Cardiac amyloidosis in non-transplant cardiac surgery:

Prevalence, diagnosis and outcomes

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Abstract

Cardiac amyloidosis is a rare infiltrative cardiomyopathy that portends a poor prognosis. There is a growing recognition of co-existent aortic valve stenosis and transthyretin cardiac amyloidosis, with some studies suggesting that dual pathology may be associated increased risk of complication and mortality during surgical intervention. This review aims to evaluate the available literature on non-transplant cardiac surgical interventions in patients with cardiac amyloidosis, with particular focus on diagnosis, surgical risk and areas of uncertainty that require further research.

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Introduction

Amyloidosis is a group of rare heterogeneous diseases characterized by the abnormal extracellular deposition of beta-sheet fibrillar protein within different tissues, resulting in organ dysfunction. The term amyloid was first coined by the German botanist Mathias Schleiden in 1838 to describe the starchy amylaceous constituent of plants. It was subsequently ascribed to a macroscopic tissue abnormality exhibiting a positive iodine staining reaction by the famous pathologist Rudolph Virchow in 1854 (1).

Amyloidosis is classified into systemic and localised subtypes. Systemic forms include primary amyloidosis associated with plasma cell dyscrasias, and secondary reactive forms associated with chronic inflammation or malignancy (2).

Cardiac involvement is particularly severe and is reported to have an incidence of 18-55 per 100000 person years (3). It is commonly associated with primary systemic (AL) and transthyretin-type (ATTR) amyloidosis. AL amyloidosis is a result of plasma cell dyscrasia (e.g. multiple myeloma) that leads to extracellular deposition of fibril-forming monoclonal immunoglobulin light chains. Transthyretin is a transport protein that carries thyroxine and retinol-binding protein bound to retinol in the serum and cerebrospinal fluid. It is encoded by the TTR gene located on chromosome 18. Transthyretin (ATTR) amyloidosis is either hereditary due to mutation in the transthyretin gene (hATTR), or wild-type ATTR (previously known as senile systemic) which is predominantly associated with male gender and increasing age. Point mutations within TTR destabilise the tetramer and increase the chance of amyloidogenesis; familial amyloid polyneuropathy is most commonly associated with the replacement of valine by methionine at position 30 (4); and 3.9% of the Afro-Carribean

population carry a mutation where valine is replaced by isoleucine at position 122, the most common cause of familial amyloid cardiomyopathy (5).

Amyloid deposition within the myocardium results in expansion of the extracellular space around myocytes, fibre bundles and capillaries. It causes increased cardiac and vascular stiffness resulting in impaired relaxation in diastole. A restrictive cardiomyopathy results and dominates with reduced end-diastolic volumes, and diastolic followed by systolic heart failure. Other complications include electrical conduction disorders, embolic events, and syncope. Microvascular amyloid deposition can lead to coronary syndrome-X where angina is present without evidence of epicardial coronary artery disease. Prognosis is often poor, with AL cardiac amyloidosis (CA) reported to have a median survival of 24-66 months and ATTR 75 months (6).

There appears to be an increased prevalence of ATTR amyloidosis in patients with cardiac disease (e.g. aortic stenosis, hypertrophic cardiomyopathy, heart failure with preserved ejection fraction and conduction disease). In this review, we aim to evaluate the available literature on non-transplant cardiac surgical interventions in patients with CA to focus our attention on diagnosis, possible risks of surgery as well as identify potential areas for improvement and future research.

DIAGNOSIS

Clinical diagnosis of CA represents a significant challenge to the clinician, and unfortunately is often made late in advanced stages disease. Until recently, diagnosis of CA mandated biopsy, but by using a combination of echocardiography, cardiac magnetic resonance imaging and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) scintigraphy, non-invasive diagnosis is now both sensitive and specific. The most important step enabling diagnosis is increasing clinical awareness of the condition, with a low threshold to investigate.

