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# Treatment of End Stage Heart Failure Related to Cardiac Amyloidosis

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Additional information is available at the end of the chapter

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## 1. Introduction

Amyloidosis is a disease characterized by deposition of extracellular proteinaceous material known as amyloid in tissues. Amyloidoses are classified according to the protein composition and the clinical characteristics of the disease [1]. Amyloid protein can accumulate at various speeds in multiple organ systems and the disease can have localized or systemic manifestations depending on organ involvement. Amyloidotic cardiomyopathy or cardiac amyloidosis is characterized as a restrictive cardiomyopathy associated with increased ventricular wall thickness caused by the accumulation of amyloid in the heart [2]. Cardiac amyloidosis is of special interest since its occurrence usually has a significant impact on morbidity and prognosis.

### 1.2. Subtypes of amyloid disease with cardiac manifestations

At least 27 different precursor proteins for amyloidosis have been identified [3]. Although almost every amyloidogenic protein can deposit in the heart, a few specific types of amyloid have a predilection to involve this organ and are responsible for most clinical presentations. Of the nine proteins that have been shown to potentially involve the heart, two proteins: the immunoglobulin light chain and the serum protein transthyretin are responsible for the two clinically most important types of cardiac amyloidosis. Immunoglobulin light chain is involved in AL amyloidosis and transthyretin (TTR) is involved in both familial- ATTR and senile-SSA amyloid types. Other rare amyloid types that involve the heart (such as apolipoprotein A1) and amyloid types unusual to involve the heart such as secondary amyloid (AA) [4] or hemodialysis associated ( $A\beta 2M$ ) will not be discussed in this chapter. Another more recently described type of cardiac amyloidosis results in isolated atrial deposition. Deposited

atrial amyloid resembling natriuretic peptides [5] was initially thought to be of questionable clinical significance. This subtype, found mostly in elderly women, is increasingly associated with atrial fibrillation [6],[7] and remodeling [8] but tends not to be associated with the classical clinical findings of cardiac amyloidosis.

### **1.3. Light chain (AL) Amyloidosis**

This is the most common systemic amyloidosis in the United States and the most common cause of cardiac amyloidosis. It occurs equally in men and women usually over the age of 50. The incidence of AL in the United States is between 2000 and 2500 cases a year [9],[10]. This is a systemic disease most commonly involving more than one organ system which may include the kidneys, liver, nerves, and blood vessels. Therefore, most patients have clinical evidence of extra cardiac involvement including proteinuria, peripheral and autonomic neuropathy and evidence of liver and skin involvement. Periorbital purpura is a relatively rare, but characteristic finding. Amyloid can be detected in the heart in almost every case but clinical cardiac involvement is encountered in about half of cases. However, when present, cardiac amyloidosis will usually dominate the clinical presentation and has the greatest impact on survival [11]. The amyloid is derived from monoclonal light chains (intact or fragmented) produced from a population of clonal plasma cells. It is generally thought that organ dysfunction in AL is primarily due to infiltration by the amyloid deposits, but there is increasing evidence for a direct toxic effect of the amyloidogenic light chain [12],[13]. To support this paradigm, after successful chemotherapy patients with AL amyloidosis frequently have improvement in heart failure symptoms associated with decrease in biomarkers despite unchanged echocardiographic findings [14].

There is little overlap with the most common plasma cell dyscrasia- multiple myeloma. Only 10-15% of myeloma patients also develop AL amyloidosis and most AL patients do not develop overt myeloma [9]. These two diseases, however, share several features, that is, excess bone marrow plasma cells and increased monoclonal proteins in the blood and urine. Light chain deposition disease of the heart is a rare condition to be differentiated from AL cardiomyopathy in which cardiac dysfunction may occur due to deposition of immune light chains that do not form amyloid in the myocardium [15],[16]. This condition is related to plasma cell dyscrasias such as multiple myeloma or Waldenstrom's macroglobulinemia and like AL amyloidosis may improve after chemotherapy directed at the underlying bone marrow clone is administered [17].

### **1.4. Transthyretin amyloidosis**

Transthyretin (TTR) is a hepatically synthesized plasma protein. The gene is coded on chromosome 18 and includes 4 exons. In the serum the protein circulates as a homotetramer, in which each monomer is comprised of 127 amino acids arranged as 8 antiparallel beta pleated sheet domains [18]. This structure is prone to form beta pleated sheet fibrils, the building blocks for amyloid deposition [19]. Transthyretin can accumulate in the heart to cause cardiac amyloidosis in two clinical syndromes: familial amyloidosis (ATTR) or senile amyloidosis (SSA), the latter of which is more recently been called age-related amyloidosis.

### **1.5. Familial amyloidosis (ATTR)**

This disease is most commonly due to a mutation in the TTR protein, and is transmitted as an autosomal dominant trait. To date, about 100 different amyloidogenic TTR point mutations have been described [20]. The prevalence and severity of cardiac disease varies with different mutations. Penetrance may vary resulting in some individuals with a mutated genotype that may not develop clinical disease. Males and females are equally affected. Interestingly the cardiac amyloid deposits consist of both wild type as well as mutant TTR [21]. The disease frequently affects the heart and/or the nervous system. Other manifestations include ocular involvement with opacities of the vitreous humor [18]. A “scalloped pupil” is pathognomonic to the disease but is rarely encountered [22]. Carpal tunnel syndrome is another common feature [18]. Nervous system involvement occurs as a polyneuropathy that usually starts with paresthesias and dysesthesias in the lower extremities and ascends centripetally [23], with possible later motor dysfunction. Autonomic nervous system involvement is common, including dyshidrosis, bowel irregularities, orthostasis, erectile dysfunction, and urinary retention or incontinence. Although the CNS is usually not involved, certain rare mutations are associated with leptomeningeal amyloidosis. In contrast to AL amyloidosis, renal involvement is unusual in TTR associated amyloidosis and neither is liver deposition or macroglossia a prominent feature. Patients may present with neuropathy, cardiomyopathy or a combination of both and specific TTR mutations usually determine the organs of primary involvement [24].

