

Primary Cardiac Amyloidosis

A Review of the Literature

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SUMMARY

A review of the literature on primary cardiac amyloidosis is presented. Its differentiation from constrictive pericarditis, both on clinical and haemodynamic grounds, is outlined. The importance of antemortem endomyocardial biopsy in establishing a definitive diagnosis of this relatively rare condition is stressed. Finally, an updated overview of the classification and immunological pathogenesis of this disease is given.

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CLASSIFICATION OF AMYLOIDOSIS

Several different systems of classification of amyloidosis have been described,¹⁻³ reflecting the unexplained pathogenesis. Previous attempts to classify the condition on the basis of the postmortem distribution of involved organs have been superseded by a working classification which recognizes that clinical manifestations may overlap a great deal. The following classification may be employed: (a) primary amyloidosis — with or without associated plasma cell and lymphoid neoplasm; (b) secondary amyloidosis — associated with chronic disease such as tuberculosis, ulcerative colitis, syphilis, osteomyelitis, or rheumatoid arthritis; (c) familial systemic amyloidosis, as in familial Mediterranean fever and Portuguese limb neuropathy; (d) amyloidosis associated with ageing ('senile amyloidosis'); (e) amyloidosis of endocrine glands, as in medullary thyroid carcinoma and multiple endocrine neoplasia.

Previously there was doubt whether primary amyloidosis represented a distinct entity, and it was suggested that primary amyloidosis was a pathological variant of primary plasma cell proliferation,⁴ since amyloid deposits often precede the skeletal manifestations of multiple myeloma. They may be classified together because of the presence of the 'amyloid L chain' protein in primary and myeloma-associated amyloidosis.

Senile amyloidosis⁵ corresponds to the condition which develops in younger people after infection, for example tuberculosis or lymphogranulomatosis but, like primary amyloidosis, it need not be associated with infections. The senile amyloidotic triad consists of amyloid deposition in brain, cardiac muscle and pancreatic islets. The number of organs involved increases with ageing, but in contrast to secondary amyloidosis, spleen, liver and kidney are usually unaffected.

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AETIOLOGY AND PATHOGENESIS

The homogeneous extracellular eosinophilic material which characterizes amyloidosis may be derived from several proteins, including L-chain fragments and hormones. It consists of long fibrils with a diameter of 100 - 150 Å arranged in an antiparallel and B-pleated sheet structure.^{6,7} Amyloid deposits may originate from a precursor protein present in the circulation or from a locally produced protein. The possibility that primary and secondary amyloidosis may share a common pathogenetic mechanism, associated with an underlying immune disorder, remains to be disproved.

Amyloid fibrils appear to be composed of two types of protein, singly or in combination. Primary amyloid is composed of fragments of immunoglobulin light chains which may arise from overproduction of, or failure of degradation of, light chains in serum. The amyloid fibrils may be separated into lambda and kappa types, but the frequency of lambda-related proteins is greater than that of protein of the kappa-chain class. The proteins comprising primary amyloid are called the amyloid L-chain (AL) protein^{8,9} and have a molecular weight of 5 000 - 25 000 daltons. Amyloid deposits appear to be derived directly from this circulating precursor, which is also found in the myeloma-associated amyloid.

In contrast, overproduction of an unrelated protein, amyloid A (AA) protein, is associated with secondary amyloidosis and familial forms, for example, familial Mediterranean fever. AA protein appears to be derived from an antigenically related large protein, the serum amyloid A-related (SAA) protein with molecular weight of 12 000 - 14 000 daltons, while AA protein has a molecular weight of 8 000 daltons. SAA is produced in response to B lymphocyte stimulation. SAA and AA protein are cleaved by proteases liberated by monocytes to small peptides or AA-like molecules. Individuals appear to vary in their ability to process these intermediate products and those in whom AA intermediates persist appear to have a predisposition to develop amyloid under conditions of increased SAA production. Variations in the ability to degrade SAA may be genetically determined, but could also be influenced by the presence of protease inhibitors which normally inhibit SAA and AA degradation, except in several disease states during which their activity falls.

