Amylose cardiaque et scintigraphie

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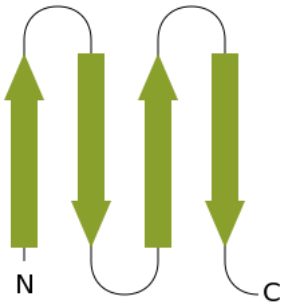
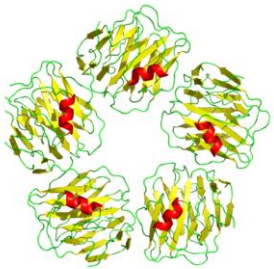
Physiopathologie

Dépôt extracellulaire de feuillets béta-amyloïde

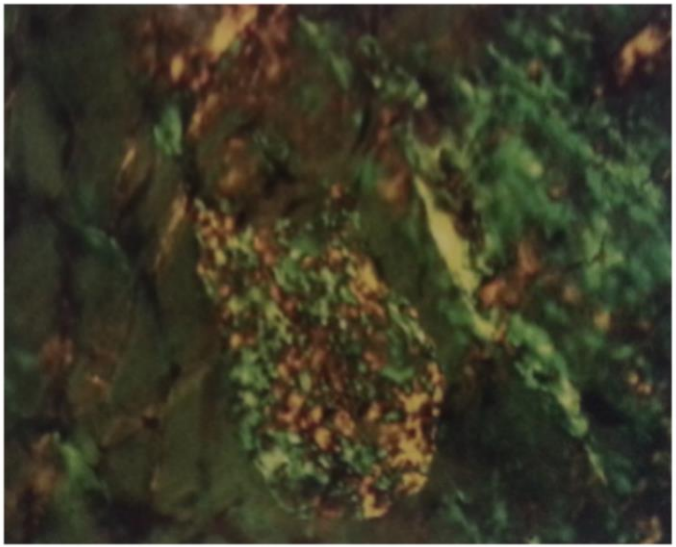
Liés par le P-component : protéine en forme de pentagone calcium dépendante





Physiopathologie

- Colorés par Rouge Congo : biréfringence jaune-vert en lumière polarisée
- Spectroscopie de masse : gold standard dans la caractérisation du type



Physiopathologie

Infiltration extracellulaire des tissus

- Cardiopathie hypertrophique restrictive
- ↘ relaxation diastolique : ↘ volume télédiastolique
- Troubles de la conduction et du rythme
- Paralysie atriale : thrombus
- Insuffisance cardiaque droite : facteur de gravité

Physiopathologie

Types d'amylose :

- AA : inflammatoire
- AL : chaîne légère d'immunoglobuline
- ATTR
  - ATTRm : mutation
  - ATTRwt : « amylose sénile »

Physiopathologie

AL

- Prévalence : 6-10 cas par million d'habitants
- Myélome λ ++
- Concerne 20% des myélomes symptomatiques
- 60-80% d'atteinte cardiaque

- Médiane de survie : 5,4 mois

Gertz, M. A., Benson, M. D., Dyck, P. J., Grogan, M., Coelho, T., Cruz, M., … Merlini, G. (2015). Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. Journal of the American College of Cardiology, 66(21), 2451–2466. doi:10.1016/j.jacc.2015.09.075

Physiopathologie

- Transthyrétine
  - Produite par le foie +++
  - Transporte les hormones thyroïdiennes et la *retinol-binding protein*

ATTRm

- Mutation du gène de la Transthyrétine
- > 110 mutations
- Portugal ++, Japon et Suède
- Val30Met : la plus fréquente

Adams, D., Lozeron, P., Theaudin, M., Mincheva, Z., Cauquil, C., … Adam, C. (2012). Regional difference and similarity of familial amyloidosis with polyneuropathy in France. Amyloid, 19(sup1), 61–64.

Physiopathologie

- Transthyrétine
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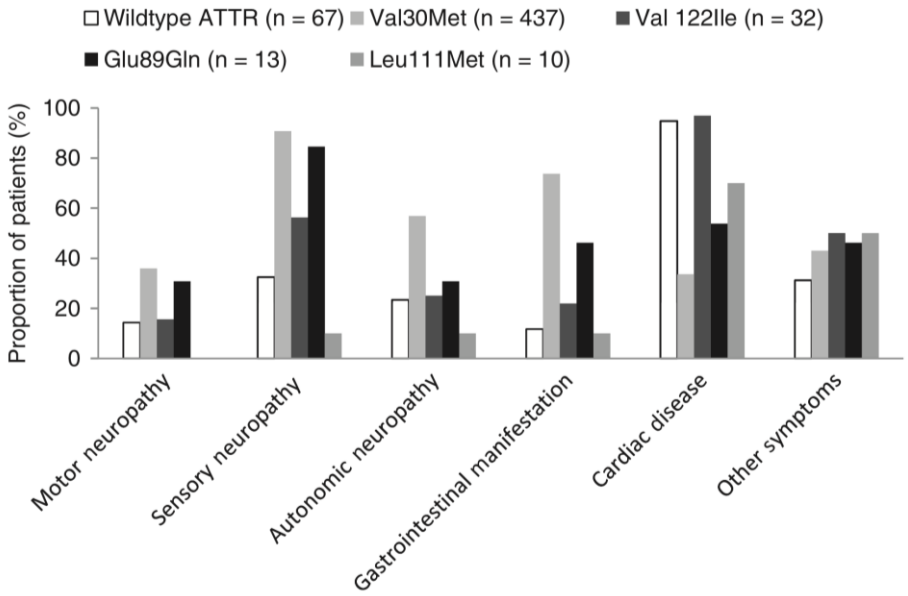
ATTRm