Several common mutations warrant specific consideration. Isoleucine to valine substitution at position 122 (Val122Ile) is among the most common, present in 4% of African Americans [25]. These patients present with severe cardiomyopathy usually by age 60, with little or no neuropathy [26]. Valine to Methionine substitution at position 30 (Val30Met) is probably the most studied TTR mutation worldwide. It is prevalent in a few specific locations (also termed endemic) in Japan [27], Portugal [28] and northern Sweden [29]. In Japan and Portugal patients usually manifest with neuropathy in the mid 30s, and cardiomyopathy is rare, typically occurring after the sixth decade. By contrast the same mutation in Sweden usually manifests later (mid 50s), and has slower progression and lower penetrance [30]. The threonine to alanine substitution at position 60 (Thr60Ala) usually manifests with predominantly cardiac amyloidosis and minimal neuropathy.

### **1.6. Senile amyloidosis (SSA) or age related amyloidosis**

This is a non-hereditary form of transthyretin related amyloidosis. It is almost exclusively a disease of the elderly (>70 years old) and occurs more commonly in men. The disease involves deposition of amyloid from normal unmutated transthyretin (wild type). Wild type transthyretin deposits almost exclusively in the heart and when extensive enough is associated with cardiac disease. The only other manifestation may be carpal tunnel syndrome often preceding heart failure by 3-5 years. The finding of some transthyretin amyloid deposition is common in the elderly (up to 25% of autopsies in subjects over the age of 80) and not always associates with clinical cardiac amyloidosis [31].

## 2. Specific features of cardiac amyloidosis

### 2.1. Pathology

Grossly, amyloid can be seen to infiltrate any or all cardiac structures including the myocardium (atrial and ventricular), valves, conduction system, coronary and large arteries [32]. This usually results in thickening of all 4 chambers, biatrial dilatation, normal or mildly dilated right ventricle and normal or small left ventricular cavity. The conduction system is usually involved. Valve infiltration may lead to thickening or nodule formation. Valve regurgitation is generally mild but can be severe.

Microscopically, myocardial cells separate and are distorted by amyloid deposition [33]. Amyloid deposits stain pink with Hematoxylin and Eosin and show an apple-green birefringence when stained with Congo red and viewed under polarized light. By electron microscope the fibrils are non-branching with a consistent diameter of 7.5 to 10 nm [34]. Additionally, the intramyocardial vessels are frequently infiltrated by amyloid [34]. Rarely this small vessel involvement will cause the initial presentation with only minimal myocardial infiltration. Involvement of epicardial vessels is rare but may mimic atherosclerotic plaques. There may be differences in patterns of deposition between AL and SSA amyloid to suggest more vascular involvement in the former [35].

### 2.2. Clinical manifestations

In AL amyloidosis, cardiac manifestations are rare to occur without associated systemic manifestations such as gastrointestinal symptoms or heavy proteinuria [36]. Age at presentation is typically in the fifth to sixth decade, and is rare in patients younger than 30 [36]. ATTR may present with or without neurologic manifestations. SSA usually does not involve other organs, with the exception of carpal tunnel symptom and will manifest usually in an older patient.

Heart failure is the usual cardiac manifestation, typically with preserved left ventricular ejection fraction. Biventricular failure is usually present, but the presenting symptoms are often those of right heart failure including ascites and peripheral edema. This can help differentiate from cardiac hypertrophy due to hypertension alone, where right heart failure is less common on presentation. Other non specific symptoms include fatigue and orthostatic hypotension. Due to the high prevalence of ATTR in the African American population, symptoms of right heart failure in an African American in his/her sixth decade with ventricular wall thickening should alert the physician to suspect familial amyloidosis (transthyretin, Val Ile122) rather than hypertensive heart.

Other cardiac manifestations include arrhythmias and dysrhythmias. Atrial fibrillation is common and may worsen heart failure symptoms. Possible causes of atrial fibrillation are atrial infiltration, elevated left atrial pressure due to the diastolic dysfunction and older age (in SSA amyloidosis). Syncope and sudden death can occur. Differential diagnosis includes orthostatism and arrhythmias. Arrhythmias can include brady-arrhythmias such as caused by conduction delays. Ventricular tachy-arrhythmias are described but sustained VT is uncom-

mon and most cases of monitored sudden death were due to electro-mechanical dissociation [37]. Chest pain due to small vessel disease is a rare (1-2%) presentation of AL amyloidosis [38]. In some of these cases imaging studies may be positive but coronary angiography will demonstrate normal epicardial vessels.

Another clinical aspect is the tendency for thromboembolic events. As stated above atrial fibrillation is a common finding, especially with advanced disease. Atrial standstill can occur due to amyloid infiltration even in the presence of sinus rhythm and contribute to thrombus formation. In AL amyloid nephrotic syndrome can also contribute to hypercoagulopathy and thrombus formation. Although debated, these risks may warrant a relatively liberal use of anticoagulation as discussed below [39]-[41] [42].

### **2.3. Diagnosis**

The diagnosis of cardiac amyloidosis can be challenging. A high level of suspicion is needed since diagnosis can often be missed, especially with the transthyretin amyloidosis. Patients may be misdiagnosed with more common causes of heart failure associated with cardiac hypertrophy such as hypertensive cardiomyopathy. Clinical suspicion usually arises during evaluation for right sided heart failure, because other manifestations of cardiac amyloidosis occur less commonly. Systemic manifestations typical of each type of cardiac amyloidosis may be supportive of the diagnosis. Further basic evaluation includes electrocardiography and echocardiography. More advanced evaluation including MRI and radioisotope and hemodynamic studies may also be utilized to substantiate the diagnosis. Definite diagnosis is generally made by cardiac biopsy and pathological evaluation but may not be needed in every case.

### **2.4. Cardiovascular directed physical examination**

An irregular rhythm due to atrial fibrillation occurs in 10-15% of the patients. Blood pressure is often low and can further decrease with standing. Manifestations of right heart failure due to restrictive cardiomyopathy will include an elevated jugular venous pressure but Kussmaul's sign is rarely present (in contrast to constrictive pericarditis). The apex beat is frequently impalpable. The first and second heart sounds are usually normal. A left ventricular S3 is rare but a right ventricular S3 may be heard. A fourth heart sound is almost never present, possibly due to atrial dysfunction [9]. On chest examination rales are uncommon but pleural effusion may occur both due to heart failure as well as to amyloid involvement [43]. Hepatomegaly is common, due to either congestion or AL amyloid infiltration (causing a rock-hard organ in the latter case). Peripheral edema may be profound, especially if nephrosis co-exists.

