How to Use Nuclear Cardiology for Early Diagnosis ofATTR-CM

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Agenda

- Which Pts Should Undergo PYP Scintigraphy?
- Significance of Carpal Tunnel Syndrome
- Late Iodine Enhancement & ECV in TAVI/RFCA Planning CT
- Natural History of ATTR-CM Detected by Bone Scintigraphy
Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

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Diagnostic Algorithm for Cardiac Amyloidosis

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

99mTc-DPD/PYP/HMIDP Scintigraphy with SPECT & Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Scintigraphy grade 0
Haematologic tests -

AL/ATTR cardiac amyloidosis unlikely

If suspicion persists consider CMR followed by biopsy

Scintigraphy grade 1-3
Haematologic tests -

Grade 2-3
Cardiac ATTR amyloidosis

TTR genetic testing
ATTRwt / ATTRv

Scintigraphy grade 0
Haematologic tests +

AL amyloidosis?

Histological confirmation (cardiac/extracardiac) to diagnose

CMR negative

Amyloidosis unlikely

CMR + or inconclusive

Histological confirmation (cardiac/extracardiac) to subtype

Cardiac amyloidosis
ESC Myocardial WG position paper


**SUSPECT**

Screen if

Left ventricle wall thickness ≥ 12 mm

&

≥ 1 Red Flag or Clinical Scenario

**DIAGNOSIS**

Diagnostic criteria

<table>
<thead>
<tr>
<th>Invasive (all types)</th>
<th>Non-Invasive (only for ATTR)</th>
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<tbody>
<tr>
<td>Cardiac biopsy positive for amyloid</td>
<td>Grade 2 or 3 cardiac uptake at diphosphonate Scintigraphy</td>
</tr>
<tr>
<td>or</td>
<td>+ Negative serum free light chains &amp; negative serum and urine immunofixation (SPEI &amp; UPIE)</td>
</tr>
<tr>
<td>Extracardiac biopsy positive for amyloid</td>
<td>+ Echocardiographic/CMR criteria</td>
</tr>
<tr>
<td>Echocardiographic/CMR criteria</td>
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</tr>
</tbody>
</table>

Diagnostic algorithm

99m-Tc-DPD/PYP/HMDP Scintigraphy with SPECT & Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to CMR and/or biopsy according to results

**TREATMENT**

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.
Screening for Cardiac Amyloidosis

Left Ventricular Wall Thickness $\geq 12$ mm

+ $\geq 1$ of

- Heart failure in $\geq 65$ years
- Aortic stenosis in $\geq 65$ years
- Hypotension or normotensive if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history

Diagnostic Algorithm for Cardiac Amyloidosis

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

\[ ^{99m} \text{Tc-DPD/PYP/HMDP Scintigraphy with SPECT} \quad & \quad \text{Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)} \]

<table>
<thead>
<tr>
<th>Scintigraphy grade 0</th>
<th>Scintigraphy grade 1-3</th>
</tr>
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<tbody>
<tr>
<td>Haematologic tests -</td>
<td>Haematologic tests -</td>
</tr>
</tbody>
</table>

- Scintigraphy grade 0: Haematologic tests -
  - AL/ATTR cardiac amyloidosis unlikely
    - If suspicion persists consider CMR followed by biopsy

- Scintigraphy grade 1: Haematologic tests -
  - Cardiac ATTR amyloidosis
    - TTR genetic testing

- Scintigraphy grade 2-3: Haematologic tests -
  - Cardiac ATTR amyloidosis
    - Cardiac/extra cardiac
      - Grade 1
        - Histological confirmation
          - Cardiac/extra cardiac
            - AL amyloidosis?
              - CMR negative
                - Amyloidosis unlikely
              - CMR + or inconclusive
                - Histological confirmation
                  - (cardiac/extra cardiac)
                    - to subtype

Pts Flow Chart for PYP Positivity Criteria

441 patients underwent $^{99m}$Tc-PYP scintigraphy at Kumamoto University Hospital between January 2012 and December 2018

228 patients aged < 70 years

8 patients with no electrocardiographic data available
14 patients with a paced ventricular rhythm
10 patients with no laboratory examination data available

