Amyloid heart disease

Heart involvement can have devastating consequences. The clinical consequences will depend on the type of amyloid, the extent of systemic involvement and treatment options. Patients in whom disease recognition is late have poor outcomes, because of the severity of cardiac compromise and the necessarily aggressive treatments.

The amyloidoses are a group of diseases that are part of the wider category of protein-folding disorders. In amyloidosis, proteins comprising both normal plasma constituents and mutations of such proteins undergo a change in structural conformation. This mechanical change results in circulating protein instability with consequent misfolding. The final common pathway is the creation of semi-insoluble, highly ordered fibrillar aggregates that make up the amyloid matrix. This substrate is deposited extracellularly forming a nidus for further expansion. More than 20 different proteins have been identified that can form amyloid deposits. In addition to the fibrils, several other components are common to most types of amyloidosis. These include serum amyloid P component (SAP), amyloid enhancing factor, glycosaminoglycans and other basement membrane components.

Types of amyloidosis affecting the heart

Three main types of amyloidosis affect the heart (*Table 1*); light chain (AL) amyloidosis (previously termed primary amyloidosis), senile systemic amyloidosis and familial amyloidosis, the latter most commonly resulting from a mutation in transthyretin. Each of these types has a very different prognosis when the heart is involved. The remaining forms of amyloidosis either involve the heart rarely, as in secondary amyloidosis (AA), or in a form that does not produce clinically apparent problems, such as isolated atrial amyloidosis.

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How does amyloid deposition cause heart dysfunction?

The heart is compromised by amyloid deposition through several different mechanisms. The most obvious is infiltration of the myocardium and conduction system as a result of the physical presence of amyloid in the intercellular matrix. Valvular amyloid deposition is also common, but rarely leads to significant valvular dysfunction. Small vessel amyloid deposition may lead to chronic myocardial ischemia by impairing arteriolar vasodilation. A third mechanism is through a direct toxicity effect of circulating immunoglobulin light chains (Liao et al, 2001). Finally, the systemic nature of many of the amyloidoses means that the cardiovascular system may be indirectly compromised from other organ involvement. Examples of this include severe hypotension caused by autonomic neuropathy, exacerbation of heart failure as a result of amyloid-induced hypothyroidism and, rarely, pulmonary hypertension caused by extensive pulmonary amyloid infiltration.

Clinical features of heart involvement

Amyloidosis affects all chambers of the heart, so although the clinical manifestation is often that of severe right-sided heart failure, biventricular heart failure is usually present. Peripheral oedema may be profound from markedly elevated right-sided pressures, not uncommonly aggravated (in AL amyloidosis) by concomitant nephrotic syndrome. Ascites may also be present in advanced

Table 1. Amyloid type and degree of heart involvement

Amyloid type	Amyloid sub-units	Extent of heart involvement
Light chain amyloidosis	Immunoglobulin light chains	Frequent and severe
Transthyretin amyloidosis (familial)	Mutant (and wild type) transthyretin molecules	Severe with particular mutations (Leu55Pro, Val30Met, Val122Ile, Tyr78Phe)
Hereditary apolipoprotein A1 amyloidosis (familial)	Mutant apolipoprotein A1 molecules	Severe heart involvement can occur
Hereditary fibrinogen amyloidosis (familial)	Mutant fibrinogen molecules	Severe heart involvement can occur
Gelsolin amyloidosis (familial)	Gelsolin	Rare, but heart involvement can occur
Isolated atrial amyloidosis	Atrial natriuretic peptides	Severe heart involvement possible in the elderly
Senile systemic amyloidosis (sporadic)	Wild type (non-mutant)	Severe heart involvement possible transthyretin
Reactive (secondary) systemic amyloidosis	Amyloid protein A	Rare, but severe heart involvement can occur

disease. Unlike dilated cardiomyopathy with heart failure, a fourth heart sound and left-sided third heart sound is rarely present in the restrictive cardiomyopathy of amyloidosis and, if attention is not given to the elevated neck veins, a diagnosis of heart failure may initially be missed. This may be particularly so if the echocardiogram shows a near-normal ejection fraction and attention has not been paid to indices of diastolic function. However, careful physical examination will point to a cardiac aetiology.

