Case report

Transthyretin cardiac amyloidosis: A case report

Abstract:

Introduction : Cardiacamyloidosisis due to an extracellular accumulation of insoluble fibrillarproteinswhichprogressively alter the functioning of the myocardium. The prognosisdepends on the severity of the cardiacinvolvement. Transthyretinamyloidosis (TTR) is the mostfrequent. They can bewild-type (ATTRwt) or hereditary (ATTRv) or senile (wild TTR). The diagnosis of cardiacamyloidosis has greatlyimproved over the pasttenyears and isbased on multi-modalityimagingwithmainlyechocardiography and bonescintigraphy. **Case report:**we report the case of a male patient hospitalized for heart failure due to transthyretin cardiac amyloidosis**.Conclusion :** Recognition of thispathologyis essential because the cardiological management isspecific and conventionaltreatments for heartfailure can bedeleterious. Onlyspecifictreatments can slow down or stop the infiltration process.

Keywords: Cardiac amyloidosis, diagnostic imaging,bonescintigraphy, TTR-stabilizing therapy.

Introduction:

Amyloidosis is a systemic disease characterized by an extracellular accumulation of insoluble fibrillar proteins that deposit and invade tissues, preventing their normal function . This process is dynamic and active, as fibrils multiply and divide. Amyloidosis is classified according to the biochemical nature of the amyloid protein involved in deposit formation. Around twenty proteins can form amyloid fibrils (transthyretin, immunoglobulin light chain, fibrinogen, apo A1, etc…) (1).While more than 30 proteins are known to be responsible of amyloidosis, only 9 can accumulate in the myocardium to cause significant cardiac disease.

The most common cardiac amyloidosis is transthyretin amyloidosis (2). Transthyretin (TTR) is a protein synthesized by the liver in monomeric form. These monomers assemble into tetramers, which carry proteins (e.g. thyroid hormone, vitamin D) into the bloodstream. Transthyretin amyloidosis (TRTA) is of two types:

- Wild-type ATTR, formerly known as senile systemic amyloidosis: where the precursor is unmutated TTR (ATTRwt), occurring almost exclusively as hypertrophic cardiomyopathy (HCM) in men over 50. The cause of this amyloidosis is unknown, but is associated with aging. This disease has long been underestimated in cardiological syndromes. It accounts for 13% of heart failure with preserved left ventricular ejection fraction (LVEF) and 16% of aortic stenosis in men undergoing transcatheter aortic valve implantation (TAVI) (2).
- Hereditary ATTR: the familial form in which TTR is mutated (ATTRv, v for variant) (2). Transmission is autosomal dominant. Over 120 pathogenic mutations in the gene encoding TTR have been identified, and their prevalence varies according to country

and the improvement in cardiological diagnosis (3). Tissue damage varies according tothe mutation, giving rise to different phenotypes: cardiological, neurological or mixed. In a multicenter study, 6% of hypertrophic cardiomyopathies were associated with a TTR gene mutation (4). The Val122Ile mutation is the most common worldwide, occurring in 3.6% of Afro-Caribbean subjects. The first mutation identified was Val30Met, which is observed mainly in patients of Portuguese origin and results in the onset of neuropathy at the age of 25 to 30 years, with a slow but fatal course. The penetrance of these ATTR mutations varies according to geographical origin. Cardiac amyloid infiltration is complicated by thickening of the myocardium, valves and pericardium, and conduction disorders. Initially, cardiac involvement is suggestive of hypertrophic cardiomyopathy (HCM), followed by restrictive cardiomyopathy.

Case report:

A 78 years old man known with a medical history of: diabetes mellitus,ischemic heart disease and hypertrophic cardiomyopathy, under appropriate therapy, was admitted forNYHA class IV dyspnea with orthopnea and increased lower limb volume.

