
Restrictive Cardiomyopathy

Pathogenesis · morphology · clinicopathologic correlation

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Learning objectives

- Define ventricular restriction as a diastolic filling abnormality.
- Relate myocardial or endocardial lesions to chamber morphology.
- Distinguish amyloid, endomyocardial fibrosis and eosinophilic disease.
- Recognize major mimics and the limits of morphology alone.

Cardiomyopathy: Primary myocardial dysfunction

- Cardiomyopathies arise from intrinsic myocardial dysfunction.
- Primary forms predominantly involve the myocardium.
- Secondary forms reflect systemic disease affecting cardiac muscle.
- Coronary, hypertensive, valvular and congenital causes require separate consideration.

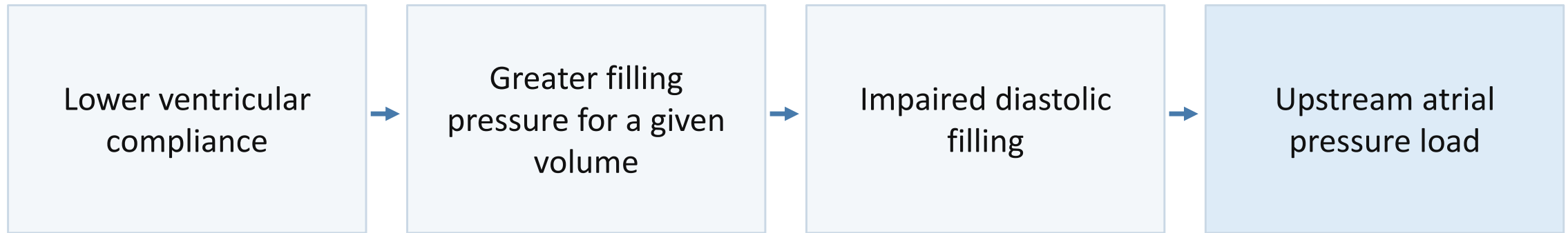
Three major functional cardiomyopathy patterns

Phenotype	Dominant physiological problem	Typical morphological emphasis
Dilated	Systolic failure	Dilation of cardiac chambers
Hypertrophic	Diastolic impairment	Increased ventricular wall mass
Restrictive	Diastolic impairment	Stiff ventricles; atrial enlargement

Restrictive cardiomyopathy: Defining abnormality

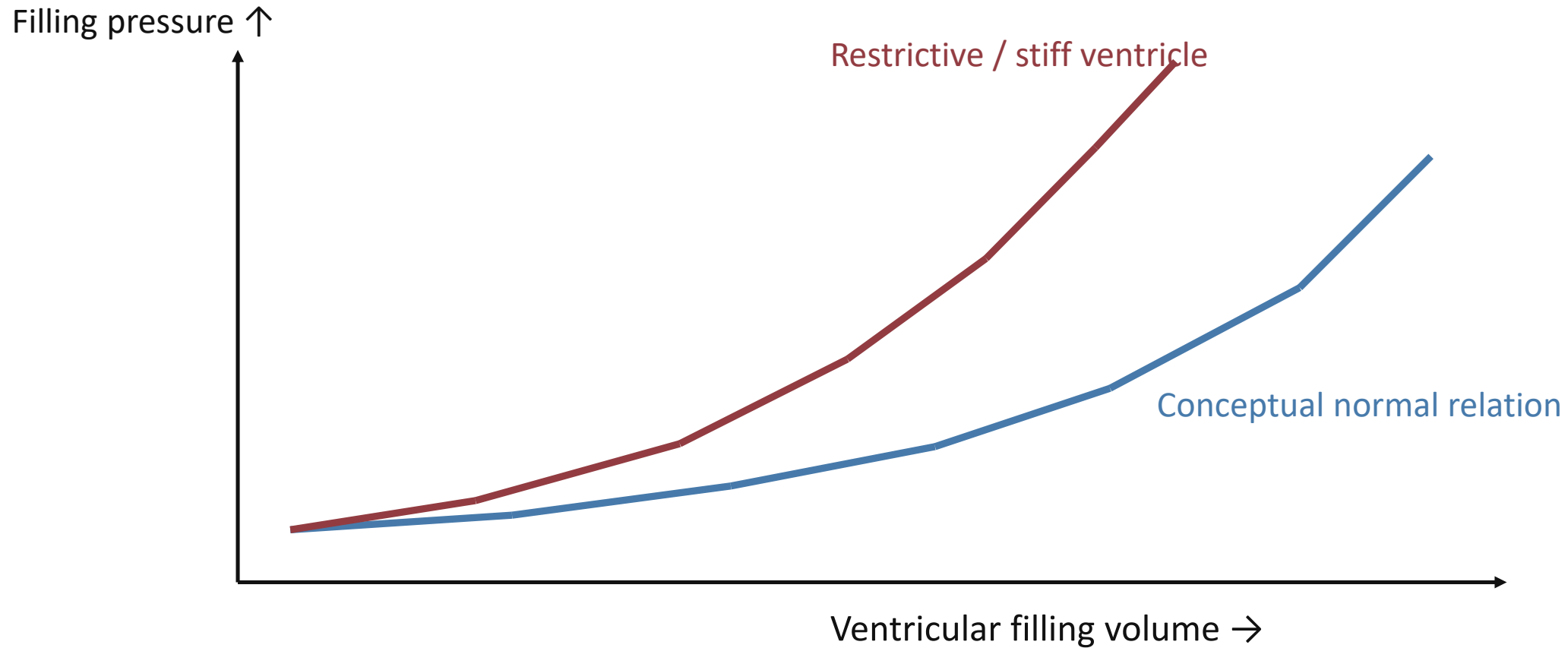
- The primary defect is reduced ventricular compliance.
- Impaired relaxation-phase filling is the functional consequence.
- The defining problem is diastolic rather than principally systolic.

