UNDERSTANDING THE RELATIONSHIPS OF CARDIAC DIAGNOSTICS IN PATIENTS WITH AMYLOID TRANSTHYRETIN CARDIAC AMYLOIDOSIS

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Disclosures

Dr. Diego Delgado is a member of the Canadian Advisory Board for Akcea, Pfizer, and Alnylam pharmaceuticals. In addition, he is a principal investigator for ATTR-ACT (NCT01994889), ATTR-ACT Extension, and ENDEAVOUR (NCT02319005) studies. Furthermore, Dr. Delgado receives funding in the form of a research grant from Pfizer Global for studying novel biomarkers of ATTR amyloidosis.

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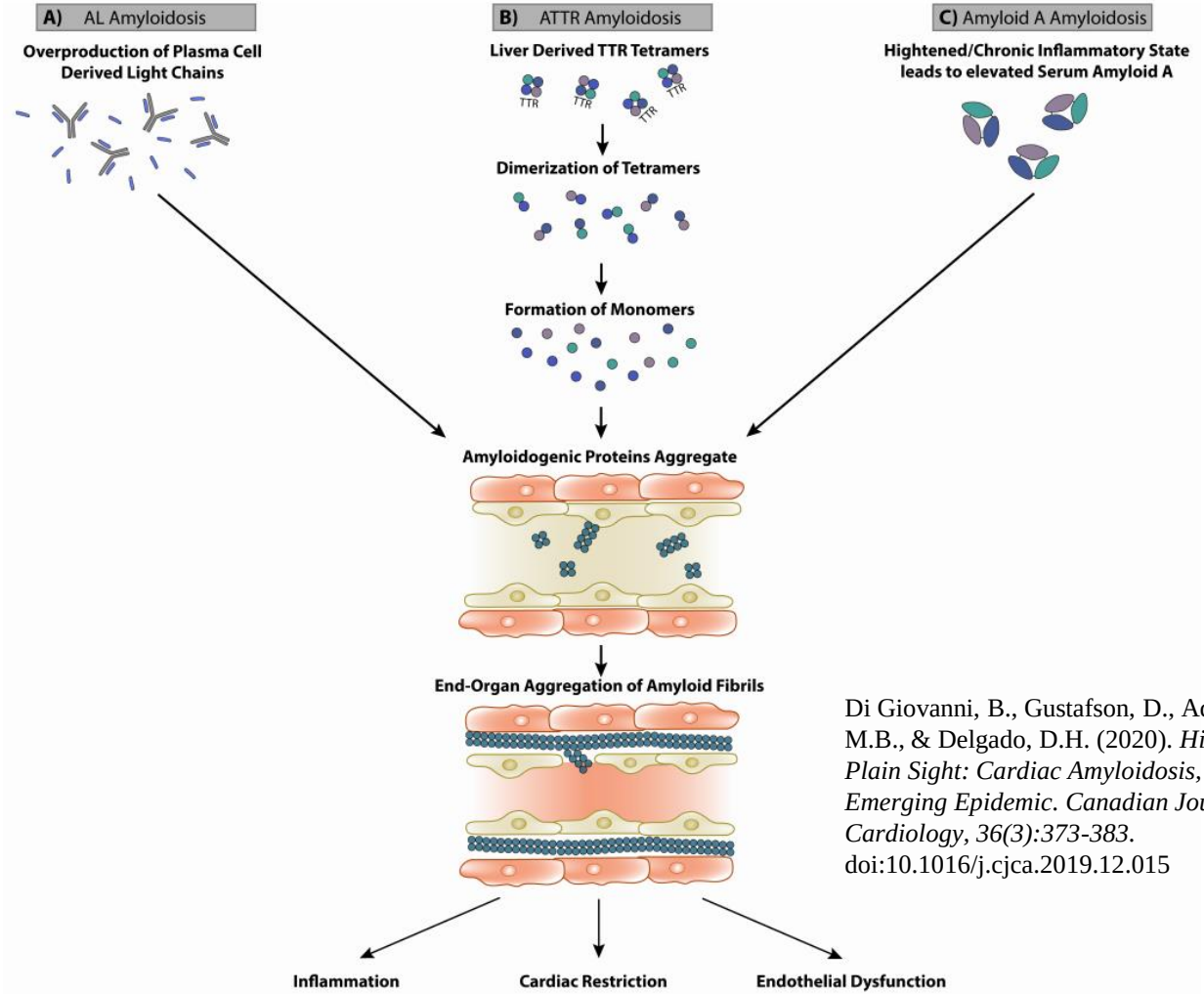
Background