### **2.5. Systemic findings**

The diagnosis of systemic amyloid involvement and findings of monoclonal immunoglobulin light chain may suggest AL amyloidosis. In detecting serum light chain, immunofixation is preferred to electrophoresis since the amount of paraprotein may be small. Serum free light chain assay is even more sensitive than immunofixation [44]. The finding of a monoclonal protein is not necessarily pathological and differential diagnosis includes monoclonal gamm-

opathy of uncertain significance (MGUS). A monoclonal protein as an incidental finding (MGUS) can be found in up to 5-10% of patients more than 70 years old [45]. Not all cases are benign and the quantitative serum free light chain assay may predict progression in some cases [46]. The combination of abnormal kappa/lambda ratio and positive immunofixation identified 99% of patients with AL amyloidosis [47]. When considering the serum immunoglobulin free light chain, elevations of either the serum kappa or lambda free light chain in the context of a normal ratio between the two does not suggest a clonal process, like what one sees in AL. Renal failure and non-specific inflammation can cause elevation of both types of light chain, and the normal ratio is preserved. Light chain elevations associated with a clonal process will also include an abnormal ratio. Amyloid deposition can be found in abdominal fat needle aspiration and used for tissue confirmation of systemic amyloidosis [48],[49]. Eventually bone marrow biopsy is necessary to assess the percentage of plasma cells and rule out myeloma and other disorders such as Waldenstrom's macroglobulinemia.

In the case of ATTR amyloidosis systemic evaluation should focus on a thorough neurological evaluation including eye examination. Genetic analysis may be helpful if ATTR is suspected, especially if a familial trait is identified and may be utilized in consulting siblings.

## 2.6. Electrocardiography

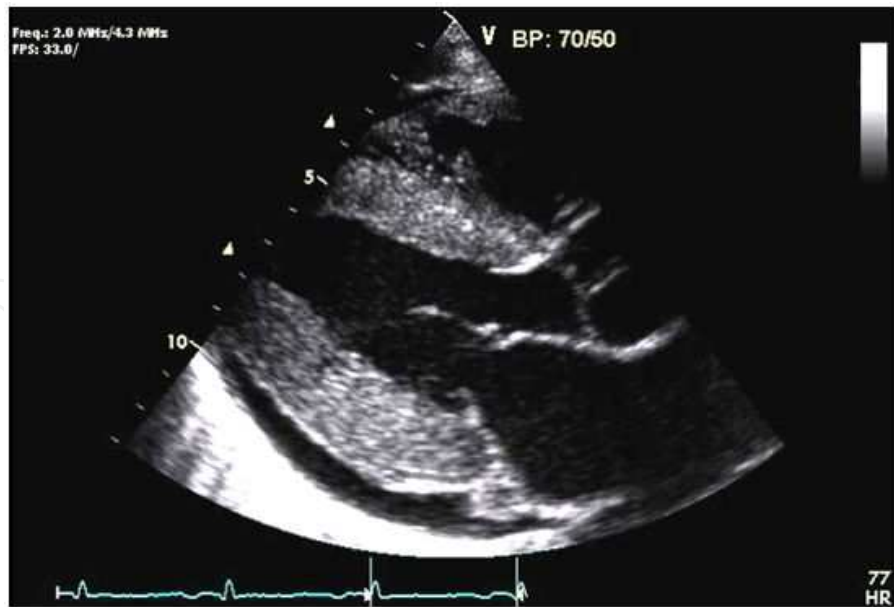
Low voltage QRS (<5mm in all limb leads) [50] is one of the hallmarks of the disease. However the lack of low voltage does not rule out the disease and in very rare cases, an unusual presentation with EKG features of left ventricular hypertrophy has been described. Other common observations include pseudoinfarct pattern, repolarization alterations and T-wave abnormalities, and atrial fibrillation [51]. Atrial involvement may lead to delayed atrial conduction and a long PR interval. Interestingly, bundle branch blocks tend to be uncommon [9]

## 2.7. Echocardiography

Usually ventricular wall thickening in the absence of left ventricular cavity dilatation is seen. Ejection fraction is often normal. Trans-mitral Doppler and tissue Doppler frequently suggests elevated left ventricular filling pressure [52],[53]. A decreased transmitral A wave can be due to the direct effect of atrial infiltration and not only the restrictive physiology therefore a normal E wave deceleration time with small A wave can be encountered [54] [55]. Pericardial effusion is common. A typical echocardiographic image is shown in figure 1.

Clues to differentiate LV thickening due to amyloidosis from LV hypertrophy include:

1. Disproportional impairment of longitudinal motion. Subendocardial fibers are particularly susceptible to damage in amyloidosis. Since these are longitudinal, the longitudinal contraction of the heart is impaired early in the disease process. This can be diagnosed using tissue Doppler as well as strain and strain rate [56],[57].
2. Involvement of other cardiac structures including RV free wall thickening, prominent biatrial dilatation and valvular thickening.



**Figure 1. Representative echocardiographic image in a patient with cardiac amyloidosis.** Parasternal long axis echocardiographic view showing granular myocardium with increased left and right ventricular wall thickness in a 77 year old with cardiac amyloidosis. Note the pericardial effusion.

3. Absence of high voltage QRS on surface EKG despite the appearance of a thickened left ventricle. The opposite may occur with decreased voltage as ventricular mass is increased [58].

In about 5% of patients cardiac amyloidosis can mimic hypertrophic cardiomyopathy echocardiographically [59],[60]. Unlike true hypertrophic cardiomyopathy ventricular hypertrophy on the EKG limb leads is almost never seen and systolic anterior motion of the mitral leaflet is uncommon, although chordal anterior motion may be present.