Compliance links pressure to volume



A physiological sequence, not a measured relationship

A stiff ventricle has an altered filling relation

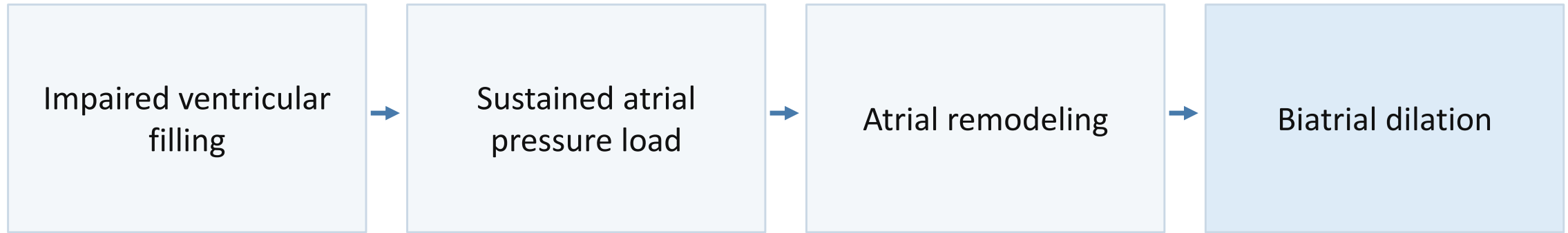


Qualitative schematic; Not patient data or a measured curve

The functional lesion is not necessarily poor contraction

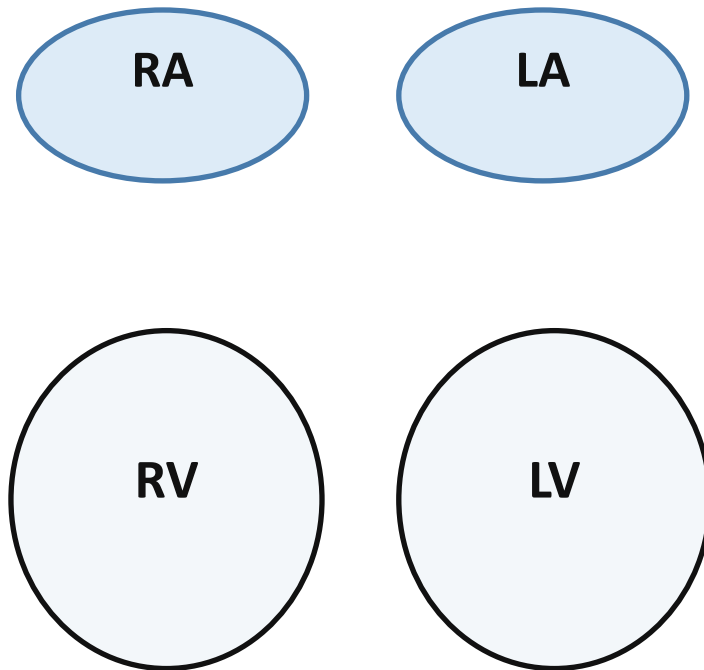
- Left-ventricular contractile function is usually relatively unaffected.
- Normal or near-normal contraction does not imply normal filling.
- Restrictive disease can therefore be confused with other diastolic disorders.

