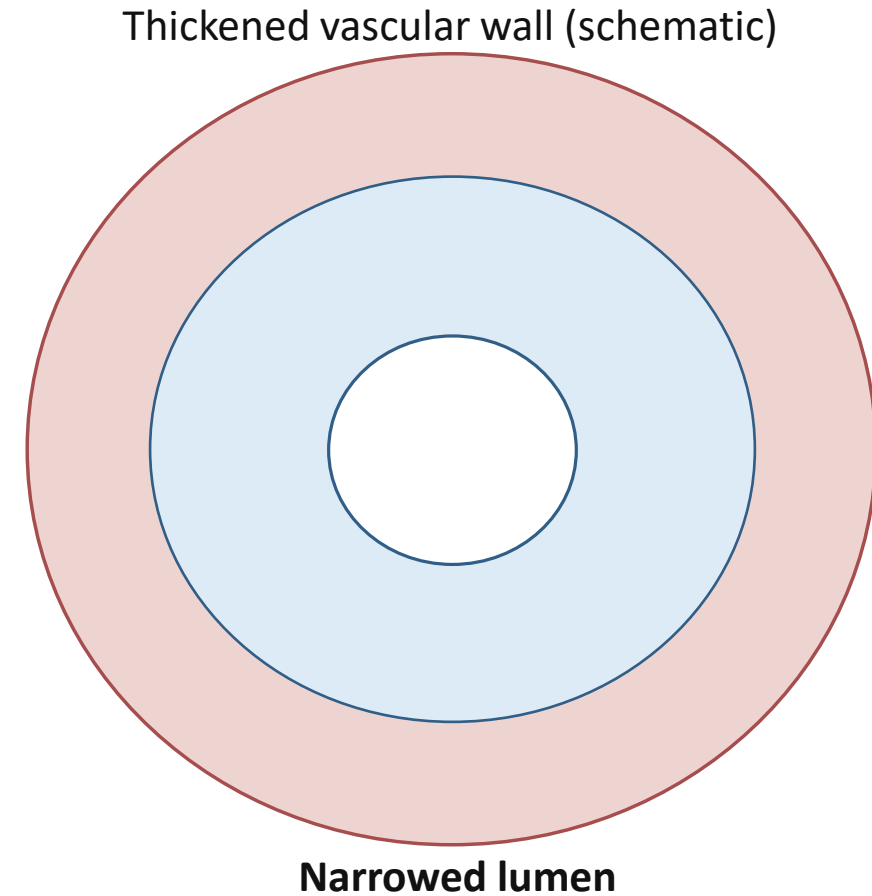
- Interstitial collagen accumulates among cardiomyocytes
- Replacement fibrosis marks loss and substitution of myocardial tissue
- Fibrosis contributes to increased stiffness and electric heterogeneity
- The distribution and extent can vary between affected hearts



Schematic

Fibrotic narrowing of intramural arteries

- Small intramural coronary vessels may have thickened, fibrotic walls
- A reduced vascular lumen can compromise myocardial perfusion
- Small-vessel changes help explain ischemia without epicardial CAD
- Vascular and interstitial abnormalities coexist with myocyte changes



Schematic

Four microscopic elements in HCM

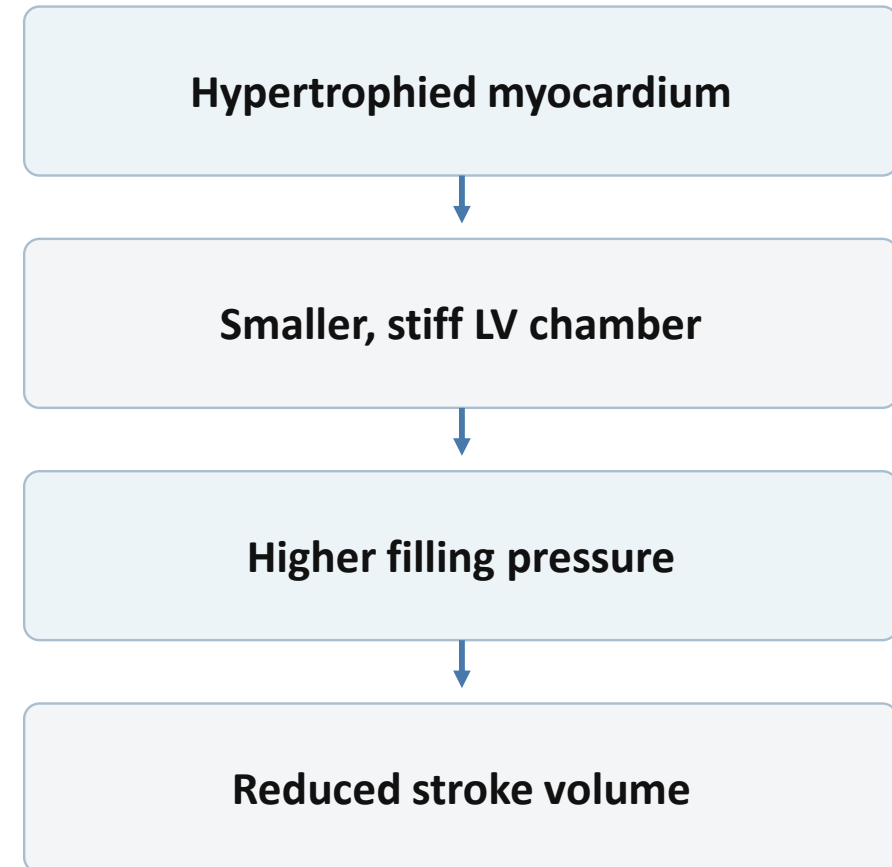
- Marked myocyte hypertrophy
- Haphazard myofiber disarray
- Fibrotic thickening of small intramural arteries
- Interstitial and replacement myocardial fibrosis

Myocyte	Vessel	Interstitium
Hypertrophy	Wall fibrosis	Fibrosis
Disarray	Lumen narrowing	Replacement scar
Abnormal topology	Ischemic substrate	Stiffness

Schematic

Structural remodeling creates functional stiffness

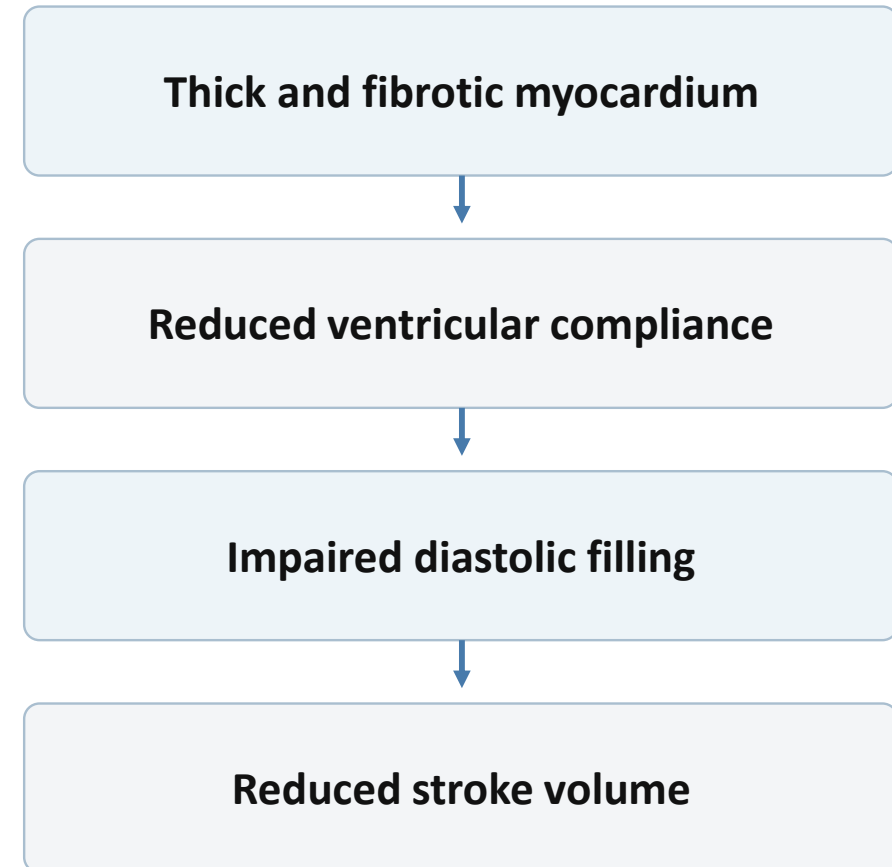
- Hypertrophied cells increase myocardial mass
- Fibrotic interstitium resists ventricular expansion
- A reduced chamber further limits filling
- These combined changes underlie a major diastolic defect