Clinical examination reveals global heart failure signs:the patient was tachycardic, polypneicwith 90% oxygen saturation, orthopnea, lower limb oedemas reaching the knees, turgidity of jugular veins and crepitus rales in 1/3 of the 2 lung fields.No friction rub nore heart murmurs were noted.

Hiselecrtrocardiogram hasshowensinusalrythmwith ventricular rate of 75bpm, a low voltage in peripheral derivations andantero-septo-apical R wave abrasion with no conductive disorders.Chest X ray showed bilateral pleural effusion of low abundance with no parenchymal abnormalities and a normal cardiac silhouette.

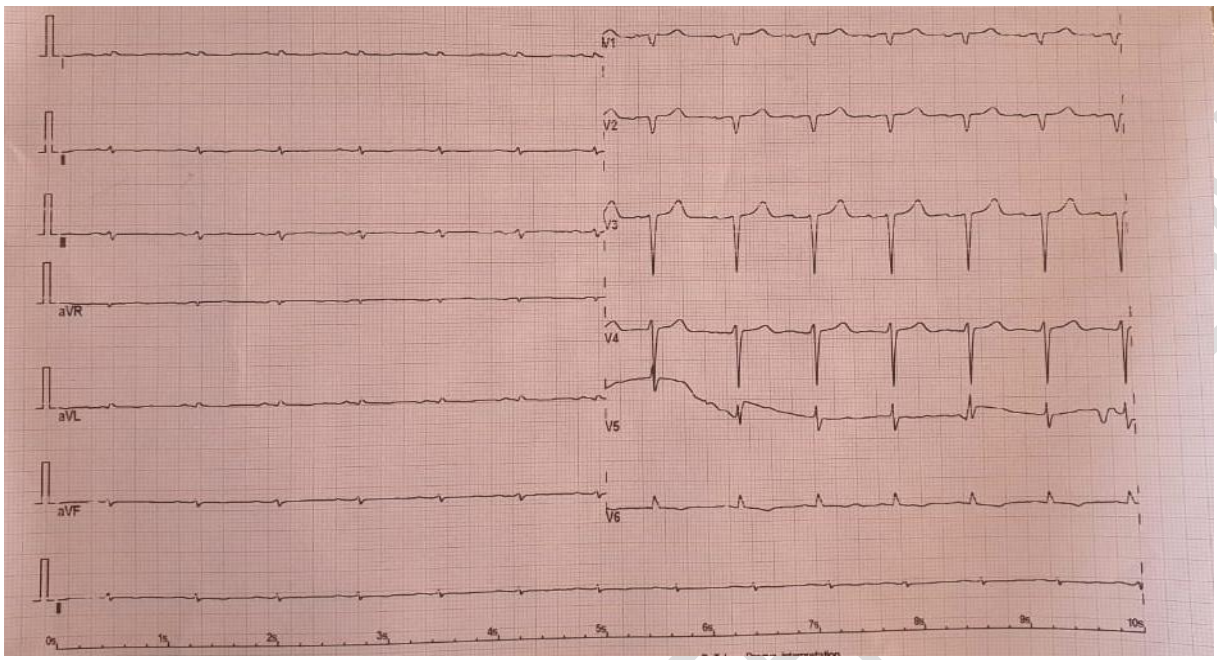
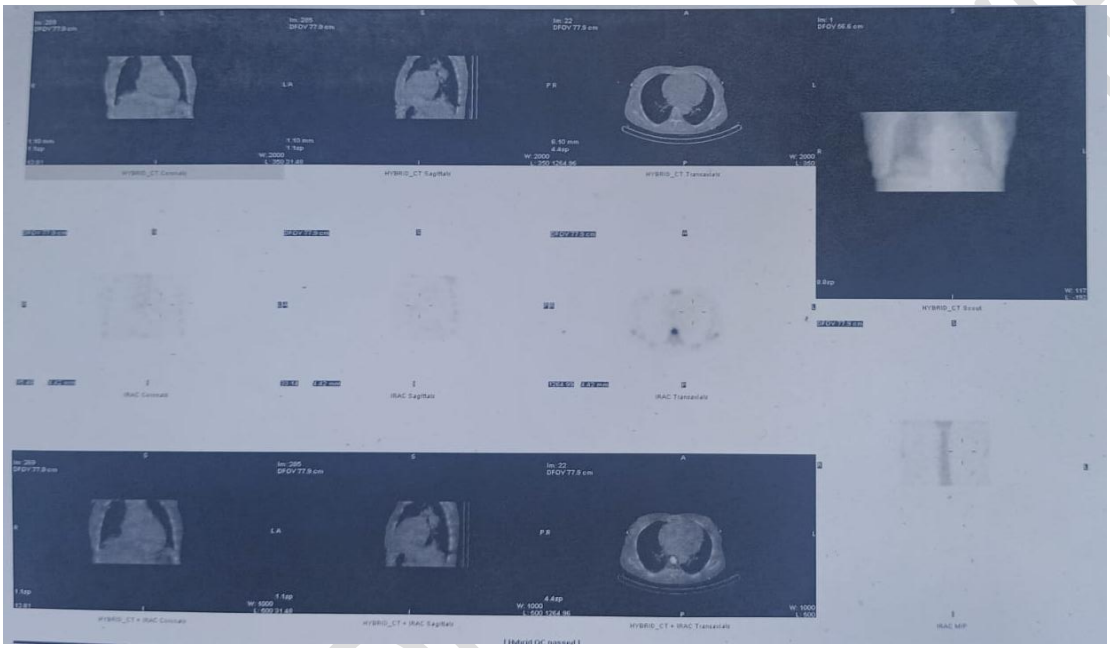