181 patients with suspected cardiac amyloidosis in the analysis

Clinical Diagnoses in the 99m Tc-PYP Negative

(n=111)

Unclassified, 28 (25%)
Hypertrophic cardiomyopathy, 28 (25%)
Aortic stenosis, 23 (21%)
AL amyloidosis, 7 (6.3%)
Dilated cardiomyopathy, 6 (5.4%)
Hypertensive heart disease, 5 (4.5%)
Sarcoidosis, 4 (3.6%)
Connective tissue disease, 4 (3.6%)
Inflammatory amyloidosis, 2 (1.8%)
Aortic regurgitation or mitral regurgitation, 2 (1.8%)
ATTRm, 1 (0.9%)
Old myocardial infarction, 1 (0.9%)

ROC Curve for 99m Tc-PYP Positivity

A. hs-cTnT

Best Cut-Off Value: 0.0308 ng/ml (sensitivity: 0.80 specificity: 0.59)

AUC, 0.730
95% CI, 0.658–0.802,
\(P<0.001\)

B. LV posterior wall thickness

Best Cut-Off Value: 13.6mm (sensitivity: 0.70 specificity: 0.87)

AUC, 0.859
95% CI, 0.803–0.915,
\(P<0.001\)

Using hs-cTnT ≥0.0308 ng/mL, LV posterior wall thickness ≥13.6 mm, and wide QRS (QRS ≥120 ms), we created a new index to predict 99mTc-PYP positivity, named the Kumamoto Criteria. We calculated the index by adding 1 point for each factor.

The proportion of pts with 99m Tc-PYP positivity increased as the number of points increased.

<table>
<thead>
<tr>
<th>Number of variables present</th>
<th>99mTc-PYP scintigraphy (%)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>13%</td>
</tr>
<tr>
<td>1</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>96%</td>
</tr>
</tbody>
</table>

Number of patients of $^{99m}$Tc-PYP positivity / total number of patients

7/55 12/57 29/46 22/23

New diagnostic strategy for ATTR-CM

Suspected cardiac amyloidosis

Kumamoto Criteria

- hs-cTnT ≥ 0.0308 ng/mL
- LV posterior wall thickness ≥ 13.6 mm
- Wide QRS (QRS ≥ 120 ms)

Score 0
- Consider other diagnoses, and performing $^{99m}$Tc-PYP scintigraphy based on other factors (e.g. known TTR mutation and carpal tunnel syndrome)

Score 1
- $^{99m}$Tc-PYP scintigraphy is helpful

Score 2
- If negative, rule out other type of cardiac amyloidosis

Score 3

Utility of Kumamoto Criteria in Diagnosing ATTR-CM in Real-World Practice


438 patients aged ≥70 years who simultaneously underwent electrocardiography, echocardiography and high-sensitivity cardiac troponin T analysis from April 2019 to October 2019

368 patients evaluated score of Kumamoto criteria

- Acute coronary syndrome (n=16)
- Decompensated heart failure (n=8)
- eGFR<15 mL/min/1.73 m² (n=20)
- Ventricular pacing rhythm (n=26)

Score: 0 (n=246)
Score: 1 (n=86)
Score: 2 (n=26)
Score: 3 (n=10)

Low score: 90%

High score: 10%
Percentage of ATTR-CM with Each Score on the Kumamoto Criteria


- LIE on CT (-): 1
- PYP Scintigraphy (-): 3
- Amyloid Detection on EMB (-): 1
- ATTR-CM s/o: 1

Score 0: 0.4% (245)
Score 1: 2% (84)
Score 2: 46% (14)
Score 3: 90% (9)
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Don’t Miss History of Carpal Tunnel Release

Ope. Scar of Bil. CTR

own experiments; Department of Cardiovascular Medicine, Kumamoto University
Important Red-Flags of ATTR-CM: Carpal Tunnel Syndrome

Complicated by CTS in 45% of ATTRwt-CM
CTS & Amyloidosis, HF, and Adverse CV Outcomes

A  Cumulative Incidence of Amyloidosis

B  Cumulative Incidence of Heart Failure

C  Cumulative Incidence of Death

(J Am Coll Cardiol. 2019;74:15-23)
Case: Early Dx of ATTRwt-CM by Hx of CTS

Male 64 y.o.