Schematic

Diastolic dysfunction is central

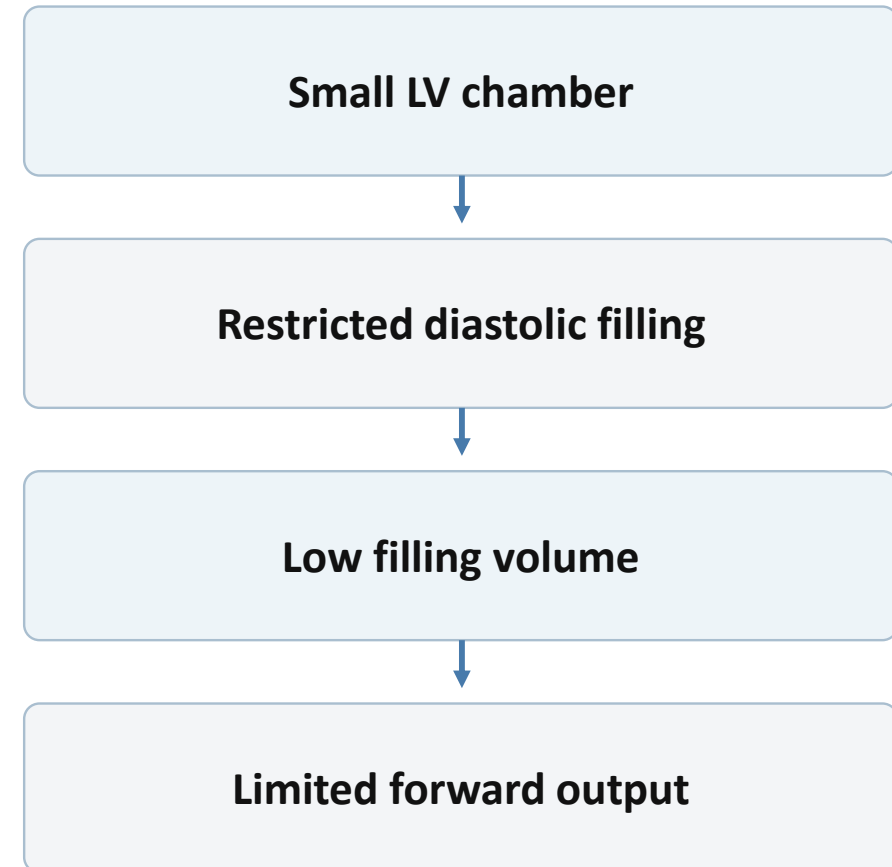
- The LV is poorly compliant and requires more pressure to fill
- Thick walls reduce the effective filling capacity
- Even preserved contractile function may coexist with reduced stroke volume
- The result is impaired cardiac performance during demand



Schematic

Reduced stroke volume despite hypercontraction

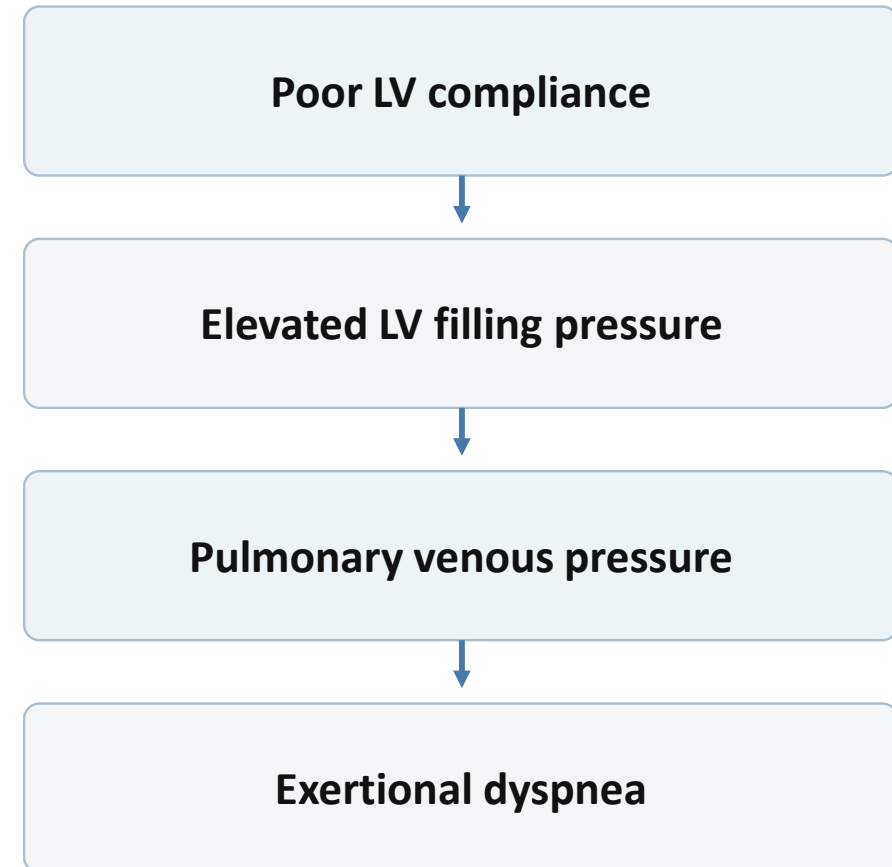
- The amount ejected depends on the amount entering during diastole
- A hypercontracting, small cavity can still deliver inadequate forward output
- Exercise increases the demand for cardiac flow
- Symptoms may arise despite preserved conventional systolic measures



Schematic

Why pulmonary venous pressure rises

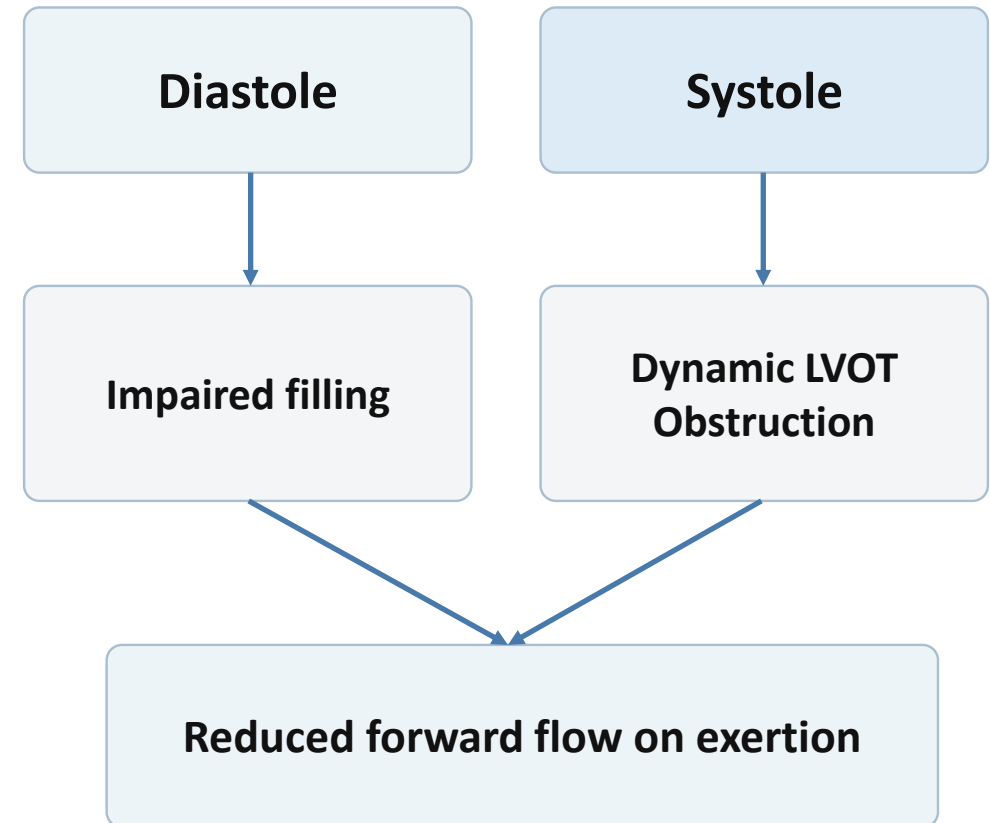
- Poor LV filling produces higher pressure upstream
- The left atrium and pulmonary veins face increased filling pressure
- This contributes to exertional dyspnea
- Clinical symptoms link diastolic mechanics with pulmonary congestion