Why the atria enlarge

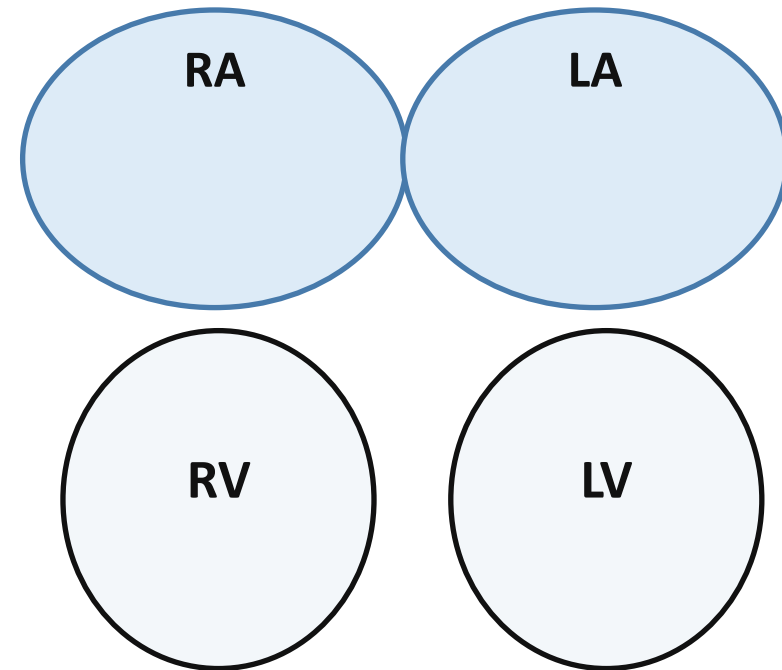


Chamber configuration in restriction

Reference configuration



Restrictive pattern

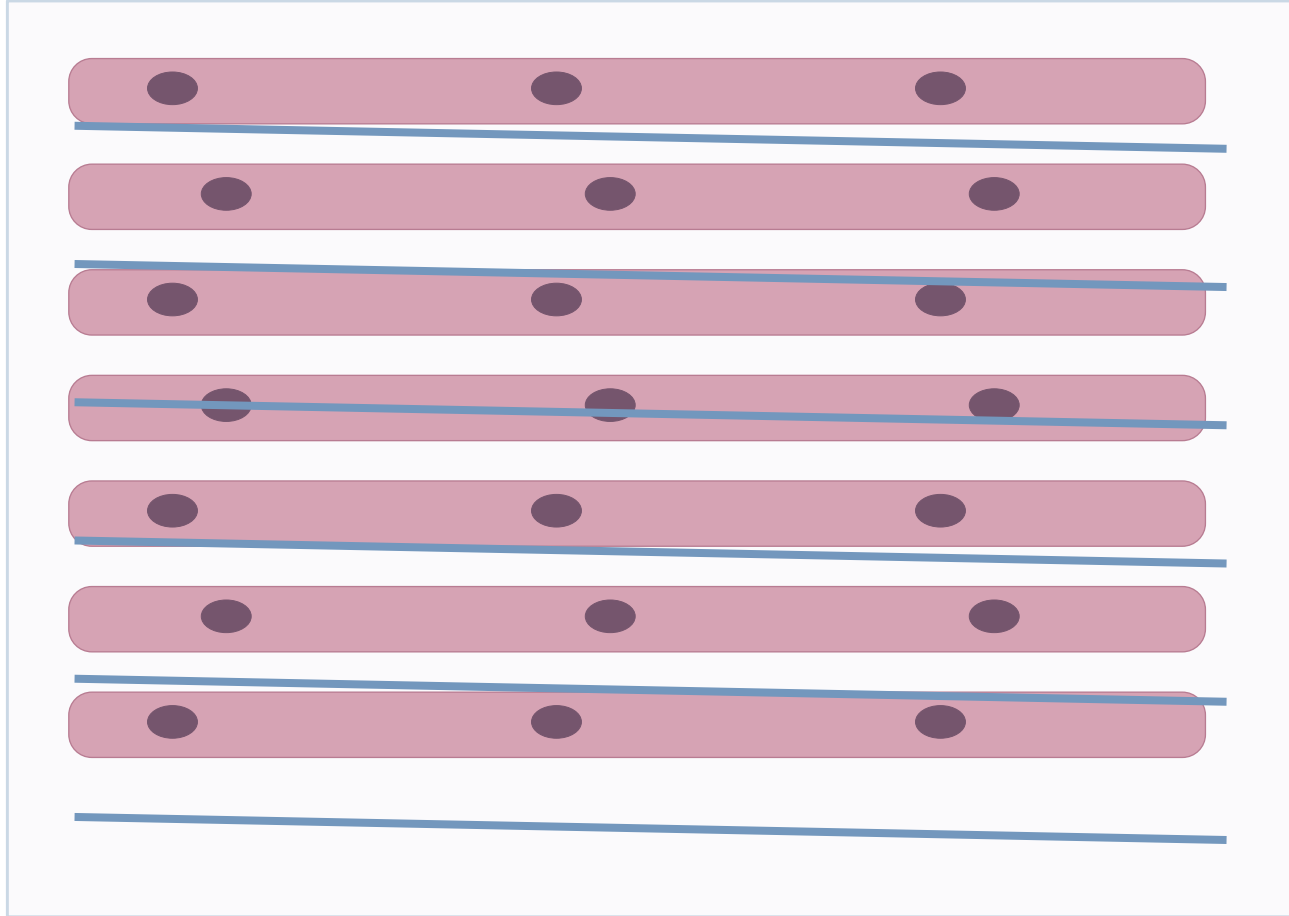


Atrial enlargement with relatively nondilated ventricles · schematic

What gross examination can—and cannot—show

- Biatrial enlargement is common.
- Ventricular size is near normal or only slightly increased.
- Ventricular cavities usually lack overt dilation.
- The remaining myocardium may look largely unremarkable.

Nonspecific interstitial fibrosis



Simplified tissue schematic — not a histology image

Collagen between myocytes

- Fibrous tissue increases passive stiffness
- Distribution may be patchy or diffuse
- Amount of fibrosis varies by cause

Fibrosis is not a universal diagnostic signature

- Microscopic fibrosis ranges from minimal to extensive.
- Lesion distribution may be patchy or diffuse.
- A nondiagnostic biopsy does not itself exclude restriction.

Etiologies: Idiopathic and secondary forms

Idiopathic

No cause identified

Functional phenotype defined

Secondary

Distinct myocardial disorder

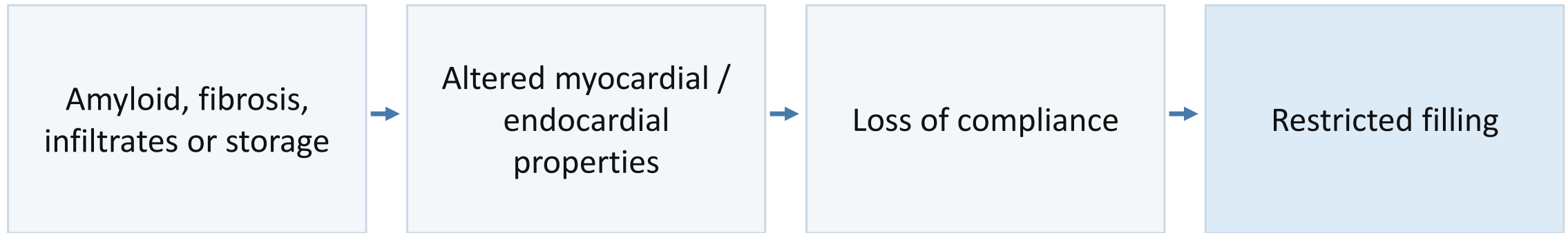
Specific pathologic substrate

A restrictive phenotype does not specify its cause.

Conditions associated with a restrictive phenotype

Pathobiologic setting	Examples directly named in Robbins
Protein deposition	Amyloidosis
Granulomatous / infiltrative	Sarcoidosis; metastatic tumors
Fibrotic injury	Radiation-induced fibrosis
Metabolite accumulation	Inborn errors of metabolism
Endocardial disease	Endomyocardial fibrosis; Loeffler disease; fibroelastosis

A shared physiology can reflect distinct lesions



Infiltration versus fibrosis: Distinct substrates

Infiltrative disease

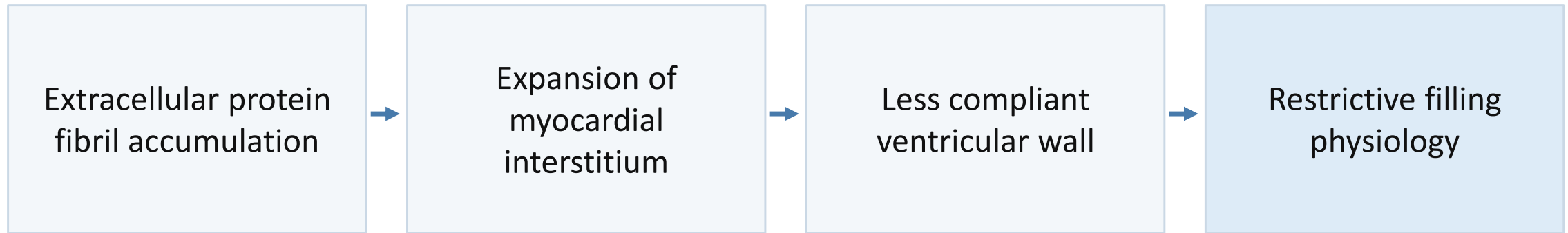
- Extracellular deposits or cellular infiltrates
- Myocardium stiffens despite limited chamber dilation
- Examples: Amyloid, sarcoid, metastatic disease

Fibrotic disease

- Interstitial or endocardial scarring
- Scarring mechanically impairs distensibility
- Examples: Radiation injury, tropical EMF

Both mechanisms can produce a similar hemodynamic phenotype.

