

Cardiac amyloidosis

Myocardial protein deposition and restrictive dysfunction

Etiology · morphology · clinicopathologic interpretation

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Learning objectives

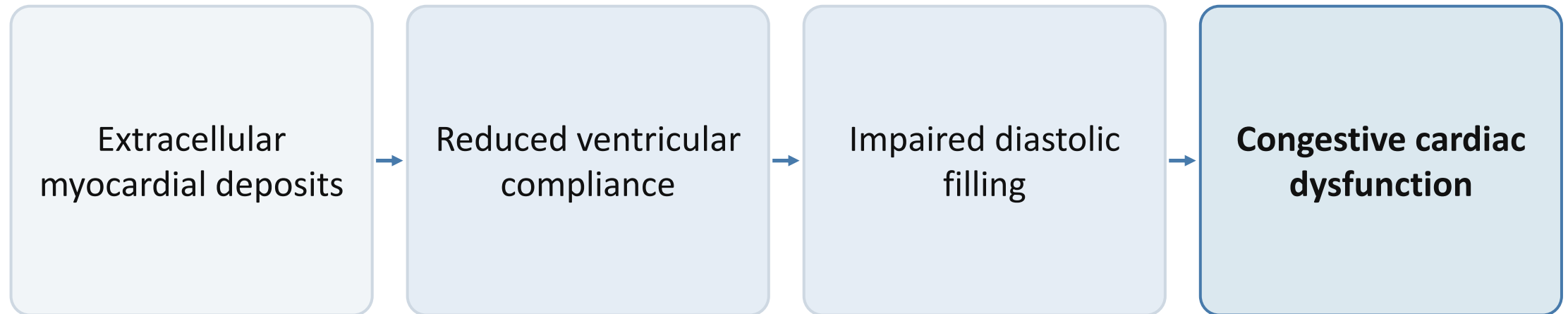
- Define cardiac amyloidosis and identify its relationship to restrictive cardiomyopathy.
- Compare AL, wild-type ATTR, variant ATTR and inflammation-related AA amyloid.
- Interpret myocardial distribution, H&E and Congo red findings.
- Connect deposition sites to diastolic dysfunction, arrhythmias and ischemic features.

Cardiac amyloidosis: Defining lesion

- Insoluble amyloid fibrils accumulate extracellularly within cardiac tissues.
- The deposited proteins adopt a cross- β -pleated sheet architecture.
- Accumulating amyloid alters tissue architecture and impairs cardiac function.
- The classic presentation is a restrictive cardiomyopathy.

Amyloid is a protein deposit, not an inflammatory cellular infiltrate.

Why it is a restrictive cardiomyopathy



The principal initial functional abnormality is impaired relaxation/filling, not a primary valve lesion.

Systemic and predominantly cardiac disease

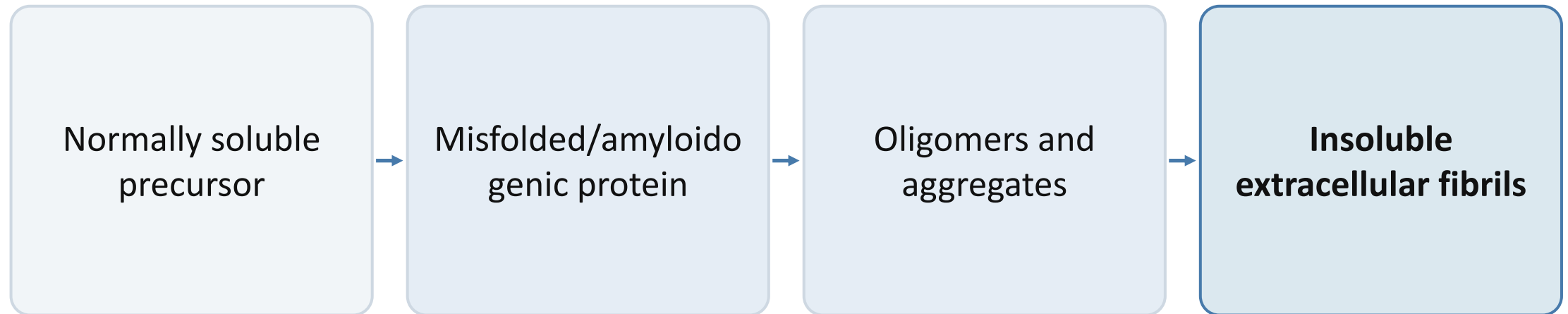
Systemic amyloidosis

- Circulating amyloidogenic precursor
- Heart plus one or more extracardiac tissues may be involved

Predominantly cardiac disease

- Often age-associated ATTRwt
- Deposits may be concentrated in the heart, with possible connective-tissue deposits

From native protein to amyloid fibril



Misfolding and aggregation—not simple protein abundance alone—define amyloid formation.

The cross- β structure explains staining

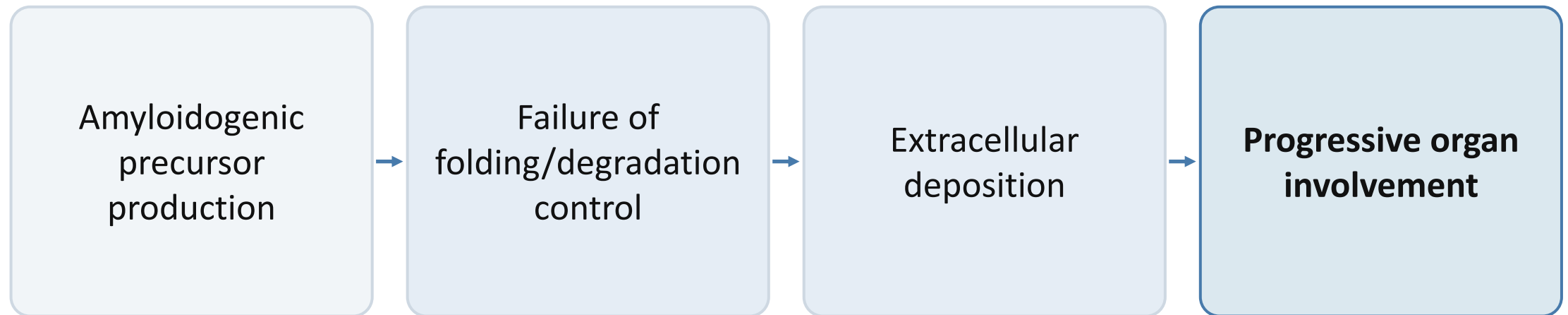


The classic polarized-light finding reflects the molecular organization of amyloid.

Amyloid is not starch

- The historical name reflects earlier staining similarities to amylose.
- Amyloid is composed of abnormal protein fibrils and associated molecules.
- Deposits additionally bind proteoglycans, glycosaminoglycans and serum amyloid P.
- “Amyloid” describes a shared deposit phenotype, not a single protein.

Why extracellular protein accumulates



Both high precursor supply and intrinsic amyloidogenic sequence/structure may contribute.