- Mutation du gène de la Transthyrétine
- > 110 mutations
- Portugal ++, Japon et Suède
- Val30Met : la plus fréquente

- Val122Ile (Afrique et Amérique latine) & Leu111Met : atteinte cardiaque
- ¾ : homme
- Toute mutation confondue : 42% d'atteinte cardiaque



Coelho T, Maurer MS, Suhr OB. THAOS: The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin 2013;29:63–76.

Physiopathologie

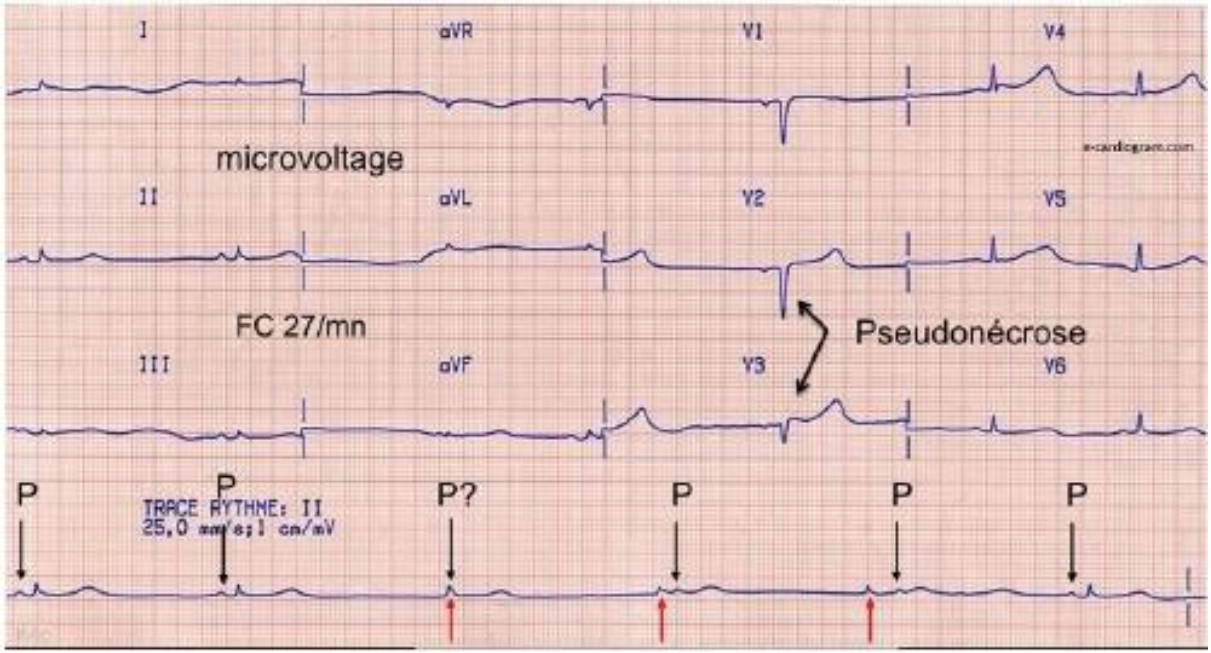
ATTRwt

- Wild-Type amylose = amylose sénile = SSA
- 90%-99% chez l'homme > 60 ans
- Médiane de survie : 60 mois
- 17% des arrêts cardiaques à FEVG conservée

- Associée à 50% de syndrome du canal carpien
- Canal carpien idiopathique : 34% de dépôts amyloïdes
- Symptôme précoce de l'ATTRwt ?

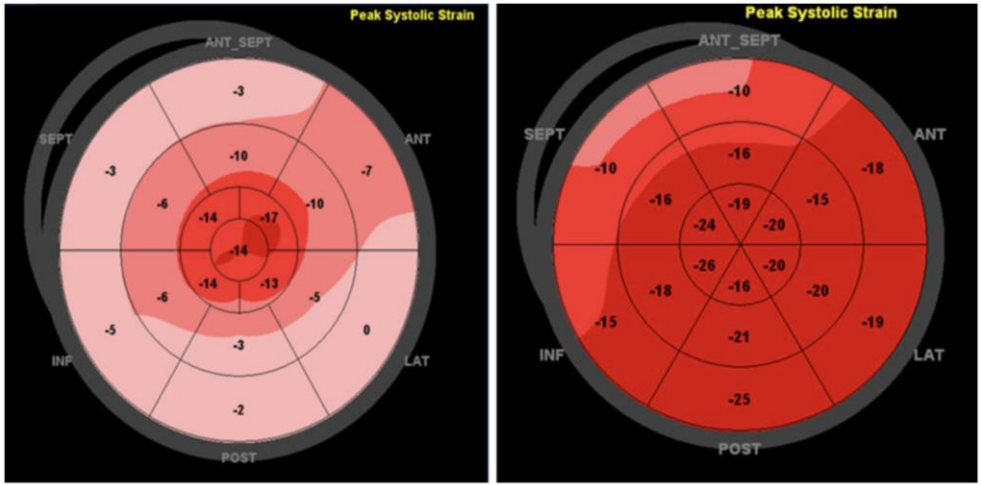
Sekijima Y, Uchiyama S, Tojo K, et al. High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: a common cause of carpal tunnel syndrome in the elderly. Hum Pathol 2011;42: 1785–91.