Investigations of cardiac involvement

Cardiac amyloidosis is usually first suspected from the appearances on echocardiography (*Figures 1* and *2, Table 2*). The heart walls are usually globally thickened and characteristically this often includes the inter-atrial septum. The myocardium shows increased echogenicity although this is not unique to amyloidosis. Valve leaflets and the pericardium may be thickened and there is often a modest pericardial effusion. In contrast to the normal-sized ventricular cavities, the atria are usually dilated and often appear not to contract, giving an immobile 'owl's eye' appearance. Doppler interrogation of ventricular inflow and tissue Doppler indices frequently show characteristic restrictive features of an infiltrative cardiomyopathy (*Figure 3*).

Low or normal voltage on the electrocardiogram in the presence of apparent left ventricular 'hypertrophy' on the electrocardiogram is very suggestive of heart involvement by amyloidosis. Q waves, without prior history of myocardial infarction, and an unusual axis are also frequent electrocardiographic findings (*Figure 4, Table 2*). Tissue Doppler techniques have also proved helpful in distinguishing amyloidosis from other causes of true hypertrophy and in characterizing ventricular dysfunction (Koyama et al, 2002). Diseases sometimes confused with amyloid heart disease include various forms of hyper-

Figure 1. Apical four-chamber view echocardiogram, showing bi-atrial dilatation, valve thickening, thick ventricular walls and a pericardial effusion. The ventricular chambers are not dilated, an almost universal characteristic of amyloid heart disease. The atria were immobile in real time reflecting extensive amyloid infiltration. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

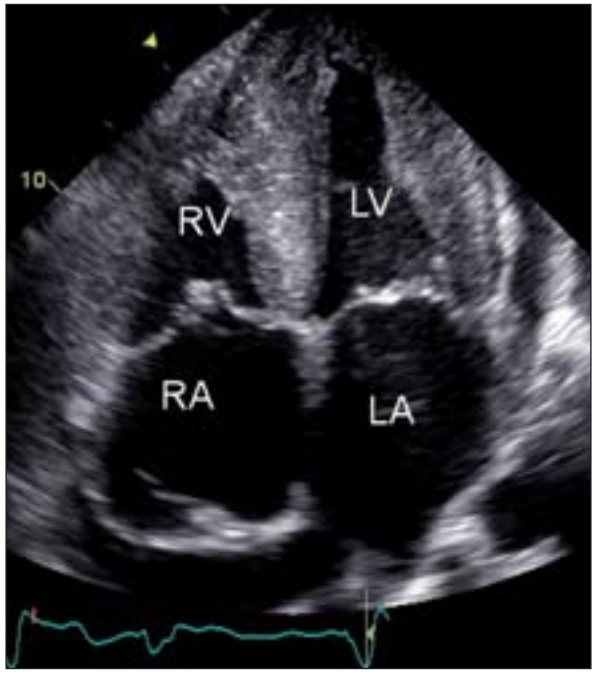


Figure 2. Subcostal four-chamber view echocardiogram, showing thickening of the right ventricular free wall and of the inter-atrial septum as a result of infiltration. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

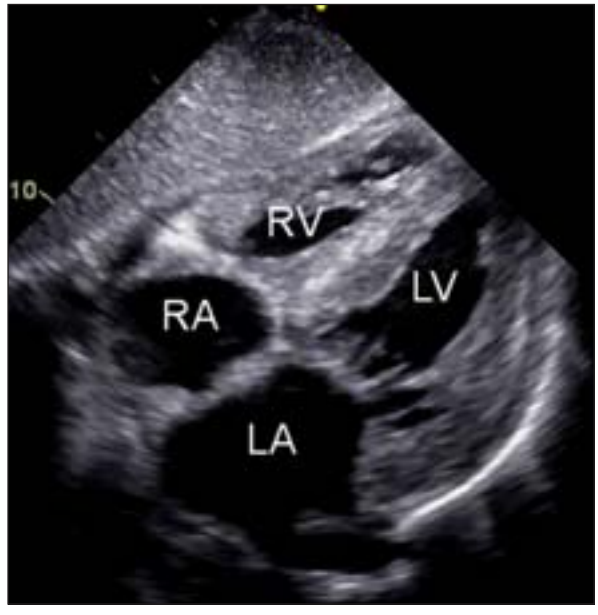


Table 2. Electrocardiographic and echocardiographic features of amyloid heart disease