Two broad routes to amyloid

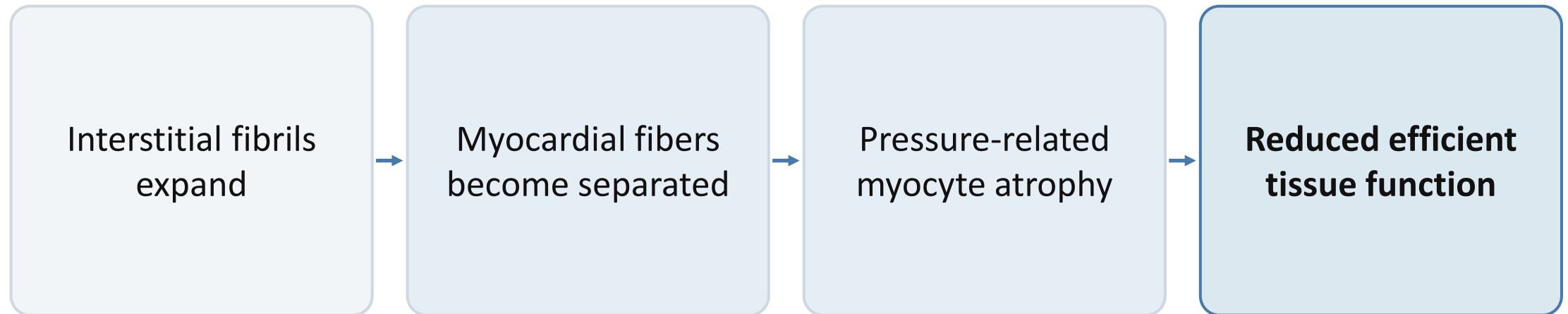
Excess production of susceptible proteins

- Monoclonal light chains or chronic inflammatory SAA
- Amyloidogenic fragments accumulate

Variant or age-dependent instability

- Mutant or wild-type transthyretin
- Misfolding produces ATTR fibrils

Why myocytes fail despite being viable



The source attributes most organ dysfunction to architectural distortion; Additional toxicity may occur.

Possible direct cellular effects

- Architectural disruption as the dominant injury mechanism.
- Some amyloidogenic proteins may perturb signaling, increase reactive oxygen species or impair calcium homeostasis.
- These proposed cellular effects supplement—but do not replace—mechanical infiltration as an explanation.

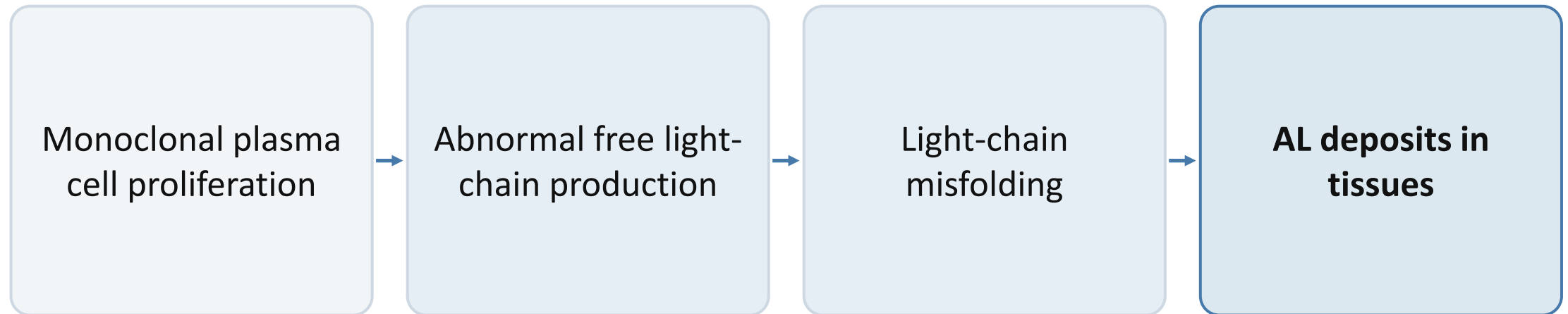
Principal cardiac anatomic sites

Anatomic site	Functional consequence
Interstitial myocardium	Impaired compliance and myocyte compression
Conduction tissue	Electrical abnormalities or arrhythmias
Small intramural coronary vessels	Luminal narrowing and ischemia
Valves/endocardium	Valvular or surface manifestations

Cardiac amyloid: Biochemical taxonomy

Amyloid	Fibril precursor	Setting
AL	Immunoglobulin light chain	Plasma cell clone
ATTRwt	Wild-type transthyretin	Age-associated aggregation
ATTRv	Variant transthyretin	Inherited TTR variant
AA	Serum amyloid A–derived fibrils	Chronic inflammation

AL amyloid begins with a plasma cell clone



Cardiac AL may occur with overt myeloma or a less conspicuous plasma-cell proliferation.

Light-chain sequence determines propensity

- Not every free immunoglobulin light chain forms amyloid.
- The specific amino-acid sequence contributes to amyloidogenic potential.
- Both κ and λ chains can form deposits; λ is more frequently represented in AL.
- An isolated light-chain laboratory abnormality is not identical to tissue-proven AL amyloidosis.

AL amyloidosis does not require overt myeloma

AL with multiple myeloma

- Overt plasma-cell tumor may produce abnormal immunoglobulins and amyloidogenic light chains.
- Amyloid is an additional pathologic consequence.

AL without overt myeloma

- A smaller clonal plasma-cell population can produce amyloidogenic light chains.
- Protein toxicity/deposition may dominate the clinical picture.

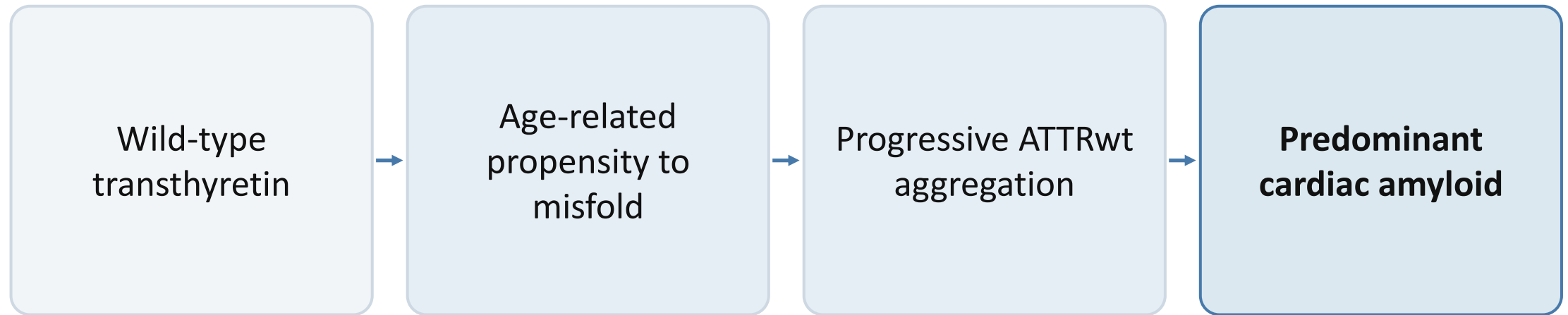
Systemic AL: Clues beyond the heart

- Renal proteinuria or nephrotic syndrome suggests glomerular amyloid.
- Peripheral nerve or autonomic dysfunction can accompany systemic deposition.
- Tongue enlargement and gastrointestinal symptoms may arise from extra-cardiac deposits.
- These findings support systemic involvement; None alone establishes fibril type.