Schematic

Dynamic obstruction compounds impaired output

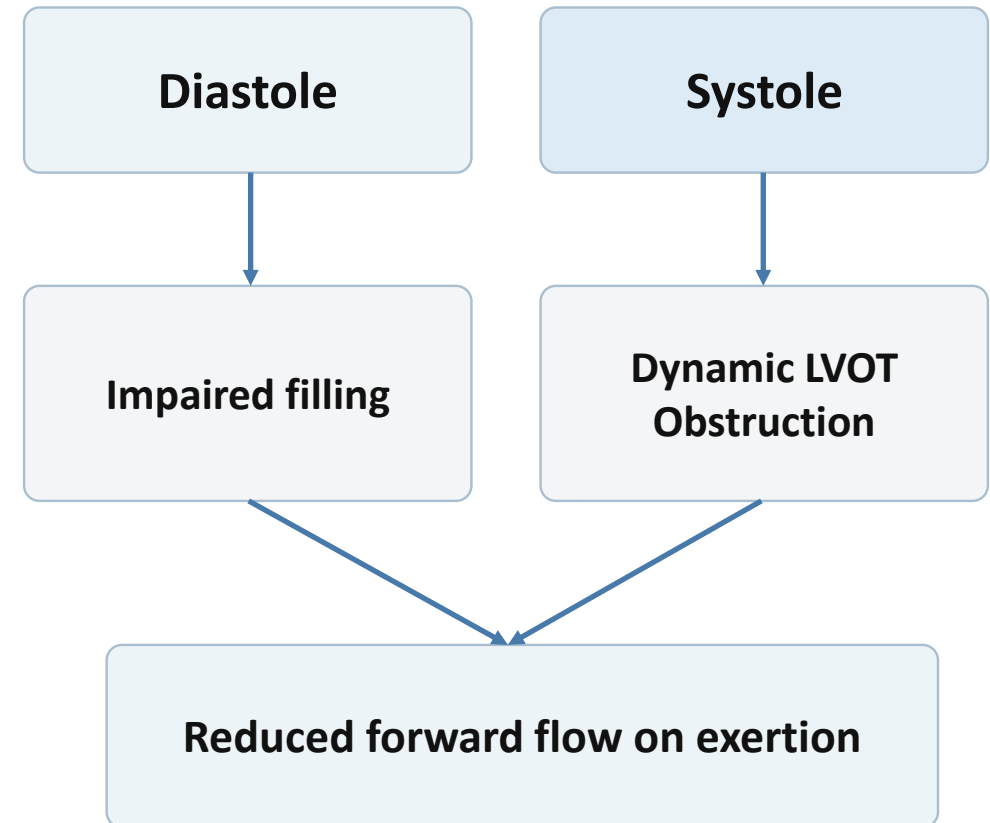
- Outflow narrowing occurs during ventricular systole
- Mitral–septal interaction adds to reduced forward flow
- Obstruction can coexist with the primary filling abnormality
- Its presence and magnitude contribute to heterogeneity



Schematic

Exertional dyspnea: Two mechanisms

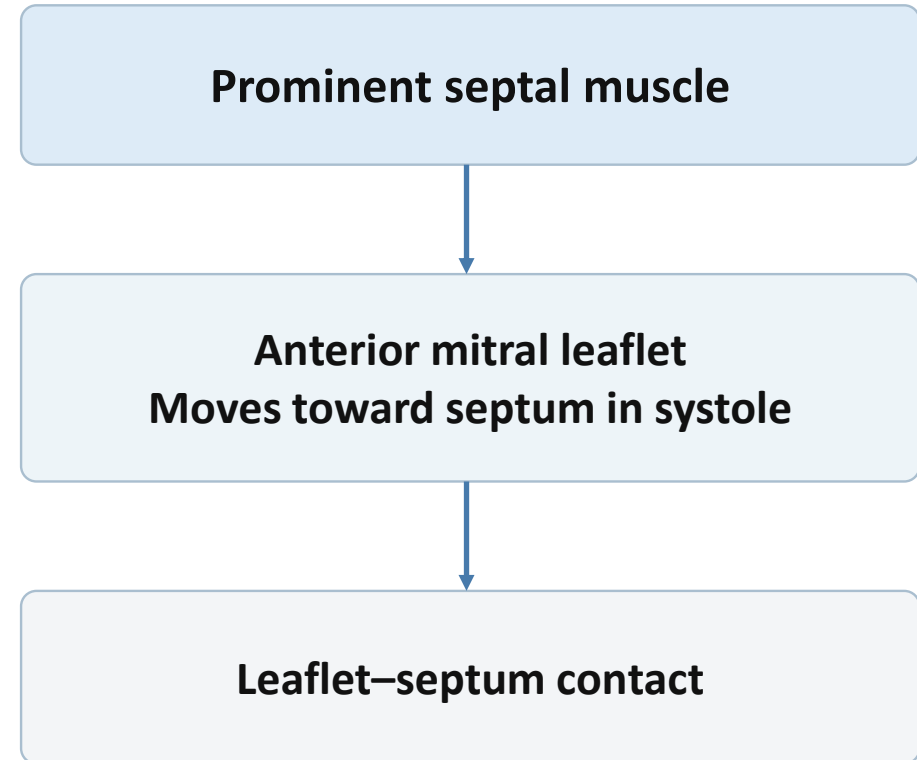
- A stiff ventricle restricts end-diastolic filling
- Pulmonary venous pressure rises as LV filling pressure increases
- Dynamic obstruction can further compromise forward cardiac output
- The combination helps explain symptoms with activity



Schematic

The systolic ejection murmur

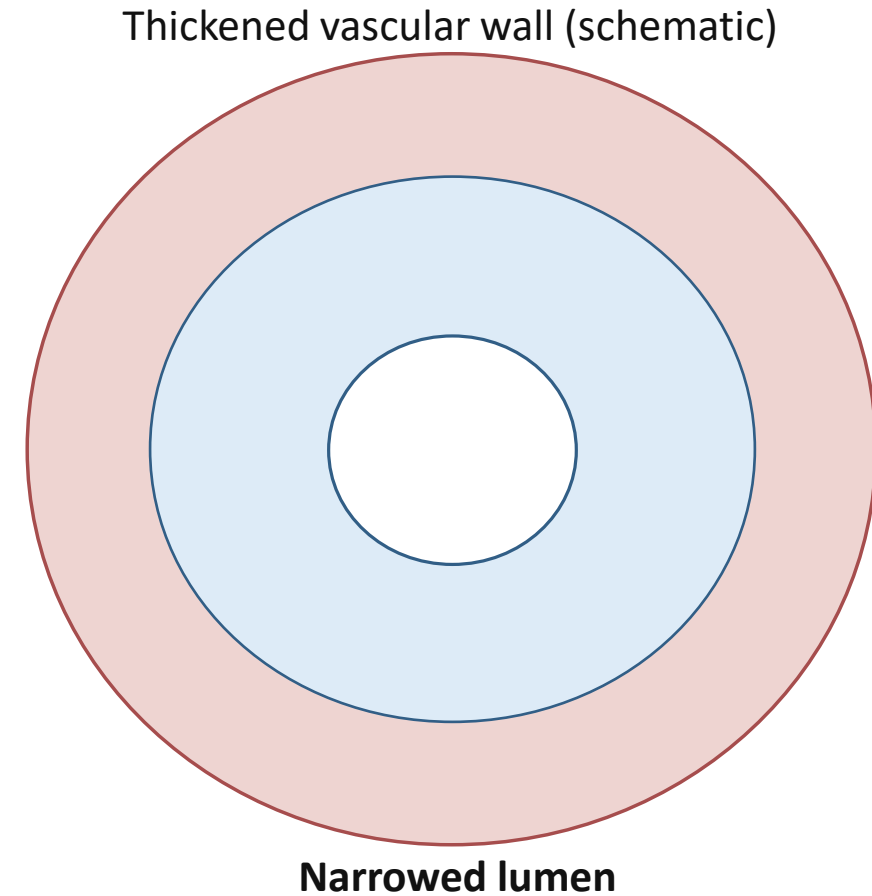
- Dynamic LV outflow obstruction produces a harsh systolic ejection murmur
- The audible finding reflects disturbed systolic outflow
- A murmur is not required in nonobstructive HCM
- Interpret auscultation with structural and functional assessment



Schematic

Myocardial ischemia without epicardial stenosis

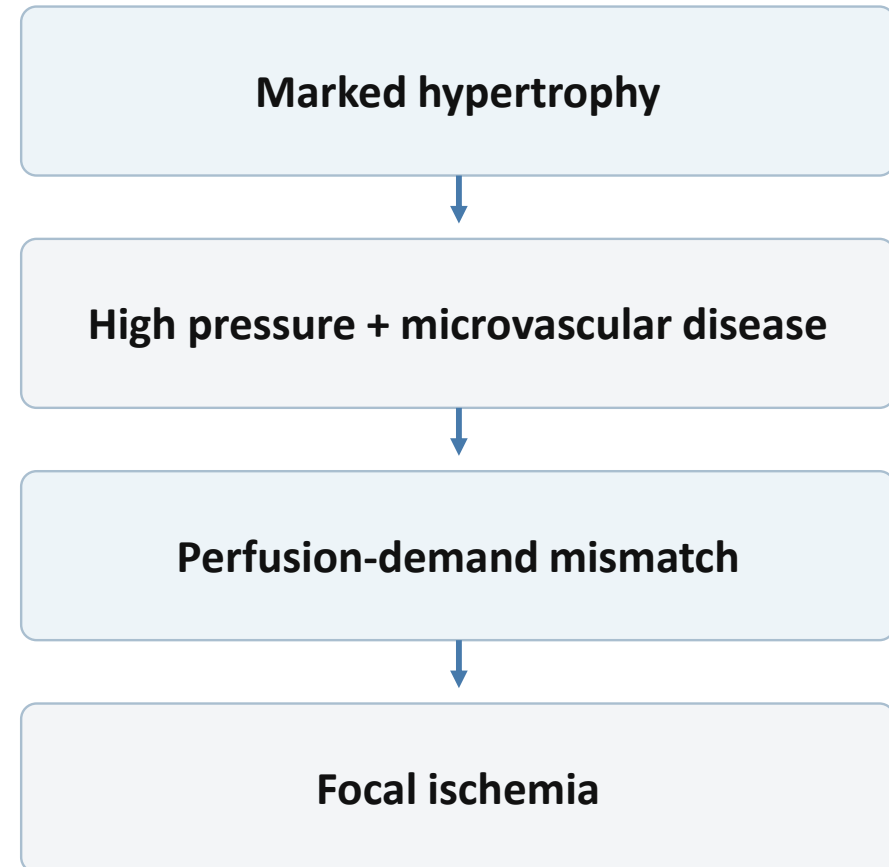
- Massive ventricular hypertrophy raises myocardial oxygen demand
- High intracavitary pressures increase wall stress
- Fibrotic small intramural vessels impair microvascular supply
- Focal ischemia may occur even without obstructive epicardial CAD