Cardiac feature	Notes
Low voltage electrocardiogram	Mean limb lead voltage less than 0.5 mV
Q-waves on electrocardiogram	Usually anterior chest leads but may be inferior leads
Thick chamber walls on echo	Not true 'hypertrophy'
Thickened RV free wall on echo	Best seen on subcostal views
Ventricles are rarely dilated	Aside from early dilatation of the right ventricle
Thickening of the inter-atrial septum	Best seen on subcostal views
Granular appearance to myocardium	Not specific to amyloid heart disease
Valves appear thickened	But, surprisingly not usually that dysfunctional
Bi-atrial dilatation	Appear static, with an 'owl eye' appearance on echocardiographic apical four-chamber view
Thrombi may be seen in chambers	Thromboembolic events may be a presenting feature
Doppler may show restrictive pattern	Shown on interrogation of ventricular inflow
Pericardial and pleural effusions	May be caused by heart failure and/or pericardial or pleural involvement

RV = right ventricle

trophic cardiomyopathy and other 'deposition' diseases including Fabry disease. Constrictive pericarditis may present with a similar clinical pattern, but the echocardiographic appearance differs, with normal wall thickness and a normal or increased early relaxation profile on tissue Doppler interrogation of the myocardium.

Magnetic resonance imaging with gadolinium enhancement may help to differentiate amyloidosis from other causes of chamber wall thickening (*Figures 5* and *6*), particularly hypertrophic cardiomyopathy (Maceira et al, 2005).

Serum amyloid P component scintigraphy scanning for amyloidosis

The extent of non-cardiac amyloid deposition, of any type, can be assessed by SAP scintigraphy (Hawkins et al, 1990). Serum amyloid P is a normal plasma protein that binds reversibly to amyloid deposits. Quantifying the whole body amyloid load, primarily in the liver, kidneys and spleen, is the main indication (*Figure 7*). Bone marrow involvement on SAP scanning is also strongly correlated with AL amyloidosis type. An additional benefit is being able to follow response to treatments. Unfortunately, SAP scintigraphy is not useful for identifying amyloid in the heart, as a result of blood pool uptake, but the finding of significant isotope uptake in other organs may be helpful in planning treatment, particularly in AL amyloidosis.

Once the disease is suspected, a confirmatory histological diagnosis needs to be made. In many cases, amyloid deposition can be found in the fat, and an abdominal fat pad biopsy is a simple procedure with a relatively high yield. A higher yield will be obtained from a cardiac biopsy in suspected cardiac amyloidosis, although this carries the usual risks of endomyocardial

Figure 3. Transmitral Doppler flow showing a diminutive A-wave characteristic of atrial failure in a patient with light chain cardiac amyloid infiltration. The patient was not initially anticoagulated and suffered a transient ischaemic attack as a result of an embolic event. (A = A-wave; E = E-wave).