【PI】
➢ Bil. finger numbness at 57y.o.
➢ Dx of CTS at 60y.o.
➢ CTR at 62y.o.: Amyloid Positive in synovial membrane (ATTRwt based on TTR mutation (-))
➢ After that, periodical f/u by UCG, biomarkers, PYP

【PH】bil. CTS, rt. rotator cuff injury, lumbar canal stenosis

【FH】Amyloidosis (-)

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Synovial Membrane Biopsy

Hematoxylin-Eosin Stain

Congo Red Statin

Immunohistochemical Stain → TTR positive

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Electrocardiogram

own experiments; Department of Cardiovascular Medicine, Kumamoto University
## Laboratory Data

<table>
<thead>
<tr>
<th>Hemogram</th>
<th>Serum Chemistry</th>
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<tbody>
<tr>
<td>WBC 8700/μl</td>
<td>TP 7.4 mg/dL</td>
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<tr>
<td>RBC 4.99×10^6/μl</td>
<td>Alb 4.5 mg/dL</td>
</tr>
<tr>
<td>Hb 15.7 g/dL</td>
<td>T-bil 0.4 mg/dL</td>
</tr>
<tr>
<td>Ht 46.6 %</td>
<td>BUN 20.7 mg/dl</td>
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<tr>
<td>Plt 31.0×10^4/μl</td>
<td>Crea 1.10 mg/dl</td>
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<tr>
<td></td>
<td>Na 139 mEq/L</td>
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<tr>
<td></td>
<td>K 4.7 mEq/L</td>
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<tr>
<td></td>
<td>Cl 107 mEq/L</td>
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<tr>
<td></td>
<td>LDH 180 IU/l</td>
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<td>AST 17 IU/l</td>
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<td>ALT 13 IU/l</td>
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<td>CK 91 IU/l</td>
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<td>CKMB 13 IU/l</td>
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<td>CRP 0.06 mg/dL</td>
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<tr>
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<td>BNP 47.1 pg/mL</td>
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<tr>
<td></td>
<td>Bence-Jones Protein: negative</td>
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<tr>
<td></td>
<td>Free light chain κ 25.1 mg/L</td>
</tr>
<tr>
<td></td>
<td>λ 17.8 mg/L</td>
</tr>
<tr>
<td></td>
<td>κ / λ ratio 1.41</td>
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<tr>
<td></td>
<td>HbA1c 5.8%</td>
</tr>
</tbody>
</table>

own experiments; Department of Cardiovascular Medicine, Kumamoto University
Serial Change of UCG Findings

2017/6/21

IVS 12.3
PW 11.4
E/A 0.8
e' 4.3
E/e' 12.1

2018/6/21

IVS 12.3
PW 12.2
E/A 0.5
e' 2.9
E/e' 11.2

2019/4/22

IVS 13.9
PW 13.9
E/A 0.6
e' 3.5
E/e' 14.8

own experiments; Department of Cardiovascular Medicine, Kumamoto University
### Serial Change of PYP Findings

<table>
<thead>
<tr>
<th>Date</th>
<th>Value</th>
<th>Date</th>
<th>Value</th>
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<tbody>
<tr>
<td>2017/6/20</td>
<td>1.15</td>
<td>2018/4/20</td>
<td>1.26</td>
</tr>
<tr>
<td>2017/6/20</td>
<td>1.15</td>
<td>2019/4/22</td>
<td>1.33</td>
</tr>
</tbody>
</table>

own experiments; Department of Cardiovascular Medicine, Kumamoto University
Serial Change of CMR Findings

own experiments; Department of Cardiovascular Medicine, Kumamoto University
Endomyocardial Biopsy

Hematoxylin-Eosin Stain

Congo Red Stain

Non AA Amyloid: positive

own experiments; Department of Cardiovascular Medicine, Kumamoto University
Regarding the following sentences, which is the “wrong” description?