ECG


I
aVR
V1
V4
microvoltage
II
aVL
V2
V5
FC 27/mn
Pseudonécrose
III
aVF
V3
V6
P
P
TRACE RYTHME: II
25,0 mm/s; 1 cm/mV
P?
P
P
P

Echographie

- Epaississement concentrique des parois – aspect brillant, granité
- Strain : raccourcissement longitudinal 93% Se & 82% Sp



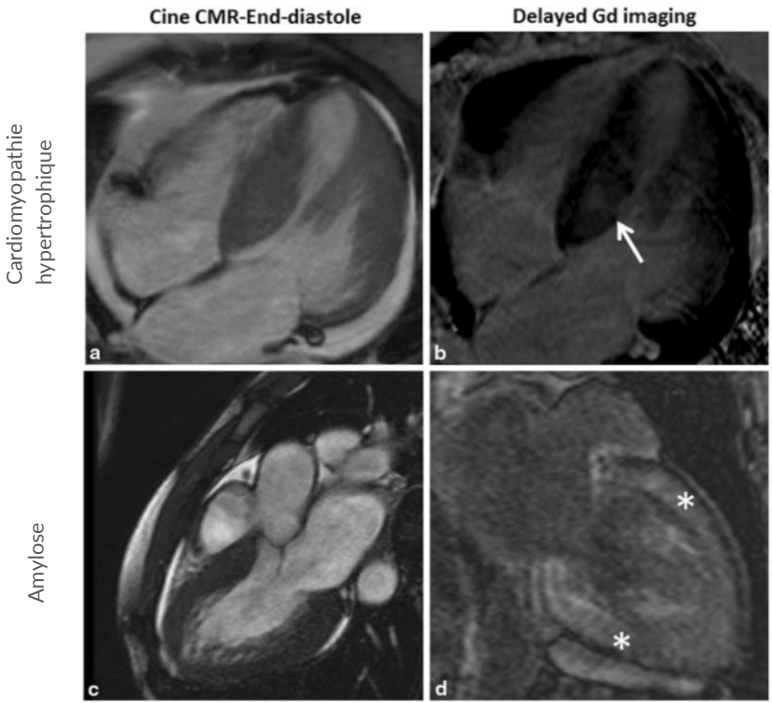
AlJaroudi, W. A., Desai, M. Y., Tang, W. H. W., Phelan, D., Cerqueira, M. D., & Jaber, W. A. (2013). Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: State of the art review and focus on emerging nuclear techniques. Journal of Nuclear Cardiology, 21(2), 271–283. doi:10.1007/s12350-013-9800-5

IRM

- Réhaussement Gd tardif des parois
- Hypertrophie
- Impossibilité de régler le T1

- Se : 80%
  Sp : 94%

- Caractérisation des types d'amylose difficile



Dungu JN, Valencia O, Pinney JH, et al. CMRbased differentiation of AL and ATTR cardiac amyloidosis. J Am Coll Cardiol Img 2014;7:133–42.

^{123}I-MIBG[49]	Sympathetic cardiac innervation	Decreased H/M ratio and increased washout rate reflect sympathetic cardiac denervation	No
^{123}I-BMIPP[50]	Fatty acid Metabolism	Very limited role	No
^{99m}Tc(V)-DMSA[51]	Metabolism and avid uptake	Limited role due to physiological uptake in the blood pool	No
^{201}Tl redistribution[52]	Perfusion	Higher washout rate associated with amyloidosis Limited data; non-specific	No
Blood pool ventriculography[51]	Assesses peak filling rate and time to peak filling	Can detect features of restrictive physiology but not specific to cardiac amyloidosis	No
^{99m}Tc-Aprotinin[51]	Amyloid deposit (*antiproteases*)	5/5 biopsy proven cases had + tracer uptake	No
^{99m}Tc-DPD[53,54,57]	Amyloid deposit (*high calcium content*)	More useful for extra-abdominal uptake 15/15 + uptake in ATTR vs 0/10 in AL Another study: 1/3 of patients with AL had mild uptake Has Prognostic value Not Available in the USA	Yes
^{99m}Tc-MDP[55]	Amyloid deposit (*high calcium content*)	Mixed results likely secondary to combining patients with AL and ATTR	Not well known
^{99m}Tc-PYP[56]	Amyloid deposit (*high calcium content*)	SN 97%, SP 100%, AUC 0.992	Yes
^{67}Ga-citrate[58]	Unknown mechanism for deposition	Limited case reports. Less uptake than ^{99m}Tc-PYP. No role in cardiac amyloidosis	Not known
^{111}In antimyosin[50]	Binds to areas of myocardial necrosis	7/7 patients had positive uptake Non-specific Only 1 case report	No
^{123}I-Serum amyloid protein[59]	Labels the amyloid pool	Not FDA approved. Only used in 2 European centers Not suitable for cardiac amyloidosis due to movement, blood pool content and lack of fenestrated endothelium in the myocardium Detects visceral uptake in AL but not ATTR	No
^{11}C-BF-227[66]	Binds to aggregated amyloid fibrils	First PET tracer to be used One case report: correctly identified ATTR deposition in the heart	Not known
^{11}C-PIB[67]	Binds to amyloid fibrils of any type	10/10 patients (ATTR and AL) had uptake and 0/5 volunteers had uptake	No
^{18}F florbetapir[68]	Binds to amyloid fibrils of any type	5/5 patients (3 ATTR, 2 AL) had decreased myocardial washout. 0/2 healthy controls had uptake	No