Transthyretin is a circulating transport protein

- Transthyretin is synthesized principally in the liver.
- In plasma it transports thyroxine and retinol-binding protein.
- Both ordinary wild-type and sequence-variant TTR can form extracellular amyloid fibrils.
- Biochemical identity, not gross myocardial appearance, distinguishes ATTR from AL.

Wild-type ATTR: Age-associated deposition

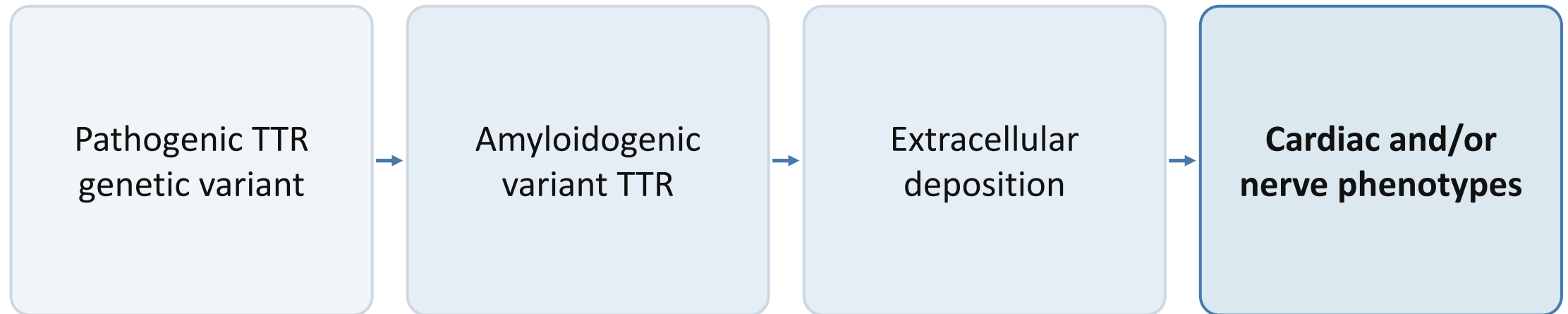


Cardiac disease in older adults, especially men.

ATTRwt is not necessarily heart-exclusive

- ATTRwt commonly deposits in the aging heart.
- Transthyretin amyloid may also be found in connective tissues, including ligaments.
- A cardiac-dominant presentation does not require every other organ to be amyloid-free.
- Distribution should be described precisely rather than labeled automatically “localized.”

Variant ATTR: An inherited protein disorder



ATTRv is autosomal dominant, with variable penetrance and organ involvement.

TTR genotype and organ phenotype differ

Cardiac-predominant variant

- Amyloid deposition mainly involves myocardium.
- Familial ATTR cardiomyopathy may result.

Neuropathy-predominant variant

- Deposits favor peripheral and autonomic nerves.
- Amyloid polyneuropathy may predominate.

One TTR variant, variable penetrance

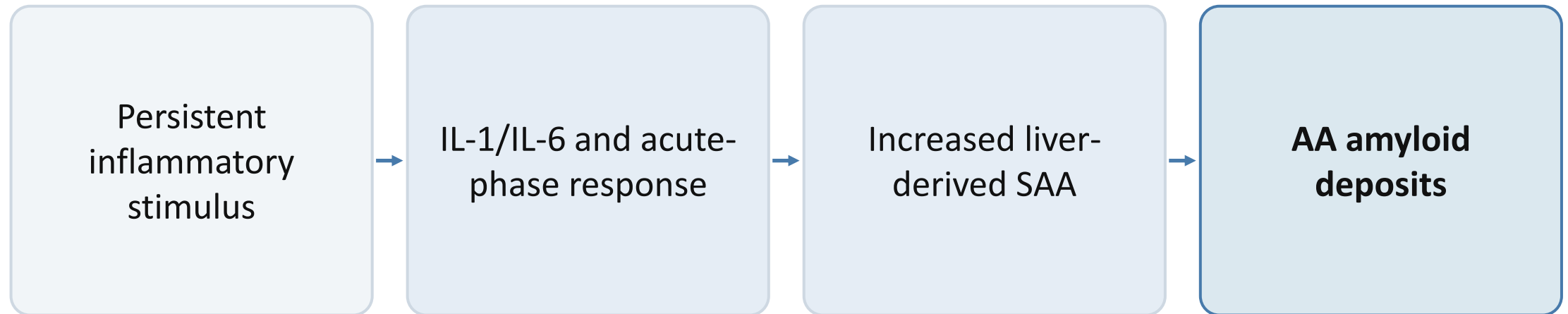
- A West African founder-associated TTR substitution: Val122Ile.
- Individuals with the variant may develop cardiac amyloidosis, but expression varies markedly.
- Both heterozygous and homozygous carriers may be affected.
- Carrier status alone does not establish clinical cardiac involvement.

Variant nomenclature follows the supplied textbook; Genetic testing requires appropriate clinical interpretation.

ATTRwt versus ATTRv

Feature	ATTRwt	ATTRv
Precursor	Wild-type TTR	Sequence-variant TTR
Origin	Age-associated	Hereditary, autosomal dominant
Principal tissues	Heart; Sometimes ligaments	Heart and/or peripheral nerves
Clinical pattern	Often late-onset cardiac	Variable phenotype and penetrance

AA amyloid: Inflammatory precursor pathway



Chronic inflammation can generate systemic amyloid; Cardiac involvement is possible but not its distinctive distribution.

AA differs from AL and ATTR

Type	Underlying process	Important pattern
AL	Light-chain-producing plasma cell clone	Heart, kidney and other organs
ATTR	Wild-type or variant TTR	Heart and/or peripheral nerves
AA	Sustained inflammatory SAA production	Often kidney, liver and spleen

Not all amyloid proteins explain cardiac disease

- A β deposition is characteristic of cerebral plaques and some cerebral vessels.
- β_2 -microglobulin amyloid is classically associated with long-term dialysis and periarticular tissues.
- Atrial natriuretic factor can produce isolated atrial amyloid.
- A tissue diagnosis requires characterization of the actual deposited protein.

Macroscopic appearance may be subtle

- A heart with amyloid deposits can look nearly normal grossly.
- Consistency may vary from ordinary to firm and rubbery.
- Chamber dimensions are often preserved, despite substantial functional impairment.
- A normal-looking heart does not exclude clinically important deposition.

Wall thickening does not always imply hypertrophy

Amyloid infiltration

- Extracellular deposits expand the wall.
- Increased apparent wall thickness can coexist with myocyte atrophy.

Myocyte hypertrophy

- Cardiomyocytes themselves enlarge.
- Wall thickening arises from increased myocyte mass.