Clinical signs

Diagnostic red flags include unexplained left ventricular hypertrophy, carpal tunnel disease (particularly if bilateral), biceps tendon rupture, peripheral neuropathy, neuropathic pain, orthostatic hypotension, and hypertrophic cardiomyopathy after the 6th decade of life (7). Familial amyloid cardiomyopathy should be considered in all patients of African origin presenting in heart failure.

Biochemical Markers

Laboratory investigations may show a raised N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) to >332 ng/L (in absence of renal failure), and cardiac troponin levels >0.035 micrograms/L) (8). Serum and urine electrophoresis and immunofixation assays detect an abnormal result in 99% of patients with AL amyloidosis (9)

Electrocardiograms

Electrocardiograms are frequently abnormal, with low voltage QRS complexes and poor R wave progression (10).

Echo

The hallmarks of CA on echocardiogram include infiltrative/restrictive cardiomyopathy with increased left ventricular wall thickness >12mm and a 'speckled/sparkling granular' appearance, as show in in figure 1 (11). Other signs include pericardial effusion, global longitudinal strain with relative sparing of the apex (12), doppler mitral annular S' of <6cm/s (13), and a high E/A ratio (14). Surgeons should be suspicious in patients with a severe low-flow, low-gradient aortic stenosis phenotype, which is particularly prevalent in ATTR-CA (15). In a recent prospective cohort study of patients with degenerative aortic stenosis referred for aortic valve replacement, Longhi et al conducted bone scintigraphy in patients identified with pre-selected echocardiographic 'red flags'; increased thickness of the atrioventricular valves, interatrial septum or right ventricular wall; pericardial effusion; and myocardial granular sparkling. Remarkably all patients (n=5/43) identified subsequently showed uptake on bone scintigraphy and amyloid deposition on endomyocardial biopsy (16).

CMRI

Radiological investigation is key in allowing non-invasive diagnosis, and multiparametric cardiac magnetic resonance (CMR) has a useful diagnostic role. CMR diagnosis utilises late gadolinium enhancement (17), T1 mapping (18) and extracellular volume fraction (19). Figure 2 details typical MRI findings in CA.

Bone Scintigraphy

99mTcDPD scintigraphy has recently emerged as a remarkably sensitive method enabling non-invasive diagnosis of ATTR CA. Castano et al (20) showed scintigraphy to demonstrate 91% sensitivity and 92% specificity for detecting ATTR with a area under the curve of 0.960 (95% CI .930-.981). The classical appearances of ATTR-CA on scintigraphy are show in in Figure 3.

Biopsy

Ultimate diagnosis is through tissue biopsy and histological analysis using the alkaline Congo red stain, and microscopic inspection in bright polarized light by green bifringence, with further subclassification by immunohistochemistry (21-22).

Treatment

Medical therapy is directed at relief of symptoms of cardiac failure primarily using loop diuretics and aldosterone antagonists. Patients with severely restrictive physiology have a fixed end diastolic volume, and regulation of cardiac output is subsequently dependent on heart rate. Medications including digoxin, calcium channel blockers and beta-blockers must therefore be used with caution. Equally vasoactive ACE inhibitors and angiotensin II inhibitors are poorly tolerated often resulting in profound hypotension, even at low doses.

Targeted therapy directed against the plasma cell dyscrasia responsible for AL amyloidosis involves chemotherapy +/- autologous stem cell transplantation. In wtATTR amyloidosis, Tafamidis (a drug which stabilizes the transthyretin tetramer and may reduce the formation of

ATTR amyloid) has recently been shown to improve survival, as well as lower the rate of decline in distance for the 6-minute walk test (23).

Heart Transplantation in cardiac Amyloidosis.

Cardiac transplantation was initially considered a contraindication, but with advances in chemotherapy and hematopoietic stem cell transplantation outcomes are now acceptable in highly selected patients (24). Currently, reported case series are small, but nevertheless a 5-year survival of 65% appears achievable.