Schematic

Ischemic substrate: Demand and supply

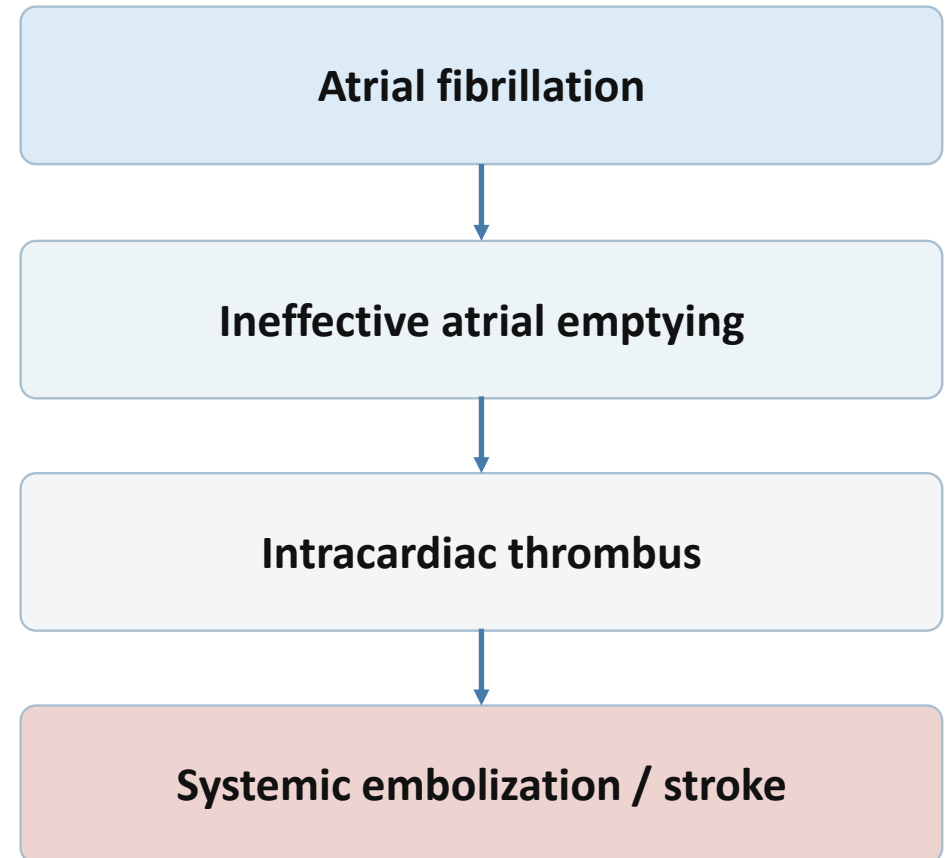
- Greater muscle mass increases perfusion requirements
- Small-vessel narrowing limits local blood delivery
- The net supply–demand imbalance produces focal myocardial ischemia
- Ischemia may add to scarring and functional deterioration



Schematic

Atrial fibrillation: A major complication

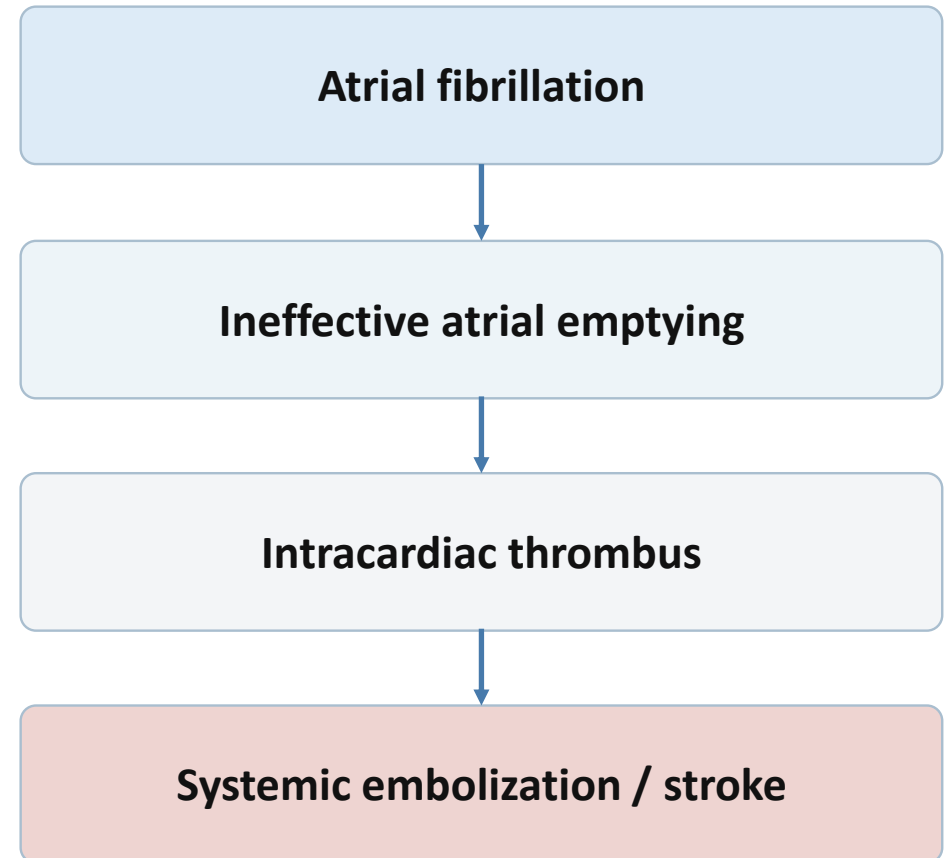
- Altered filling and atrial pressure create a clinically important atrial burden
- Atrial fibrillation is a major problem in HCM
- Loss of coordinated atrial activity can worsen diastolic filling
- Rhythm disturbance can initiate a thromboembolic sequence



Schematic

From atrial arrhythmia to embolic stroke

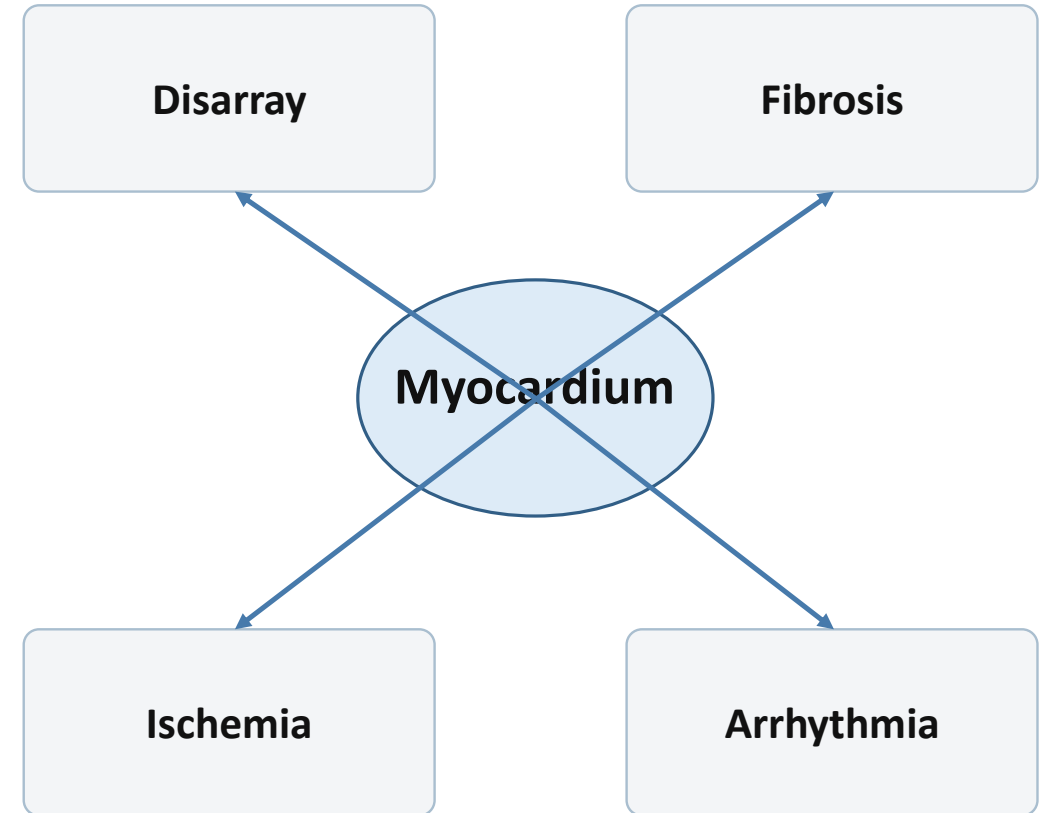
- Atrial fibrillation can be associated with intracardiac thrombus formation
- Thrombus may embolize from the heart
- Systemic arterial embolization can involve cerebral circulation
- Stroke prevention is therefore clinically important in affected patients



