Non-invasive diagnosis and investigation of TTR cardiac amyloidosis

Claudio Rapezzi, Italy
TTR-CM: the great pretender
Diagnostic pathways to TTR-CM (Bologna, 2000–2014)

- Cardiologic screening after FAP diagnosis
- Cardiologic screening after diagnosis of AL amyloidosis
- Family screening

TTR-CM (N=178)

- Heart failure, hypertensive heart disease, CAD, HCM, bradyarrhythmias
- Other, including incidental myocardial DPD uptake

Numbers:
- 52
- 7
- 8
- 85
- 26
HF of indeterminate etiology (n=27)

HF of indeterminate etiology + bradyarrhythmias (n=5)

Bradyarrhythmias (n=9)

“HCM” with/without HF (n=6)

“HHD” with/without HF (n=9)

Severe calcific AS “low flow – low gradient” (n=2)

AL CMP (n=4)

Incidental positive DPD scan (n=9)

wt-TTR AC (n=71)
Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*

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Received 6 March 2007; revised 27 June 2007; accepted 16 July 2007
Sarcomeric HCM

TTR Amyloidosis

Anderson-Fabry

Glycogenosis (Danon)
HCM: Prevalence of different etiologies in a cohort of 1807 pts, London & Bologna

- Sarcomeric HCM (N = 1378 – 76.2 %)
- Noonan (N = 25 – 1.4 %)
- AFD (N = 84 – 4.6 %)
- AL amyloidosis (N = 114 – 6.3 %)
- Mitochondrial disease (N = 24 – 1.3 %)
- Diabetic mother (N = 3 – 0.2 %)
- LEOPARD (N = 8 – 0.4 %)
- GSD (N = 16 – 0.9 %)
- Neuromuscular diseases (N = 17 – 0.9 %)
- Danon (N = 4 – 0.2 %)
- SSA (N = 48 – 2.7 %)
- ATTR (N = 86 – 4.7 %)

Diabetic mother (N = 3 – 0.2 %)
HCM: Prevalence of different etiologies in a cohort of 1807 pts, London & Bologna
All-cause mortality and HTx in sarcomeric HCM and phenocopies
Towards the definite diagnosis of TTR-CM

Clinical evaluation, ECG, Echocardiogram

Histology +/- proteomic +/- DNA +/- immunohistochemistry

≪bone tracers≫ scintigraphy

CMR
General Profile of TTR-CM patients with Exclusively Cardiac Phenotype

- **Male** gender
- Average age ~ 72 yrs
- **No apparent family history** of ATTR
- Heart failure symptoms
- Frequent history of CTS
- Symmetric “LV hypertrophy”
- Absent or mild LV dilatation
- Mild LV systolic **dysfunction**
- Normal or near normal QRS voltages but reduced QRS voltage / LV thickness
“Senile Systemic Amyloidosis” (wtTTR-related Amyloidosis)
Prevalence of carpal tunnel syndrome in different subsets of systemic amyloidosis
(435 patients, Bologna, Italy)

- AL
- TTR-related Amyloidosis
- ATTR
- Wild-type
- ATTR with CMP
- ATTR without CMP

*P <0.0001*
*n.s.*
Prevalence of carpal tunnel syndrome in different subsets of systemic amyloidosis according to gender

(435 patients, Bologna, Italy)
 Estimates from competing risk regression model*
Cumulative incidence function of carpal tunnel syndrome

ATTR Vs AL: HR 14.5, 95%CI 6.7-31.5, p<0.001
SSA Vs AL: HR 7.1, 95%CI 2.8-18.3, p<0.001

*Adjusted by gender, year and age at the onset of amyloidosis
Panel B, incidence of cardiac involvement

SHR 1.8, 95% CI 1.2-2.6, p<0.01

*Adjusted by gender, year and age at the onset of amyloidosis, and amyloidosis etiology

Carpal tunnel syndrome*

*Adjusted by gender, year and age at the onset of amyloidosis, and amyloidosis etiology
Standardized incidence ratios of carpal tunnel syndrome reported by years before the diagnosis of amyloidosis.
Towards the definite diagnosis of TTR-CM