Non-transplant cardiac surgery in CA

Other than transplantation, it is difficult to justify cardiac surgical intervention in patients with CA. Not only is life expectancy often limited and frailty status high, but the pathophysiology of CA restrictive cardiomyopathy copes poorly with the physiological insult of cardiac surgery, cardiopulmonary bypass and myocardial ischaemia, and this cohort are at high risk for post-operative low cardiac output syndrome.

Cardiac amyloidosis and aortic valve surgery

The coexistence of ATTR CA and aortic stenosis (AS) has been recently reported in several studies. Aortic stenosis (AS) is the most common valvular heart disease in Western developed countries, affecting 3% of individuals aged >75 years (25). It shares a common patient demographic and clinical profile with ATTR-CA. Several patterns of AS have been described, pertaining to valve area, flow rate, gradient and left ventricular ejection fraction (LVEF). The pathophysiology of low-flow, low-gradient AS shares similarities with that of

ATTR-CA; cardiac remodelling in both results in hypertrophied LVs with low stroke volume even if LVEF is still preserved. Excessive cardiac remodelling and restrictive physiology of CA is often mistaken for afterload induced LVH and decompensation due to AS (26). Emerging studies suggest that a significant proportion of patients undergoing aortic valve replacement (AVR) for AS have undiagnosed CA, and it has been previously suggested that this may explain high rates of permanent pacemaker insertion following transcatheter aortic valve implantation (TAVR) (27).

In a cohort of 20 patients with AS who underwent TAVR but subsequently had the valve explanted (autopsy n=17, surgery n=3), Nietlispach et al found histological evidence of valvular amyloid deposition in one third of cases (28). In a further histological study of 150 explanted heart valve specimens, Kristen et al found evidence of amyloid valve disease in 83/150 case, the highest prevalence being in aortic stenosis (74/100) (29). Until recently, it has not been possible to diagnose ATTR-CA without resorting to endomyocardial biopsy, but this is now possible with the use of multiparametric cardiac magnetic resonance imaging (CMR) in combination with ^{99m}Tc-DPD scintigraphy (30). Subsequent studies have shown the rates of wtATTR-CA in patients referred for aortic valve replacement (surgical/ TAVR) to be between 4.1 and 16% (10,12,13, 31). Current evidence for the co-existence of ATTR-CA and AS is summarised in Table 1.

The high prevalence of concomitant ATTR-CA in AS compared to the general population suggests an underlying pathophysiological relationship. However, it remains unknown whether ATTR-CA is the consequence or the cause of AS. Whilst pressure overload secondary to AS has deleterious effects on myocardial remodelling and may induce ATTR

deposition, it may be that amyloid deposition induces or worsens AS, and further research is required to delineate this (32).

The presence of CA has significant implications for aortic valve intervention, but data on the role of valve surgery in the treatment of these patients is limited to small cohort studies (10, 26, 32, 33) and case reports (34-38). In a prospective cohort of 146 patients with severe AS referred for SAVR, using a combination of CMR and intraoperative biopsies Triebel et al identified ATTR-CA in 6/146 patients. Patients with amyloid deposition subsequently underwent genotyping and ^{99m}Tc-DPD bone scintigraphy. The hazard ratio for postoperative death within the amyloid subgroup was 9.5 [95% confidence interval 2.5-35.8, P=0.001]. However, due to the low patient numbers there was no adjustment for potential confounders (10). Recently, Java et al published a retrospective cohort study of 16 patients with amyloidosis and aortic stenosis who underwent SAVR (n=11) or TAVR (n=5) with 100% 1-year survival. 4 patients died within the follow up period, all more than 1 year post-operatively (33). Unfortunately, the study was limited as it did not refer to the degree of myocardial amyloid infiltration, and included those with localized amyloidosis of the skin (n=1), Pharynx (n=1) and seminal vesicles (n=2). Amyloidosis encompasses both mild systemic and severe cardiac forms, and the lack of clarification and inclusion of patients with localized amyloidosis stops broader conclusions being made. Galat et al reported no procedural-related mortality in their series of 11 patients with ATTR-CA who underwent AVR (10 SAVR and 1 TAVR), but 40% of SAVR patients passed away during the follow up period (2-78 months) (32). Using multiparametric magnetic resonance imaging, Cavalcante et al identified CA in 9/113 patients with severe aortic stenosis, 4 of whom proceeded to SAVR (26); CA remained associated with all-cause mortality (HR 2.92, 95% CI 1.09-7.86, P=0.03) after adjustment for aortic valve replacement modelled as a time-dependent covariate, society