Figure 1: electrocardiogram of our patient revealing sinusalrythm with ventricular rate of 75bpm, a low voltage in peripheral derivations and antero-septo-apical R waveabrasion

An echocardiography transthoracic was performed and showed:a biventricular hypertrophic cardiomyopathy with a 22mm symmetrical left ventricular wall thickness, a scintillating myocardial appearance and a preserved systolic function out of 56%.Thus a spontaneous echo contrast casts doubts on an eventual thrombosis.The right ventricle was hypertrophic and slightly dysfunctional .Both atriums were dilated. Doppler stated for a restrictive mitral profileand a grade II tricuspid regurgitationwith a cocardial strain appearance. TTE also showed a pericardial effusion measuring 10mm circumferentially.

The patient underwent medical depletion therapy and a panel of investigations. The hemogram was normal and liver function was preserved. Urine Bence Jones protein was negative. Serum immunoelectrophoresis was normal. Salivary gland biopsy revealed no

amyloid deposits. Cardiac MRI was performed and showed increased T1 mapping with late subendocardial gadolinium enhancement, indicating probable cardiac amyloidosis. A radioisotope was avidly taken up by the myocardium, equivalent to a grade 3 uptake on Tc-Pyrophosphate scintigraphy. **Cardiac amyloidosis was therefore diagnosed, and TTR-stabilizing therapy was initiated.**Unfortunately our patient passed away three months after tafamidis treatment.