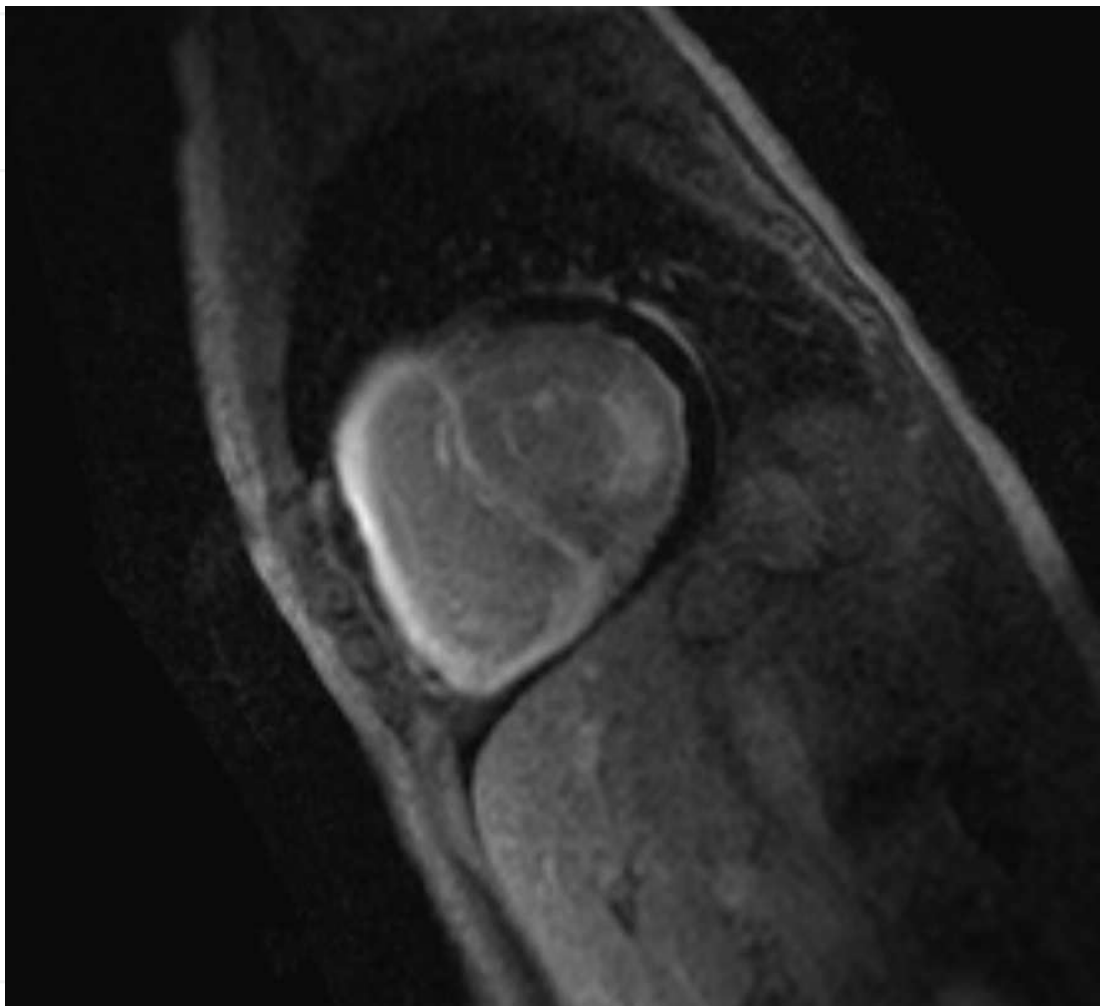
Echocardiographically distinguishing the different types of cardiac amyloidosis is challenging. Ventricular cavity is usually smaller and ventricular walls thicker in SSR compared to AL amyloidosis [61]. One clue to differentiate ATTR and AL amyloidosis may be that QRS voltage may be higher due to the amount of ventricular thickening in ATTR as compared to AL amyloidosis [62]. Subtle differences in strain and strain rate were described between the two [57]. These are possibly related to the toxic effects of the light chains in AL, absent in ATTR amyloidosis [12].

## 2.8. Magnetic Resonance Imaging (MRI)

Gadolinium tends to accumulate in the amyloid infiltrated cardiac interstitium. Therefore a distinctive pattern in cardiac MRI can be highly suggestive of the diagnosis. This consists of faster washout than usual from blood and myocardium, and later a diffuse, predominantly subendocardial delayed gadolinium uptake pattern [63]-[68]. A representative MRI is shown in figure 2. Less commonly a focal distribution with variable trans-mural extension is seen, more often in the mid-ventricle [69]. The analysis of gadolinium kinetics may have prognostic



value as well as diagnostic utility [70]. The use of gadolinium may be restricted by the potential harm of causing nephrogenic systemic fibrosis in patients with renal impairment (especially in AL amyloidosis) and therefore the possible utility in substantiating the diagnosis should be carefully weighed against this possible risk.



**Figure 2. Magnetic resonance image in cardiac amyloidosis.** Cardiac MRI showing a short axis myocardial delayed enhancement image obtained 10 minutes following gadolinium administration demonstrating diffuse abnormal enhancement (white) of the right ventricular free and inferior walls as well as focal abnormal enhancement of the inferolateral left ventricular myocardium in a subendocardial distribution. The diffuse abnormal enhancement involving both right and left ventricles is characteristic of cardiac amyloid deposition.

## 2.9. Radioisotope imaging

Serum amyloid P binds in a calcium dependent way to amyloid and <sup>123</sup>I-labeled serum amyloid P component has been used to identify amyloid deposits. However its use in the heart is hampered by blood pool uptake [71] and it is available only in a few highly specialized centers. <sup>99m</sup>Tc-aprotinin may be fairly specific for cardiac amyloidosis but experience with this technique is limited [72].

## 2.10. Hemodynamics

Amyloid cardiomyopathy physiology is typically restrictive. Left ventricular end diastolic pressure (LVEDP) is typically elevated with a dip and plateau waveform. Since the left ventricle does not dilate the patients are usually sensitive to volume loading and even small reductions in contractility may cause significant reduction in stroke volume. However hemodynamics displayed by catheterization are not always typical. Among 38 patients with ATTR cardiac amyloidosis one had an RV pressure curve dip and plateau, 34% had elevated wedge pressure. Interestingly 29% patients did not display hemodynamic diastolic abnormalities at rest [73].

Differentiation from constrictive pericarditis may necessitate a simultaneous right and left hemodynamics study. Early observations suggested that unlike constrictive pericarditis, in amyloidosis LVEDP is elevated at least 7mmHg above right ventricular end diastolic pressure [74]. Later reports have argued this is not always the case and amyloidosis can masquerade constriction hemodynamics [75]. Pulmonary systolic pressure >50mmHg is another parameter thought to be less likely in pure constriction and if occurs may suggest restrictive physiology such that occurs with amyloidosis. Currently accepted parameters that best differentiate constriction from restrictive cardiomyopathy include exacerbated interventricular dependence (demonstrated by increased inspiratory rise in RV pressure and fall in LV pressure as measured by the systolic area index) and dissociation between intrathoracic and intracardiac pressures [76] [77].