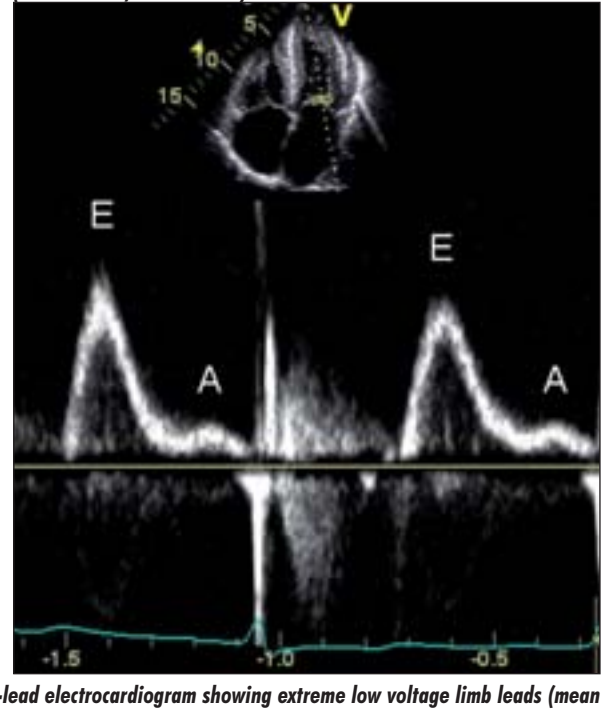


Figure 4. Resting 12-lead electrocardiogram showing extreme low voltage limb leads (mean voltage <0.2 mV) and Q waves in the anterior chest leads C1 through C3. Both features are highly characteristic of AL amyloid heart disease.

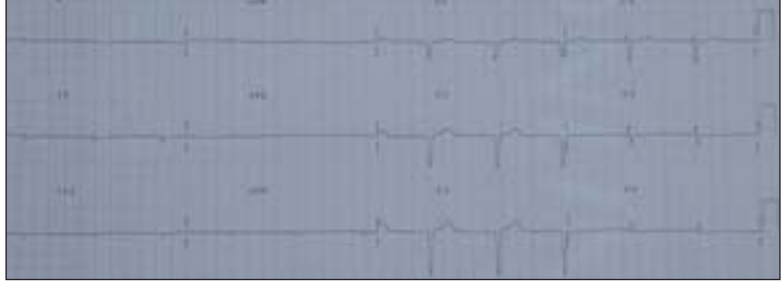


Figure 5. Cardiac magnetic resonance scan showing a short axis view with global late gadolinium enhancement, mainly in the epicardial portion, typical of cardiac amyloid.

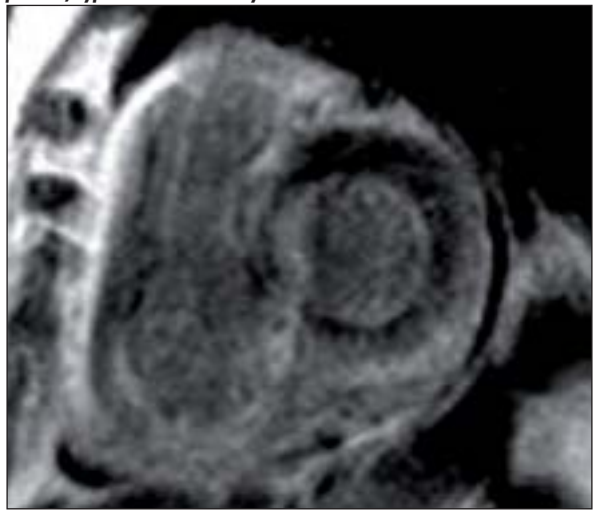
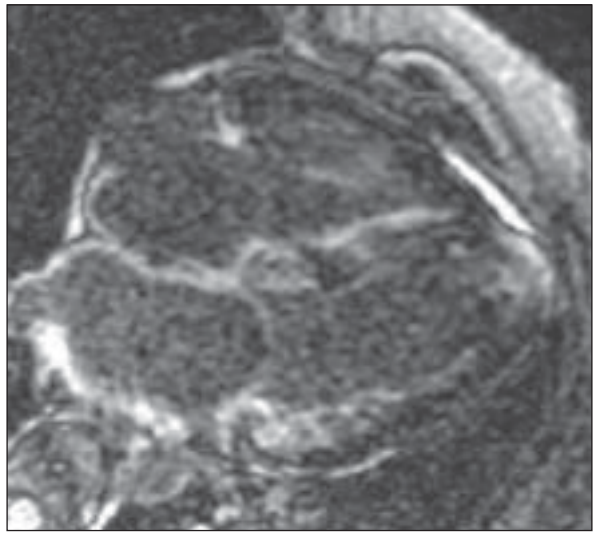


Figure 6. Cardiac magnetic resonance scan from a different patient to that shown in* Figure 5*, showing a long axis view with global late gadolinium enhancement predominantly in the epicardial portion.



biopsy. A negative cardiac biopsy in suspected cardiac amyloidosis usually rules out the disease, as infiltration is widespread and is almost always found in a biopsy specimen. Once a positive biopsy has been obtained, it is critical to determine the type of amyloid (Lachmann et al, 2002), as this determines the treatment. Immunohistochemistry has a high specificity, but it is critical that it is performed in a laboratory with appropriate experience.

