CARDIAC AMYLOIDOSIS; DIFFERENTIAL DIAGNOSIS & EVIDENCE

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I THE CORE DIFFERENTIAL DIAGNOSIS (LEFT VENTRICULAR HYPERTROPHY PHENOCOPIES)

- **The Diagnostic Challenge:** Because Cardiac Amyloidosis (CA) presents with concentric or asymmetric **Left Ventricular Wall Thickening (12 mm or greater)** and preserved ejection fraction, it is frequently misdiagnosed as other conditions causing increased LV wall thickness:
- **Hypertrophic Cardiomyopathy (HCM):** The primary inherited sarcomeric phenocopy.
- **Hypertensive Heart Disease (HHD):** The most common acquired pressure-overload phenocopy.
- **Severe Calcific Aortic Stenosis (AS):** Both a hemodynamic mimic and a frequent **concomitant dual pathology** in elderly patients.
- **Metabolic and Lysosomal Storage Phenocopies: Anderson-Fabry Disease (*GLA*)**, **Danon Disease (*LAMP2*)**, **PRKAG2 Cardiomyopathy**, and mitochondrial cardiomyopathies.

II DIFFERENTIAL EVIDENCE: CARDIAC AMYLOIDOSIS VS. HYPERTROPHIC CARDIOMYOPATHY (HCM)

- **12-Lead Electrocardiogram (The Voltage-to-Mass Discordance Rule):**
  - **Cardiac Amyloidosis:** Classic **discordance** between thick LV walls on echocardiography and **low QRS voltage** in the limb leads (<=5 mm in all limb leads, or low Sokolow-Lyon voltage-to-mass ratio), accompanied by a **"pseudo-infarction" QS pattern** in anterior/inferior leads (in 50 to 70 percent of patients with normal coronaries) and AV conduction delay.
  - **Sarcomeric HCM:** Prominent **high QRS voltages** fulfilling LVH criteria, deep narrow lateral/inferior **"dagger" Q waves** (from septal hypertrophy), or giant negative precordial T waves (in Apical HCM).
  - **2D Speckle-Tracking Echocardiography (Strain Polar Map):**
  - **Cardiac Amyloidosis:** Pathognomonic **"Relative Apical Sparing" ("Cherry-on-Top" bull's-eye sign)**—severely depressed basal and mid-ventricular longitudinal strain with preserved apical strain (**Relative Apical Longitudinal Strain ratio >= 1.0**, validated by Phelan et al. with **93 percent sensitivity and 82 percent specificity** for differentiating CA from HCM and aortic stenosis). Also shows concurrent **RV free-wall thickening (>5 mm)**, **interatrial septal and AV valve thickening**, and a small pericardial effusion.
  - **Sarcomeric HCM:** Focal longitudinal strain reduction localized to the site of maximal septal or apical hypertrophy **without** a basal-to-apical gradient, plus **Systolic Anterior Motion (SAM)** of the mitral valve and dynamic LVOT obstruction.
  - **Cardiac Magnetic Resonance (LGE Distribution and Gadolinium Kinetics):**
  - **Cardiac Amyloidosis: Global, diffuse circumferential subendocardial or transmural Late Gadolinium Enhancement (LGE)** (often involving both atria and the RV) coupled with **abnormal inversion-time (TI) nulling kinetics** (the amyloid myocardium nulls **before or at the same inversion time as the blood pool** on the TI scout).
  - **Sarcomeric HCM: Patchy, mid-wall focal LGE** localized to the **anterior and posterior Right Ventricular septal insertion ("hinge") points** and segments of maximal hypertrophy, with normal blood-pool nulling kinetics.

III DIFFERENTIAL EVIDENCE: CARDIAC AMYLOIDOSIS VS. HYPERTENSIVE HEART DISEASE (HHD)

- **Clinical and Structural Clues:** HHD patients have long-standing severe hypertension without orthopedic red flags (carpal tunnel syndrome, spinal stenosis, biceps tendon rupture); in contrast, CA patients frequently exhibit **spontaneous normalization of prior hypertension ("auto-cure")** and intolerance to ACEi/ARBs/Beta-blockers, alongside **thickened AV valve leaflets, thickened interatrial septum, RV hypertrophy, and severe Grade III restrictive diastolic filling**.
- **CMR Parametric Mapping (The ECV Cut-off):**
  - **Cardiac Amyloidosis: Extreme Extracellular Volume (ECV) expansion (>40 percent, often 50 to 70 percent)** and markedly elevated **Native T1 (>1,100 to 1,150 ms at 1.5T)** caused by massive extracellular fibril deposition.
  - **Hypertensive Heart Disease: Normal or only mildly elevated ECV (<30 to 32 percent)** and mildly increased Native T1, because wall thickening in HHD is predominantly intracellular cardiomyocyte hypertrophy with mild reactive interstitial collagen.