of thoracic surgery predicted risk of mortality and left ventricular ejection fraction. This study however is limited by small sample size.

CA is itself associated with poor prognosis, and it is also not clear if relief of co-existing AS portends any survival benefit; Sperry et al reported no significant difference in 2-year survival in a retrospective cohort of ATTR-CA (n=144, 2-year survival 37%) Vs. ATTR-CA and concomitant AS (n=27; 11 of whom underwent SAVR; 2-year survival 37%); HR1.21 [95% CI .62-2.42]; P=0.566]. However, this study is limited as longer term follow up is required to fully assess if valve replacement confers any survival benefit (39). Further prospective studies comparing patients with ATTR-AS treated with medical therapy Vs. SAVR/TAVR are required to guide future treatment strategies.

Several case reports have been published noting successful aortic valve replacement in patients with CA; including in patients with severe aortic regurgitation (34), isolated valvular CA (35) and infective endocarditis (36). Reported outcomes have not been uniformly successful, including operative mortality due to post-operative low cardiac output syndrome after SAVR (37), and left ventricular rupture during transapical TAVR (38). Further details of the case reports are listed in Table 2.

Mitral valve surgery

Whilst it is increasingly recognised that CA occurs in patients with concomitant AS, the prevalence in mitral valve disease is less clear. In their histological analysis of 150 surgically resected heart valve specimens, Kristen et al reported amyloid deposition in 2/7 cases of mitral stenosis and 7/24 of mitral regurgitation (29). In a recent retrospective cohort study,

Xu et al reported evidence of valvular or myocardial amyloid deposition in 0.2% (n=15/7733) of cases undergoing mitral valve surgery over a ten-year period. Surgical outcomes were excellent with no complications or deaths at a mean follow-up of 1023 days (40). The study is limited by small sample size, and the authors did not comment on the degree of myocardial amyloid infiltration.

Five further cases of mitral valve surgery in patients with concomitant CA have been reported, one of successful valve replacement (41), one of successful repair (44), two cases complicated by profound postoperative LCOS and death (43,44), and one case where the patient was unable to be weaned from cardio-pulmonary bypass and died on the operating table (45). Further details are listed in table 3

Surgical Revascularisation

It is well described that in the absence of epicardial coronary artery disease, angina in CA is a result of obstructive intraluminal microangiopathy – cardiac syndrome-X (46, 47). Whilst not typical in CA, if angiographic coronary artery disease co-exists and the patient is investigated for chest pain, there is a risk of attribution of symptoms and misdiagnosis. Once labelled with ischaemic heart diseases, routine echocardiogram is usually undertaken and focuses on valvular and systolic LV function, and subtle signs of CA such as LV hypertrophy and diastolic dysfunction can easily be overlooked. It is therefore possible for surgical revascularisation to be undertaken without recognition of CA and the excessive risks it carries with it. On review of the literature, case reports of co-existing CA and surgical revascularisation report universally poor post-operative outcomes (48-52). In five cases, a post-operative irreversible low cardiac output state developed. One case has been reported of a CA patient successfully discharged

following CABG, only to succumb to electromechanical complications of CA months later (51). There is clearly a publication bias, however, as successful cases of surgical revascularization in CA patients are far less likely to be reported in the literature. Table 4 provides a summary of cases.