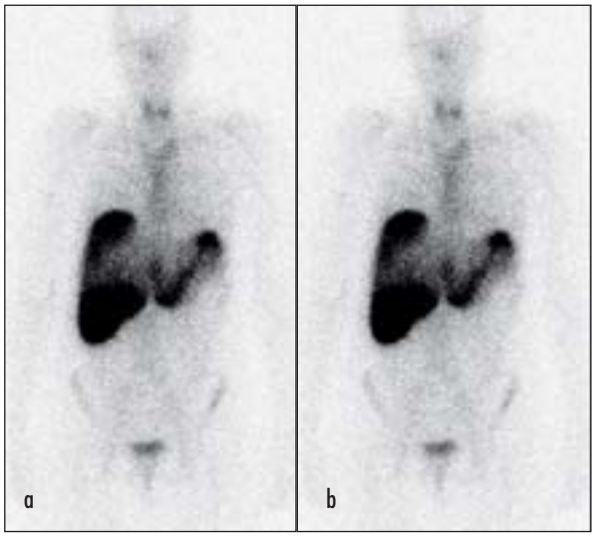
Management of amyloid heart disease

Patients with cardiac amyloidosis may benefit symptomatically from conventional heart failure therapies, although those with AL amyloidosis tend to respond poorly. Careful titration of diuretics and salt restriction remains the mainstay of management. There is no evidence of a beneficial effect of beta blockers except in atrial fibrillation, and even in this condition they should be used with caution because of their negative inotropic effects. Calcium-channel blockers may worsen heart failure, possibly by an increased myocardial concentration as a result of binding to amyloid fibrils.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are rarely tolerated in AL amyloidosis and may provoke profound hypotension if used. In senile cardiac amyloidosis, in which autonomic nervous system involvement is not a feature, angiotensin-converting enzyme inhibitors are better tolerated.

There is no role for digoxin for patients in sinus rhythm and the risk of digoxin toxicity may be increased, possibly related to abnormal binding of the drug to amyloid fibrils. In patients with atrial fibrillation, cautious use of digoxin may aid in heart rate control.

Figure 7. Serum amyloid P component scan. a. Anterior whole body scintigraphy with iodine-123 labelled serum amyloid P demonstrating diagnostic tracer uptake within the liver and the spleen. b. A posterior whole body image additionally showing tracer uptake into amyloid deposits within the kidneys and skeleton.



Hypotension in AL cardiac amyloidosis may be caused by low cardiac output or autonomic neuropathy. If the latter is present, the alpha agonist midodrine can be very effective, although the effect is usually modest. Orthostatic hypotension may require thigh-length support stockings. Fludrocortisone is generally not tolerated in cardiac amyloidosis because of its sodium-retaining effects.

If permanent pacing is needed for atrioventricular block, strong consideration should be given to biventricular pacing, as right ventricular pacing alone may further decrease the already impaired stroke volume. Unless sustained ventricular tachycardia has been documented, there appears to be little role for implantable defibrillators as most cases of sudden death in cardiac amyloidosis are the result of electromechanical dissociation.

Specific management of AL amyloidosis

In AL amyloidosis, chemotherapy is used to try and stop or at least reduce production of amyloidogenic monoclonal immunoglobulin light chain. A reduction in levels of circulating free light chains by chemotherapy is a marker of enhanced survival (Sanchorawala et al, 2005). The 5-year survival of AL amyloidosis patients with more than 50% reduction in their free light chains is 88%, compared to 39% in those whose free light chains did not fall by half (P<0.0001) (Lachmann et al, 2003).

Combined oral melphalan and prednisolone is of modest benefit in AL amyloidosis and more dose intensive regimens are now usually pursued. Intermediate dose chemotherapies, such as vincristine, adriamycin and dexamethasone or monthly intravenous melphalan with dexamethasone (Guidelines Working Group of UK Myeloma Forum et al, 2004) have, in some centres, been replaced by regimens of oral melphalan, lenalidomide or bortezomib in conjunction with oral dexamethasone.