## 2.11. The role of cardiac biopsy

In treating a patient with suspected cardiac amyloidosis, the clinician may be faced with the dilemma whether to perform a cardiac biopsy, most commonly in the setting of TTR. A careful risk benefit evaluation is warranted for every case since, while this procedure may provide useful diagnostic information [78],[79], the risks are not negligible. Myocardial biopsy has a good negative predictive value (since cardiac involvement is widespread). Biopsy of the myocardium (or any involved tissue) provides information on the type of amyloid. The most accurate technique appears to be molecular analysis of the amyloid fibrils using mass spectrometry [80]. In patients with a confirmed diagnosis of systemic amyloidosis via biopsy proof of another tissue, ventricular wall thickening and low or normal voltage EKG, the diagnosis of cardiac amyloidosis is probable and biopsy should be avoided. If the patient is hypertensive and there is uncertainty regarding cardiac involvement, biopsy may be useful. The most accessible tissue to biopsy is that abdominal fat, which has sensitivities for AL of about 80% and for TTR of about 40%. If suspicion of amyloidosis is high, and there is no other organ involvement, cardiac biopsy may be needed to confirm the diagnosis. Since small amounts of amyloid deposition are a common finding in the very elderly [81] caution should be taken when interpreting the results in this population, especially if the amyloid deposits are sparse and the echocardiographic appearance is not convincing. In an elderly patient with clinical and echocardiographic findings consistent of cardiac amyloidosis and free light chain in the serum the differential will include coincidental SSA amyloid and MGUS versus AL amyloid. If other tissue is not available or yields negative results, endomyocardial biopsy with typing

using laser capture mass spectrometry or immunochemistry or immunogold electron microscopy may be needed to differentiate ATTR from AL.

## 2.12. Prognostic markers

The type of amyloidosis by itself is an important determinant of survival and every type should be considered separately when discussing prognostic issues. Patients with AL amyloidosis generally carry the worst prognosis and most of the current research on prognostic evaluation is focused on this group. Clinical features such as low ejection fraction and low voltage pattern were associated with increased mortality [82]. Cardiac biomarkers may be elevated in patients with AL and are being utilized to estimate prognosis. Cardiac troponins may be elevated due to myocyte death or injury and elevated levels predict worse prognosis in AL patients [83]. Elevated brain natriuretic peptide (BNP) may reflect both congestive HF as well as compression by adjacent amyloid deposits [84],[85] and has also been associated with worse survival. Staging using serum levels of BNP or its n-terminal portion (NT-proBNP) together with serum troponin is used to aid in risk assessment and prognosis in AL amyloidosis [86],[87]. More recently, a risk stratification score using cardiac troponin, NT-proBNP and uric acid was developed to assess early death among AL patients [88]. Even more recently, an additional risk score that includes NT-proBNP, troponin T, and serum immunoglobulin free light chain adds further prognostic discrimination[89].

## 2.13. Prognosis

In the absence of treatment, the natural history of AL amyloidosis is dismal (80% two year mortality) [90]. Although prognosis has improved over the years with the advancement of treatment [88], mortality remains high, especially in the presence of heart failure symptoms (median survival 4-6 months) [11]. The course in ATTR amyloidosis is generally more indolent, with 92% 1 year survival [62] and heart failure may be easier to control. Genotypes differ in prognosis, and patients with the Val30Met mutation tend for better prognosis compared to other mutations [24]. Senile amyloidosis is also associated with better survival compared to AL amyloidosis, despite older age of presentation and thicker myocardium by echocardiography [61]. In one report median survival was 60 months, compared to 5.4 months for AL amyloidosis [91]. Similar results were shown in a larger series comparing the 3 major cardiac amyloidosis syndromes [73].

# 3. Treatment

## 3.1. Disease specific treatment

Cardiac dysfunction in AL amyloidosis may be caused by direct toxicity of the circulating serum free light chains, in addition to the deposited amyloid tissue [13]. Therefore, treatment of the underlying plasma cell dyscrasia in AL amyloid involving chemotherapy [92] can cause a reduction in the cardiac biomarker NT-proBNP and improve survival [14],[93]. A range of

chemotherapies ranging from low dose melphalan and dexamethasone to high dose melphalan with autologous hematopoietic stem cell transplantation are among the most commonly used therapies. One of the more promising, but least well studied drugs, that is directed against the plasma cell clone is bortezomib. Bortezomib is a proteasome inhibitor and utilizing it, a hematological response can be achieved more rapidly (in about a month) in high percentages of patients [94],[95], but clinical trials using this drug have typically excluded those AL patients with the most significant cardiac dysfunction. Other treatments using thalidomide or lenalidomide may also be effective, but these drugs have been shown to exacerbate cardiac failure in a percentage of patients [96]. Despite the advancement in hematological treatment, mortality in patients with severe heart failure is still high [97]. Moreover, worsening of cardiac function may occur during the course of treatment and an ejection fraction below 40% is considered a contraindication to high dose chemotherapy with autologous hematopoietic stem cell transplantation. The complexity and potential deterioration of cardiac function during treatment warrants cardiologist involvement during evaluation for chemotherapy and during follow-up after treatment in every case, even if cardiac involvement seems minor.

Stabilization of the tetrameric structure of transthyretin using small molecule ligands is under investigation [98] and may assist patients with TTR associated amyloidosis. The non-steroidal anti-inflammatory drug Diflunisal has been found to have this effect [99],[100] but chronic use is limited due to possible worsening of fluid overload and renal function. Tafamidis is a novel transthyretin kinetic stabilizer which has been recently investigated clinically [101]. In a randomized trial this agent was well tolerated and showed a trend for delaying peripheral neurologic impairment in patients with ATTR [102]. While showing promise, this agent is not yet in routine clinical use.