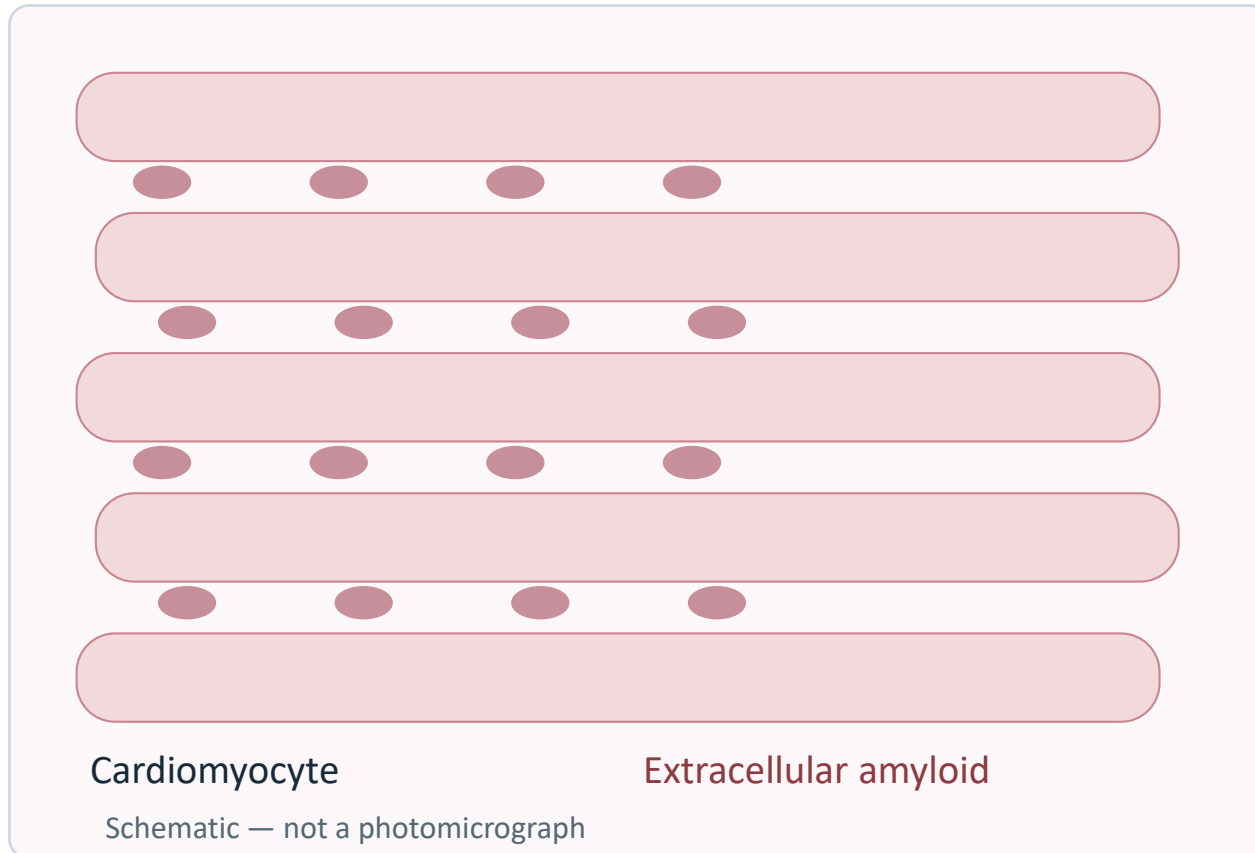
Cardiac chambers may be normal or dilated

- Chambers are usually of normal size in the classic restrictive phenotype.
- Myocardial walls can appear thickened.
- Chamber dilation is nevertheless documented in some cases.
- Avoid treating any single gross configuration as obligatory.

Atrial endocardial wax-like nodules

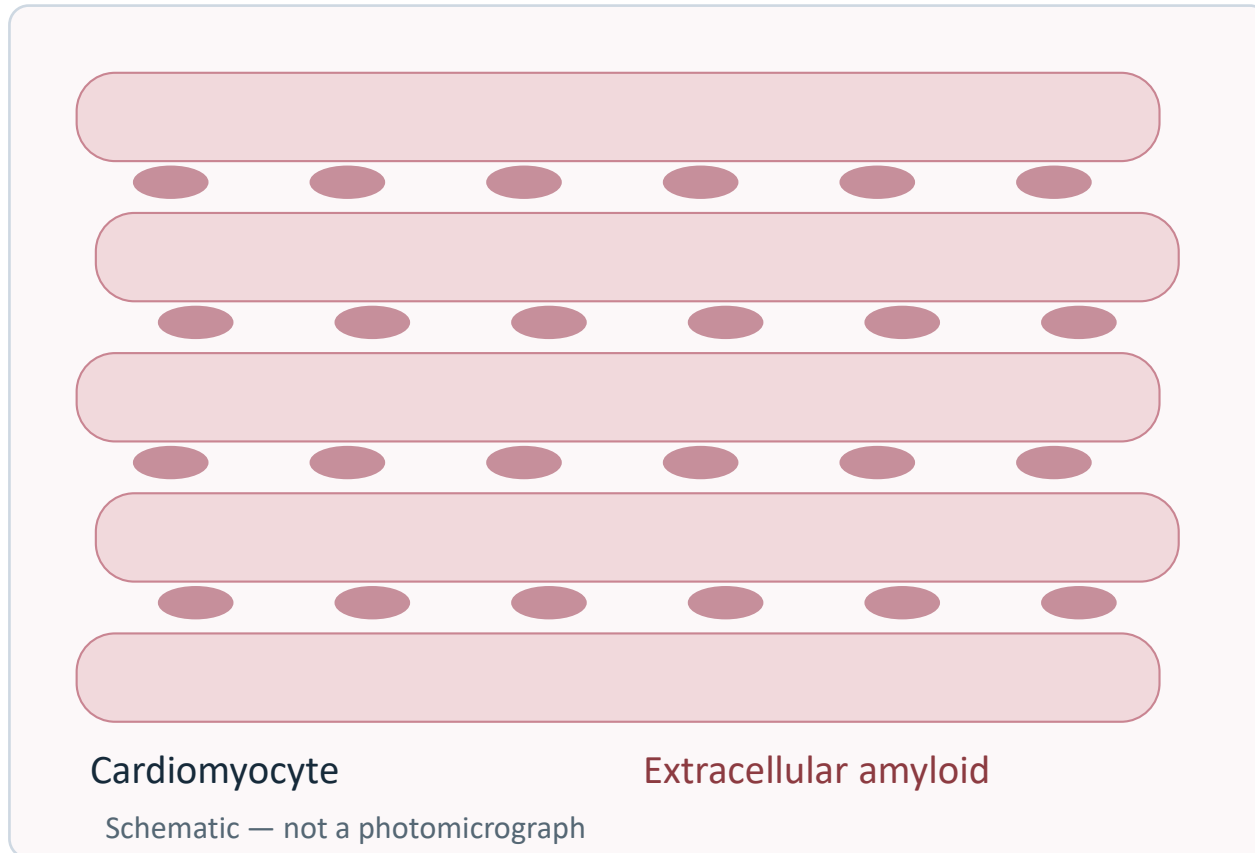
- Small semitranslucent nodules can appear along the atrial endocardial surface.
- The left atrial surface is a particularly noted site.
- The gross appearance is likened to drips of wax.
- This finding can prompt targeted tissue sampling but is not alone diagnostic.