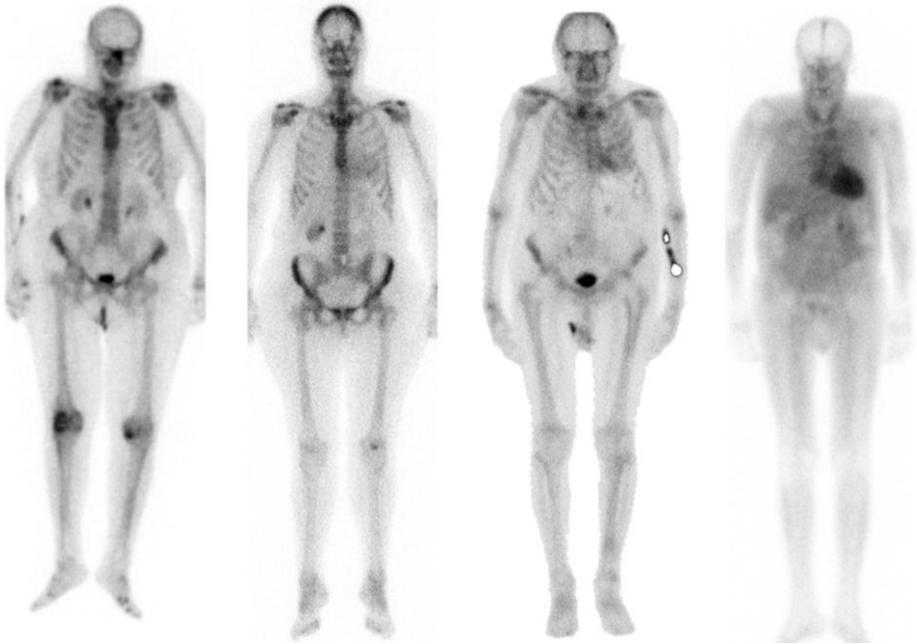
AlJaroudi, W. A., Desai, M. Y., Tang, W. H. W., Phelan, D., Cerqueira, M. D., & Jaber, W. A. (2013). Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: State of the art review and focus on emerging nuclear techniques. Journal of Nuclear Cardiology, 21(2), 271–283. doi:10.1007/s12350-013-9800-5

Scintigraphie osseuse

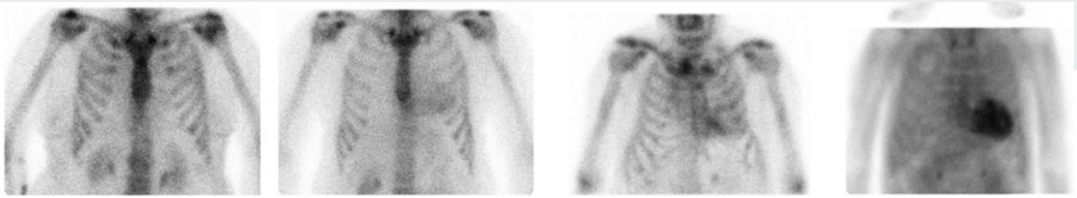
- 2 acquisitions
  - Précoce : 5-10min
  - Tardive : 3h
- Caractérisation du type AL vs ATTR
- Pas d'évènement ischémique aigu
- Diagnostic précoce avant signe échographique

Rapezzi, C., Quarta, C. C., Guidalotti, P. L., Pettinato, C., Fanti, S., Leone, O., … Salvi, F. (2011). Role of 99mTc-DPD Scintigraphy in Diagnosis and Prognosis of Hereditary Transthyretin-Related Cardiac Amyloidosis. JACC: Cardiovascular Imaging, 4(6), 659–670. doi:10.1016/j.jcmg.2011.03.016

Echelle visuelle



Score 0 Score 1 Score 2 Score 3



Performance diagnostique

ATTR tout patient

- Score ≥ 1 : Se > 99% Sp 86%
- Score ≥ 2 : Se 91% Sp 97%

ATTR avec biopsie myocardique

- Score ≥ 1 : Se > 99% Sp 68%
- Score ≥ 2 : Se 91% Sp 87%
- Score ≥ 2 ET absence d'Ig monoclonale sérique/urinaire et FreeLite chain urinaire : Sp 100%