a. In the European statement, grade 2-3 uptake on PYP scintigraphy with SPECT is gold standard for thr ATTR-CM.

b. TTR amyloid deposition can be observed in synovial membrane exenterated during carpal tunnel release.

c. The combination of wide QRS, thicker LVPW, and elevated hs-TnT ing CT is associated with positive PYP scintigraphy.

d. AL amyloidosis can be ruled out when PYP scintigraphy positive.
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Diagnosis of ATTRwt-CM Complicated by AS

- ATTRwt-CM in 6% of Elderly (>65y.o.) Aortic Stenosis Pts
- ATTRwt-CM in 16% of Pts Undergoing TAVI
- Poor Prognosis in these pts

(Circ Cardiovasc Imaging. 2016 ;9:e005066.)
(Eur Heart J. 2017;38:2879–2887)
Originally for the assessment of the aortic valve complex and access routes

- **CT Scanner**: 320-detector row CT scanner (Aquilion ONE/Genesis Edition, Canon)
- **Contrast Media Volume**: 540 mgI/kg
- **Protocol**: Cardiac CT + Aortic CT + Myocardial Iodine Enhance
LIE & ECV on TAVI Planning CT can Detect ATTRwt-CM

Global ECV = 50%
※ ECV normal range = 25-28%

Dx as ATTRwt-CM by Positive in PYP Scintigraphy

99mTc-Pyrophosphate (PYP) Scintigraphy

(visual grade 3)

Extracellular Volume (ECV) by Delayed-Enhancement CT

ECV = (ΔHUm/ΔHUb)·(1 − Hct), where ΔHUm is the change in myocardial CT attenuation, in Hounsfield units (HU), ΔHUb is the change in CT attenuation of the blood, and Hct is the hematocrit.

Figure adapted from Martin Ugander (SCMR 2014)
Incidental Dx of ATTRwt-CM by RFCA-Planning CT

Male 60’s

【PI】
➢ Dx of AFL (atrial flutter), Hypertrophic CM in 2017
➢ Heart Failure Deterioration in 2019
➢ Refer to our department for AFL RFCA Request

【PH】No Hx of CTS

【Labo.】BNP: 460.5 pg/ml, hs-cTnT: 0.0676 ng/ml, Cr: 1.29 mg/dl, eGFR: 45 ml/min

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own experiments; Department of Cardiovascular Medicine, Kumamoto University
UCG Findings

IVS/PW: 14.5/15.3
Dd/Ds: 41.1/32.8   EF: 55%

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AFL RFCA-Planning CT

Diffuse LIE mainly detected in endomyocardial zone

Elevated ECV Value by 54%

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PYP Scintigraphy

PYP: Grade 3
H/CL: 2.05

CMR

Contrast MRI: diffuse LGE
Native T1: 1451ms (normal 1250ms)
ECV: 69%

TTR positive in Endomyocardial Biopsy

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Incidental Dx of ATTRwt-CM by Bone Scintigraphy

Male 80’s

【PI】

➢ Operation due to Prostate Ca. at 70’s
➢ Bone Scintigraphy (99mTc-HMDP) for Bone Meta Screening in 2013
➢ Consult to Cardiologist for LV Hypertrophy in 2013=>Start f/u
➢ Consult again to Cardiologist for enhanced uptake on Bone Scintigraphy

【PH】Hx of CTR due to rt. CTS

99mTc-HMDP Scintigraphy

2013/6/25

H/CL=1.70

2019/9/9

H/CL=2.32

2013/7/2

HR:71 PQ:158ms, QRS:94msec

2019/9/9

HR:75 PQ:152ms, QRS:94msec

Serial UCG Findings

2013/5/14

IVS: 9.8
PW: 9.7

EF: 63.2%

2015/9/30

IVS: 13.2
PW: 10.5

EF: 66.8%

2019/9/4

IVS: 13.0
PW: 12.7

EF: 60.8%

Serial Change of Biomarkers

Biopsy

Non AA Amyloid: positive

Hematoxylin-Eosin Stain

Congo Red Statin

Sincere Appreciation for Your Attention!