Throughout the literature, it is noticeable that the cause of death in CA patients post cardiac surgery is frequently secondary to a profound and irreversible low cardiac output state. This can be explained by several pathophysiological mechanisms. Cardiopulmonary bypass induced haemodilution and systemic inflammatory response in combination with vasoplegic anaesthetic agents results in dysregulation of circulating volume. In the amyloid heart, a restrictive cardiomyopathy dominates, and the myocardium is unable to increase its contractile performance to compensate for such sudden changes. A low cardiac output state is therefore potentiated, which standard treatment fails to resolve. In our experience, even the use of conventional ionotropic agents and counter pulsation, fail to help in this low cardiac output state (52).

It is also noteworthy that current pre-operative risk stratification models (Euroscore II and the Society of Thoracic Surgery score) are invalid in patients with CA; the risk portended by severe restrictive cardiomyopathy, diastolic dysfunction and myocardial amyloid deposition are not taken into account and therefore operative risks grossly under-estimated.

Conclusions

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Cardiac amyloidosis is a rare disorder that portends a poor prognosis. There is a growing body of evidence for the co-existence of ATTR-CA and AS in approximately 4-16% of patients referred for SAVR/TAVR, with significantly increased peri-operative risk. Even if successful, the impact of relieving aortic stenosis on the long-term prognosis of CA is unclear and further prospective studies are required to guide management.

The few cases of surgical revascularization in patients with CA and concomitant epicardial coronary artery disease paint a very bleak picture. These patients are at high risk of post-operative low cardiac output state and death. Potential grave risks of CABG in CA are not to be underestimated, but as the literature is limited to case reports and small series there may be a publication bias.

Further prospective studies are required to enable formulation of guidelines aiding non-invasive pre-operative identification of this cohort of patients, utilising echocardiogram, cardiac magnetic resonance imaging and 99mTcDPD scintigraphy, so that appropriate risk stratification can guide treatment modalities. Current pre-operative risk stratification tools are invalid in CA and should not guide treatment. Ultimately, surgeons must have a high index of suspicion of CA to aid pre-operative diagnosis and protect patients from potentially futile interventions.

Figure Legends

Table 1: Current evidence for the co-existence of ATTR-CA and AS

Table 2: Case reports of aortic valve surgical intervention in patients with CA

Table 3: Case reports of mitral valve surgical intervention in patients with CA

Table 4: Case reports of surgical revascularization in patients with CA

Figure 1: 2 dimensional Echo 4-chamber view showing marked interventricular septal hypertrophy with a sparkling granular appearance

Figure 2

A – Four Chamber (4Ch) cine still image showing marked concentric left ventricular hypertrophy, more subtle right ventricular hypertrophy, biatrial dilatation and a right pleural effusion.

B – Native (pre-contrast) T1 map of the same 4Ch view showing a markedly elevated myocardial T1 at 1140ms in the left ventricular septum (normal 1025+/-60ms).

C – Late gadolinium enhancement image showing marked transmural gadolinium enhancement in the left and right ventricular myocardium. The artefact lines across the images are due to breathing.

D – Extracellular volume fraction (ECV%) map – each voxel represents an ECV%. The ECV% in the left ventricular septum is markedly elevated at 49%(normal 26+/-3%).

Figure 3

99mTcDPD scintigraphy showing typical myocardial uptake seen in cardiac amyloidosis

References

1) Virchow R. Archiv fur pathologischeanatomie and physiologie und fur klinischemedicin. Berlin 6; 354-368. 1854

2) Guvenc I (2011). Localized Amyloidosis of the Head and Neck, *Amyloidosis – An Insight to Disease of Systems and Novel Therapies*.