1217 patients, 374 avec biopsie myocardique, multicentrique
99mTc-DPD / 99mTc-PYP / 99mTc-HMDP

Gillmore, J. D., Maurer, M. S., Falk, R. H., Merlini, G., Damy, T., Dispenzieri, A., … Hawkins, P. N. (2016). Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis CLINICAL PERSPECTIVE. Circulation, 133(24), 2404–2412. doi:10.1161/circulationaha.116.021612

Performance diagnostique

Méta analyse pour un Score ≥2 :

-> Pas de différence significative entre les traceurs

99mTc-DPD	**Se : 94.6%**	Sp : 88.4%
99mTc-HMDP	Se : 85.7%	**Sp : 97.5%**

Globale

- Se : 92.2%
- Sp : 95,4%

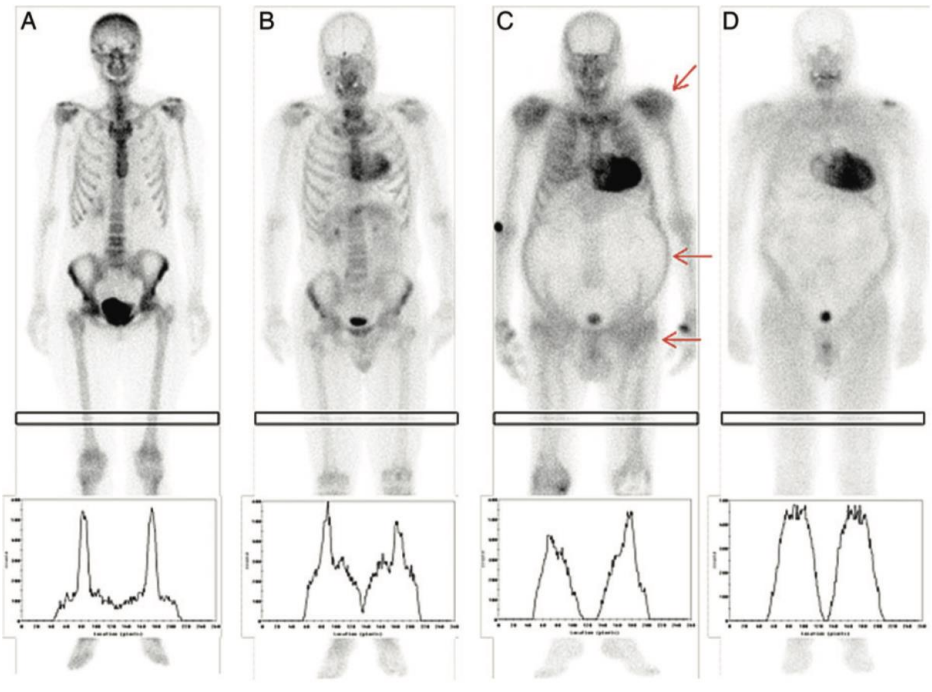
6 études, 529 patients avec biopsie myocardique

Treglia, G., Glaudemans, A. W. J. M., Bertagna, F., Hazenberg, B. P. C., Erba, P. A., Giubbini, R., … Slart, R. H. J. A. (2018). Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. European Journal of Nuclear Medicine and Molecular Imaging. doi:10.1007/s00259-018-4013-4

Score visuel

- Captation des tissus mous

ATTRwt et V122I



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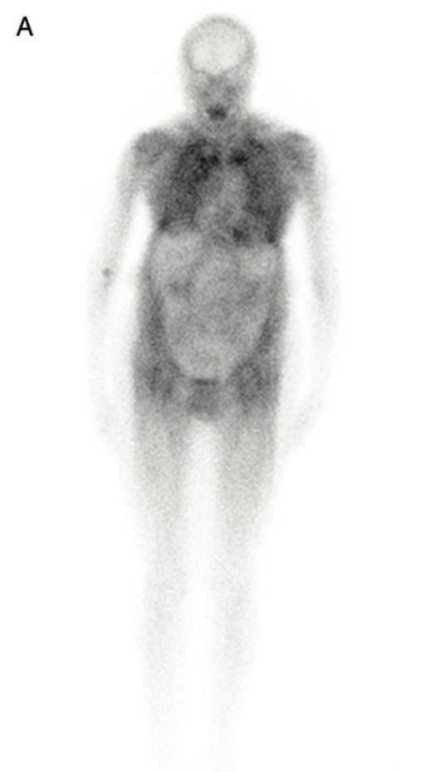
Score visuel