### **3.2. Conventional heart failure treatment**

It is important to differentiate AL from ATTR amyloid. While in AL amyloid “conventional” heart failure treatment including beta blockers and angiotensin pathway inhibitors is usually not well tolerated, these medications may be better tolerated in ATTR patients who do not suffer from significant autonomic neuropathy. Calcium channel blockers with negative inotropic effects have no role in AL amyloid and may cause harm [103] [104]. Compared to other causes of heart failure there is no evidence for remodeling effects from beta blockers and therefore they are not indicated for patients in sinus rhythm [105]. They may be used to slow atrial fibrillation response if needed, but take care if your patient decompensates after institution. Amiodarone and digoxin may be preferred for rate control. Due to their impaired cardiac function (and restrictive LV filling), some of these patients require mild tachycardia to maintain cardiac output. There is also no role for digoxin for patients in sinus rhythm but it also may help slow atrial fibrillation response. Possible increased toxicity by increased binding of digoxin to amyloid fibrils has been reported [106] and therefore lower dosing and caution is probably justified when using this medication. Angiotensin pathway inhibitors (both angiotensin converting enzyme inhibitors and receptor blockers) may provoke hypotension (possibly due to impaired sympathetic nervous system function and reduced and relatively fixed stroke volume) and therefore should be administered only if being used to treat hyper-

tension [32]. Patients with SSA amyloid tend to tolerate these medications better than patients with AL amyloid. Diuretics and salt restriction remains the mainstay of medical treatment in cardiac amyloidosis. Careful titration is utilized since reduced preload with reduced ventricular filling pressures can decrease cardiac output and cause hypotension. Higher doses may be needed if albumin is low as a result of nephrotic syndrome (with AL). If absorption is impaired due to anasarca, intravenous treatment may be necessary sometimes in association with IV albumin.

Ancillary treatment in patients with autonomic neuropathy includes compression stockings and alpha adrenergic agonists such as midodrine [107]. Fludrocortisone is usually less well tolerated due to its sodium retaining effects and worsening of edema. Patients with erectile dysfunction can be aided by phosphodiesterase inhibitors [108].

The question of anticoagulation is complex since both a thrombotic tendency as well as a bleeding tendency (especially in AL) may occur. ATTR patients tend to bleed less than AL patients. Due to an increased risk, anticoagulation with warfarin is probably indicated when atrial fibrillation occurs, even in the absence of other risk factors. The decision is more complex in patients with sinus rhythm. Because of an increased tendency for thrombotic events and the occurrence of atrial stand-still, anticoagulation should be considered. Though this must be counterbalanced by the increased risk of bleeding, especially from the GI tract. The head and neck purpura may also be a challenge to manage among patients on anticoagulation. Atrial thrombi were indeed identified in patients with AL amyloid in sinus rhythm [39]. A small transmitral A wave (<20cm/s) can suggest impaired atrial function with more tendency to form thrombi and can be used as another clue to decision making. Transesophageal echocardiography may help to identify patients in sinus rhythm with higher risk for thrombosis such as those with spontaneous echo contrast or low left atrial appendage velocities. A cutoff of <40cm/sec was initially suggested [109] but this may be considerably lower (reported as  $13\pm 5$ cm/sec for patients with and  $27\pm 15$ cm/sec for patients without thrombosis) [41].

### 3.3. Arrhythmia, pacing and defibrillators

Maintenance of sinus rhythm seems important in the stiff restrictive amyloidotic hearts, possibly due to the importance of the atrial kick and avoiding tachycardia. Therefore careful consideration should be given to electrical cardioversion for atrial flutter or fibrillation. Amiodarone can be useful to help maintain sinus rhythm. If pacing is needed strong consideration should be given to biventricular pacing since RV pacing and the resulting dysynergy may decrease stroke volume.

Sudden death is common in patients with cardiac amyloidosis. Early studies using holter monitoring suggested a high incidence of ventricular arrhythmia [110]. However, it is presently thought that the cause of death is less often rapid ventricular arrhythmias but may include electromechanical dissociation [111] and advanced heart block. Among 19 patients with either non-sustained ventricular tachycardia or high grade ventricular arrhythmia treated with an ICD only 2 received appropriate shocks for sustained VT, while 6 died of electromechanical dissociation [112]. Thus, there seems to be little role for implantable pacemakers in cardiac amyloid patients, unless a sustained ventricular arrhythmia was documented.

Amiodarone has been used to try and prevent arrhythmias and sudden death although there is no clear evidence of benefit.

## 4. Advanced heart failure treatment

### 4.1. Cardiac transplantation in AL amyloidosis

The negative impact of cardiac involvement on survival, the rapidly deteriorating clinical manifestations and the potential for hematologic treatment led clinicians as early as the 1980's to consider cardiac transplantation in AL amyloid. While initial reports based on individual cases generated optimism [113],[114], subsequent experience highlighted suboptimal outcomes [115] calling for careful and specialized patient selection and management, including disease modifying hematological treatment such as bone marrow transplant. In selected patients with both cardiac and renal failure, combined heart kidney transplant may be offered [116]. All these considerations necessitate that transplant for this complex population is carried out in highly specialized centers with high volumes.

### 4.2. Patient selection

Patient selection for patients with cardiac amyloidosis is usually a complex decision that is to be based on careful evaluation involving multiple disciplines. Considerations include the routine assessment utilized in "ordinary" cardiac transplant including factors such as age, frailty, the advancement of cardiomyopathy and co-morbidities. Additional evaluation specific to the AL includes evaluating whether other organs are involved, ruling out multiple myeloma, and collaboration with a hematologist regarding chemotherapy. Baseline evaluation before considering heart transplant includes therefore bone marrow aspirate and biopsy, echocardiogram, serum and 24-hour urine monoclonal protein studies, serum immunoglobulin free light chain assay, a chemistry panel including creatinine, liver function tests and renal clearance estimates (table 1). Major involvement of other organ systems will render the patients as less optimal candidates. This includes evidence of peripheral neuropathy, autonomic neuropathy, gastrointestinal symptoms (diarrhea), hepatic involvement, and renal failure. Patients with significant proteinuria (>500 mg/day) are usually considered higher risk due to kidney involvement. Hepatic involvement may be suspected with elevated alkaline phosphatase and hepatomegaly and a liver biopsy may be needed to differentiate it from right heart failure. Since amyloidosis is a vascular disease, the mere presence of vascular involvement in the liver would not render a patient ineligible for cardiac transplant. The acronym DANGER was suggested for evaluation of tissue involvement and adverse outcome in the context of pre-transplant evaluation for AL amyloid. It includes *Diarrhea*, *Autonomic nervous* involvement, *poor Nutritional status*, *Gastrointestinal involvement* (bleeding), *Elimination* (renal) or *Respiratory* dysfunction[117]. Recurrent pleural effusion (more common in AL amyloidosis) is also an ominous sign for bad prognosis [43].