Cardiac amyloidosis as a restrictive cause



Why amyloid deposits persist

- Amyloid comprises extracellular protein fibrils.
- Fibrils adopt insoluble β -pleated-sheet architecture.
- Accumulation may involve myocardium and multiple cardiac structures.

Systemic versus predominantly cardiac amyloid

Systemic involvement

- Cardiac disease as part of systemic amyloidosis
- May accompany plasma-cell neoplasms or inflammation-associated amyloid
- Look beyond the heart for the underlying disorder

Predominantly cardiac involvement

- Amyloid may be largely confined to the heart
- Recognized particularly in older individuals
- Wild-type transthyretin is prominent in this form

Both can alter ventricular compliance.

ATTRwt: Transthyretin deposition in older adults

- Wild-type transthyretin (ATTRwt) is a normal circulating protein.
- It is produced by the liver.
- It transports thyroxine and retinol-binding protein.
- Cardiac deposition is particularly recognized in older adults.

Hereditary transthyretin can accelerate deposition

- Transthyretin variants may increase amyloidogenic propensity.
- Hereditary transthyretin amyloidosis can involve the heart.
- Genetic variation should be distinguished from acquired wild-type deposition.

Cardiac territories that amyloid may involve

Interstitialium	Conduction system	Vasculature	Valves / serosa
Myocyte separation Reduced compliance	Electrical involvement Rhythm abnormalities	Small-vessel narrowing Potential ischemia	Valves, endocardium Pericardium

Distribution helps explain heterogeneity of presentation.

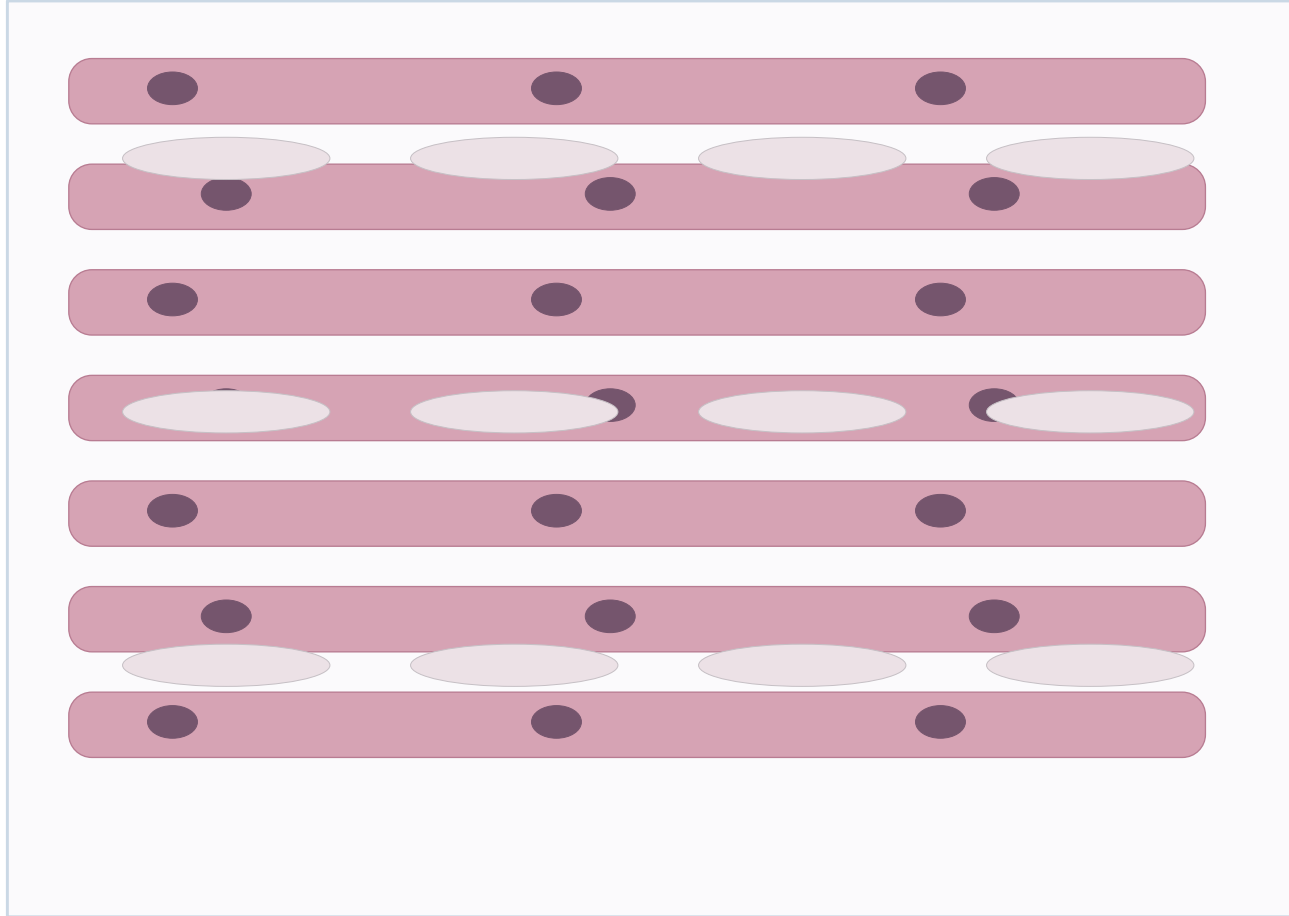
Amyloidosis can have several cardiac phenotypes

- Restrictive dysfunction is the most frequent presentation.
- Cardiac deposition may also be asymptomatic.
- Dilation, arrhythmias or ischemic/valvular mimics can occur.
- The location of deposition influences the clinical picture.

Gross appearance of an amyloid heart

- Consistency can range from normal to firm and rubbery.
- Chambers are often normal sized but may be dilated.
- Ventricular walls may be thickened.
- Atrial endocardium may show wax-like, semitranslucent nodules.