Schematic

Ventricular arrhythmias and sudden death

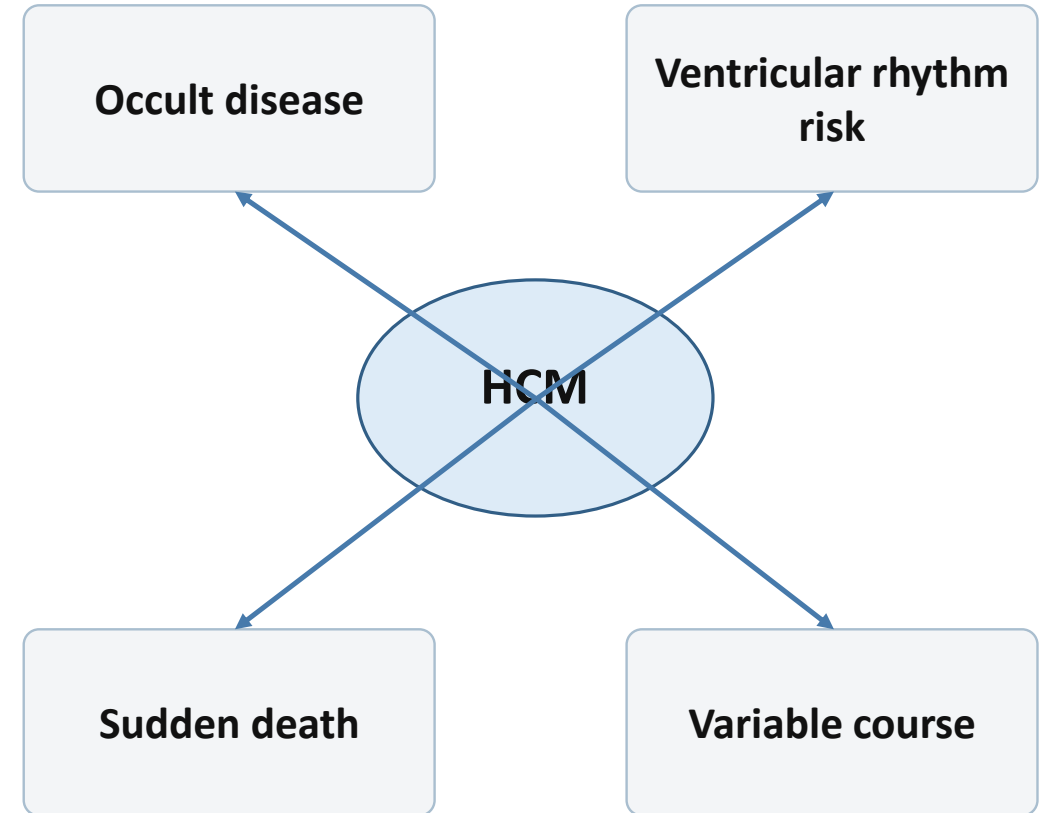
- Ventricular arrhythmias are a major complication
- Hypertrophied, disarrayed, ischemic and fibrotic myocardium provides an arrhythmogenic substrate
- Sudden death can occur, including in young individuals
- Risk varies and must not be assigned from wall thickness alone



Schematic

HCM and sudden death in young athletes

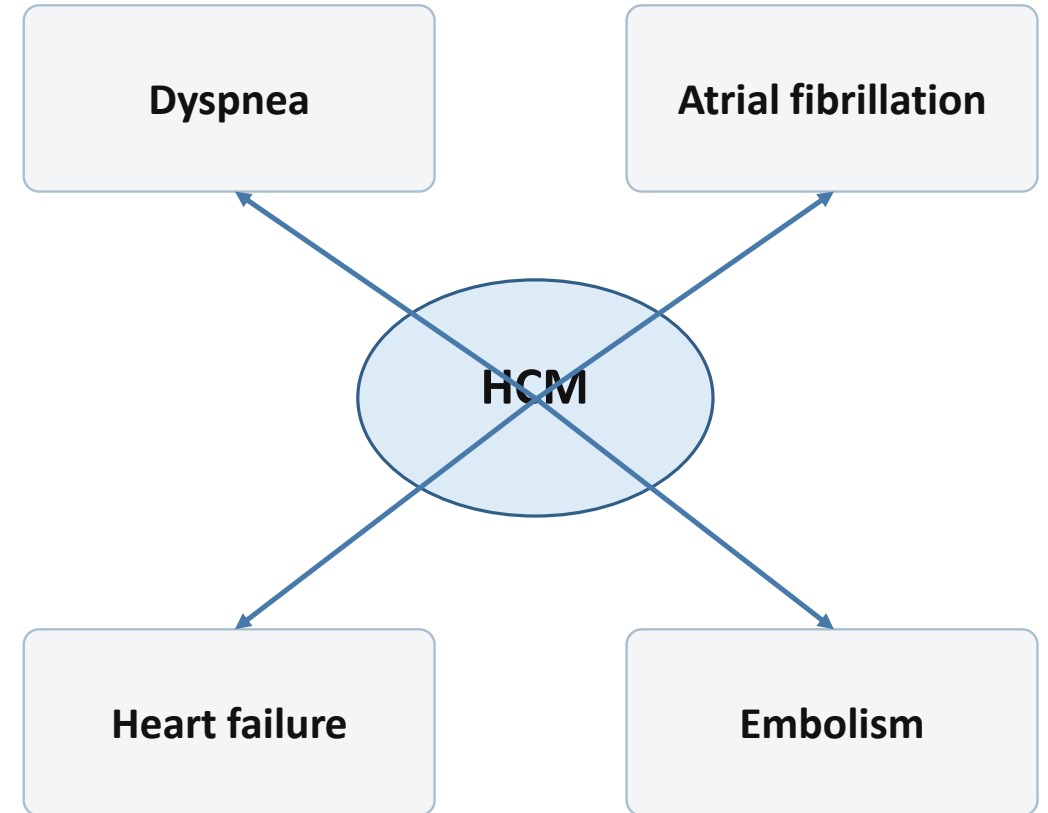
- HCM as an important cause of sudden death in young athletes
- An apparently healthy or highly active individual may have unrecognized disease
- A single exercise-related event should not be generalized to all patients
- The natural history remains highly variable



Schematic

Other major clinical consequences

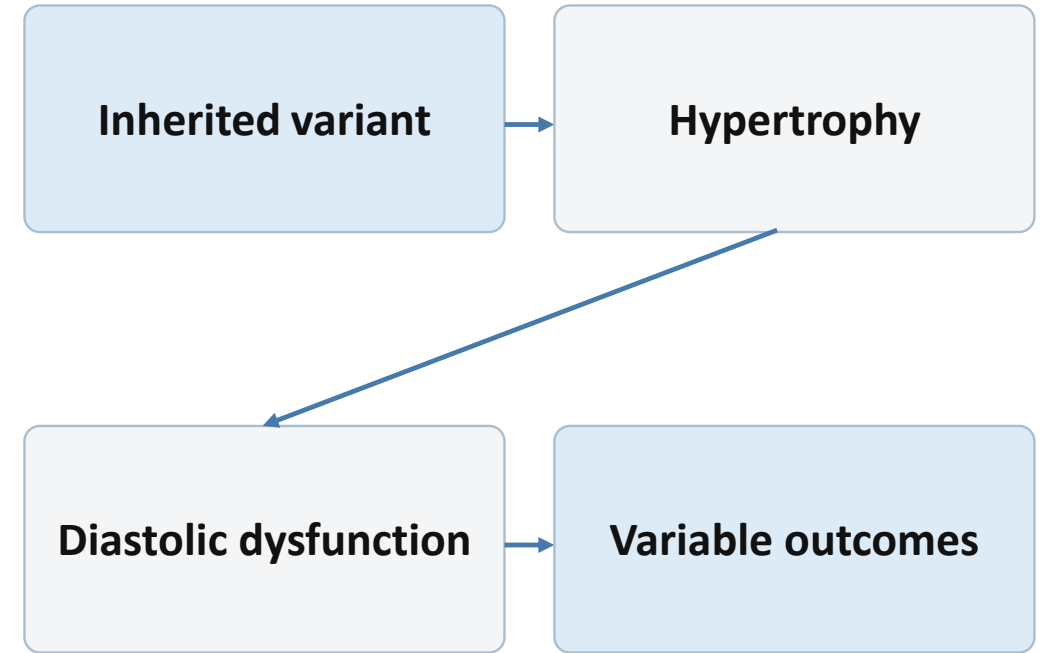
- Reduced filling and outflow obstruction may impair exertional tolerance
- Atrial fibrillation can worsen symptoms and predispose to thrombus
- Progressive cardiac failure can occur
- Arrhythmia, embolization and sudden death are distinct clinical hazards