Following success with its use in myeloma, thalidomide has been tried both alone and in combination with chemotherapy (Seldin et al, 2003), although high dose thalidomide is not well tolerated by subjects with AL amyloidosis (Dispenzieri et al, 2003). The combination of thalidomide and intermediate dose dexamethasone is effective in a proportion of patients (48%) who are refractory to therapy. Again, as with high dose thalidomide, treatment-related toxicity was frequent (65%) (Palladini et al, 2005). While dexamethasone is quite effective in suppressing light chain production, it tends to produce fluid retention in patients with cardiac amyloidosis. Thus, careful monitoring of the patient is mandatory during treatment, with frequent adjustment of diuretics.

The proteasome inhibitor bortezomid has been successful in myeloma and trials of this drug are underway in AL amyloidosis. Bortezomib prevents destruction of ubiquinated (proteins labelled for catabolism via proteasome-mediated proteolysis) molecules within the cell.

As yet there is no therapy that has been proven to promote amyloid regression, although many candidate drugs have been tested. Studies using a doxorubicin derivative (I-DOX), a cytotoxic anthracyclin, suggested promise (Gianni et al, 1995), but subsequent data were inconclusive (Gertz et al, 2002), and it is notably toxic, so is no longer used.

High-dose chemotherapy and autologous stem cell transplantation

High-dose chemotherapy with melphalan supported by autologous stem cell transplantation has been used increasingly in AL amyloidosis (Comenzo et al, 1998). Response rates in terms of clonal disease remission are encouraging with specialized centres reporting a complete haematological response in as many as 40% of eligible patients. However, eligibility criteria usually exclude patients with significant cardiac involvement, and mortality rates are appreciable with experienced centres reporting numbers between 13 and 20% (Mollee et al, 2004; Skinner et al, 2004). The overall impression is that patients with advanced disease, particularly with cardiac decompensation, tolerate this therapy poorly.

A multicentre French study (Jaccard et al, 2007) compared a regimen of oral melphalan and dexamethasone to high-dose chemotherapy and stem cell transplantation in patients with AL amyloidosis and found no difference in outcome. Early mortality was higher in the high-dose group. These findings underscore the need for a cautious approach to high-dose chemotherapy, especially in patients with cardiac disease, and indicate the importance of careful patient selection and treatment in highly experienced centres.

Management of hereditary amyloidosis

In hereditary amyloidosis the amyloidogenic protein is predominantly produced by the liver (transthyretin and fibrinogen mutations). Orthotopic liver transplantation provides a treatment by removing the source of the mutant protein (Holmgren et al, 1993; Zeldenrust et al, 2003). Initial hopes for liver transplantation as a cure for progressive transthyretin cardiac amyloidosis have been tempered by reports of progression of amyloid deposition in native hearts (Dubrey et al, 1997). It appears that wild-type transthyretin may continue the amyloid deposition after liver transplantation has eliminated the transthyretin variant which initiated the amyloidogenic process (Yazaki et al, 2000).

A drug that targets serum amyloid P is already being tested in patients with the goal of eliminating serum amyloid P from amyloid deposits, in the hope that this may reduce amyloid deposition and/or accelerate amyloid clearance. Small molecule ligands that stabilize the native tetrameric structure of transthyretin and prevent its fibrillogenesis are being actively investigated for prophylaxis and therapy in transthyretin amyloidosis (Oza et al, 2002). Diflusinal has been found to stabilize the tetrameric structure of transthyretin, reducing tetramer dissociation and subsequent monomer misfolding and aggregation into amyloid (Sekijima et al, 2006). A trial of its clinical efficacy in transthyretin amyloidosis is in progress and several similar, and possibly more potent, agents are in development (Miller at al, 2004).

Experience with apolipoprotein A1 amyloidosis and cardiac involvement is less well described. Patients with mutations of the apolipoprotein A1 molecule may require combined heart and kidney transplantation, because of a predilection for Apo A1 amyloid deposition in the kidneys with resultant renal failure.