Interstitial myocardial amyloid



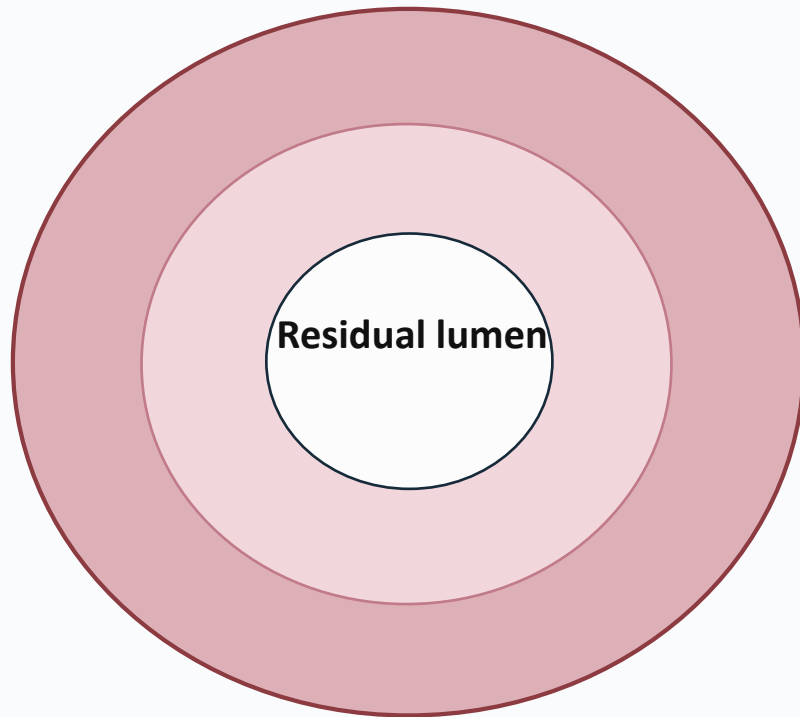
- Amorphous eosinophilic material occupies spaces between myocardial fibers.
- Interstitial expansion reduces normal tissue organization.
- Progressive deposits may compress adjacent cardiomyocytes.

Deposition around myocytes



- Amyloid is extracellular, not a cytoplasmic storage inclusion.
- Perimyocyte deposits can form broad, nearly confluent interstitial bands.
- Pressure atrophy offers a structural explanation for progressive dysfunction.

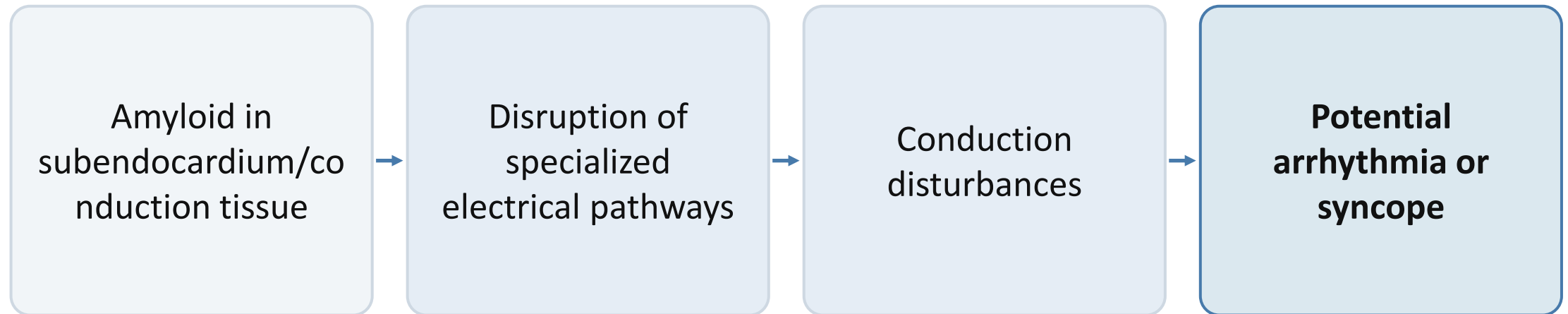
Small-vessel cardiac amyloid



Amyloid within vessel wall
Schematic — not a histologic specimen

- Amyloid can deposit within walls of intramural coronary arteries and arterioles.
- Wall expansion may narrow or occlude the vascular lumen.
- Small-vessel ischemia can occur without a large epicardial plaque.