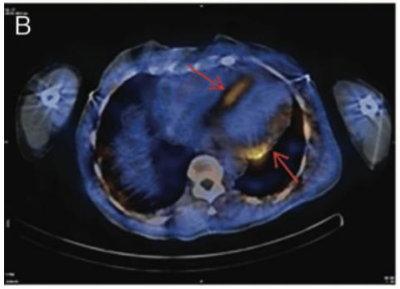


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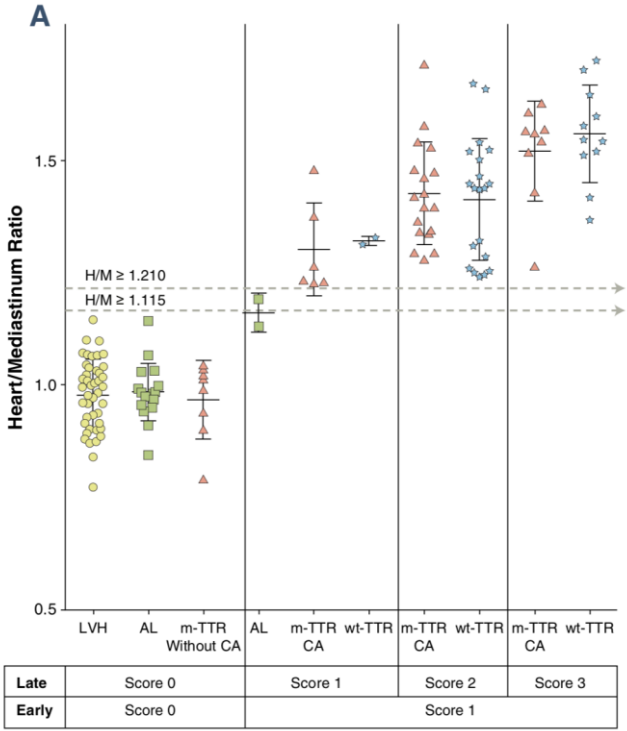
Image précoce

Rapport Cœur / médiastin précoce prédictif d'un score visuel ≥ 1

H/M ≥ 1.210 Se et Sp = 100%



Galat, A., Van der Gucht, A., Guellich, A., Bodez, D., Cottereau, A.-S., Guendouz, S., … Rosso, J. (2017). Early Phase 99 Tc-HMDP Scintigraphy for the Diagnosis and Typing of Cardiac Amyloidosis. JACC: Cardiovascular Imaging, 10(5), 601–603. doi:10.1016/j.jcmg.2016.05.007

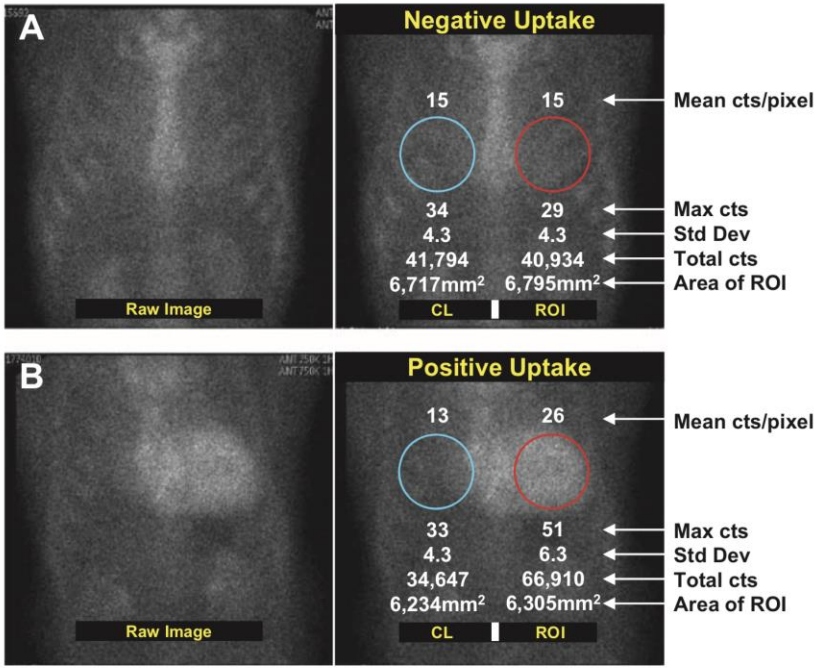
Performance diagnostique

- Se 97% Sp 100%

Heart/contralateral ratio
H/CL > 1,5 : ATTR

99mTc- Pyrophosphate
45 patients

Bokhari S, Castaño A, Pozniakoff T, et al. 99mTc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013;6: 195–201.



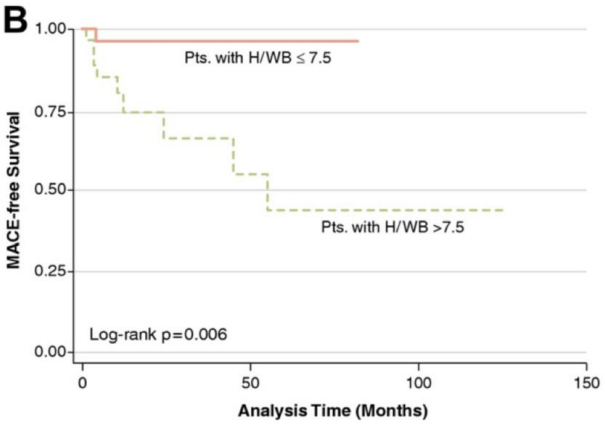
Pronostic

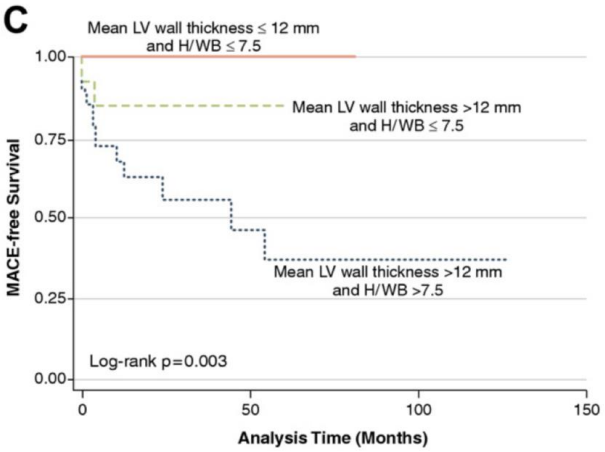
- Heart/whole body > 7.5 risque majoré de MACE