Interstitial amyloid: Histologic concept



Simplified tissue schematic — not a histology image

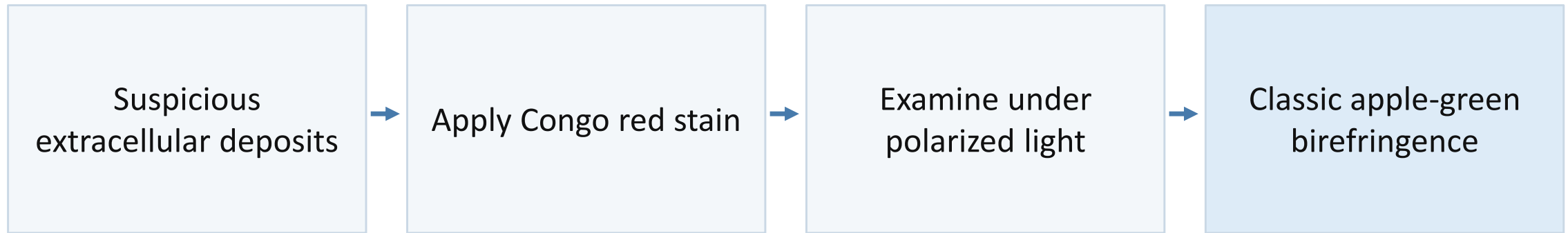
Deposits between myocardial fibers

- Extracellular material expands interstitium
- Myocytes become separated by deposits
- Specific deposition requires appropriate stain

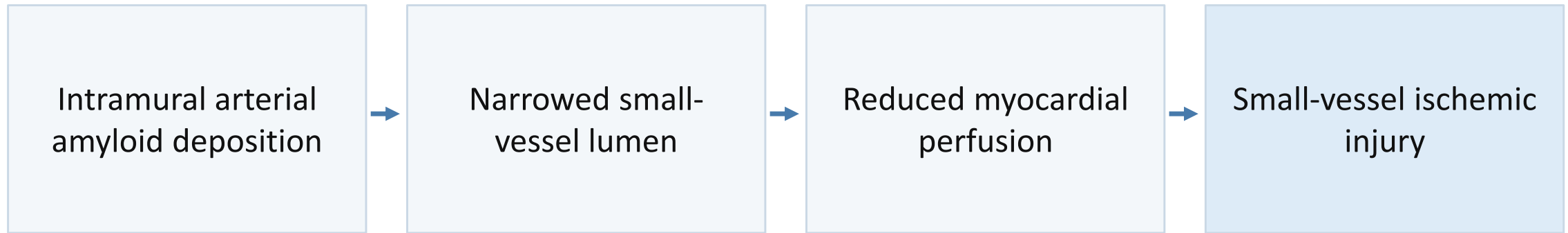
Histologic amyloid is extracellular and hyaline

- Routine sections can show amorphous eosinophilic deposits.
- Deposits may involve interstitium and vascular walls.
- Conduction tissue and valves may also be affected.
- Appearance alone does not establish amyloid protein type.

Congo red establishes amyloid deposition



Vascular amyloid and myocardial ischemia



Specific etiology matters beyond the label “RCM”

- The same physiological restriction has several causal substrates.
- Tissue findings may suggest an underlying systemic disease.
- An etiologic label can be more informative than morphology alone.

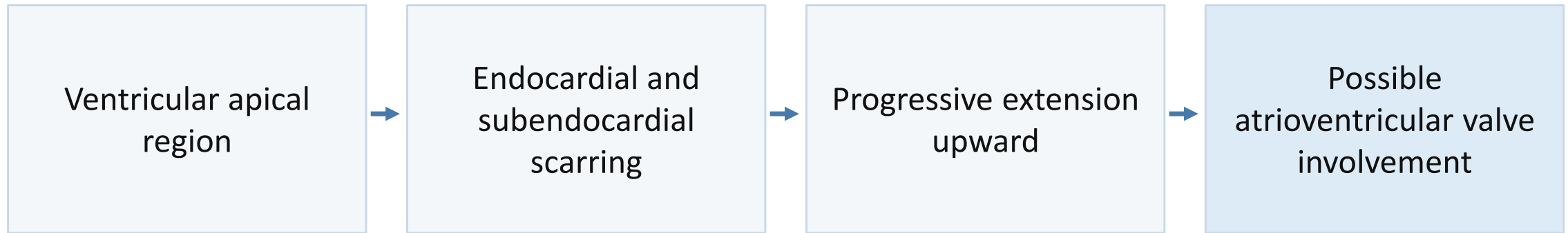
Endomyocardial restriction: A separate lesion family

Entity	Main pathologic emphasis	Clinical context in Robbins
Endomyocardial fibrosis	Apical endocardial/subendocardial scarring	Young people; tropical regions
Loeffler endomyocarditis	Eosinophilic injury, mural thrombi, fibrosis	Often peripheral/systemic eosinophilia
Endocardial fibroelastosis	Fibroelastic LV endocardial thickening	Predominantly infants

Endomyocardial fibrosis: Geographical setting

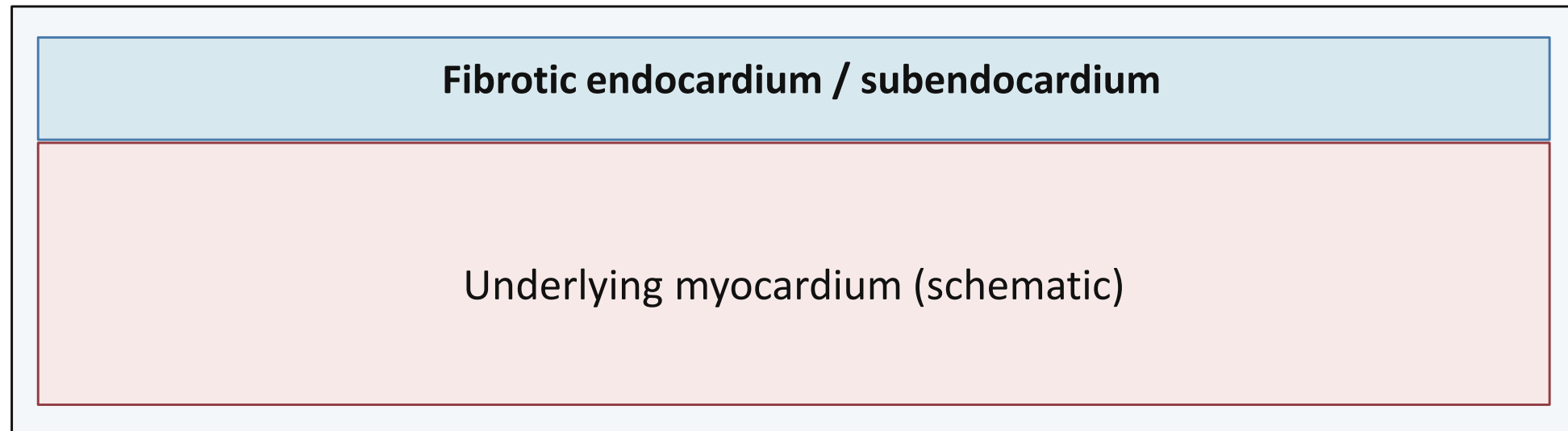
- Principally affects children and young adults.
- Described in Africa and other tropical areas.
- A major restrictive disorder worldwide.
- Morphology is dominated by ventricular endocardial scarring.