- Clinical evaluation
- ECG
- Echocardiogram
- «bone tracers» scintigraphy
- Histology +/− proteomic +/− DNA +/− immunohistochemistry
- CMR
Looking for the infiltrative phenotype hidden within the hypertrophic one

- Increased symmetric parietal thickness of LV in the absence of any other plausible cause
- Increased thickness of atrioventricular valves
- Increased thickness of interatrial septum
- Small pericardial effusion
- Granular sparkling of myocardium
- Increased thickness of RV free wall

Rapezzi et al. Nat Rev Cardiol 2010; Rapezzi C et al Eur Heart J 2012
Normal speckle strain imaging, showing relatively homogenous longitudinal LV contraction
Amyloid strain
Averaged regional function (LS & RS)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>AL</th>
<th>ATTRm</th>
<th>ATTRwt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LS (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASAL</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>MID</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>APICAL</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

| **RS (%)** |         |       |       |        |
| BASAL  | ![Graph](image) | ![Graph](image) | ![Graph](image) | ![Graph](image) |
| MID    | ![Graph](image) | ![Graph](image) | ![Graph](image) | ![Graph](image) |
| APICAL | ![Graph](image) | ![Graph](image) | ![Graph](image) | ![Graph](image) |

Quarta CC et al, Circulation 2014
ECG characteristics
### Baseline characteristics of 233 patients with amyloidotic cardiomyopathy

Baseline characteristics of 233 patients with amyloidotic cardiomyopathy are presented below:

<table>
<thead>
<tr>
<th></th>
<th>AL (n=157)</th>
<th>SSA (n=15)</th>
<th>ATTR (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB, n (%)</td>
<td>6/146 (4)</td>
<td>6 (40)</td>
<td>4/60 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total QRS score, mV</td>
<td>92 ± 36</td>
<td>120 ± 37</td>
<td>112 ± 34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low QRS voltage, n (%)</td>
<td>88/146 (60%)</td>
<td>6 (40%)</td>
<td>15/60 (25%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Rapezzi C et al, Circulation 2009:120:1203-1212
Paradigm shift:

- From low QRS voltage to QRS voltage / LV wall thickness
QRS score (mV) vs Indexed LV mass (g/m²)

- **HCM**
- **Hypert.**
- **AMYLOID**

Quarta CC et al, Eur Heart J 2010 (abstr)
Suggested criterion: SOKOLOW INDEX

CSA*

*CSA = cross-sectional area of LV wall

\[ \text{CSA} = \frac{\pi((LVEDD/20) + \text{mean LV thickness}/10)^2 - \pi(LVEDD/20)^2}{\text{BSA}} \]
A simple voltage/mass index improves the diagnosis of amyloidotic cardiomyopathy

An electrocardiographic and echocardiographic study of 767 patients with increased left ventricular wall thickness due to different causes

767 patients:

- 324 amyloidotic CMP
  - 191 AL
  - 88 ATTRm
  - 45 ATTRwt
- 173 sarcomeric HCM
- 270 hypertensive heart disease

First cohort:
469 patients:
- 262 AMI (161 AL)
- 106 HCM
- 101 HHD

Validation cohort:
298 patients:
- 62 AMI (30 AL)
- 67 HCM
- 169 HHD

Rapezzi et al. Bologna & Pavia, submitted
Total QRS/LVWT/h^{2.7} \leq 36
Diagnostic performance of ECG, ECHO and combined ECG/ECHO for the identification of TTR-related cardiac amyloidosis among patients with echocardiographic increased LV wall thickness