Conduction-system deposits

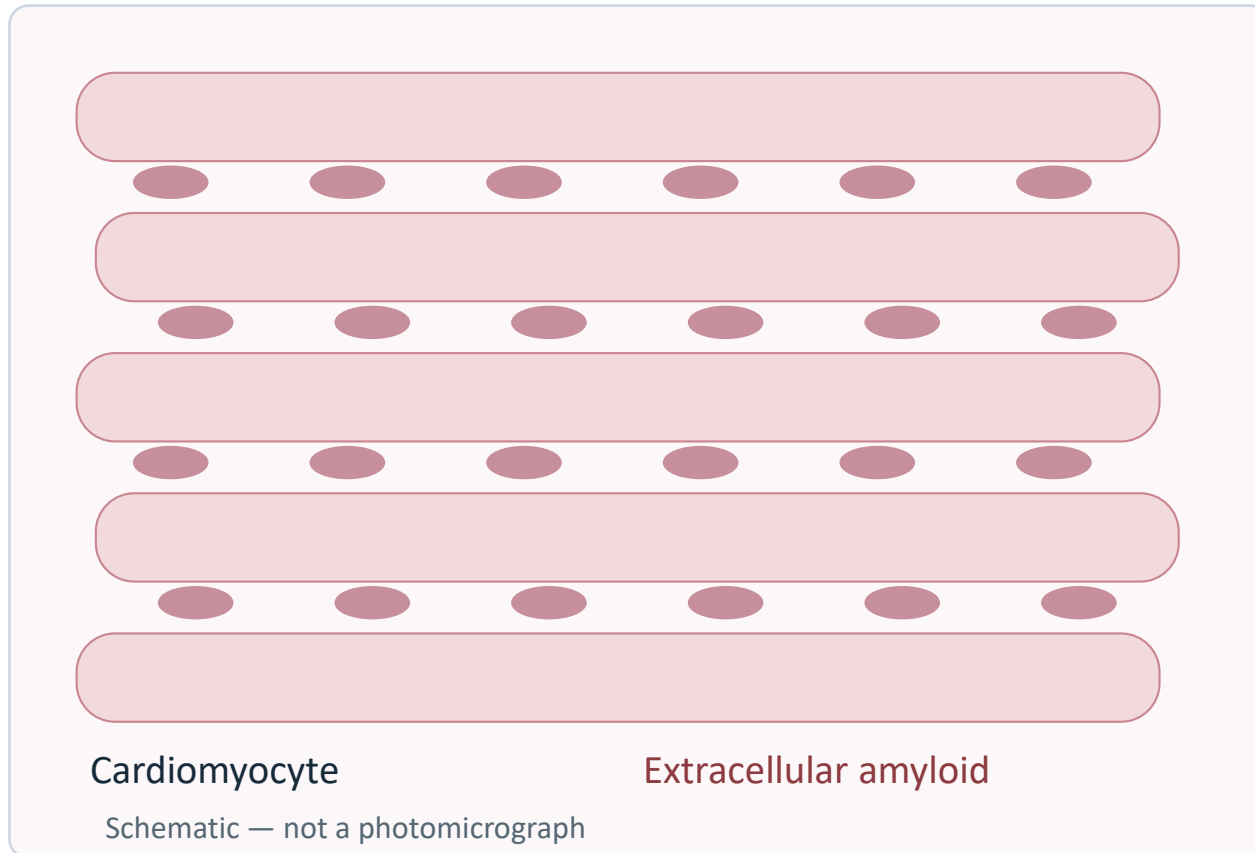


The site of amyloid deposition helps explain apparently disproportionate electrical symptoms.

Valve, endocardial and pericardial deposits

- Valves, endocardium and pericardium among possible cardiac sites.
- Location determines whether the disease resembles valvular pathology or other cardiac conditions.
- Valve involvement should be distinguished from a primary degenerative or inflammatory valve lesion.

Histology on routine H&E



- Amyloid appears as extracellular, amorphous, hyaline eosinophilic material.
- Deposits may encircle myocytes or accumulate in vessel walls.
- H&E suggests amyloid but does not identify its fibril composition.

H&E cannot distinguish amyloid from all hyaline

Amyloid on H&E

- Eosinophilic, extracellular and amorphous.
- Requires a confirmatory stain.

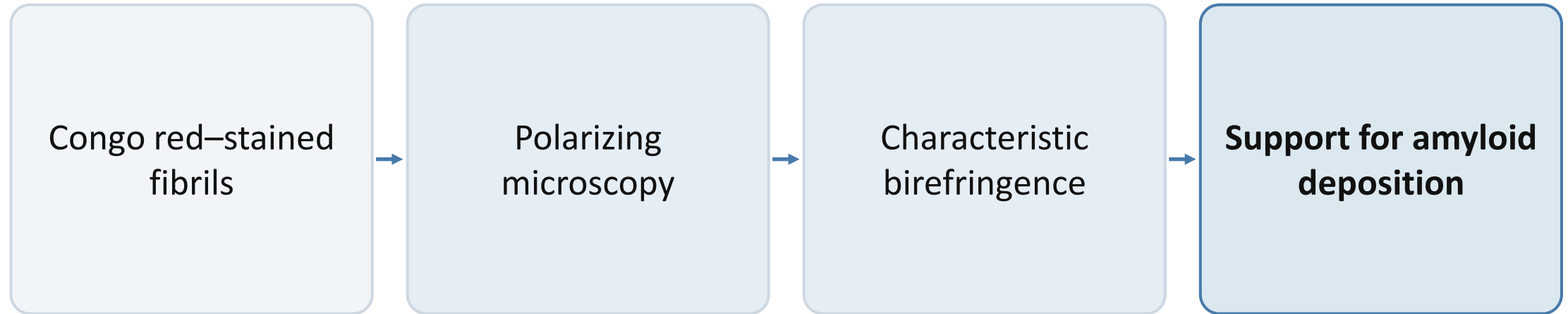
Other hyaline materials

- Collagen or fibrin may resemble amyloid.
- Morphology alone risks misclassification.

Congo red in ordinary light

- Congo red binds amyloid deposits and gives them a pink-red to red-orange appearance.
- Detection must be interpreted in an appropriate tissue and histologic context.
- The stain confirms amyloid-like fibrils but not whether the precursor is AL, ATTR or AA.

Congo red under polarization



Classic apple-green birefringence. The actual color can depend on optical conditions.

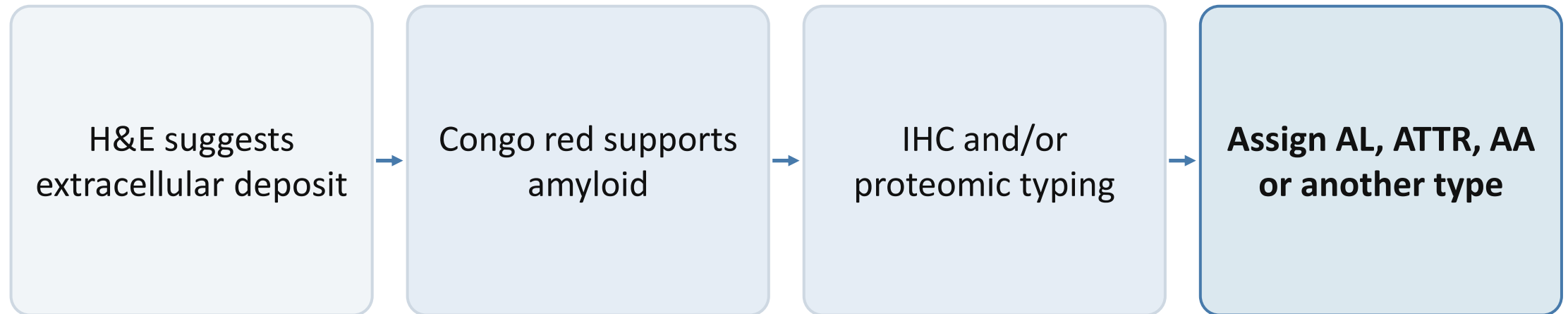
Sulfated Alcian blue is an alternative

- The cardiac chapter cites sulfated Alcian blue as another histochemical aid.
- Histochemical positivity can help distinguish amyloid deposits from other extracellular substances.
- A special-stain result does not replace biochemical amyloid typing.

Electron microscopy: Fibrillar confirmation

- Nonoriented thin extracellular fibrils on electron microscopy.
- Ultrastructure corroborates a fibrillary deposit rather than a homogeneous intracellular inclusion.
- Electron microscopy is confirmatory, not a substitute for typing the precursor.

Confirming deposit $\neq$ identifying protein



Correct amyloid typing matters because the etiologic disease differs fundamentally among types.