Endomyocardial fibrosis advances from the apex



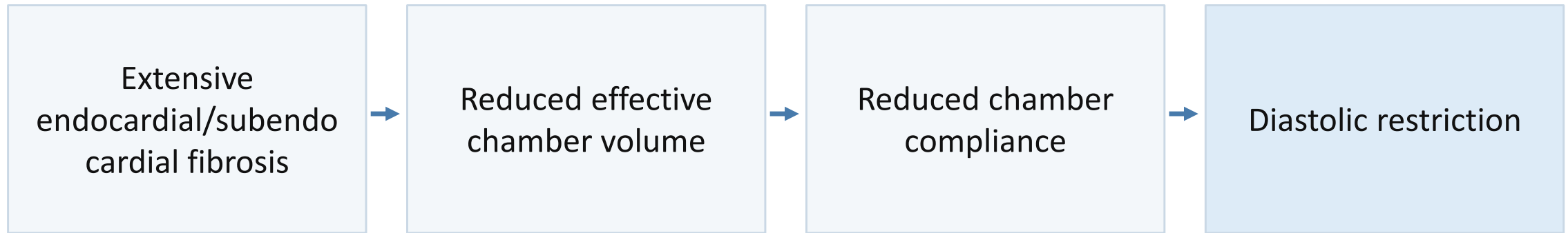
Endomyocardial fibrosis alters the wall surface

Ventricular wall with endocardial/subendocardial fibrosis



Layer thicknesses are exaggerated for explanation; Not histologic measurements

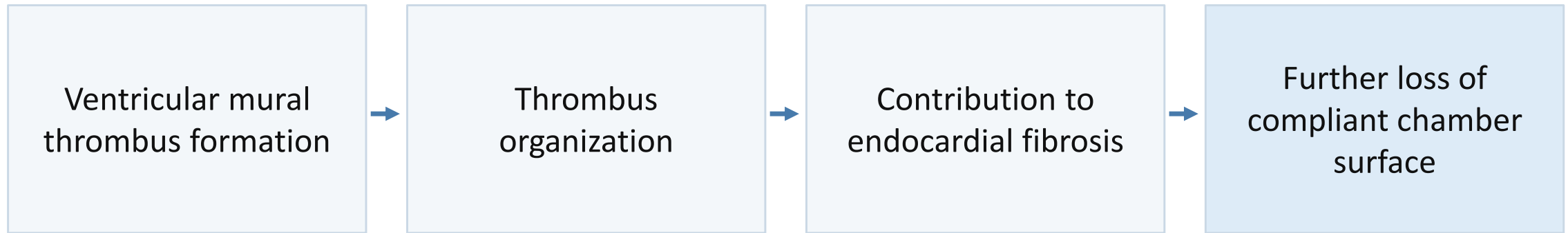
Why an endocardial plaque restricts filling



Valve involvement changes the anatomy

- Fibrosis can spread from the apex toward the atrioventricular valves.
- The tricuspid and mitral valves may eventually be involved.
- The precise gross distribution is important in anatomical assessment.

Mural thrombi and organized fibrosis



Proposed associations of tropical EMF

Nutritional context

Nutritional deficiencies

Association—not proof of cause

Inflammatory context

Parasitic infections

Possible eosinophilia

These as linked factors, not a single established mechanism.

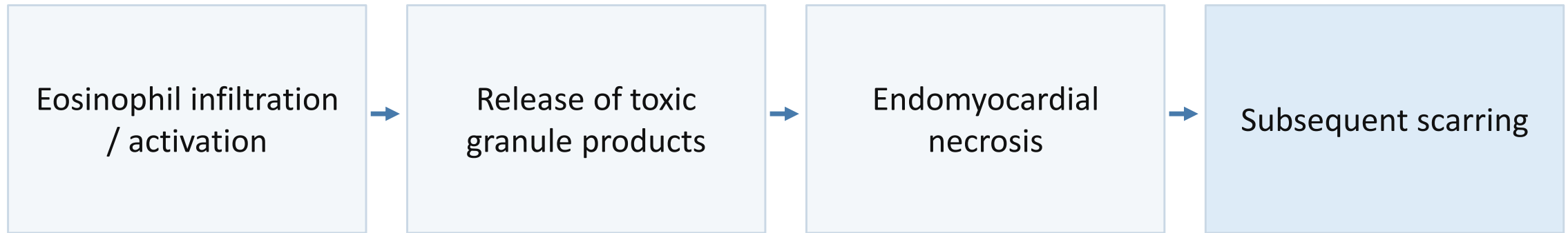
Loeffler endomyocarditis: Similar endpoint

- Produces endomyocardial fibrosis, often with large mural thrombi.
- Overall cardiac morphology resembles tropical endomyocardial fibrosis.
- A prominent eosinophilic systemic context distinguishes the syndrome.