The concentration of SAA increases with ageing, values at the 8th or 9th decade being 10 times greater than in the first 5 decades. Its concentration increases during chronic diseases including amyloidosis, infections, cancer, rheumatoid arthritis, multiple myeloma, macroglobulinaemia, lymphoma and pregnancy. It behaves as an acute phase reactant after acute infections or acute-on-chronic infections, when its level quickly returns to normal. In addition a similar fibrillary structure may be formed from

insulin and glucagon. Also, thyrocalcitonin has been identified in the amyloid of medullary carcinoma of the thyroid gland.

It has also been postulated that amyloid may be synthesized in the tissues which reflect its distribution. A locally synthesized precursor may produce L-chain immunoglobulins which, when processed, form the characteristic fibrillary structure adjacent to sites of synthesis, for example, in the vicinity of massive plasma cell infiltrates. Most amyloid deposits also contain a minor component, the 'p' or 'doughnut' component, a protein with a molecular weight of 180 000 daltons whose significance is at present unclear.

It has recently been postulated that amyloidosis is a primary disorder of the immune system,¹⁰⁻¹² and that the manifestations of primary and secondary amyloidosis merely reflect differences in the degree of antigenic stimulation of the reticulo-endothelial system. Support for this hypothesis is based on the association between primary amyloidosis and plasma cell dyscrasias, while secondary amyloidosis is accompanied by excess immunoglobulin production in rheumatoid arthritis, tuberculosis, and leprosy (Hansen's disease). Experimental studies in mice appear to suggest that disturbed immunoregulatory function plays an important role in amyloidosis. It has been proposed that macrophage activation by lymphokines represents the initial step in the pathogenesis of amyloid disease. Massive short-term antigenic stimulation of the reticulo-endothelial system leads to accumulation and deposition of AA protein in connective tissue, possibly accompanied by immunoblast proliferation and T-cell suppression.

Less intense but more sustained stimulation of the macrophages results in monoclonal proliferation of plasma cells and L-chain deposition in the form of amyloid fibrils.

Normal T-cell function inhibits amyloid disease by controlling excessive macrophage activation and B-cell proliferation despite constant antigenic challenge. Definite proof of synthesis of amyloid by B-cells or macrophages is lacking, but both primary and secondary amyloid may represent B-cell dysplasia which differs only in the degree of antigenic stimulation.

CARDIAC AMYLOIDOSIS

Pathological Features

The macroscopic and microscopic features of cardiac amyloidosis have been fully and frequently documented.¹³ Like other organs affected by amyloidosis, the heart tends to be peculiarly firm, and its weight moderately increased. Any part of the heart may be affected and the amount of amyloid varies greatly. The pericardium is frequently involved. The endocardium is sometimes affected and amyloid may extend to the valvular as well as the parietal endocardium. The greatest amount of amyloid, however, is found in the myocardium of both atria and ventricles. The myocardium is peculiarly stiff, as if fixed, so that the chambers do not collapse. Presumably this decrease in myocardial compliance is the main factor responsible for the restricted ventricular filling.

Vascular involvement varies from occasional segmental

lesions in the media to extensive replacement of all coats of the vessel wall and myocardial ischaemic fibrosis.

Under the light microscope, in the average case, the heart muscle cells are surrounded by rings of amyloid apparently deposited on the cell surface or on the reticulum framework. In very severe cases the myocardial fibres appear necrotic, atrophic or completely replaced by amyloid. In the less damaged areas surviving fibres may show hypertrophy. Patchy amyloid in the myocardium is not uncommonly found post mortem in old people but does not commonly cause deterioration of cardiac function.¹⁴ The ultrastructural features have been described:¹⁵ the amyloid was fibrillary and beaded with fibrils varying in width from 140 to 450 Å. Some fibrils were disposed haphazardly, while others were arranged in bundles. The amyloid deposits were present in relation to the basement membranes of heart muscle cells, around capillaries and in the interstitial tissues. No instance of intracellular amyloid was observed.