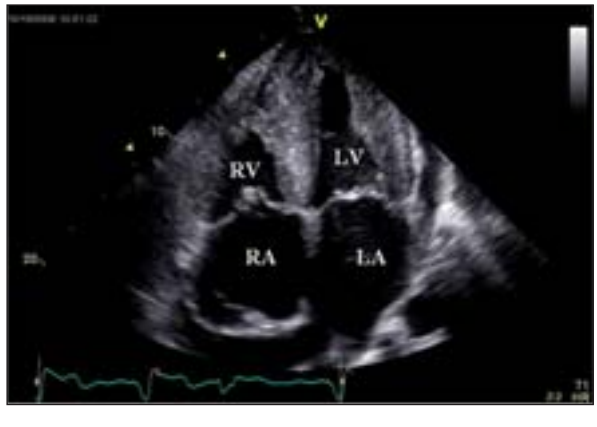
Senile systemic amyloidosis

In senile systemic amyloidosis wild-type transthyretin is deposited, almost exclusively, in the heart (Bergstrom et al, 2005). Wild-type transthyretin amyloid deposition (senile systemic amyloidosis) is found at autopsy in about 25% of individuals over the age of 80 years although, in most cases, the deposits are generally found in small quantities. The only other clinical extra-cardiac feature is a propensity to carpal tunnel syndrome. Cardiac deposition of wild-type transthyretin may sometimes be massive, resulting in severe heart failure. The echocardiographic appearance is typical of other forms of amyloidosis (*Figure 8*), but there is no neuropathy or other major extracardiac involvement. It is almost exclusively a disease of elderly men.

Management of senile systemic amyloidosis

Treatment of senile systemic amyloidosis is usually symptomatic, with diuretics remaining the mainstay. Atrial fibrillation is common and warfarin anticoagulation should be used, as the thromboembolic risk is very high. High-degree atrioventricular block occasionally occurs and, if pacing is needed, strong consideration should be given to biventricular pacing in order to prevent further decrease in stroke volume by right ventricular stimulation.

Figure 8. Apical four-chamber view echocardiogram of a patient with severe cardiac involvement as a result of senile amyloidosis. Appearances are similar to those for AL amyloidosis. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.



AA amyloidosis

AA amyloidosis is a rare complication of chronic inflammatory disorders. The fibrils are derived from the acute phase reactant serum amyloid A protein. Although cardiac deposits are often present at histology, echocardiographic abnormalities and clinical symptoms of cardiac AA amyloidosis are extremely rare, occurring in about 2% of cases. The prognosis is substantially better than in cases of AL amyloidosis (Dubrey et al, 1996). Treatment involves suppressing the underlying disease.

Isolated atrial amyloidosis

Atrial natriuretic peptide is synthesized locally by atrial myocytes, and can be deposited locally within the atria as amyloid. It may be important in the development of atrial conduction abnormalities and atrial fibrillation, particularly after cardiac surgery. Isolated atrial amyloidosis is a disease of the elderly, with a female preponderance that contrasts with senile transthyretin amyloidosis. There are no clinical or echocardiographic features of isolated atrial amyloidosis, and its pre-mortem diagnosis is usually an incidental finding noted on surgically removed atrial tissue at the time of cardiac surgery. The prevalence of isolated atrial amyloidosis in elderly hearts is high, with one autopsy study describing isolated atrial amyloidosis in 91 of 100 hearts (Kawamura et al, 1995). No specific therapy exists to treat isolated atrial amyloidosis and management centres on controlling rhythm disturbance.

Heart transplantation

The decision to consider a patient with amyloid heart involvement for heart transplantation is a complex one. Particularly difficult are patients with AL amyloidosis, the majority of whom have significant involvement of other organs that renders them unsuitable for cardiac transplantation. Furthermore, cardiac transplantation does not affect the underlying systemic disorder and amyloid deposition will continue unless the underlying plasma cell dyscrasia is addressed.