MACE : major adverse cardiac events

- Mort de causes cardiovasculaires
- Hospitalisation pour IC
- BAV3
- FA/Flutter
- SCA

63 patients, 40 avec ATTR





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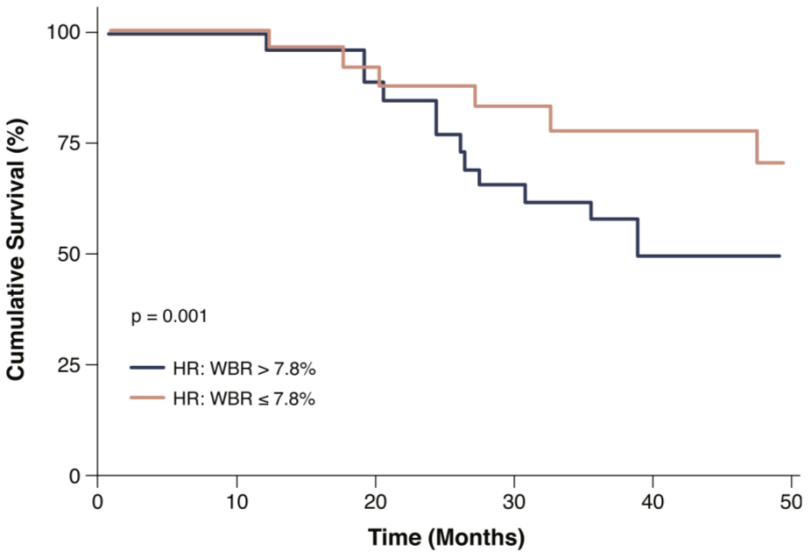
Pronostic

- H/WB > 7,8
- Mortalité toute cause
- 70 patients dont 51 avec biopsie myocardique



Kristen, A. V., Scherer, K., Buss, S., aus dem Siepen, F., Haufe, S., Bauer, R., … Steen, H. (2014). Noninvasive Risk Stratification of Patients With Transthyretin Amyloidosis. JACC: Cardiovascular Imaging, 7(5), 502–510. doi:10.1016/j.jcmg.2014.03.002

Traitements ATTR

- Diurétiques : réduisent la précharge

- Transplantation hépatique : utile chez patient avec manifestations précoces (neurologiques) mais peu chez les patients avec atteinte cardiaque (morbidité et progression de l'atteinte)

Drug	Phase	TTR Type	Organs	Study Number
Doxycycline + tauroursodeoxycholic acid	II	Wild type and mutant	Cardiac, nerve	NCT01171859
Revusiran (ALN-TTRsc), Alnylam Pharmaceuticals Cambridge (Cambridge, Massachusetts)	III	Mutant	Cardiac	NCT02319005
Tafamidis	III	Wild type and mutant	Cardiac	NCT01994889
Diflunisal	II/III	Mutant	Nerve	NCT01432587
Patisiran (ALN-TTR02), Alnylam Pharmaceuticals Cambridge (Cambridge, Massachusetts)	III	Mutant	Nerve	NCT01960348
ISIS-TTR_{Rx} Isis Pharmaceuticals (Carlsbad, California)	III	Mutant	Nerve	NCT01737398
SOM0226, SOM Biotech SL (Barcelona, Spain)	I-II	Mutant	Nerve	NCT02191826

Gertz, M. A., Benson, M. D., Dyck, P. J., Grogan, M., Coelho, T., Cruz, M., … Merlini, G. (2015). Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. Journal of the American College of Cardiology, 66(21), 2451–2466. doi:10.1016/j.jacc.2015.09.075