Clinical Features

The clinical presentation of primary cardiac amyloidosis is essentially that of a 'restrictive' cardiomyopathy (or 'stiff heart' syndrome) in a patient generally older than 50 years. Exertional dyspnoea is the most common early symptom but as the disease progresses orthopnoea usually appears. Paroxysmal cardiac (nocturnal) dyspnoea is fairly common, occurring when the disease process affects predominantly the left side of the heart, and the majority of patients present with symptoms of cardiac failure. Palpitations with or without syncopal episodes secondary to an arrhythmia may be the presenting complaint. Congestive cardiac failure develops in more than half of these cases and is usually insidious. The average duration of symptoms in these cases is 14 months.¹⁶ It is important to appreciate that the clinical features of the cardiomyopathy (and even other types of cardiomyopathy, to a lesser degree) may mimic those of constrictive pericarditis.^{17,18,21} Thus, Kussmaul's sign (paradoxical increased distension of neck veins on inspiration) may be present but is certainly not pathognomonic of 'restrictive' cardiomyopathy. Some astute examiners will notice that the 'a' and 'v' waves are prominent, followed by a deep and steep early diastolic 'y' descent and a shallow but less steep systolic 'x' descent. Pulsus paradoxus, as in constrictive pericarditis and other conditions such as severe acute asthma, is also seen.

Arterial hypotension²⁰⁻²¹ may be either supine or orthostatic in nature and occurred in some 12% of a series of 118 patients,²² indicating that it is not a reliable sign of cardiac involvement. In another series²¹ of 15 patients hypotension was seen only in those with renal or gastrointestinal disease or peripheral neuropathy; this symptom may be a clue to involvement of these systems.²³ The clinical features of primary cardiac amyloidosis may also be very closely simulated in constrictive endocarditis (endocardial fibro-elastosis, endomyocardial fibrosis and Loeffler's endocarditis).

Ischaemic heart disease may be incorrectly diagnosed in some patients because of typical or atypical angina pectoris.^{25,31,34} Pseudomyocardial infarction patterns have also been described (see 'Electrocardiographic Features').

On examination the apex beat is unremarkable with little precordial pulsation. The heart sounds are usually soft but can be of normal intensity. A remarkable feature on auscultation at the pulmonary area is the behaviour of the second heart sound. On inspiration there appears to be a 'quickening' of the pulmonic component due to the aortic component moving away from it, rather than the pulmonic component coming closer (see 'Phonocardiography'). This physical sign is also quite characteristic of constrictive pericarditis. Additional diastolic sounds are common and suggest the presence of restriction. This, can, however, be confused with the 'pericardial knock' of constrictive pericarditis which occurs earlier during diastole. Murmurs are conspicuous by their absence, but rheumatic valvular heart disease may be mimicked by the presence of mitral pansystolic murmurs as in our case.³⁰ Controversy exists as to whether such valvular abnormalities can contribute or give rise to cardiac dysfunction.^{21,25,36}

Patients with 'restrictive' ('constrictive') cardiomyopathy may at some stage also show features of 'congestive' cardiomyopathy with progression of the disease.³⁷ Mural intraventricular thrombosis with subsequent systemic embolism has been described.³⁸ Another possible consequence of development of a mural thrombus is organization of the latter, with replacement fibrosis contributing further to the restrictive process.

Electrocardiographic Features

It is generally accepted that the ECG is always abnormal in patients affected by primary cardiac amyloidosis³⁹⁻⁴³ but there is no pathognomonic pattern. Low-voltage QRS complexes, especially in the standard extremity leads, are the most common abnormality in most series,⁴⁴⁻⁴⁶ probably due to extensive infiltration and replacement fibrosis of myocardial tissues.