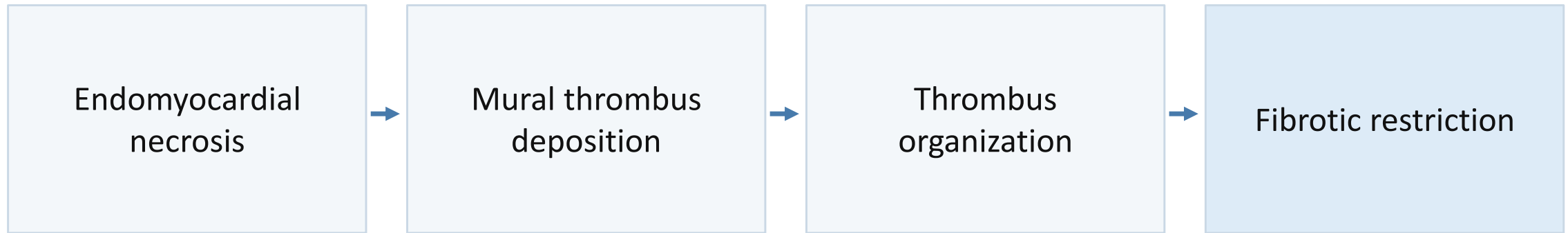
The eosinophilic component

- Peripheral eosinophilia is often present.
- Eosinophilic infiltration may involve myocardium and other organs.
- Eosinophil products are implicated in endomyocardial injury.

Major basic protein as a proposed mediator



Loeffler lesion: An injury-to-scar sequence



Why the thrombus may be prominent

- The damaged endocardial surface becomes layered by thrombus.
- Large mural thrombi are characteristic in many cases.
- Organized thrombus can contribute to fibrotic thickening.

A hematologic clue to a cardiac lesion

- A subset of patients has a myeloid neoplasm with eosinophilia.
- Acquired rearrangements may involve tyrosine kinase genes.
- An eosinophilic cardiac lesion therefore warrants etiologic evaluation.

Why identifying a kinase-driven disorder matters

Myeloid neoplasm
with eosinophilia



Tyrosine kinase gene
rearrangement



Tyrosine kinase
inhibitor therapy



Reported
hematologic and
endocardial
improvement

Tropical EMF versus Loeffler disease

Feature	Tropical endomyocardial fibrosis	Loeffler endomyocarditis
Clinical setting	Young people in tropical areas	Often peripheral eosinophilia
Dominant pathology	Apical endocardial fibrosis	Fibrosis and often large mural thrombi
Proposed association	Nutritional/inflammatory factors	Eosinophil granule toxicity
Additional concern	Valve extension	Possible kinase-driven myeloid neoplasm

Endocardial fibroelastosis: Characteristic lesion

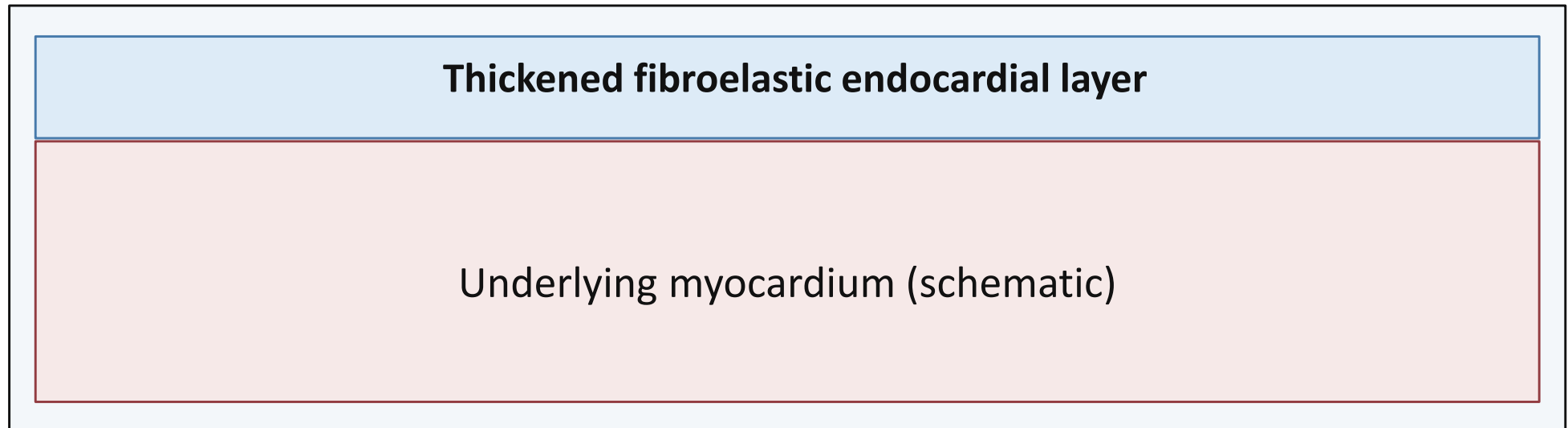
- An uncommon cause of endocardial thickening.
- Fibroelastic tissue accumulates along the endocardium.
- Left ventricular endocardium is typically involved.

The disease is principally pediatric

- Most often encountered in the first two years of life.
- Some cases accompany aortic valve obstruction.
- Other congenital cardiac abnormalities may coexist.

Endocardial fibroelastosis: Layer schematic

Left-ventricular endocardial fibroelastic thickening



Layer thicknesses are exaggerated for explanation; Not histologic measurements

Potential etiologic pathways in fibroelastosis

Infectious insult

Proposed prenatal viral injury

Example: Intrauterine mumps

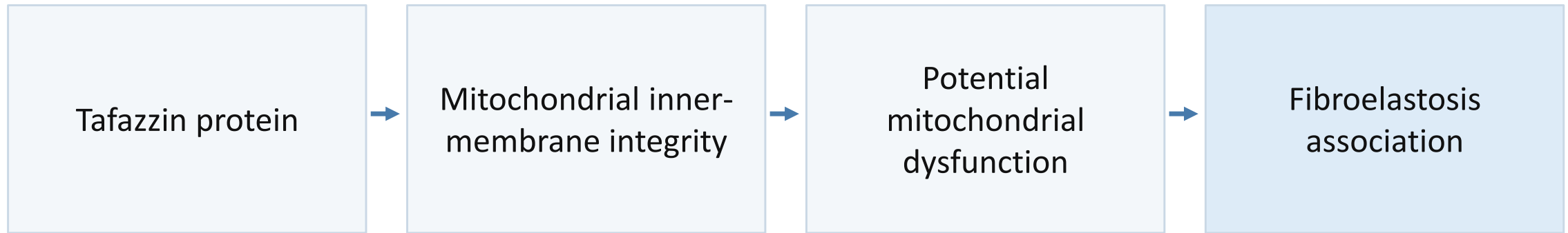
Genetic insult

Tafazzin mutations

Mitochondrial inner membrane

Fibroelastosis may be a shared morphologic endpoint of different injuries.