<table>
<thead>
<tr>
<th></th>
<th>Symmetric LV hypertrophy</th>
<th>LQRSV</th>
<th>Carroll’s Index *</th>
<th>Total QRS/LVWT/h2.7 ≤ 36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTR vs other (HCM+HHD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91%</td>
<td>28%</td>
<td>53%</td>
<td>72%</td>
</tr>
<tr>
<td>Specificity</td>
<td>27%</td>
<td>93%</td>
<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>44%</td>
<td>76%</td>
<td>74%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>TTR vs HCM</strong></td>
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<td>96%</td>
<td>71%</td>
<td>85%</td>
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<tr>
<td>Diagnostic accuracy</td>
<td>75%</td>
<td>64%</td>
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<td>80%</td>
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Rapezzi et al. Bologna & Pavia, submitted
Towards the definite diagnosis of TTR-CM

- Histology +/- proteomic +/- DNA +/- immunohistochemistry
- "bone tracers" scintigraphy
- CMR
- Clinical evaluation, ECG, Echocardiogram
Patterns of amyloid myocardial infiltration
Role of Cardiac Magnetic Resonance Imaging in the Detection of Cardiac Amyloidosis

Imran S. Syed, MD,* James F. Glockner, MD, PhD,† DaLi Feng, MD,*
Philip A. Araoz, MD,† Matthew W. Martinez, MD,*† William D. Edwards, MD,‡
Morie A. Gertz, MD,§ Angela Dispenzieri, MD,§ Jae K. Oh, MD,*
Diego Bellavia, MD, PhD,* A. Jamil Tajik, MD,|| Martha Grogan, MD*

Rochester, Minnesota; and Scottsdale, Arizona
Amyloid GAD kinetic on MRI

Characteristic GAD kinetic:

- High avidity for GSD of amyloidotic myocardium
- At a short TI large part of myocardium goes to “null point” earlier than the LV blood pool, so myocardium gets black earlier than blood
Equilibrium-Contrast CMR

Key features:
- A bolus of Gadolinium followed by continuous infusion to achieve blood:myocardial contrast equilibrium
- A blood test to measure blood contrast volume of distribution (1-hematocrit)
- T1 measurement before and after contrast equilibrium to calculate changes in tissue signal

Precise estimation of myocardial contrast volume of distribution

Quantification of Extracellular Matrix Expansion by CMR in Infiltrative Heart Disease

François-Pierre Mongeon, MD, SM,*† Michael Jerosch-Herold, PhD,‡
Otávio Rizzi Coelho-Filho, MD, MPH,*§ Ron Blankstein, MD,* Rodney H. Falk, MD,*
Raymond Y. Kwong, MD, MPH*

Boston, Massachusetts; Montreal, Quebec, Canada; and Campinas, São Paulo, Brazil
J Am Coll Cardiol Img 2012

Kruskal-Wallis p < 0.0001

MECVF

p = 0.13

p = 0.0003

p < 0.0001

p = 0.0001

BX Clinical Non AMYL CMP Volunteer

Cardiac Amyloidosis
Noncontrast T1 Mapping for the Diagnosis of Cardiac Amyloidosis

Karamitsos et al. (J Am Coll Cardiol Img 2013;6:488–97)

![Graph showing T1 time distributions for different groups with statistical significance](image-url)

- Normal: T1 Time (ms) range
- Amyloid, No Cardiac Involvement: T1 Time (ms) range
- Amyloid, Possible Cardiac Involvement: T1 Time (ms) range
- Amyloid, Definite Cardiac Involvement: T1 Time (ms) range
- Aortic Stenosis: T1 Time (ms) range

Statistical Significance:
- P = 0.3
- P < 0.001
- P < 0.001
- P = 0.003
R. Magritte: Les Amants
Towards the definite diagnosis of TTR-CM

Clinical evaluation, ECG, Echocardiogram

Histology +/- proteomic +/- DNA +/- immunohistochemistry

«bone tracers» scintigraphy

CMR
TcDPD Scintigraphy

A

B

C

D

Perugini et al, J Am Coll Cardiol 2005
Paradox!
$^{99m}$Tc-PYP uptake.
Total-body $^{99m}$Tc-DPD scintigraphy

**Visual score** of heart retention of $^{99m}$Tc-DPD:

- **Visual score 0** = absent myocardial uptake, normal bone uptake;
- **Visual score 1** = mild myocardial uptake, less than bone uptake;
- **Visual score 2** = moderate myocardial uptake, attenuated bone uptake;
- **Visual score 3** = strong myocardial uptake, very attenuated bone uptake.
Tc DPD myocardial uptake among AL and wtTTR patients