- Amyloid transthyretin (ATTR) cardiac amyloidosis (CA) is an increasingly recognized cause of:
  - restrictive cardiomyopathy
  - heart failure with preserved ejection fraction (HFpEF)
- Patients often experience delayed diagnosis
- Limited interpretation of routine cardiac testing in ATTR-CA, including:
  - Cardiac biomarkers (troponins, brain natriuretic peptide (BNP))
  - Echocardiography
- Technetium-99m pyrophosphate (^{99m}Tc-PYP) scintigraphy is increasingly used for non-invasive diagnosis of ATTR-CA

Background

- ATTR-CA is divided into two major subtypes
  - Wild-type (no mutation)
  - Variant (also referred to as hereditary)
- In both subtypes, amyloid fibrils form, aggregate/deposit and damage tissues



Di Giovanni, B., Gustafson, D., Adamson M.B., & Delgado, D.H. (2020). *Hiding in Plain Sight: Cardiac Amyloidosis, an Emerging Epidemic. Canadian Journal of Cardiology, 36(3):373-383.* doi:10.1016/j.cjca.2019.12.015

Table 1. Differences in presentation of ATTR amyloidosis in relation to genotype.

Wild-type	References	Variant	References
• Elderly • Predominantly cardiac involvement • Generally asymptomatic (sporadic cardiac symptoms) • Disease process progresses slowly • No identified TTR gene mutation	[5,6]	• Early or late onset • Predominantly neurological and/or cardiac involvement • Symptomatic (symptoms experienced often reflect variant) • Neuropathy can be autonomic, sensory, and motor • Disease process generally progresses slowly • Identified TTR gene mutation which is considered pathogenic (autosomal dominant inheritance)	[7,8]

Di Giovanni, B., Gustafson, D., & Delgado, D. H. (2019). *Amyloid transthyretin cardiac amyloidosis: diagnosis and management. Expert Review of Cardiovascular Therapy, 1–9.* doi:10.1080/14779072.2019.1662723