3) Gilstrap L, Dominici F, Wang Y, El-Sady S, Singh A, Di Carli M, Falk R, Dorbala S. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations among fee-for-service medicare beneficiaries in the united states. Circulation: Heart Failure. 2019:12 (6):e005407

4) Saraiva MR. Transthyretin mutations in health and disease. Hum Mutat. 1995:5(3):191-6

5) Jacobson DR, Pastore RD, Yaghoubian R, Kane I, Gallo G, Bucks FS, Buxbaum JN. Variant-sequence transthyretin (isoleucine 122) in late onset cardiac amyloidosis in black Americans. N. Engl. J. Med. 1997;336(7):466-73

6) Mankad AK, Seray I, Shah KB. Light-chain cardiac amyloidosis. CurrProbl Cancer. 2017;41:144-56

7) Maurer MS, Elliot P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation. 2017;135(14):1357-1377.

8) Longhi S, Lorenzini M, Garliardi C, Milandri A, Marzocchi A, Marrossini C, Saia F, Ortolani P, Biagini E, GUidalotti PL, Leone O, Rapezzi C. Coexistence of Degenerative Aortic Stenosis and Wild-Type Transthyretin-Related Cardiac Amyloidosis. JACC

Cardiovas Imaging. 2016;9:325-327

9) Dispenzieri A, Gertz MA, Kyle RA, et al. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood. 2004;104:1881-87

10) Piper C, Butz T, Farr M, Faber L, Oldenburg O, Horstkotte D. How to diagnose cardiac amyloidosis early: impact of ECG, tissue Doppler echocardiography, and myocardial biopsy. Amyloid. 2010;17(1):1-9

11) Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, Jaccard A. Cardiac amyloidosis; updates in diagnosis and management. Arch Cardiovasc Dis. 2013;106(10):528-40

12) Phelan D, Collier P, Thavendiranathan P, Popovic SB, Hanna M, Plana JC, Marwick TH, Thomas JD, Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012;98(19):1442-8

13) Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, Roberts N, Hutt DF, Rowczenio DM, Whelan CJ, Ashworth MA, Gillmore JD, Hawkins PN, Moon JC. Occult transthyretin cardiac amyloidosis in severe calcific aortic stenosis. CircCardiovasc Imaging. 2016;9(8):e005066.

14) Knight DS, Zumbo G, Barcella W, Steeden JA, Muthurangu V, Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Kotecha T, Francis R, Rezk T, Quarta CC, Whelan CJ, Lachman HJ, Wechalekar AD, Gillmore JD, Moon JC, Hawkins PN, Fontanta

M.Cardiac structural and functional consequences of amyloid deposition by cardiac magnetic resonance and echocardiography and their prognostic roles. JACC Cardiovasc Imaging. 2019;12(5):823-833

15) Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. 2017;38:2879-2887

16) Katzmann JA, Abraham RS, Dispenzieri A, Lust JA, Kyle RA. Diagnostic performance of quantitative {kappa} and {lambda} free light chain assays in clinical practice. Clin Chem 2005; 51: 878–881.

17) FontantaM, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, Maestrini V, Barcella W, Rosmini S, Bulluck H, Sayed RH, Patel K, Mamhood S, Bucciarelli-Ducci C, Whelan CJ, Herrey AS, Lachmann HJ, Wechalekar AD, Manisty CH, Schelbert EB, Kellman P, Gillmore JD, Hawkins PN, Moon JC. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2015;132(16):1570-1579

18) KaramitsosTD, Pichnik SK, Banypersad SM, Fontana M, Ntusi NB, Ferreira VM, Whelan CJ, Myerson SG, Robson MD, Hawkins PN, Neubauer S, Moon JC. Non contrast T1 mapping for the diagnosis of cardiac amyloidosis. JACC:Cardiovascular imaging. 2013;6(4):489-497

19) Banypersad SM, Sado DM, Flett AS, Gibbs SD, Pinney JH, Maestrini V, Cox AT, Fontana

M, Whelan CJ, Wechalekar AD, Hawkins PN, Moon JC. Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: an equilibrium contrast cardiovascular magnetic resonance study. CircCardiovasc Imaging. 2013;6(1):34-39