Routine cardiac transplantation evaluation with the following additional studies:	<ul style="list-style-type: none"> <li>• Serum protein electrophoresis</li> <li>• Urine protein electrophoresis (24-hour urine)</li> <li>• Factor X and thrombin time (special coagulation studies)</li> <li>• Bone marrow biopsy with aspirate, labeling index and smear</li> <li>• Labeling index in peripheral blood with number of circulating plasma cells</li> <li>• Serum carotene</li> <li>• <math>\beta_2</math>-microglobulin</li> <li>• C-reactive protein</li> <li>• 24-hour urine creatinine clearance</li> <li>• 48-hour stool collection for fat</li> <li>• Subcutaneous fat aspirate</li> <li>• Metastatic bone survey with single views of humeri and femurs</li> </ul>
Pulmonary assessment will proceed as follows:	<p>Recurrent pleural effusions, refractory to treatment will necessitate:</p> <ul style="list-style-type: none"> <li>• Chest CT</li> <li>• Possible lung biopsy dependent on CT findings</li> </ul>
Liver assessment will proceed as follows:	<ul style="list-style-type: none"> <li>• If alkaline phosphatase &lt;1.5-fold upper limit of normal (350), then proceed with transplant evaluation</li> <li>• If alkaline phosphatase 1.5- to 3-fold upper limit of normal, then proceed to liver biopsy: <ol style="list-style-type: none"> <li>1. If there is portal tract amyloid deposition, then there is an absolute contraindication</li> <li>2. If vascular amyloid only, then proceed with transplant evaluation</li> </ol> </li> <li>• If alkaline phosphatase is <math>\geq 3.0</math>-fold upper limit of normal (750), absolute then there is a contraindication to HT</li> </ul>
Renal assessment will proceed as follows:	<p>Lothalamate clearance should exceed 50 ml/min/1.73 m<sup>2</sup></p> <ul style="list-style-type: none"> <li>• If urinary albumin is &lt;250 mg/24 hours, then proceed with transplant evaluation</li> <li>• If urinary albumin is 250 to 1,000 mg/24 hours, then proceed to renal biopsy <ol style="list-style-type: none"> <li>1. If vascular amyloid only, is present then proceed with transplant evaluation</li> <li>2. If interstitial or glomerular amyloid is present, then there is an absolute contraindication to cardiac transplant</li> </ol> </li> </ul>
Blood/marrow plasma cell labeling index assessment will proceed as follows:	<p>Plasma cell labeling index</p> <ul style="list-style-type: none"> <li>• If plasma cell labeling index is <math>\geq 2\%</math>, then exclude from consideration for transplant evaluation</li> <li>• If plasma cell labeling index is <math>\geq 1\%</math>, then proceed to metastatic bone survey to exclude myeloma-associated bony lesions</li> </ul>

- If plasma cell labeling index is <1%, then proceed with transplant evaluation

Peripheral blood labeling index

- If peripheral blood plasma cell labeling index is  $\geq 1\%$ , then absolute contraindication to cardiac transplant

Plasmacytosis

- If plasma cell differential on marrow aspirate is <10%, then proceed with transplant evaluation
- If plasma cell differential on marrow aspirate is 10% to 20%, then do metastatic bone survey to exclude myeloma-associated bony lesions
- If plasma cell differential on marrow aspirate, marrow biopsy or cytoplasmic immunoglobulin-positive plasma cells are  $\geq 20\%$ , then contraindication to there is an absolute cardiac transplant

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Intestinal assessment will proceed as follows: • 48-hour stool collection for fecal fat to rule out malabsorption

- Serum carotene if low level could indicate malabsorption
- Endoscopic and flexible sigmoidoscopic evaluation with biopsy
  1. If vascular amyloid deposition only, then proceed with transplant evaluation
  2. If mucosal amyloid deposition, then there is an absolute contraindication to cardiac transplantation

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Adopted from Lacy MQ et al. 2008.

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**Table 1.** Pre-transplant evaluation of AL amyloid patients.

#### **4.3. High dose chemotherapy with autologous hematopoietic stem cell transplant (ASCT) after heart transplant in patients with AL**

Since the clinical course of these patients is usually rapidly progressive once heart failure occurs, death rates on the transplant list tend to be high. Cardiac transplant alone does not halt the ongoing amyloid deposition and although it results in temporary improvement, this is followed by an overall poor prognosis [114],[115]. Unless therapy directed at the underlying plasma cell clone is effective, the amyloid may also recur in the transplanted heart at a later stage, despite initial clinical improvement of heart failure [118]. Therefore, the treatment strategy should be to follow the heart transplant with chemotherapy, usually within 6 months to a year after the heart transplant to allow for healing from the surgery and tapering down of the immunosuppression. Initial experience was described in 5 patients, of whom 2 died of progressive amyloid and 3 survived [119]. With increasing experience with patient selection and treatment results are improving [120] and in selected patients prognosis may be comparable to non-amyloid patients [117]. This strategy has been shown to be feasible and associated with improved survival with carefully selected patients [121]. Although there are some reports of late recurrence of cardiac amyloidosis [122] despite ASCT this is considered still the strategy that offers the best chance for long term good outcomes.



Since the disease is rapidly progressive and patients will generally wait 4-6 months after heart transplant to be fit for ASCT. Therefore timing of heart transplant is especially crucial in this patient setting since patients might miss the window of opportunity for hematologic treatment. Extended donor criteria have been advocated and may be utilized to facilitate a timely transplant in selected cases [123]. Another approach would be to consider heart transplant after successful hematological treatment including ASCT [124], but this strategy is fraught with more hazard, because of the high risk of death among ASCT AL patients with cardiac amyloid bad enough to require cardiac transplantation.. Newer chemotherapeutic agents that are better tolerated may be used to achieve partial remission [95] and may halt the progression of cardiac symptoms by decreasing serum levels of light chains with potential toxic myocardial effects, and thereby facilitate survival on the waiting list for heart transplant.

#### **4.4. Outcomes of heart transplant in AL cardiac amyloidosis**

Survival in transplanted patients with amyloidosis is generally poorer when compared to patients without amyloidosis. Five year survival rates reported from the European registry were 38%, with prevalent progression of the systemic disease [125]. Analyzing results of the United Network of Organ Sharing for 69 patients with amyloid heart disease, 1 year actuarial survival was 74.6% compared to 81.6% for all other heart transplanted patients and 5 year survival was 54% versus 63.3% respectively. The authors included all types of amyloid and did not detail treatment for the underlying disease [126]. Data from other registries suggests poorer prognosis for patients transplanted with AL amyloidosis compared to other types of cardiac amyloidosis [127]. As described above, survival may be improved if bone marrow transplantation is performed after cardiac transplant. In carefully selected patients survival utilizing this strategy can reach about 60% in five years which is comparable to the general heart transplant population [121],[128],[129].