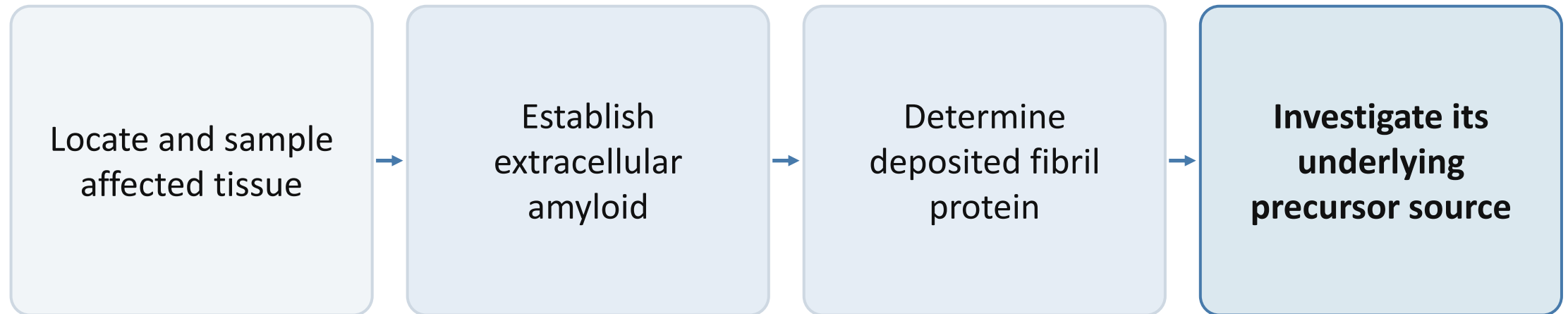
Immunohistochemistry for amyloid typing

- The systemic amyloidosis chapter describes immunostaining for AA, AL and TTR.
- A subtype result requires appropriate interpretation of staining performance and specificity.
- The aim is to identify the constituent fibril protein, not merely to demonstrate a deposit.

Mass spectrometry for biochemical typing

- Mass spectrometry as an available approach to typing amyloid.
- Proteomic identification provides the basis for classifying otherwise similar Congo red–positive deposits.
- Histology and protein identity answer different but complementary diagnostic questions.

Diagnostic reasoning from tissue to etiology

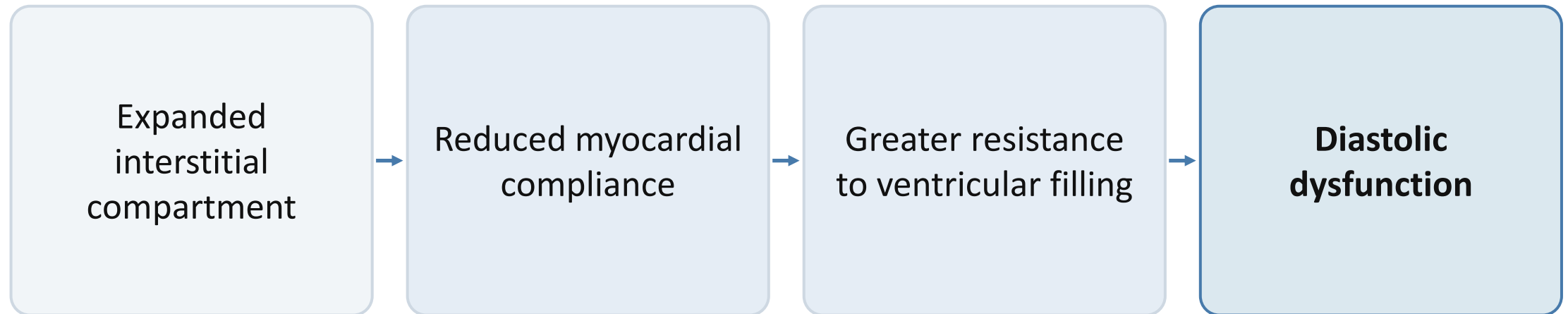


Do not infer “AL” solely from detecting an M protein in a patient with cardiac amyloid.

The clinical spectrum is wide

- Cardiac amyloid can be an unsuspected microscopic or asymptomatic finding.
- Other patients show progressive restrictive heart failure.
- Arrhythmia, dilation, valvular features or an ischemic mimic can predominate.
- Clinical variation follows the location and burden of deposits.

Mechanics of a stiff infiltrated ventricle



The restrictive physiology arises from deposition within myocardium—not from external pericardial restraint.

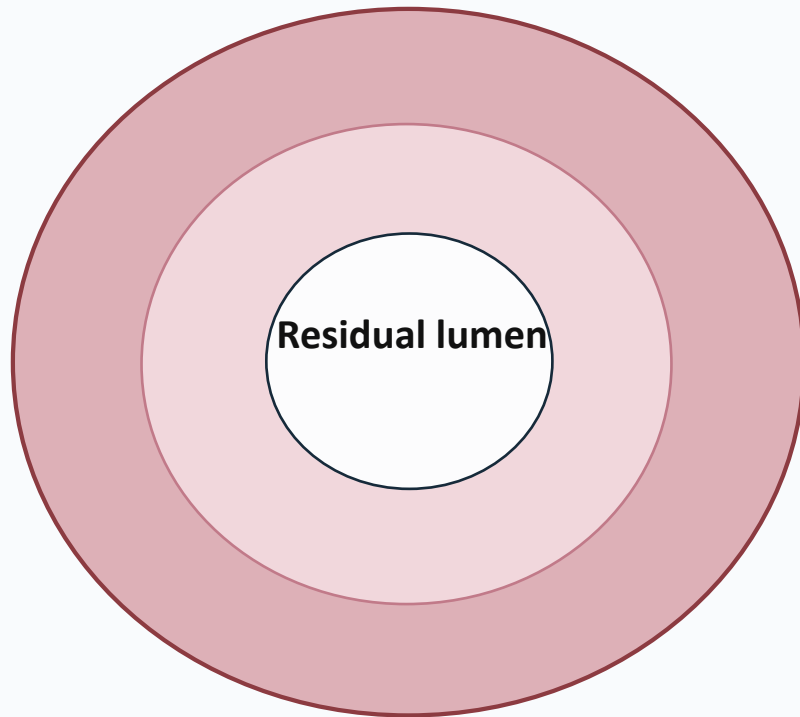
Heart failure in cardiac amyloidosis

- Cardiac amyloid may produce insidious congestive heart failure.
- The classical restrictive pattern links reduced compliance to raised filling pressures.
- Symptoms may overlap with other cardiac diseases and are not pathognomonic.
- Morphology establishes mechanism; Clinical findings establish physiologic impact.

Electrical complications can dominate

- Conduction tissue is a documented site of deposition.
- The clinical consequences can include rhythm disturbance and syncope.
- That conduction abnormalities and arrhythmias may be fatal.
- Risk relates to distribution, not simply total visible myocardial amyloid.

An ischemic presentation without large-vessel disease



Amyloid within vessel wall
Schematic — not a histologic specimen

- Intramural vascular amyloid narrows small coronary lumens.
- Microvascular obstruction limits local myocardial perfusion.
- The resulting syndrome may mimic ischemic heart disease.

How cardiac amyloid mimics valve disease

- Valvular and endocardial amyloid deposition can alter the presenting cardiac phenotype.
- Coexisting chamber changes and arrhythmias can complicate bedside interpretation.
- A valve-like clinical presentation does not establish a primary valve etiology.

Why the phenotype can appear dilated

- Most cases are restrictive, but Robbins explicitly recognizes chamber dilation.
- A dilated appearance does not rule out amyloid protein deposition.
- The diagnosis therefore requires structural and tissue correlation, rather than naming by silhouette alone.

Recognizing a silent amyloid burden

- Amyloid deposition may precede clinically overt mechanical impairment.
- An incidental biopsy/autopsy finding should be interpreted by type and distribution.
- Incidental deposition and symptomatic cardiomyopathy are not interchangeable labels.