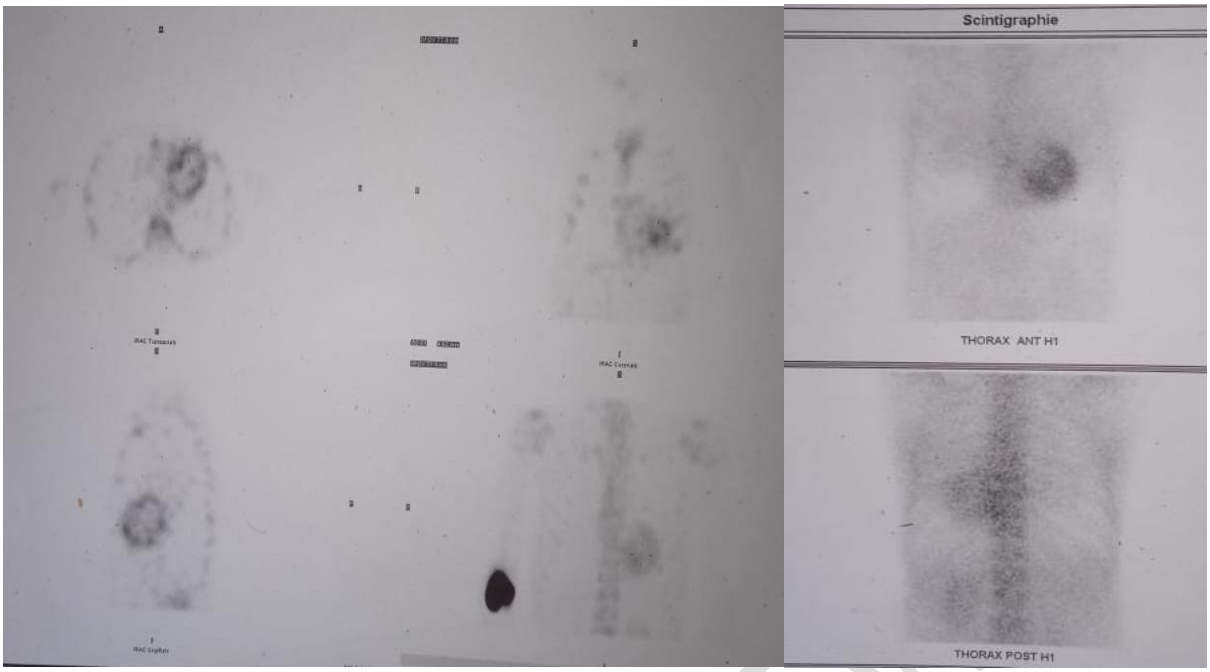


Figure 2: Tc-Pyrophosphate scintigraphy proving a grade 3 uptake

Discussion:

TTR is a liver synthesized protein normally involved in the transportation of the hormone thyroxine and retinol-binding protein.ATTR can be inherited as an autosomal dominant trait caused by pathogenic variants in the TTR gene *(ATTRv) or by the deposition of ATTRwt*(wild-type transthyretin protein), previously called senile cardiac amyloidosis.It can infiltrate other organs, most often the autonomic and peripheral nervous systems, but cardiac involvement, when present, defines the prognosis.

Both AL-CA and ATTR-CA lead to diffuse amyloid fibril deposition in the heart causing thickening of both ventricles resulting in a nondilated ventricle that is stiff and poorly compliant leading to a progressive diastolic filling abnormalities. The atria are universally involved with interatrial septal thickening, then poor atrial function and increased rates of atrial fibrillation (ATTR++). The valves are usually thickened, usually with mild to moderate regurgitation. Coronary involvement has been reported with ischemia and angina while epicardial coronary arteries remain normal,otherwise systolic function remains preserved. Pericardial involvement can lead to small pericardial effusions.

Cardiac manifestations are non-specific and include symptoms of heart failure and/or conductive and rhythmic disturbances (flutter and atrial fibrillation). Q waves are frequently observed on the electrocardiogram, and are related to the amount of amyloid infiltrate (5).

ATTR-CM can be an obscure diagnosis as its presentation can mimic other well-established cardiac problems, most commonly aortic stenosis, hypertrophic cardiomyopathy, and AL amyloidosis. Patients typically presents with heart failure but preserved EF with left congestive signs: dyspnea on exertion is common; however it can also present with more right-sided heart failure symptoms. The first manifestation of CA may be rhythmic with an atrial fibrillation or complete heart block and or cardioembolic complication. Angina with

normal coronaries can occur, leading rarely to cardiogenic shock due to diffuse ischemia. Due to low cardiac output , it may also presents with fatigue and weakness, especially on elderly patients. Low to normal blood pressure in a previously hypertensive patient that leads to discontinuation or reduction of antihypertensive therapy can be the first sign.