The total UK experience was reported in 2004 for all 24 patients (17 AL and seven non-AL amyloidosis) who had undergone heart transplantation up to that date (Dubrey et al, 2004). Regardless of the use of adjunctive chemotherapy, the 5-year survival after heart transplantation for cardiac AL amyloidosis was generally poorer than following heart transplantation for other indications. Progression of the systemic disease contributed to the increased mortality. Early experience from the United States was disappointing in AL amyloidosis patients undergoing heart transplantation, but few, if any of these patients had subsequent treatment of their plasma cell dyscrasia, and the initial selection criteria were not well described (Hosenpud et al, 1991). Heart transplantation followed by autologous stem cell transplantation has been tried in a limited number of patients. A report from the UK describes five patients undergoing combined sequential transplants. Two of these patients died of progressive amyloidosis and the remaining three were well at censor without evidence of intracardiac or extracardiac amyloid deposition (Gillmore et al, 2006).

The Columbia Presbyterian Medical Centre has described their experience with cardiac transplantation in 12 patients (ten with AL and two with familial amyloidosis) with cardiac amyloidosis. Eight patients with AL amyloidosis also underwent high-dose chemotherapy with autologous stem cell transplantation and the two familial patients underwent liver transplantation in addition to heart transplantation. The 1-year survival of the group was 75%, compared to 25% in patients who were evaluated but did not receive a heart (Maurer et al, 2007). The Mayo Clinic has presented preliminary data on 11 patients who underwent cardiac transplantation followed by chemotherapy and autologous stem cell transplantation. Two patients died within 100 days of chemotherapy and eight of the remaining patients had a haematological remission. Three more patients died from 55 to 66 months after chemotherapy, four remain in continued remission, one has relapsed and one has failed to improve (Lacy et al, 2008).

In a study from Germany, seven patients with AL (mean age 41.8 years) and five patients with transthyretin amyloidosis (mean age 42.6 years) were successfully transplanted with an actual survival rate of 91.6%. One patient died 8 months after transplant as a result of infection. Five AL patients received chemotherapy and stem cell transplantation and one transthyretin amyloidosis patient had a liver transplant. Three AL patients showed complete remission of amyloidosis. The authors noted the rapid progression of cardiac amyloidosis and stressed the importance of considering heart transplantation early in the course of the disease, rather than waiting until severe congestive heart failure supervenes. They concluded that cardiac amyloidosis is a potentially curative disease after heart transplantation, when combined with both chemotherapy and stem cell transplantation (for AL amyloidosis) or liver transplant (for transthyretin amyloidosis). However, a potential cure in AL amyloidosis requires a complete haematological response to chemotherapy, and long-term data evaluating relapse rates are not yet available (Sack et al, 2008).

In the UK, two cardiac transplants have been performed for senile systemic amyloidosis (wild-type transthyretin amyloidosis); both patients were male and, unusually, presented before age 60 years (Dubrey et al, 2004). Cardiac transplantation therefore seems a very reasonable approach in patients with severe wild-type cardiac amyloidosis who present at a sufficiently young age.

Conclusions

Early detection of cardiac amyloidosis is the best method to obtain the best possible outcome, as it allows for a broader range of therapeutic options. Clinical awareness

of the disease and a high index of clinical suspicion are critical to early diagnosis, but, unfortunately, many cases are diagnosed late in the disease. Once a case of amyloidosis is recognized, it is vital to precisely determine the type of amyloid as the prognosis and treatment differ considerably among the types. **BJHM**

Conflict of interest: Dr SW Dubrey has received payments from J and J Pharmaceuticals for study in AL amyloidosis. Dr RH Falk is consultant to Fold Rx, for a study on drug therapy in transthyretin amyloidosis and consultant to J and J Pharmaceuticals for a study in AL amyloidosis.

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KEY POINTS

- Suspect amyloid heart disease in any patient with a thick-walled heart in combination with a low voltage electrocardiogram.
- Consider amyloid disease in patients with heart failure coexisting with proteinuria, elevated alkaline phosphatase levels, neuropathy or periorbital purpura.
- Determination of amyloid type is critical to prognosis and to choice of therapy.
- Treatment is aimed at elimination of the source of precursor protein.
- Patients with light chain amyloidosis and significant cardiac involvement tolerate high dose chemotherapy poorly.