Schematic

Natural history is highly variable

- Some individuals have an indolent or minimally symptomatic course
- Others develop obstruction, arrhythmias or cardiac failure
- Different mutations and myocardial phenotypes contribute to variability
- Clinical assessment must integrate structure, function and symptoms



Clinical identification starts with a pattern

- Recognize otherwise unexplained LV hypertrophy
- Establish whether the dominant physiology is impaired filling
- Assess for septal thickening and systolic anterior mitral motion
- Exclude conditions that cause similar wall thickening

Phenotype recognition

Exclude mimicking causes

Relate structure to symptoms

Cardiac imaging and the morphologic phenotype

- Imaging can assess ventricular wall distribution and chamber dimensions
- A thickened septum and reduced chamber can support the phenotype
- Echocardiographic SAM documents leaflet movement toward the septum
- Morphology must still be interpreted with competing etiologies in mind

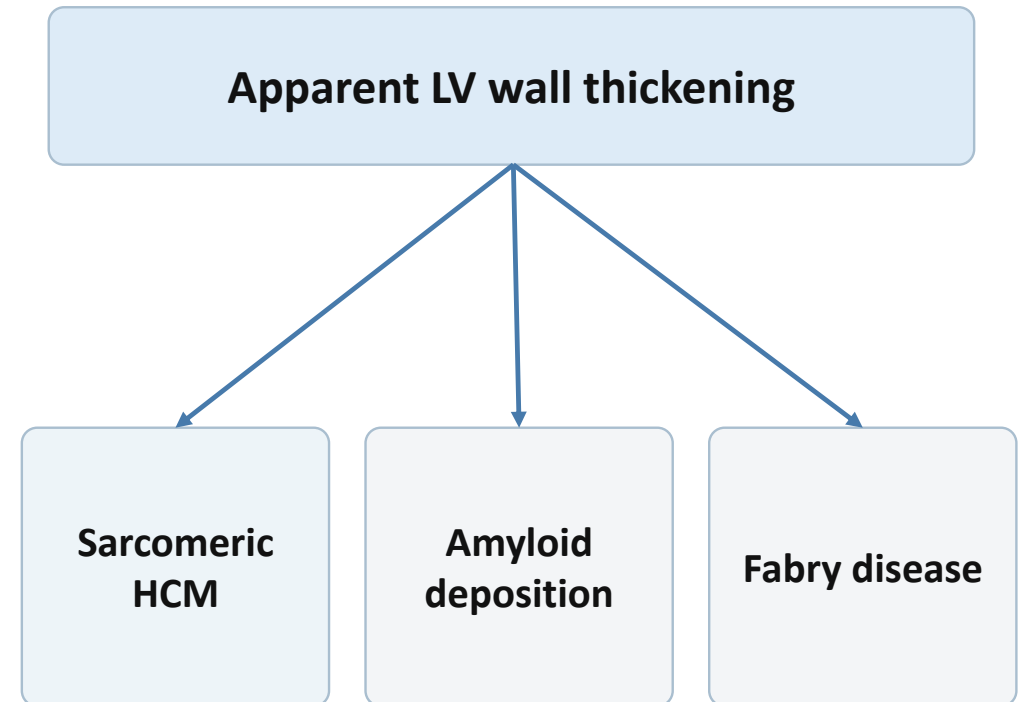
Wall distribution and cavity

LV outflow / leaflet motion

Contextual differential diagnosis

Mimic 1: Deposition-related myocardial disease

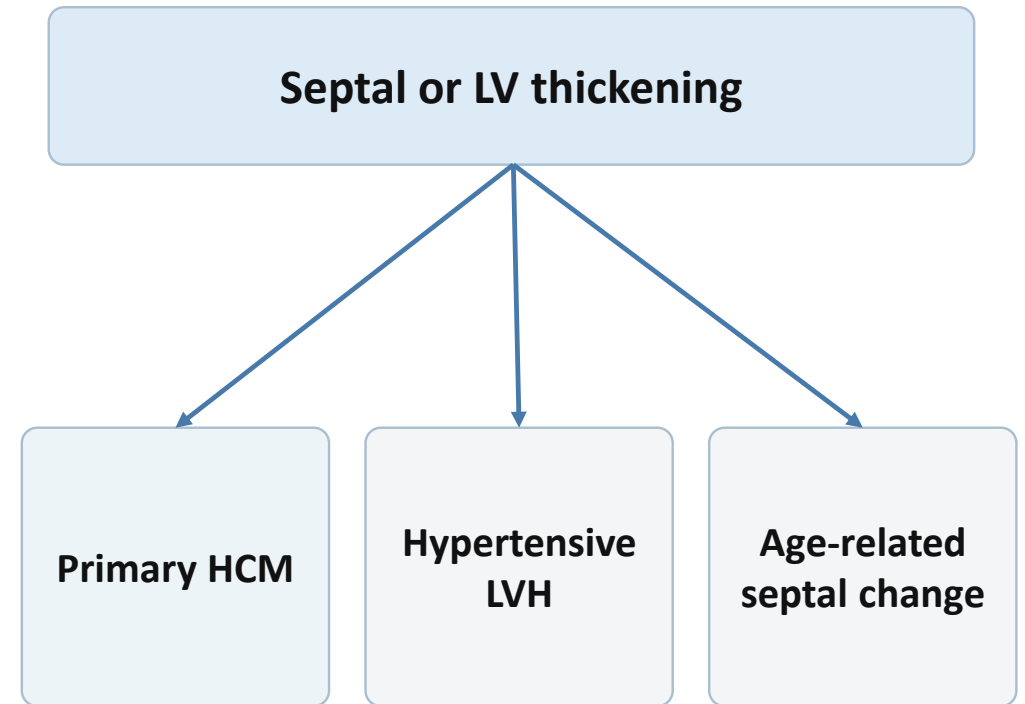
- Amyloidosis and Fabry disease as important HCM mimics
- Myocardial thickening may arise from accumulation rather than sarcomeric hypertrophy
- The mechanism and associated pathology differ
- A thick ventricular wall is therefore a phenotype, not the complete diagnosis



Schematic

Mimic 2: Hypertensive heart disease

- Longstanding hypertension can cause LV hypertrophy
- Age-related subaortic septal hypertrophy can add to the resemblance
- Clinical pressure-loading context is diagnostically important
- Do not label any prominent septum as genetically mediated HCM



Schematic

Mimic 3: Fixed outflow stenosis

- Valvular aortic stenosis is an important alternative explanation
- Congenital subvalvular aortic stenosis can also mimic obstruction
- Fixed valvular/subvalvular lesions differ from dynamic mitral–septal contact
- Correct diagnosis requires attention to obstructive anatomy

Dynamic HCM

Septal thickening

Systolic mitral motion

Variable obstruction

Fixed stenosis

Valve/subvalvular lesion

Fixed narrowing

Alternative cause of LVH

Schematic

HCM, DCM and restrictive disease compared

- HCM is typically thick-walled and nondilated
- DCM predominantly has a dilated, poorly contracting ventricle
- Restrictive cardiomyopathy has impaired filling, often without striking hypertrophy
- Functional overlap makes morphologic interpretation necessary

Attribute	HCM	Restrictive
LV wall	Marked thickening	Often not marked
Diastole	Abnormal	Abnormal
LV cavity	Usually not dilated	Not dilated
Myocyte disarray	Characteristic	Not defining

Schematic

Therapeutic principle: Reduce cardiac work

- β -adrenergic blockade as beneficial for many patients
- Lower heart rate allows more time for ventricular filling
- Reduced contractility can attenuate hyperdynamic physiology
- Treatment details require patient-specific specialist assessment