The prognosis of cardiac amyloidosis is mainly related to the heart. The median survival rate is of 50% at 3 years (9).

Extracardiac manifestations are diverse, and for the most part occur several years before cardiac manifestations (6). They could help to detect ATTRs earlier (6). They vary according to the type of amyloidosis: carpal tunnel syndrome, deafness (7), rupture of the long biceps tendon, narrow lumbar canal and, more rarely in ATTRv as in AL, periorbital ecchymosis and macroglossia. In ATTRv, neurological damage predominates in the autonomic nervous system and peripheral nerves, with damage to long-dependent fibers. Involvement of the autonomic nervous system may be in the foreground (ATTRv) and affect all autonomic functions, leading to severe orthostatic hypotension, gastroparesis responsible for incoercible vomiting and dyskalemia, and disorders of genitourinary functions. All these manifestations greatly impair patients' quality of life (8).

Classic cardiac biomarkers have been shown to be persistently elevated in ATTR-CM and have been incorporated into its staging and prognosis. Serum troponin levels have been found to be persistently elevated in the absence of any apparent cardiomyopathy. Similarly, pro-B-type natriuretic peptide can be seen as elevated out of proportion to the patient’s clinical heart failure.

ECG may be of help showing non specificsigns: low voltage, a classic finding for CA,pseudo infarct pattern with Q waves in the early precordial leads mimicking a prior anteroseptal myocardial infarction and wide QRS complexes are more frequent in ATTR while low voltages are more frequent in AL CA.

Imaging remains at the heart of a noninvasive diagnosis of ATTR-CM. The three modalities that have been shown to be useful for the diagnostic for ATTR-CM are transthoracic echocardiography, cardiovascular magnetic resonance (CMR), and cardiac scintigraphy.

TTE, apical sparing on strain imaging increased the likelihood of CA diagnosis but with modest sensitivity and specificity: a symmetric left ventricle hypertrophy is common, ventricles are withusually smaller dimensions than normal while atriums are dilated with a restrictive filling pattern. Due to the thick and dense myocardium, a classic sparking or “speckled appearance” term is often used to describe the myocardium. It is not uncommon to have pleural and pericardial effusions, although they are often dismissed as trivial with respect to hemodynamic significance.Ejection fraction is usually preserved but cardiac output is low due to decreased ventricular volume. The apical sparing with the easily recognizable **bull’s-eye pattern** on polar map can help differentiate CA from other forms of LV hypertrophy such hypertension or HCM with good sensitivity and specificity (12).

MRI T1-myocardial mapping shows significantly increased native T1 times.The addition of gadolinium enhancement helps detect infiltrative cardiomyopathies. An inability to suppress the myocardial signal (inability for the gadolinium to leave the myocardium) or presence of diffuse subendocardial or transmural enhancement is suggestive of amyloidosis with impressive sensitivity and specificity.

Currently, the only imaging modality that allows accurate diagnosis of the exact type of cardiac amyloidosis is nuclear scintigraphy using bone-avid radiotracers.99mTcPYP myocardial radiotracer uptake is graded by the semiquantitative visual score of cardiac retention comparing to rib uptake.

Unlike AL amyloidosis in which there are circulating biomarkers (light chains), ATTR-CM has not been shown to have specific biomarkers for which to test. Tissue biopsy with histopathology and immunohistochemistry has been used to definitively diagnose amyloidosis. Cardiac amyloidosis is confirmed when an endomyocardial biopsy demonstrates amyloid deposits after Congo red staining irrespective of the degree of left ventricular (LV) wall thickness.It can also be confirmed if amyloid deposits within an extracardiac biopsy are accompanied either by characteristic features of cardiac amyloidosis by echocardiography, in the absence of an alternative cause for increased LV wall thickness, or by characteristic features on cardiac magnetic resonance.Identification of amyloid should be followed by classification of the amyloid fibril protein.

