CARDIAC AMYLOIDOSIS; DEFINITION AND PATHOPHYSIOLOGY

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I DEFINITION AND CLASSIFICATION

- **Definition:** Cardiac Amyloidosis (CA) is an infiltrative, restrictive-phenotype cardiomyopathy caused by the extracellular deposition of insoluble, misfolded autologous protein fibrils arranged in antiparallel **beta-pleated sheets** within the myocardial interstitium, conduction system, valves, and intramural coronary microvasculature.
- **The Clinical Result:** Progressive interstitial expansion and direct proteotoxicity cause biventricular wall thickening ("pseudo-hypertrophy"), profound diastolic stiffness (**Restrictive Cardiomyopathy**), biatrial enlargement with high thromboembolic risk, heart failure (predominantly **HFpEF** progressing to low-output systolic failure), and conduction block or arrhythmias.
- **The Two Dominant Precursor Proteins (Greater Than 95 Percent of All Cases):**
  - **Immunoglobulin Light-Chain (AL) Amyloidosis:** Derived from monoclonal **lambda (75 to 80 percent) or kappa (20 to 25 percent)** free light chains produced by a bone marrow plasma cell clone.
  - **Transthyretin (ATTR) Amyloidosis:** Derived from misfolded **transthyretin (prealbumin)** synthesized predominantly (>95 percent) by the liver, subdivided into **Wild-Type (ATTRwt)** and **Hereditary/Variant (ATTRv)** disease.
  - **Rare Secondary Subtypes (<5 Percent):** Serum Amyloid A (**AA amyloidosis** in chronic inflammatory diseases), **Apolipoprotein A-I**, isolated atrial amyloidosis (**Atrial Natriuretic Peptide [AANP]**), and heavy-chain (AH) amyloidosis.

II PATHOPHYSIOLOGY: MOLECULAR FIBRILLOGENESIS

- **AL Amyloidosis (Clonal Plasma Cell Dyscrasia + Direct Proteotoxicity):**
  - **Origin:** An indolent bone marrow plasma cell clone (or rarely overt multiple myeloma / Waldenström macroglobulinemia) secretes kinetically unstable monoclonal immunoglobulin light chains.
  - **Mechanism:** Unfolding of the light-chain variable domain exposes hydrophobic residues that self-assemble into soluble **prefibrillar oligomers** and insoluble cross-beta amyloid fibrils stabilized by **Serum Amyloid P (SAP)** and glycosaminoglycans in the cardiac extracellular matrix.
  - **ATTR Amyloidosis (Tetramer Dissociation as the Rate-Limiting Step):**
  - **Origin:** Native **Transthyretin (TTR)** is a stable 55-kDa **homotetrameric transport protein** synthesized by the liver (and in small amounts by the choroid plexus and retinal pigment epithelium) that transports **thyroxine (T4)** and **retinol-binding protein (Vitamin A)**.
  - **Mechanism:** Proteolytic cleavage and kinetic/thermodynamic destabilization of the TTR tetramer at the weaker dimer-dimer thyroxine-binding interface cause **tetramer dissociation into folded monomers**—the **rate-limiting step** of ATTR fibrillogenesis (and the exact therapeutic target of TTR stabilizers like **Tafamidis** and **Acoramidis**). These monomers subsequently misfold and polymerize into insoluble amyloid fibrils.
  - **Clinical Subtypes:**
  - **Wild-Type ATTR (ATTRwt, formerly "Senile Systemic Amyloidosis"):** Age-related oxidative modification and chaperone exhaustion cause normal, unmutated wild-type TTR tetramers to dissociate; predominantly affects **men over 65 to 70 years of age**.
  - **Hereditary / Variant ATTR (ATTRv):** Autosomal dominant single-point mutations in the ***TTR* gene** (chromosome 18) thermodynamically destabilize the tetramer, accelerating dissociation and earlier clinical onset. Key variants include **Val122Ile (p.Val142Ile)** (present in 3 to 4 percent of African Americans; predominantly cardiopathic), **Thr60Ala (p.Thr80Ala)** (mixed cardiac and neuropathic), and **Val30Met (p.Val50Met)** (classic familial amyloid polyneuropathy with conduction disease).