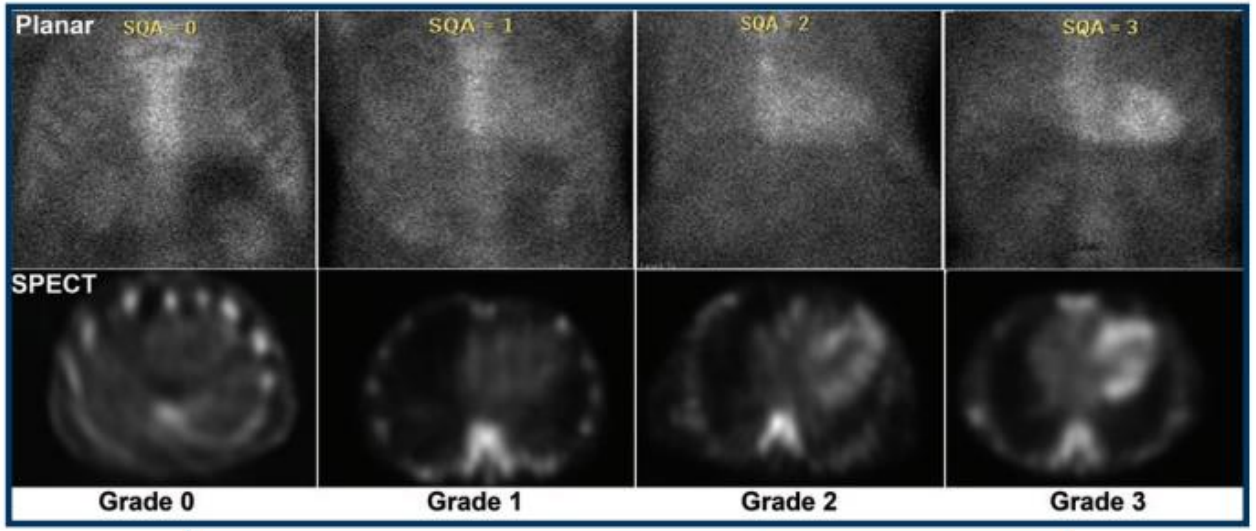
^{99m}Tc-PYP Scintigraphy for ATTR-CA

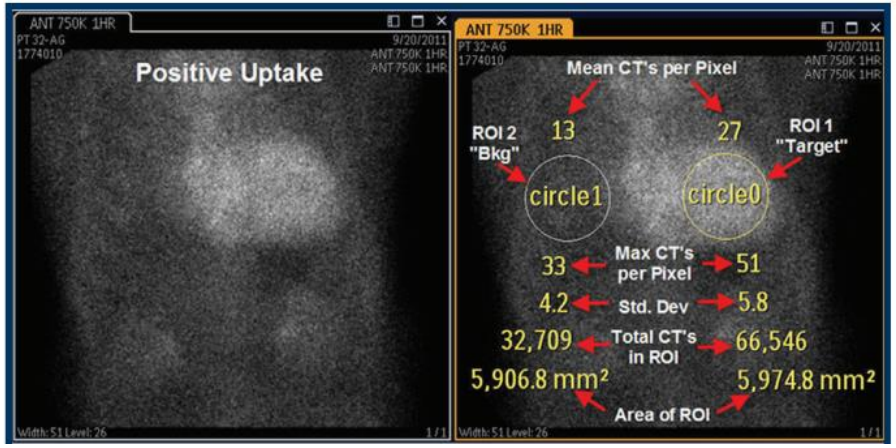
- Semi-quantitative visual grading
  - ^{99m}Tc-PYP originally developed as bone radiotracer
  - Grading visually compares uptake in the heart to uptake in bone
  - Grade 0-3 (Grade 2 and 3 are considered indicative of ATTR-CA)

- Quantitative ratio – heart to contralateral (H/CL) ratio
  - Direct comparison of uptake to produce numeric ratio
  - H/CL ratio is considered suggestive of ATTR-CA when ≥1.5

^{99m}Tc-PYP Scintigraphy for ATTR-CA

- Grade 0 : no myocardial uptake, normal bone
- Grade 1 : myocardial uptake < rib
- Grade 2 : myocardial uptake = rib
- Grade 3 : myocardial uptake > rib





American Society of Nuclear Cardiology (https://www.asnc.org/Files/Practice%20Resources/Practice%20Points/ASNC%20Practice%20Point-99mTechnetiumPyrophosphateImaging2016.pdf)

Objective

- We sought to investigate the relationship of cardiac diagnostics to standard of care non-invasive imaging modalities.

Methods

- Single-center retrospective cohort study
- Adult patients (≥18 years old) diagnosed with an identified genetic variant in the transthyretin (TTR) gene or ATTR-CA
  - We included wild-type and variant cases of ATTR-CA

- The association between PYP grade (0-3), H/CL ratios, echocardiographic variables, and cardiac biomarkers (troponin and BNP) was investigated using linear regression models

Results

- Among 140 cases, 83 utilized a PYP scan as part of their diagnostic workup

Grade compared to biomarkers:

- The association between PYP grade and presenting troponin was statistically significant for grades 1-3, using grade 0 as the referent
  - Median for Grade 1 was 79 ng/L [IQR 37-115].
  - Median for Grade 2 was 92 ng/L [IQR 10-237]
  - Median for Grade 3 was 92.5 ng/L [IQR 45-187].
- Presenting BNP which demonstrated no correlation between PYP Grade and presenting values

Results

Ratio compared to biomarkers:

- H/CL ratio did not show any statistically significant correlation with presenting biomarkers

Ratio compared to echocardiography:

- H/CL ratio was significantly positively correlated with left ventricular mass (g) 88.14 [95% CI; 41.66-134.62] ($p<0.001$)
- H/CL ratio was correlated with interventricular septal thickness at end diastole (IVSd;cm) 0.33 [95% CI; 0.17-0.49] ($p<0.001$)

Limitations

- Lack of documentation or loss of follow up before investigations completed
- Paradigm shift to a predominantly non-invasive diagnosis more apparent in recent years as opposed to endomyocardial biopsy in past
- ^{99m}Tc-PYP scintigraphy reports differ in layout and clinician interpretation based on site and experience
- Only BNP was available, no measurements of N-terminal prohormone BNP
- Cardiology specialist site, referrals may be skewed to more symptomatic patients with significant cardiac involvement

Conclusion

- We found troponins were correlated with PYP grade in patients with ATTR-CA
- Higher presenting troponins and IVSd were associated with a higher PYP grade and PYP ratio respectively
- There may be a role for scintigraphy in management of HFpEF cases of unknown etiology to rule in/out ATTR-CA
- Combinatorial approach to diagnosing ATTR-CA is essential

Future Directions

- Further evaluation of diagnostic tools in ATTR-CA, in both symptomatic and asymptomatic patients
- Continued analysis of cardiac investigations including imaging and biomarkers within patients with ATTR-CA to strengthen associations
- Consider ATTR-CA in the differential diagnosis for HFpEF and follow appropriate diagnostic algorithms; earlier diagnosis may help provide more opportunity to trend biomarkers, echocardiographic variables and scintigraphy, as well as provide available treatment options
- Continued evaluation of current and new cardiac biomarkers which may aid in earlier diagnosis or provide prognostic value