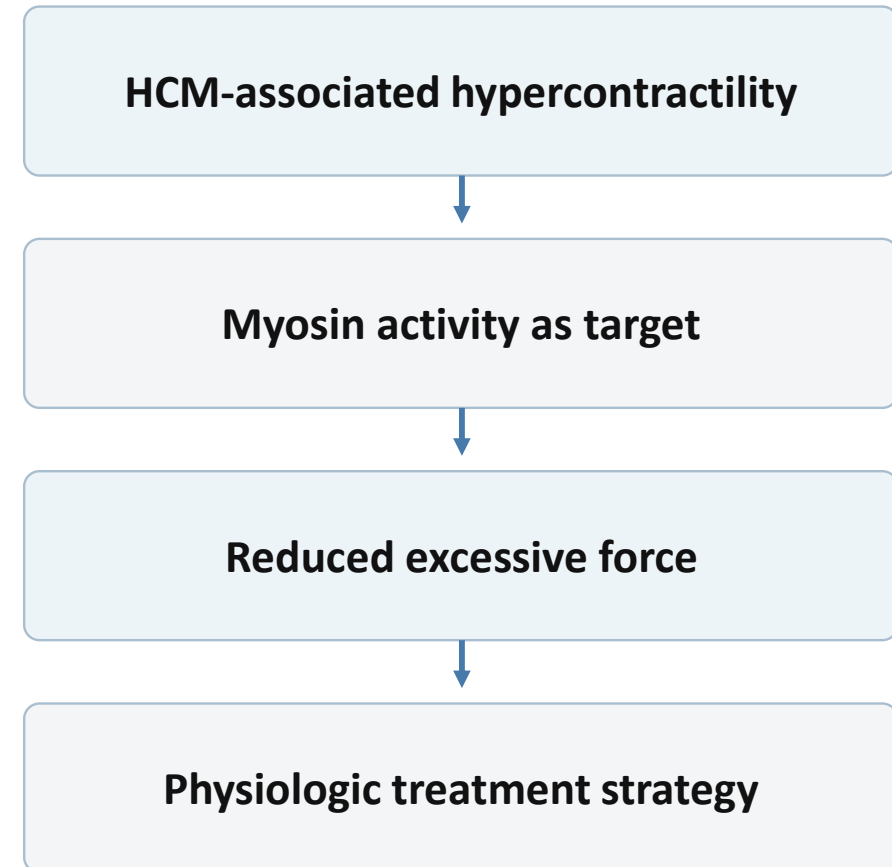
Lower heart rate

Reduce excessive contractility

Improve functional filling conditions

Myosin-directed treatment follows mechanism

- Sarcomeric hypercontractility is a mechanistic drug target
- Newer therapies based on inhibiting myosin activity
- The therapeutic logic is to modify excessive contractile activity
- This mechanistic concept is separate from prescribing criteria



Schematic

Implantable defibrillator: A distinct objective

- Some HCM patients are at risk for life-threatening ventricular arrhythmias
- An implantable cardioverter-defibrillator addresses selected arrhythmic risk
- An ICD does not remove myocardial hypertrophy or septal anatomy
- Indication requires individualized clinical risk assessment

Arrhythmic risk assessment

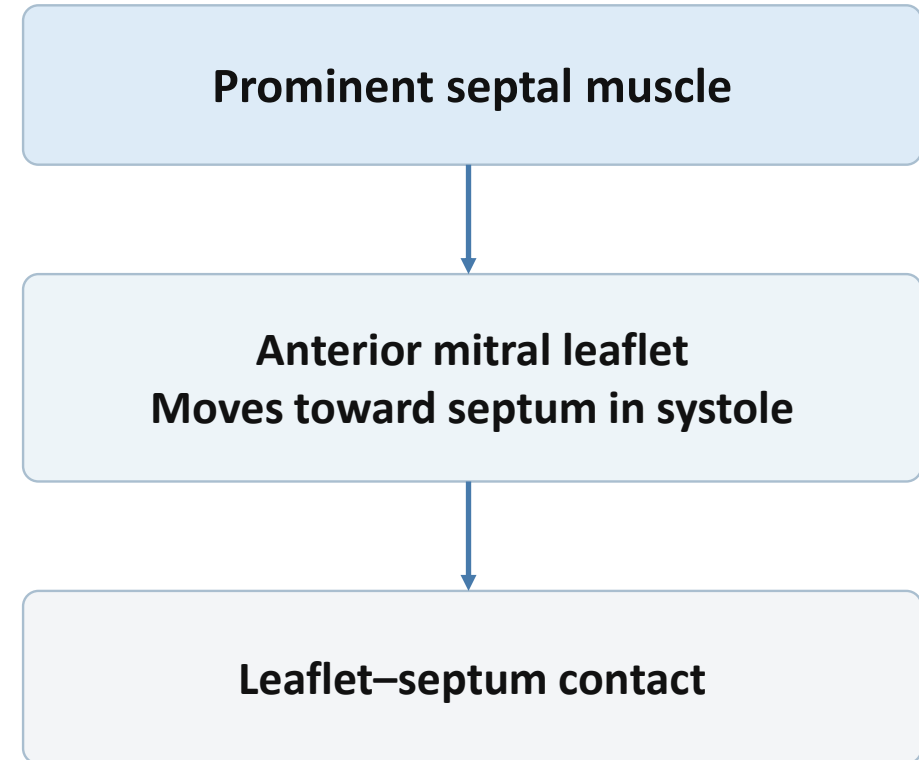
Selected ICD implantation

Prevention of fatal ventricular rhythm outcome

Schematic

Septal myectomy: Mechanical relief

- Surgical excision can reduce the mass of an obstructing septum
- The aim is to widen the LV outflow region
- This approach addresses a geometric component of obstruction
- It does not reverse the underlying inherited sarcomeric abnormality



Schematic

Alcohol septal ablation: Another strategy

- Catheter-delivered alcohol can create a carefully controlled septal infarction
- The subsequent reduction of septal muscle mass mitigates outflow obstruction
- This is an anatomically targeted therapy for selected patients
- It differs mechanistically from surgery but shares the obstruction-relief objective

Target obstructing septum

Controlled septal infarction

Reduction in obstructing muscle mass

Schematic

Matching treatment to pathophysiology

- Filling impairment suggests a role for reducing heart rate/contractility
- Ventricular rhythm risk is a separate reason to consider an ICD
- Severe obstructive anatomy may warrant septal reduction
- These treatments address distinct physiologic or clinical problems

Problem	Intervention	Goal
Rapid/hyperdynamic	β -blockade	Slow / reduce force
VT/VF risk	ICD	Arrhythmia rescue
Septal obstruction	Septal reduction	Improve outflow

Case: Exertional dyspnea and septal thickening

- A patient develops exertional dyspnea and a systolic ejection murmur
- Imaging demonstrates marked asymmetric septal hypertrophy
- The anterior mitral leaflet approaches the septum during systole
- Question: Which two processes most directly impair forward output?