Extracardiac clues orient a systemic workup

Anatomic site	Functional consequence
Kidney	Proteinuria or nephrotic syndrome
Peripheral/autonomic nerves	Sensory, motor or autonomic manifestations
Tongue and gut	Macroglossia, malabsorption or altered digestion
Skin and vessels	Fragility or bleeding manifestations

Renal involvement changes the presentation

- Amyloid frequently affects glomeruli in systemic forms.
- Progressive deposits can distort and ultimately obliterate capillary tufts.
- Proteinuria may be severe enough to cause nephrotic syndrome.
- Renal involvement raises concern for systemic disease in a patient with cardiac signs.

Neuropathy may suggest a variant ATTR phenotype

- Some ATTRv proteins preferentially deposit in peripheral and autonomic nerves.
- Other variants predominantly produce cardiac disease.
- Combined cardiac and neurologic manifestations should broaden the anatomic assessment.
- The phenotype alone does not prove a particular genetic variant.

Systemic AL can be associated with bleeding

- Deposits within vessels may increase vascular fragility.
- The text describes acquired factor X binding/inactivation in some AL cases.
- These systemic manifestations can coexist with cardiac involvement.
- They are supportive clues, not substitutes for amyloid typing.

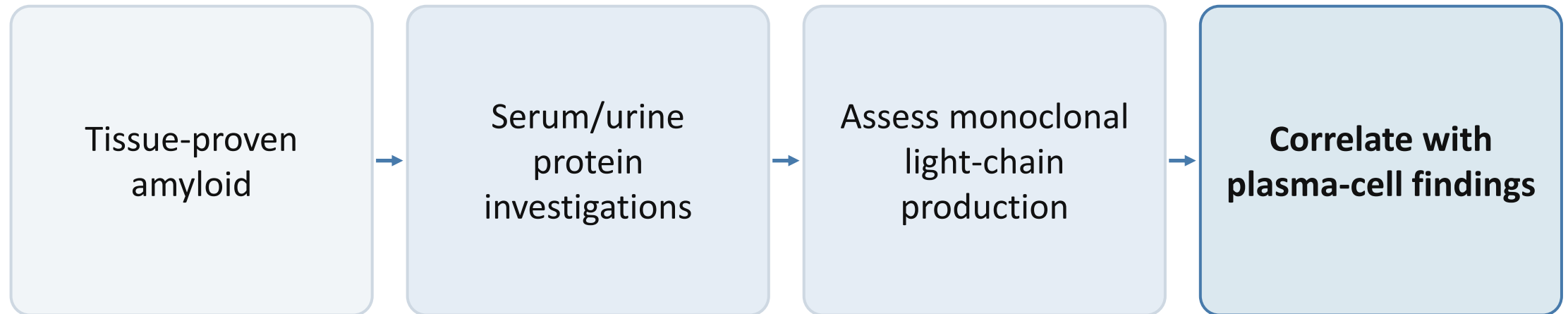
Choosing a diagnostic tissue site

- Demonstration of amyloid in a suitable biopsy specimen.
- Kidney may be sampled when renal involvement is prominent.
- Rectal or gingival samples and abdominal fat aspirates may detect systemic disease.
- Endomyocardial biopsy can identify an etiology in selected cardiac presentations.

A negative fat aspirate does not exclude amyloid

- Congo red staining of aspirated abdominal fat is an option for systemic assessment.
- High specificity but limited sensitivity.
- A negative result must be integrated with the strength of clinical suspicion and organ findings.
- Do not treat tissue sampling sites as interchangeable.

Investigating a possible AL precursor



Serum and urine electrophoretic testing and marrow examination in suspected AL.

Bone marrow findings in AL

- Marrow aspirates often show monoclonal plasmacytosis in AL amyloidosis.
- An overt myeloma phenotype may be absent.
- An underlying clonal plasma-cell population explains production of amyloidogenic free light chains.
- The presence of a clone and the amyloid fibril type should be considered together.

Cardiac amyloid versus endomyocardial fibrosis

Amyloidosis

- Extracellular protein fibrils expand the interstitium and other cardiac tissues.
- Congo red positivity is characteristic.

Endomyocardial fibrosis

- Fibrous thickening predominantly affects endocardial/subendocardial regions.
- A fibrotic rather than amyloid deposit is the key lesion.

Amyloid thickening versus hypertrophic cardiomyopathy

Cardiac amyloidosis

- Extracellular protein deposition may thicken walls.
- Amyloid around fibers is central.

Hypertrophic cardiomyopathy

- Sarcomeric disease may show myocyte hypertrophy/disarray.
- Myocyte architecture, not amyloid, defines the lesion.

Cardiac amyloid versus constrictive pericarditis

Restrictive amyloid

- The intrinsic ventricular myocardium is stiff from interstitial deposits.
- Extracellular amyloid is within cardiac tissues.

Constrictive pericarditis

- The pericardium mechanically limits cardiac filling.
- The primary pathology is pericardial constriction.

Histologic pitfalls: What H&E cannot tell you

- Amorphous pink material is not automatically amyloid.
- Congo red positivity establishes a deposit phenotype but not subtype.
- A negative extracardiac screening sample does not prove the heart is uninvolved.
- Coexisting monoclonal protein does not independently determine cardiac amyloid type.

Case: A stiff heart in later life

An older adult develops insidious heart failure with apparently thick ventricular walls.

The heart shows firm myocardium and interstitial extracellular deposits.

Congo red examination supports amyloid deposition.

Which biochemical possibilities must remain open before typing?

Case reasoning: Old age is not a fibril type

- ATTRwt is a strong etiologic consideration in older patients.
- AL amyloidosis and variant ATTR remain clinically important alternatives.
- Amyloid type must be established rather than inferred from age or gross appearance.
- The physiologic diagnosis and the biochemical diagnosis answer separate questions.

Case: Disproportionate electrical symptoms

A patient has conduction abnormalities and episodic syncope.

Histology reveals amyloid close to subendocardial conduction tissue.

There is less prominent diffuse interstitial expansion.

Which deposition site best links pathology to the clinical phenotype?

Case reasoning: Distribution predicts phenotype

- Conduction-system involvement can explain major electrical symptoms.
- Interstitial burden may explain restrictive physiology in a different presentation.
- Vascular involvement can account for ischemic manifestations.
- The anatomic distribution of deposits is a major pathologic explanatory variable.

Six clinicopathologic principles

Domain	Teaching conclusion
Protein	Amyloid is extracellular fibrillar material
Precursor	AL, ATTRwt, ATTRv and AA have distinct origins
Distribution	Interstitial, vascular, valvular and electrical tissues
Function	Usually restrictive, sometimes alternate phenotypes
Detection	Congo red with polarizing microscopy
Typing	Separate from the initial deposit identification

Reading and image provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- The Heart: cardiomyopathies / cardiac amyloidosis.
- Diseases of the Immune System: amyloid chemistry, classification and general morphologic diagnosis.
- Histology panels not reproduced: diagnostic morphology is shown only as editable conceptual schematics.