Pathophysiological Feature	AL Cardiac Amyloidosis	ATTRwt (Wild-Type) Amyloidosis	ATTRv (Hereditary) Amyloidosis
Precursor Protein & Source	Monoclonal **Lambda/Kappa Light Chains** (Bone marrow plasma cells)	Normal **Wild-Type Transthyretin** (Liver)	Mutant **Variant Transthyretin** (Liver; autosomal dominant *TTR* gene)
Myocardial Injury Mechanism	**Dual Hit:** Interstitial fibril infiltration **PLUS acute direct light-chain oligomer cardiotoxicity**	Predominantly **chronic mechanical interstitial fibril infiltration** (slower progression)	Chronic interstitial fibril infiltration (cardiac, neuropathic, or mixed phenotype)
Wall Thickness vs. Severity	**Moderate LV wall thickening** (12–15 mm) with **severe rapid HF & high NT-proBNP**	**Marked LV/RV wall thickening** (often 16–20+ mm) with more indolent HF progression	Variable wall thickening; depends on specific *TTR* mutation (*Val122Ile, Thr60Ala, Val30Met*)
Untreated Median Survival	**Less than 6 months** from HF onset (Medical Emergency)	**3.5 to 5 years** from diagnosis	**2.5 to 5 years** (worse in *Val122Ile* than *Val30Met*)

III STRUCTURAL AND HEMODYNAMIC CONSEQUENCES

- **Massive Extracellular Volume (ECV) Expansion ("Pseudo-Hypertrophy"):** Unlike true Hypertrophic Cardiomyopathy or hypertensive LVH (where individual cardiomyocytes enlarge), amyloid fibrils accumulate in the extracellular space, **expanding the Extracellular Volume (ECV) fraction to 40 to 70 percent** (normal 22 to 28 percent). This physically separates, compresses, and atrophies cardiomyocytes—explaining the classic **ECG-to-Echo discordance (thick walls on Echo with low QRS voltages on ECG)**.
- **Restrictive Diastolic Physiology and Steep Pressure-Volume Relationship:** The amyloid-stiffened left and right ventricles cannot relax or expand during diastole, shifting the **end-diastolic pressure-volume relationship (EDPVR) sharply upward and to the left**. Small increases in intravascular volume cause steep spikes in left and right ventricular filling pressures (pulmonary edema and systemic venous congestion), whereas small volume reductions from over-diuresis cause a precipitous drop in **Fixed Stroke Volume** and blood pressure.
- **Atrial Myopathy and Electromechanical Dissociation:** Primary amyloid infiltration of the left and right atrial walls—compounded by chronic restrictive elevation of atrial pressures—leads to **biatrial enlargement, loss of atrial reservoir/contractile strain, and "atrial standstill" (electromechanical dissociation)**, predisposing to **left atrial appendage thrombi and cardioembolic stroke even during sinus rhythm**.
- **Longitudinal-Before-Radial Systolic Failure ("Apical Sparing" to "Burn-Out"):** Subendocardial longitudinal myocardial fibers at the **base and mid-ventricle** are infiltrated earliest, severely depressing **Global Longitudinal Strain (GLS)** while relative sparing of the apex (**"Cherry-on-Top" pattern**) and compensatory radial contraction maintain a "normal" LVEF until late-stage cardiomyocyte strangulation causes **LVEF decline, low cardiac output, and spontaneous resolution ("pseudo-cure") of prior systemic hypertension**.

IV CELLULAR PROTEOTOXICITY, CONDUCTION AND MICROVASCULAR INJURY

- **Direct Light-Chain Cardiotoxicity in AL Amyloidosis (The Liao-Falk Mechanism):** In AL amyloidosis, circulating soluble **prefibrillar light-chain oligomers** directly enter cardiomyocytes, impair **autophagic-lysosomal flux**, and activate the non-canonical **p38 Mitogen-Activated Protein Kinase (p38-MAPK) pathway**. This generates intense **mitochondrial Reactive Oxygen Species (ROS) oxidative stress**, impairs intracellular calcium handling, directly suppresses contractility, and induces **cardiomyocyte apoptosis** (and directly stimulates *NPPB* gene transcription, explaining why **NT-proBNP is disproportionately higher and survival is far shorter in AL than ATTR for the exact same degree of LV wall thickness**, and why rapid light-chain clearance with **Daratumumab-CyBorD** improves cardiac function before physical amyloid fibrils are resorbed).
- **Infiltration of the Cardiac Conduction System and Autonomic Nerves:** Amyloid deposition and fibrosis within the **Sinoatrial (SA) node, Atrioventricular (AV) node, and infra-Hisian His-Purkinje system** produce sinus node dysfunction, bundle branch blocks, and **high-degree / Complete AV Block**, while infiltration of sympathetic/parasympathetic ganglia causes **severe autonomic neuropathy and orthostatic hypotension**.
- **Intramural Coronary Microvascular Dysfunction:** Perivascular and medial amyloid cuffs surround and narrow **intramural coronary arterioles**, severely reducing **Coronary Flow Reserve (CFR)** and causing chronic **subendocardial ischemia, angina with normal epicardial coronary arteries, and persistent low-level elevation of high-sensitivity cardiac troponin**.

KEY REFERENCES

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