Transthyretingenesequencingisused to diagnose hereditarytransthyretinamyloidosis, and only the absence of a mutation can confirm the diagnosis of ATTRwtamyloidosis in the presence of ATTR. This test shouldbeperformedsystematically for all cases of ATTR, regardless of age, sincecardiacATTRvismostoftendiagnosedafter the age of 70 (10)(14).

Therapeutic management of heart failure in amyloidosis aims to limit fluid retention by adjusting blood volume (13). Beta-blockers are particularly deleterious in severe forms, due to their negative inotropic, dromotropic and chronotropic effects: in cardiac amyloidosis, cardiac output is essentially dependent on heart rate. The causes of this dependence are a reduction in systolic ejection volume due to thickening of the ventricular walls at the expense of the ventricular cavity, and a reduction in contractility (10).

Anticoagulation is often necessary due to the high risk of thromboembolic events in patients with cardiac amyloidosis. It is imperative to search for intracardiac thrombus before performing electrical cardioversion, even if the patient has been anticoagulated for a long time, due to the possible presence of a thrombus that would contraindicate this procedure (15). Atrial arrhythmias are common in cardiac amyloidosis, and rate control may prove difficult. Pacemaker implantation may be useful in some symptomatic patients with marked chronotropic incompetence. As the pathological process is dynamic and evolving, the risk of conduction disorders (BAV3, BSA) must be constantly reassessed, with monitoring of PR and QRS spaces and their elongation. Resynchronization can be discussed in cases of preserved LVEF, or even more so if there is a risk, or especially if there is a risk.

Until recently, treatment of ATTR-CA was aimed at management of symptoms and disease-related complications. However, novel and experimental therapies for treatment of ATTR-CA wild-type (ATTRwt-CA) and hereditary/variant (ATTRv-CA) are emerging (11).

Liver transplantation remains the established treatment for variant TTR-related amyloid neuropathy and cardiomyopathy, but small molecule pharmaceuticals may prove effective alternatives to surgery. ATTR-CA treatment strategies target various steps along the ATTR-CA amyloid production process. ATTR fibrillogenesis, can eitherreduced using pharmacologic agents that bind to the thyroxine binding pockets called:stabilizer drug, such as **Tafamidis**, like diflunisal, interacts with TTR's thyroxine binding pocket an increases tetrameric stability. Other treatments aim to decrease or halt amyloid deposition by making less TTR available to dissociate and deposit in the heart and nerves by silencing TTR mRNA translation: Two gene silencer therapies :Parisiran that improves LV basal LS, NT proBNP,and ameliorated abnormal LV geometric patterns; and Inotersen thatimproves clinical manifestations. Immunotherapy is also being investigated for treatment of ATTR-CA . Another class of pharmacological agents aims to disrupt and clear the ATTR amyloid fibrils but showed modest results .

Conclusion:

ATTR occurs in up to 14% of patients with heart failure with preserved ejection fraction. Systemic involvement of the disease makes both diagnosing and treating ATTR- CA remain challenging. A tremendous advancement has been made with the therapeutic options making the prognosis better.

References:

1. S. Oghina, M.A. Delbarre, E. Poullot, K. Belhadj, P. Fanen, T. Damy .Cardiacamyloidosis: State of art in 2022.Rev Med Interne, 43 (2022), pp. 537-544.
2. J.C. Eicher, S. Audia, T. Damy .TransthyretincardiacamyloidosisRev Med Interne, 41 (2020), pp. 673-683.
3. T. Damy, A.V. Kristen, O.B. Suhr, M.S. Maurer, V. Planté-Bordeneuve, C.R. Yu, *et al.* Transthyretincardiacamyloidosis in continental Western Europe: an insight through the TransthyretinAmyloidosisOutcomes Survey (THAOS).EurHeart J, 43 (2019), pp. 391-400.Google Scholar.
4. T. Damy, B. Costes, A.A. Hagège, E. Donal, J.C. Eicher, M. Slama, *et al.* Prevalence and clinicalphenotype of hereditarytransthyretinamyloidcardiomyopathy in patients withincreasedleftventricularwallthickness .EurHeart J, 37 (2016), pp. 1826-1834 . Google Scholar.
5. T. Damy, M.S. Maurer, C. Rapezzi, V. PlantéBordeneuve, O.N. Karayal, R. Mundayat , *et al.*Clinical, ECG and echocardiographic clues to the diagnosis of TTR-relatedcardiomyopathy .Open Heart, 3 (2016), p. e000289 .CrossRefView in ScopusGoogle Scholar.
6. M. Kharoubi, M. Bézard, A. Galat, F. Le Bras, E. Poullot, V. Molinier-Frenkel, *et al.*History of extracardiac/cardiacevents in cardiacamyloidosis: prevalence and time

from initial onset to diagnosis .ESC Heart Fail, 8 (2021), pp. 5501-5512 .CrossRefView in ScopusGoogle Scholar.
7. E. Béquignon, A. Guellich, S. Bartier, M. Raynal, V. Prulière-Escabasse, F. Canouï-Poitrine, *et al.*How yourears can tell whatishidden in yourheart:wild-type transthyretinamyloidosis as potential cause of sensorineuralhearingloss in elderly-AmyloDEAFNESS pilot study . Amyloid, 24 (2017), pp. 96-100 .CrossRefView in ScopusGoogle Scholar.
8. T. Damy, D. Adams, F. Bridoux, G. Grateau, V. Planté-Bordeneuve, Y. Ghiron, *et al.*Amyloidosisfrom the patient perspective: the French daily impact of amyloidosisstudyAmyloid, 29 (2022), pp. 165-174.
9. M. Kharoubi, D. Bodez, M. Bézard, A. Zaroui, A. Galat, S. Guendouz, *et al.*Describing mode of death in three major cardiacamyloidosissubtypes to improve management and survival .Amyloid, 29 (2022), pp. 79-91.
10. M.S. Maurer, S. Bokhari, T. Damy, S. Dorbala, B.M. Drachman, M. Fontana, *et al.*Expert consensus recommendations for the suspicion and diagnosis of transthyretincardiacamyloidosis .CircHeart Fail, 12 (2019), p. e006075.
11. Stern LK, Patel J. Cardiac Amyloidosis Treatment. Methodist Debakey Cardiovasc J. 2022 Mar 14;18(2):59-72. doi: 10.14797/mdcvj.1050. PMID: 35414852; PMCID: PMC8932359.
12. Douglas Kyrouac, Walter Schiffer, Brandon Lennep, Nicole Fergestrom, Kathleen W. Zhang, John Gorcsan III, Daniel J. Lenihan, Joshua D. Mitchell : Echocardiographic and clinical predictors of cardiac amyloidosis: limitations of apical sparing.
13. Yamamoto H, Yokochi T. Transthyretin cardiac amyloidosis: an update on diagnosis and treatment. ESC Heart Fail. 2019 Dec;6(6):1128-1139. doi: 10.1002/ehf2.12518. Epub 2019 Sep 25. PMID: 31553132; PMCID: PMC6989279.
14. M. Bézard, M. Kharoubi, A. Galat, F. Le Bras, E. Poullot, V. Molinier-Frenkel, *et al.* Real-life evaluation of an algorithm for the diagnosis of cardiacamyloidosis .Mayo Clin Proc, 98 (2023), pp. 48-59.
15. O. Touboul, V. Algalarrondo, S. Oghina, N. Elbaz, S. Rouffiac, D. Hamon, *et al.* Electrical cardioversion of atrial arrhythmiaswithcardiacamyloidosis in the era of direct oral anticogulants .ESCHeart Fail, 9 (2022), pp. 3556-3564.