20) CastanoA, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, Pozniakoff T, Ruberg FL, Miller EJ, Berk JL, Dispenzieri A, Grogan M, Johnson G, Bokhari S, Maurer MS. Multicenter study of planar technetrium 99m pyrophosphate cardiac imaging. 2016;1(8):880-889

21) Linke RP, Oos R, Wiegel NM et al. Improvements and practical guide for a more precise diagnosis of amyloid and the different amyloidoses. IN: Uversky VN, Fink AL, editors. Protein misfolding, aggregation and conformational disease. New York: Springer, 2006. P. 239-76

22) Linke RL, Oos R,Wiegel NM, Nathrath WBJ. Classification of amyloidosis: misdiagnosing by way of incomplete immunohistochemistry and how to prevent it. ActaHistochem. 2006;108(3):197-208

23) Maurer MS, Schwartz JH, Gundapaneni B, Elliot PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AL, Huber P, Patterson TA, Riley S, Schumacher J, Sterwart M, Sultan MB, Rapezzi C. Tafamidis treatment for patient with transthyretinin amyloid cardiomyopathy. New England Journal of Medicine. 2018:379:1007-16

24) Sousa M, Monohan G, Rajagopalan N, Grigorian A, Guglin M. Heart transplantation in cardiac amyloidosis. Heart failure review. 2017:22:317-327

25) Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the

elderly: an echocardiographic study of a random population sample. J Am CollCardiol. 1993;21:1220-1225

26) Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, Soman P, Forman DE, Schindler JT, Gleason TG, Lee JS, Schelbert EB. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. Journal of Cardiovascular Magnetic Resonance. 2017;19:98

27) Castano A, Bokhari S, Maurer MS. Could late enhancement and need for permanent pacemaker implantation in patients undergoing TAVR be explained by undiagnosed transthyretin cardiac amyloidosis? J Am CollCardiol. 2015;65:311-312

28) Nietlispach F, Webb JG, Ye J, Cheung A, Lichtenstein SV, Carere RG, Gurvitch R, Thompson CR, Ostry AJ, Matze L, Allard MF. Pathology of transcatheter valve therapy. Jacc: Cardiovascular Interventions. 2012;5:585-590

29) Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, Koch A, Sack FU, Katus HA, Linke RP, Dengler TJ. High prevalence of amyloid in 150 surgically removed heart valves – a comparison of histological and clinical data reveals a correlation with atheroinflammatory conditions. Cardiovascular pathology. 2010;9:228-235

30) Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, Ferlini A, Longhi S, Lorenzini L, Reggiani LB, Gagliardi C, Gallo P, Villani C, Salvi F. Role of ^{99m}Tc-DPD Scintigraphy in Diagnosis and Prognosis of Hereditary Transthyretin-Related Cardiac Amyloidosis. JACC: Cardiovascular imaging. 2011;4(6):660-70

31) Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, Katsoulis M, Hartman N, Fontana M, Pugliese F, Sabharwal N, Newton JD, Kelion A, Ozkor M, Kennon S, Mullen M, Lloyd G, Menezes LJ, Hawkins PN, Moon JC. Prevalence and

outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. European Heart Journal. 2020;41(29):2759-2767

32) Galat A, Guellich A, Bodez D, Slama M, Dijos M, Zeitoun DM, Milleron O, Attias D, Dubois-Rande JL, Mohty D, Audureau E, Teiger E, Rosso J, Monin JL, Damy T. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken of the egg?. European Heart Journal. 2016;37:3525-3531.

33) Java AP, Greason KL, Dispenzieri A, Grogan M, King KS, Maleszewski JJ, Daly RC, Eleid MF, Pochettino A, Schaff HV. Aortic valve replacement in patients with amyloidosis. The Journal of Thoracic and Cardiovascular Surgery. 2018;156(1):98-103

34) Terada Y, Wanibuchi Y. Aortic valve replacement in a patient with cardiac amyloidosis. Annals of thoracic surgery. 1996;62:1565-74

35) Iqbal S, Reehana S, Lawrence D. Unique type of isolated cardiac valvular amyloidosis. Journal of cardiothoracic surgery. 2006;1:38)

36) Namaai A, Sakurai M, Sasaki O, Meguro K. Cardiac surgery in a patient with multiple myeloma combined with renal amyloidosis. 2010;58:341-43.