- Visual score 0: 43 AL
- Visual score 0: 10 TTRwt
- Visual score 1: 5 AL
- Visual score 1: 14 TTRwt
- Visual score 2: 7 AL
- Visual score 2: 14 TTRwt
- Visual score 3: 55 TTRwt
Early Diagnosis of TTR-Related Cardiac Amyloidosis in asymptomatic carriers

Rapezzi et al, JACC Imaging 2011
Senile Systemic Amyloidosis

Quarta C et al, J Am Coll Cardiol Img, 2012
Heart/Whole Body retention

SSA

ATTR

Non amyl CMP

Controls

p < 0.001

N.S.

p < 0.001

N.S.

p < 0.001

Quarta C et al, J Am Coll Cardiol Img, 2012
Towards the definite diagnosis of TTR-CM

- Clinical evaluation, ECG, Echocardiogram
- «bone tracers» scintigraphy
- Histology +/- proteomic +/- DNA +/- immunohistochemistry
- CMR
Diagnosis of «amyloidosis»

1. Demonstration of amyloid deposition in a tissue

2. Definition of the type of precursor protein
Limitations and pitfalls in tissue diagnosis of cardiac amyloidosis

- Low sensitivity of extracardiac tissue biopsy
  - AL $\geq 80\%$
  - TTR 30\% -50\%

- Low specificity of immunohistochemistry (anti-light chains and anti-TTR positivity in the same specimen)

- MGUS
What is the diagnostic standard?
What is the diagnostic standard?
Survival (%) vs wtTTR

- BO: 63 pts, 78 yrs, NYHA III-IV, 30%
- TRACS: 18 pts, 76 yrs, NYHA III-IV, 22%
- Pinney et al.: 99 pts, 73 yrs, NYHA III-IV, 30%
Expanding the Diagnosis of wtTTR

• Unexpected myocardial uptake during «bone» scintigraphies

• History of CTS in >65 year-old men

• Paradoxical «low flow low gradient» AO stenosis in the elderly

• HFpEF in the elderly
DPD Scintigraphies for Oncologic / Rheumathologic reasons (n = 12,300)

MYOCARDIAL UPTAKE (n = 45)

Cardiologic work-up

- NO (n = 31)
- YES (n = 14)

Echo confirmation of CMP

- NO (n = 0)
- YES (n = 14)

Endomyocardial biopsy (n = 7)

- Positive (TTR) (n = 7)

wt = 6
m = 1

Longhi S et al JACC Img May 2014
Prevalence of incidental myocardial uptake of 99 mTc-DPD

Longhi S et al JACC Img May 2014
AVA 1.08 cm²
ΔPm 14 mmHg
# Imaging and biomarkers of Cardiac Amyloidosis

<table>
<thead>
<tr>
<th>Phase of work-up</th>
<th>ECHO</th>
<th>MRI</th>
<th>Scintigraphy</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suspicion</strong></td>
<td>+++</td>
<td>++</td>
<td>+ (TTR)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Definite diagnosis</strong></td>
<td>+</td>
<td>++</td>
<td>+++(TTR)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Etiologic diagnosis</strong></td>
<td>±</td>
<td>+?</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Early diagnosis</strong></td>
<td>+</td>
<td>?</td>
<td>++ (TTR)</td>
<td>+?</td>
</tr>
<tr>
<td><strong>Functional evaluation</strong></td>
<td>+++</td>
<td>++</td>
<td>+(MIBG)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Prognostic stratification</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Amyloidotic burden</strong></td>
<td>-</td>
<td>+++? (ECV)</td>
<td>+?</td>
<td>-</td>
</tr>
<tr>
<td><strong>Response to therapy</strong></td>
<td>±</td>
<td>? (T1/ECV)</td>
<td>?</td>
<td>+++</td>
</tr>
</tbody>
</table>

- BNP: Brain Natriuretic Peptide