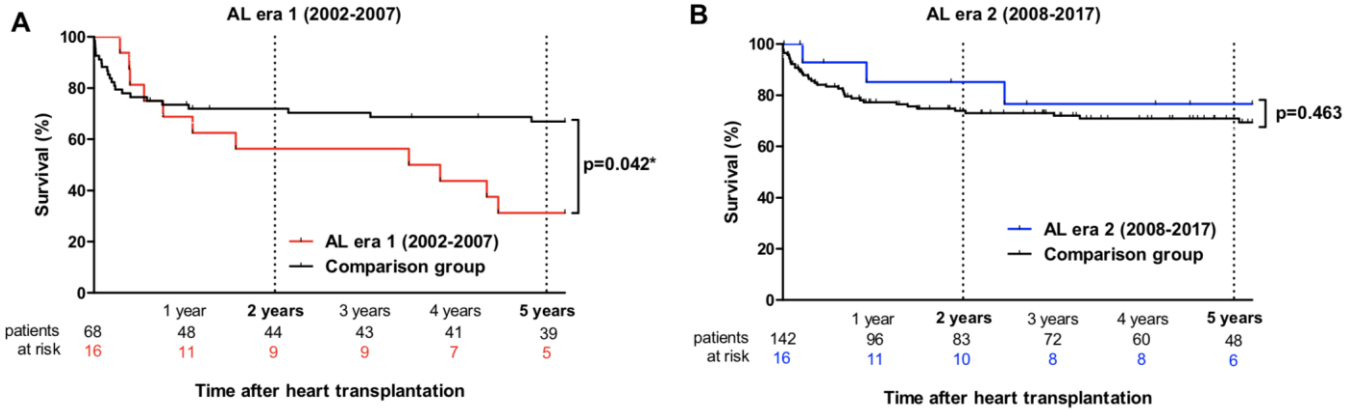
Kristen, A. V., Kreusser, M. M., Blum, P., Schönland, S. O., Frankenstein, L., Dösch, A. O., … Raake, P. W. J. (2018). Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era. The Journal of Heart and Lung Transplantation, 37(5), 611–618. doi:10.1016/j.healun.2017.11.015

Traitements AL

- Chimiothérapie à haute dose + greffe autologue
- Inhibiteur du protéasome (bortezomib) + Méphalan

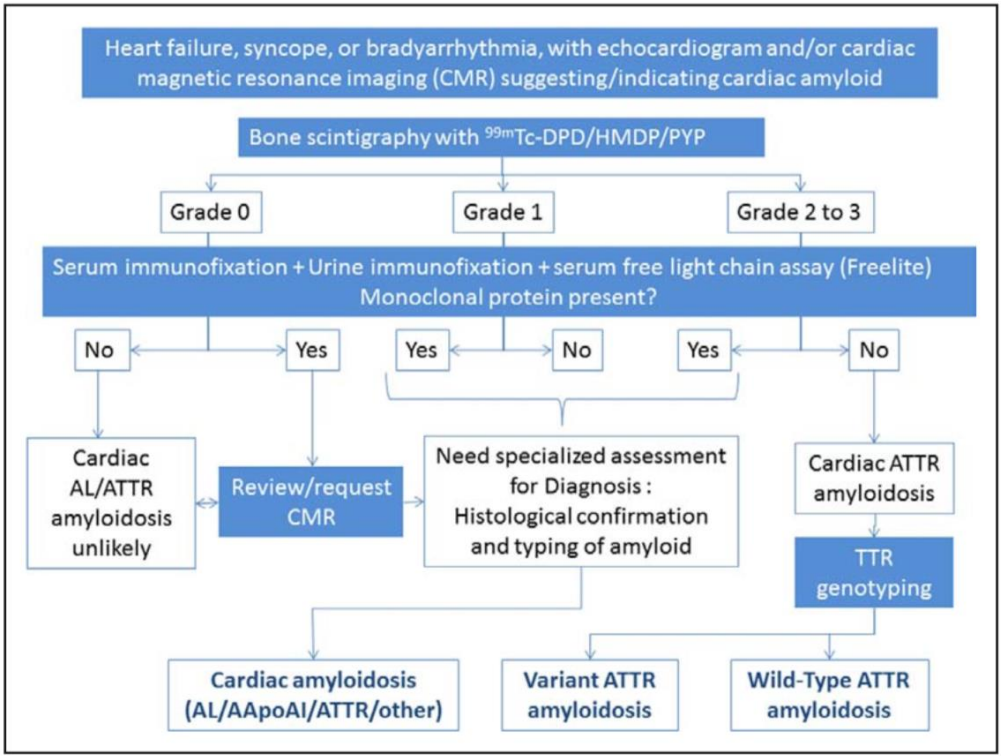
San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-17.

Traitements AL



- Transplantation cardiaque chez les patients présentant une amylose sans manifestation extra-cardiaque (16 patients par période)

Kristen, A. V., Kreusser, M. M., Blum, P., Schönland, S. O., Frankenstein, L., Dösch, A. O., … Raake, P. W. J. (2018). Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era. The Journal of Heart and Lung Transplantation, 37(5), 611–618. doi:10.1016/j.healun.2017.11.015


Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/or cardiac magnetic resonance imaging (CMR) suggesting/indicating cardiac amyloid
Bone scintigraphy with 99mTc-DPD/HMDP/PYP
Grade 0
Grade 1
Grade 2 to 3
Serum immunofixation + Urine immunofixation + serum free light chain assay (Freelite) Monoclonal protein present?
No
Yes
Yes
No
Yes
No
Cardiac AL/ATTR amyloidosis unlikely
Review/request CMR
Need specialized assessment for Diagnosis : Histological confirmation and typing of amyloid
Cardiac ATTR amyloidosis
TTR genotyping
Cardiac amyloidosis (AL/AApoAI/ATTR/other)
Variant ATTR amyloidosis
Wild-Type ATTR amyloidosis

Se : 92.2%

Sp : 95,4%

Distinction AL / ATTR

Pour un score ≥2

H/WB > 7,5

Facteur de mauvais pronostic