37) Seki T, Hattori A, Yoshida T. Hemodynamic deterioration after aortic valve replacement in a patient with mixed systemic amyloidosis. General Thoracic and Cardiovascular surgery. 2017;65:470-473

38) Monticelli FC, Kunz SN, Keller T, Bleiziffer S. Cardiac amyloidosis as a potential risk factor for transapical transcatheter aortic valve implantation. The Journal of Cardiac Surgery. 2014;29(5):623-4

39) Sperry BW, Jones BM, Vranian MN, Hanna M, Jaber WA. Recognizing Transthyretin Cardiac Amyloidosis in Patients With Aortic Stenosis: Impact on Prognosis. JACC Cardiovasc Imaging. 2016;9(7):904–906. doi:10.1016/j.jcmg.2015.10.023

40) Xu B, Godoy RC, Rodriguez ER, Tan C, Gillinov AM, Harb S, Jellis C, Griffin B. Unrecognized cardiac amyloidosis at the time of mitral valve surgery: incidence and outcomes. Cardiology. 2019;1429(4):253-258

41) Coisne D, Corbi P, SOsner P. Obstructive intramural coronary amyloidosis and papillary muscle rupture. Heart. 2003;89:e8

42) Nishi H, Mitsuno M, Ryomoto M, Miyamoto Y. Severe mitral regurgitation due to cardiac amyloidosis – a rare reason for ruptured chordae. Interactive Cardiovascular and Thoracic Surgery. 2008:1199-1200

43) Schwartz JG, Ghidoni JJ. Unsuspected amyloidosis and cardiac arrest following mitral valve replacement. International Journal of Cardiology. 1985;9(4):485-7

44) Frumkin D, Taube ET, Stangl K, Knebel F. Rapid progression of aortic and mitral stenosis in a patient with AA amyloidosis: a case report. European Heart Journal – Case Reports. 2019;3(2):

45) Engelmeier RS, O'Connell JB, Subramanian R. Cardiac amyloidosis presenting as severe mitral regurgitation. International Journal of Cardiology. 1983;4(3):325-327

46) Cantwell RV, Aviles RJ, Bjornsson J, Wright RS, Freeman WK, Oh, JK, Hoyer JD, Markovic S, Jaffe AS. Cardiac amyloidosis presenting with elevations of cardiac troponin I and angina pectoris. Clinical Cardiology. 2002;25(1):33-37

47) Whitaker DC, Tungekar MF, Dussek JE. Angina with a normal coronary angiogram caused by amyloidosis. Heart. 2004;90(9):e54

48) Massoudy P, Szabo A, Dirsch O, Wienecke H, van de Wal H, Jakob H. Amyloid of heart and lungs in a patient with low output syndrome after coronary artery bypass grafting. Herz. 2003:28(5):453-6

49) Zacek P, Medilek K, Lonsky V, Laco J. Cardiac amyloidosis in the cardiosurgical operating room – a rare but fatal trap. ThoracCardiovasc surg. 2007;55(2):65-67

50) Fitzmaurice G, Wishart V, Graham A. An unexpected mortality following cardiac surgery: A post-mortem diagnosis of cardiac amyloidosis. Gen ThoracCardiovasc Surg. 2013;61(7):417-21

51) Massias S, Vyssoulis G, Rizos I, Barbetseas I, Stefanadis C. Progressive heart failure in a patient after coronary artery bypass grafting. Hell J Cardiol. 2006;47:114-11

52) Smith A, Edlin J, Hinds C, Ambekar S. Coronary Revascularization in Cardiac Amyloidosis. Journal of Cardiac Surgery. 2020;35(11):3248-3250