Tafazzin connects a gene to mitochondria



Diffuse fibroelastosis can be clinically severe

- Diffuse endocardial involvement can compromise ventricular function.
- Some affected infants develop rapid cardiac decompensation.
- Severity relates to extent and underlying associated disease.

Where each restrictive lesion predominantly lives

Lesion	Principal tissue compartment	Morphological clue
Idiopathic/secondary RCM	Myocardium	Variable interstitial fibrosis
Amyloidosis	Interstitial / vascular / conduction	Extracellular protein deposition
Endomyocardial fibrosis	Endocardium and subendocardium	Apical-to-basal scarring
Loeffler disease	Endomyocardial surface	Thrombus plus eosinophilic injury
Fibroelastosis	Left ventricular endocardium	Fibroelastic thickening

Gross morphology provides clues, not a full diagnosis

Pattern	Expected structural finding	Interpretive limitation
General restriction	Biatrial dilation; nondilated ventricles	Nonspecific phenotype
Cardiac amyloid	Variable firmness, wall thickness	May resemble other processes
Endomyocardial fibrosis	Apical endocardial thickening	Cause may remain uncertain
Loeffler disease	Thrombus and fibrosis	Requires systemic context
Fibroelastosis	Endocardial thickening in infant	Multiple possible insults

Microscopic findings are etiologic clues

Observation	Interpretation	Additional clarification
Interstitial collagen	Fibrosing myocardial disease	Nonspecific by itself
Hyaline extracellular deposits	Consider amyloid	Congo red confirmation
Fibrous endocardial tissue	Endomyocardial scarring	Assess extent/site
Eosinophils with injury	Eosinophilic cardiac process	Consider hematologic context
Fibroelastic endocardium	Fibroelastosis	Assess pediatric associations

Cardiac imaging is useful for tissue characterization

- Imaging can assess ventricular and atrial configuration.
- Increasingly, imaging can characterize suspected myocardial infiltrates.
- An abnormal imaging pattern is not automatically an etiologic diagnosis.

What endomyocardial biopsy may contribute

- Sampling may occasionally suggest a specific etiology.
- A positive amyloid stain supports tissue deposition.
- Patchy fibrosis can limit representativeness of small samples.
- Interpret biopsy with cardiac imaging and clinical context.

Restrictive myocardial disease vs pericardial constriction

Restrictive cardiomyopathy

- Primary abnormality in ventricular myocardial compliance
- Variable myocardial infiltration or fibrosis
- Heart muscle is the principal site of disease

Constrictive pericarditis

- External mechanical limitation from pericardium
- May yield a similar diastolic filling syndrome
- Pericardial lesion is the principal anatomic process

This clinically important diagnostic confusion.

Restrictive disease versus hypertrophic cardiomyopathy

Restrictive

- Low compliance due to diverse infiltration or fibrosing lesions
- Ventricles are usually not greatly enlarged
- Batrial dilation may be prominent

Hypertrophic

- Primary myocardial hypertrophy, often asymmetric
- Poor compliance with thickened ventricular wall
- Myocyte disarray is a histologic hallmark

Both may present with diastolic dysfunction; Morphology and cause differ.

Restrictive versus dilated cardiomyopathy

Restrictive

- Impaired ventricular filling predominates
- Cavities remain nondilated in typical morphology
- Systolic function may be relatively retained

Dilated

- Ineffective contraction predominates
- Four-chamber dilation is characteristic
- Impaired ejection underlies the phenotype

Cardiomyopathy categories are patterns, not etiologic diagnoses.

Integrating phenotype and cause

Confirm a restrictive
filling phenotype



Evaluate myocardium
vs pericardium



Identify structural /
tissue clue



Correlate with
systemic cause

Clinicopathologic case: Older adult

An older adult has a stiff ventricle, enlarged atria and a firm, mildly thickened myocardium. A sample shows amorphous extracellular deposits.

Discussion

- Which etiologic category becomes likely?
- Which special stain would help confirm the deposits?
- Why might small vessels also matter?

Clinicopathologic case: Tropical endocardial disease

A young person from a tropical region has restrictive filling and fibrous thickening concentrated near a ventricular apex, extending toward an atrioventricular valve.

Discussion

- What restrictive entity does this distribution suggest?
- Why may the effective cavity volume be reduced?
- How might organized mural thrombus contribute?

Clinicopathologic case: Eosinophilia and thrombus

A patient with marked peripheral eosinophilia develops large ventricular mural thrombi and endomyocardial scarring.

Discussion

- What named disease process is suggested?
- What putative toxin mediates myocardial damage?
- Which accompanying hematologic process deserves consideration?

Clinicopathologic case: Early infancy

An infant with rapid cardiac deterioration shows diffuse thickening of the left ventricular endocardial surface containing fibroelastic tissue.

Discussion

- Which restrictive-associated condition is most consistent?
- What congenital lesion may coexist?
- What mitochondrial membrane-associated protein is mentioned?

Common interpretive errors

- Equating preserved contraction with absence of cardiac disease.
- Treating atrial enlargement alone as proof of myocardial restriction.
- Calling any interstitial fibrosis diagnostic of a specific etiology.
- Conflating endomyocardial fibrosis, Loeffler disease and fibroelastosis.

Five anatomical clues worth retaining

Myocardium

Reduced compliance

Variable fibrosis

Atria

Common dilation

Pressure load

Amyloid

Interstitial deposits

Congo red

Endocardium

Apical / LV fibrosis

Disease-specific pattern

Locate the lesion before naming the disease.

Restrictive cardiomyopathy: Integrated summary

- The primary lesion is reduced ventricular compliance and impaired filling.
- Typical chambers show enlarged atria without major ventricular dilation.
- Myocardial deposition, fibrosis and endocardial disease are major substrates.
- Specific diagnosis depends on lesion distribution and associated disease.

Reference and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th edition (2026).
- Chapter 12: The Heart — Cardiomyopathies; Restrictive Cardiomyopathy.
- Related source subsection: Amyloidosis, pp. 522–523.
- Schematics are original and editable; no textbook figure or synthetic specimen reproduced.