Diagnostic Modality / Feature	Cardiac Amyloidosis (AL / ATTR)	Sarcomeric HCM	Hypertensive Heart Disease (HHD)	Anderson-Fabry Disease (GLA)
12-Lead ECG	**Low QRS voltage / LVH discordance**; **pseudo-infarct QS**; AV block	**High LVH voltage**; deep narrow **"dagger" Q waves**; giant T-wave inversion	Normal or high LVH voltage with lateral repolarization strain	High LVH voltage; **short PR interval** (early) -> AV block (late)
Echo 2D Strain (GLS)	**"Apical Sparing" ("Cherry-on-Top")** (Apical/[Basal+Mid] ratio >=1.0)	Focal reduction in hypertrophied septum or apex (no apical sparing)	Mild diffuse basal/global reduction	Early **basal inferolateral** strain reduction
CMR LGE Pattern	**Global subendocardial or transmural LGE** + **abnormal TI nulling**	**Patchy mid-wall LGE at RV insertion points** & thickest wall	Absent LGE or minimal non-specific mid-wall fibrosis	Classic **mid-wall / subepicardial basal inferolateral LGE**
CMR Native T1 & ECV	**Very High Native T1** & **Massive ECV (>40–55%)**	Mildly elevated Native T1 & ECV in scarred segments	Mildly elevated Native T1; **ECV <30–32%**	**Pathognomonic LOW Native T1** (intracellular lipid) & normal ECV
Tc-99m PYP/DPD Scan	**Perugini Grade 2 or 3** in ATTR (with negative sFLC/SIFE/UIFE)	Grade 0 (Negative)	Grade 0 (Negative)	Grade 0 (Negative)

IV DIFFERENTIAL AND DUAL PATHOLOGY: CARDIAC AMYLOIDOSIS AND SEVERE AORTIC STENOSIS

- **High Prevalence of Dual Pathology (Castaño et al. / Scully et al. / Nitsche et al., *JACC* 2021):** Prospective bone-scintigraphy screening studies demonstrate that **11 to 16 percent of elderly patients (aged >=75 years) referred for TAVR have concomitant occult Wild-Type Transthyretin Cardiac Amyloidosis (AS-ATTR-CM)**, rising to **up to 25 to 30 percent in the Paradoxical Low-Flow, Low-Gradient (LFLG) severe AS subgroup**.

- **Clinical and Echocardiographic Red Flags for Dual AS + ATTR-CM (The RAISE Score):**
  - **R — Remodeling:** Disproportionate concentric LV wall thickening (>14 to 16 mm) and severe diastolic dysfunction/biatrial enlargement out of proportion to the aortic valve gradient.
  - **A — Age:** Age >= 85 years.
  - **I — Injury:** Chronically elevated **High-Sensitivity Troponin (hs-cTnT)**.
  - **S — Systemic:** History of **Carpal Tunnel Syndrome**, lumbar spinal stenosis, or biceps tendon rupture.
  - **E — Electrical: Right Bundle Branch Block (RBBB)** or **Low QRS Voltage** (low Sokolow-Lyon voltage-to-mass ratio).
  - **Hemodynamic Phenotype:** Classic presentation is **Low-Flow, Low-Gradient Severe AS (Stroke Volume Index <35 mL/m2, Mean Gradient <40 mmHg, AVA <=1.0 cm2)** with preserved or mildly reduced LVEF and impaired longitudinal strain (**mitral annular S' <=6 cm/s**).
  - **Pre-TAVR CT Myocardial Extracellular Volume (CT-ECV) and Bone Scintigraphy:**
  - **Opportunistic Pre-TAVR CT-ECV:** Performing a 3-to-5-minute delayed equilibrium scan during routine pre-TAVR cardiac CT to measure **Myocardial CT-ECV (cut-off >31 to 35 percent)** reliably screens for concomitant cardiac amyloidosis without requiring a separate CMR.
  - **Confirmation and Clinical Impact (TAVR is Still Beneficial):** Confirmed via **Tc-99m PYP/DPD SPECT + monoclonal light-chain exclusion**. Multicenter outcome studies (**Nitsche et al., *JACC* 2021**) prove that **TAVR significantly improves survival compared to medical therapy in dual AS + ATTR-CM** (futility is avoided), and post-TAVR initiation of **Tafamidis / Acoramidis** addresses the underlying amyloid cardiomyopathy.

V DIFFERENTIAL EVIDENCE: CARDIAC AMYLOIDOSIS VS. ANDERSON-FABRY DISEASE

- **Pathophysiology and Systemic Clues: Anderson-Fabry Disease** is an **X-linked lysosomal storage disorder** caused by deficiency of **alpha-galactosidase A (*GLA* gene)**, resulting in **intracellular** accumulation of **globotriaosylceramide (Gb3)** inside cardiomyocytes, vascular endothelium, kidneys, and nerves. Extracardiac hallmarks include **angiokeratomas** (bathing-trunk distribution), **cornea verticillata** (whorl-like corneal opacities on slit-lamp exam), **acroparesthesias** (burning neuropathic pain in hands/feet), hypohidrosis, and proteinuric CKD.
- **Definitive CMR Differentiation (Native T1 Mapping):**
  - **Anderson-Fabry Disease:** Because Gb3 is an **intracellular glycosphingolipid (fat)**, Fabry disease uniquely exhibits a **pathognomonic LOW Native T1 relaxation time** on CMR parametric mapping with a **normal ECV** (until late-stage replacement fibrosis develops in the **basal inferolateral wall**, causing focal "pseudonormalization" of T1).
  - **Cardiac Amyloidosis:** Exhibits **markedly ELEVATED Native T1 and massively expanded ECV (>40%)** because amyloid fibrils accumulate in the **extracellular** matrix.

KEY REFERENCES

- **Phelan D, Collier P, Thavendiranathan P, et al.:** Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis, *Heart*, 2012.
- **Nitsche C, Scully PR, Patel KP, et al.:** Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis, *Journal of the American College of Cardiology*, 2021.
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