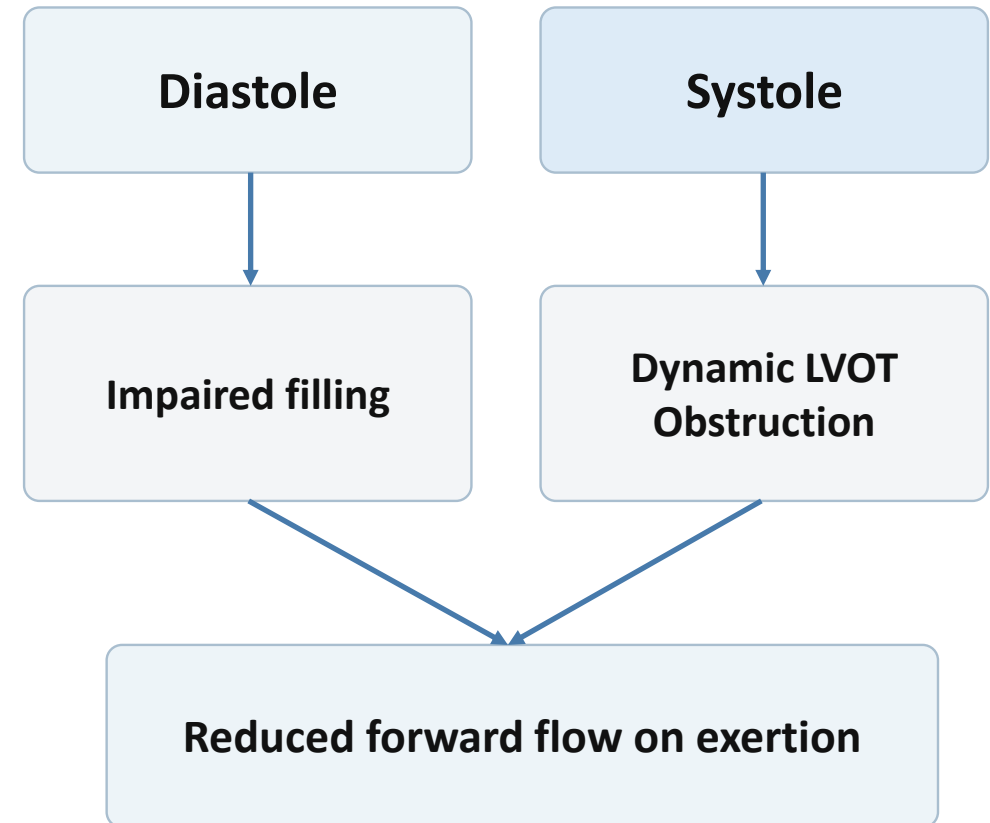
Septal hypertrophy + SAM

Reduced compliance / filling

Dynamic systolic outflow obstruction

Case reasoning: Integrate physiology

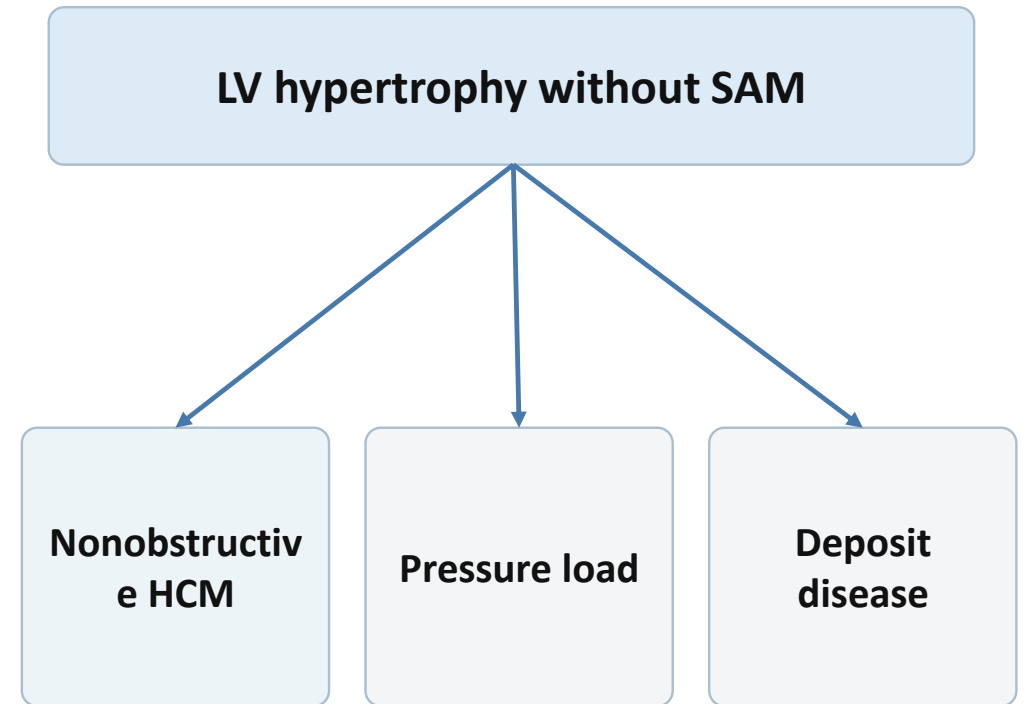
- Diastolic filling falls because the LV is small and poorly compliant
- The anterior mitral leaflet can narrow outflow during systole
- Raised filling pressure contributes to exertional dyspnea
- The combination is characteristic of obstructive HCM



Schematic

Case: Hypertrophy with no obvious obstruction

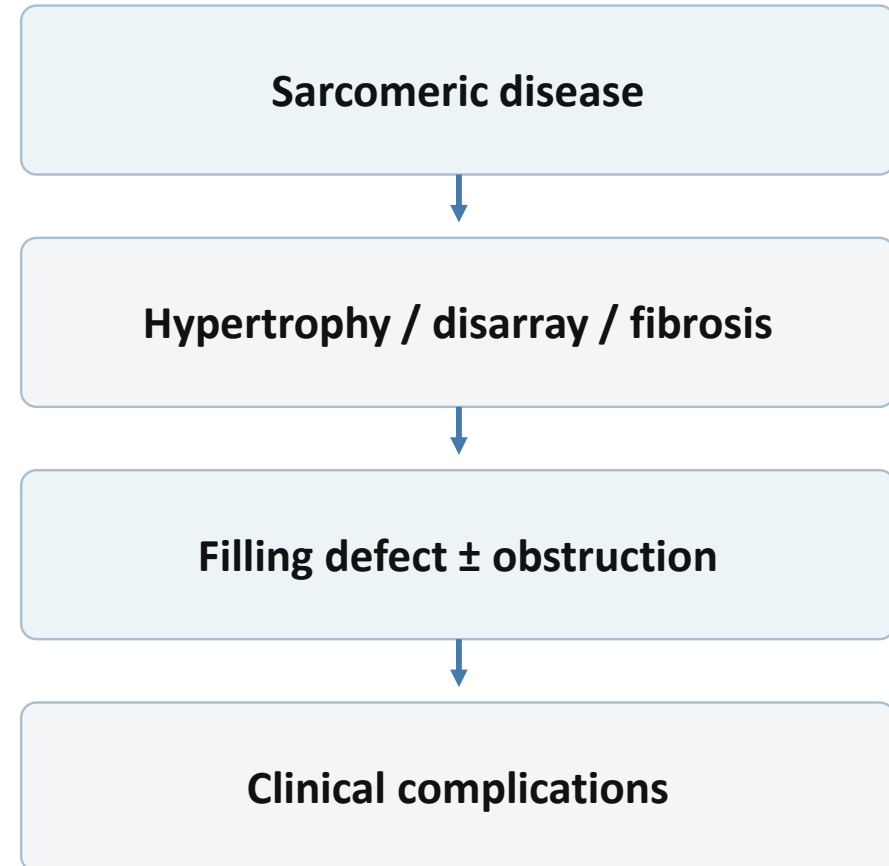
- A second patient has a thick left ventricular wall but no documented SAM
- Question: Does absence of obstruction exclude HCM?
- No: Symmetric or nonobstructive HCM phenotypes occur
- The differential must also address hypertension and infiltrative disorders



Schematic

Pathology synthesis: Molecules to events

- Sarcomeric variation alters contraction and leads to hypertrophic remodeling
- Disarray, intramural arterial disease and fibrosis alter the tissue substrate
- Reduced compliance and sometimes outflow obstruction diminish effective output
- Arrhythmias, embolism, failure and sudden death define major clinical risks

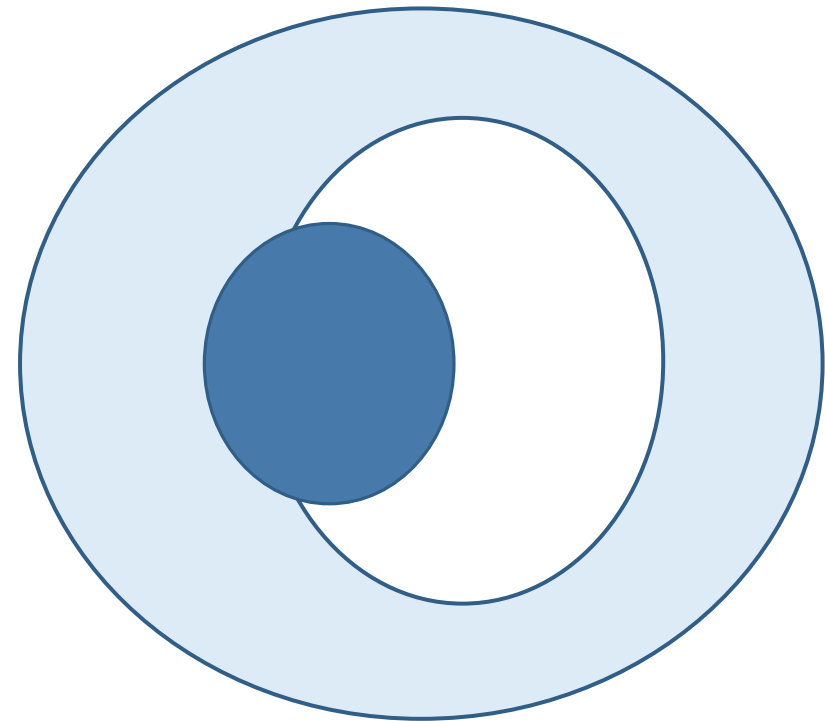


Schematic

Four findings to recognize at autopsy

- A thick and heavy ventricular myocardium
- Septal-predominant thickening with small LV cavity when classic
- Endocardial plaque at the mitral–septal contact zone in obstructive cases
- Microscopic hypertrophy, disarray, microvascular changes and fibrosis

Simplified LV cross-section



Dark blue: Septal projection White: Residual LV cavity

Schematic

Three distinctions to retain

- HCM is principally a filling disorder; DCM is principally a contractile disorder
- Hypertrophic wall thickness is not synonymous with sarcomeric HCM
- Dynamic outflow obstruction is clinically important but not universal
- A genetic result must be interpreted in phenotypic and family context

Underlying disease

Sarcomeric dysfunction

Myocyte enlargement

Disarray and fibrosis

Clinical phenotype

Diastolic impairment

± LVOT obstruction

Arrhythmic / embolic
risk

Schematic

Primary reference and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026)
- Chapter 12, The Heart — Cardiomyopathies; Hypertrophic Cardiomyopathy
- Teaching text and schematic concepts derived from the verified printed pp. 520–521
- All diagrams in this deck are original editable schematics; no diagnostic specimen images are reproduced