#### **4.5. Cardiac transplantation for transthyretin related amyloidosis**

Heart transplant for significant cardiomyopathy related to transthyretin amyloid deposition has been successfully deployed with overall good outcomes. Specific considerations include possible associated neuropathy and need for combined heart-liver transplant in ATTR amyloidosis and the advanced age of presentation in SSA amyloidosis.

#### **4.6. Patient selection**

In ATTR cardiac amyloidosis a major determinant of pre-transplant evaluation and candidacy is the presence and severity of associated neuropathy. Autonomic disturbances should be evaluated specifically including orthostatic hypotension, gastrointestinal and urinary tract dysfunction. Other factors of importance include the body mass index, patient age and degree of disability. Generally patients with SSA are not offered transplant due to their advanced age, however if presenting early, transplantation may be successfully performed [130].

#### 4.7. Combined heart and liver transplant in ATTR cardiac amyloidosis

Since the abnormal transthyretin is primarily synthesized by the liver, liver transplantation is a reasonable treatment for ATTR. Liver transplantation in ATTR can halt, and in some cases is associated with regression of amyloid deposits [131],[132]. This is especially true for certain mutations (such as Val30Met) where liver transplantation can halt neurological symptoms and improve general symptoms (gastrointestinal, nutritional, orthostasis and dyshidrosis) however this mutation less commonly causes cardiac disease [132]. Paradoxical acceleration of cardiac involvement after liver transplantation may occur in patients with mutation variants other than Val30Met [133]-[135], due to wild-type transthyretin deposition in addition to the background amyloid fibrils [136]-[138]. Therefore combined heart and liver transplantation rather heart transplant alone is considered in patients with significant cardiac involvement [139],[140]. Combined heart and liver transplantation can be performed in selected patients with results similar to heart transplant for other indications [141]. The indications for combined heart liver transplant include patients with heart failure symptoms and without advanced neurological involvement and patients with non Val30Met mutations who are candidates for liver transplant and have echocardiographic evidence of cardiomyopathy.

The liver in these patients otherwise functions normally and generally the explanted liver can be used for another patient requiring liver transplantation (domino transplant) [142]. Amyloid deposition from the implanted liver is thought to occur very slowly. Rare cases of recurrence of amyloid deposition in the liver recipient have been reported 8-10 years after the transplant [143]-[145].

The surgical approach to combined heart-liver transplant has changed over the years. Initially transplantation of the heart and maintaining the patient on cardio-pulmonary bypass during the liver transplant was used. Subsequent concerns about substantial coagulopathy and increased bleeding changed the strategy to performing liver implantation after separation from cardiopulmonary bypass [139],[146],[147]. Later, improved surgical and anesthetic techniques during liver transplant and the potential benefits to the transplanted heart to remain on cardio-pulmonary bypass during liver implantation led to revising this strategy. This technique was suggested to provide a considerably shortened liver ischemia time and decreased blood transfusion compared to the sequential approach [148]. Staged heart and liver transplantation where initial cardiac transplant is later followed by liver transplant from a different donor can be used, especially for patients that are hemodynamically unstable after cardiac reperfusion [149],[150]. However the preferred method is a single donor transplant, due to the avoidance of a second major operation early after cardiac transplant as well as certain possible immunological advantages. In cases of elevated pre-formed anti-HLA antibodies, there might be an advantage to a surgical strategy where liver transplant is performed initially, followed by sequential heart transplant. The liver is thought to sequester pre-formed anti-HLA antibodies and "protect" the heart in this scenario. This approach necessitates maximal coordination to avoid a prolonged ischemic time for the implanted heart but was successful at least in one case [151].

Interestingly, heart rejection is infrequent in combined heart-liver compared to heart alone transplantation [141]. A possible explanation may be an induction of partial tolerance. The liver has been demonstrated to shed soluble HLA antigens [152],[153]. Soluble HLA antigens may lead to tolerance of the specific allotype and permit acceptance of other transplanted organs [154]. Less intensive immunosuppression may be needed in these cases and a reduced tendency for allograft vasculopathy has been recently demonstrated [155]. Overall, potentially due to the supportive contribution of these considerations and despite a larger and more complex operation results for the heart and liver transplant are comparable to those in other heart transplant patients [125].

#### **4.8. Cardiac assist devices in patients with cardiac amyloidosis**

Left ventricular assist devices (LVAD) are currently implanted for patients with advanced heart failure and improve survival and quality of life. The number of devices implanted and medical centers involved in device implantation is rapidly increasing and newer continuous flow devices replacing the older pulsatile ones and allowing for improved durability [156]. While traditional indications for LVAD support were dilated cardiomyopathies (either ischemic or non-ischemic), LVAD implantation has been successfully administered to patients with primarily restrictive physiology. Early reports of include implantation and successful support for one patient with amyloidosis with the Jarvik-2000 device [157]. A case series recently described successful support with the HeartMate II device in patients with restrictive cardiomyopathy, several of whom had cardiac amyloidosis [158]. Candidates had transthyretin related cardiac amyloidosis since the immune suppression, coagulopathy and systemic involvement in AL amyloidosis renders them less optimal candidates for this line of treatment.

In selecting patients with cardiac amyloidosis for LVAD some important considerations should be considered. Since the assist device will not support the right ventricle, specific consideration should be given to assess the right ventricular function. Detailed directed echocardiographic evaluation as well as hemodynamic catheterization are critical to establishing candidacy. The right ventricle is anticipated to be involved in the infiltrative disease and RV dilatation may not occur despite significant dysfunction. Total artificial heart implant may be considered if right ventricular function is poor suggesting that LVAD support alone may not be sufficient. However the long-term durability of these devices has not been evaluated and therefore implantation in patients not eligible for heart transplant (such as for older patients with SSA) may be problematic. Another important consideration is the degree of systemic involvement, particularly neuropathy. This will influence considerably their ability to recuperate from the operation and the remaining degree of physical limitation and dysfunction. Patients with LVAD support often display orthostatism and this may worsen if the patient had pre-existing autonomic dysfunction due to amyloid. Overall, with careful patient selection, meticulous operative technique (with extra care for cannula positioning in the small cavity) and dedicated post-operative follow-up, assist devices can be deployed in patients with cardiac amyloidosis with success rates comparable to conventional indications [158].

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