Disturbances of atrioventricular conduction are most varied and heart block is prominent.^{25,47,48} Some workers have correlated the anatomical findings of amyloid infiltration of the conduction system with the electrocardiographic conduction abnormalities.^{31,36,49} Involvement of the sino-atrial node, with or without concomitant atrioventricular node involvement, has also been described.⁵⁰ Classic cases of sick sinus syndrome, manifesting with a variety of supraventricular arrhythmias and causing syncopal episodes, are less frequently documented.⁵¹⁻⁵⁷ Atrial fibrillation is classically associated with cardiac amyloidosis, especially at the advanced stage with cardiac failure. Other arrhythmias, such as atrial flutter, supraventricular tachycardia and junctional tachycardias, are fairly common. The most dangerous arrhythmias are commoner in patients on digitalis therapy,⁶ who are stated to be more sensitive to this drug in the presence of cardiac amyloidosis.^{14,31,58} Intriguing are the changes mimicking old transmural myocardial infarction;⁵⁹ these are usually anteroseptal or anterior in site, and are thought to be due to the atrophy and widespread replacement of myocardium by amyloid material, as several of these patients have patent coronary arteries at postmortem examination. Left axis deviation is often present as well. Of interest is the rare electrocardiographic finding of electrical alternation of the p wave, first described by Bernreiter.⁴²

Thus, in summary, the presence of low QRS voltage in the limb leads, accompanied by inversion of the QRS complexes in the right precordial leads, should alert one to the possibility of cardiac amyloidosis whether symptoms are present or not.

Phonocardiography

Premature closure of the aortic valve in primary cardiac amyloidosis was described for the first time by the present authors.⁶⁵ This feature, initially thought to be characteristic of constrictive pericarditis,⁶⁰ is probably due to the relative non-compliance of atria and ventricles, thus causing an altered pressure-volume relationship.

Echocardiographic Features

The advent of echocardiography has made possible the presymptomatic detection of many conditions, especially the cardiomyopathies. Characteristic features have been well documented in the hypertrophic cardiomyopathies, obstructive or non-obstructive, as well as the congestive cardiomyopathies. More recently, Borer *et al.*⁶¹ have delineated the changes seen in the infiltrative cardiomyopathies,⁶² as exemplified by amyloidosis. This latter group of conditions gives rise to so-called 'restrictive' features.⁶³ With cardiac amyloidosis, specifically, there is marked thickening of the ventricular walls which gives rise to a non-compliant and 'stiff' ventricle (especially the left) displaying a usually normal cavity size. Because of reduced left ventricular compliance the left atrium is as a rule dilated.⁶⁴

Decreased diastolic compliance of the left ventricle leads to increased resistance to early diastolic filling with subsequent reduction in the 'mitral valve slope' (E-F slope).⁶⁵ This measurement was one of the earliest reported with regard to mitral valve motion.^{66,67} Quinones *et al.*⁶⁸ demonstrated that an E-F slope of less than 60 mm/s (normal range 60 - 110 mm/s) in the absence of mitral valve obstruction, was closely correlated with impaired left ventricular filling secondary to decreased diastolic compliance. However, a reduced mitral valve slope is also seen in mitral stenosis, atrial myxoma, aortic stenosis, aortic insufficiency, primary pulmonary hypertension, and idiopathic subaortic stenosis.^{69,70} Recently, this reduction has also been reported in scleroderma heart disease.^{61,71} Borer *et al.*⁶¹ demonstrated that the left ventricular free wall and septum were thickened (more than 11 mm) in all of their 19 patients with infiltrative disease of the heart (4 of whom had systemic amyloidosis). However, the septal/posterobasal free wall thickness ratio⁷² was always less than 1.3. Contractility of the left ventricle, as represented by the ejection fraction, was preserved (exceeded 60%) in 18 of the 19 cases. Other studies^{73,74} have also shown reduced ventricular wall motion with a striking increase in the septal and free posterior wall thickness (but with normal ratios) in the absence of ventricular dilatation.

Some workers^{75,76} have stressed abnormal or paradoxical interventricular septal motion (movement of the septum anteriorly during systole) as a feature of constrictive pericarditis. Although this was noted in some of the patients of Voelkel *et al.*⁷⁷ it was regarded as not specific, having been described following cardiopulmonary bypass,⁷⁸

and also in ischaemic heart disease, conduction defects and right ventricular volume overload.⁷⁹

It is interesting to note that a pattern of diastolic posterior wall 'flatness', which might be expected to occur with infiltrative diseases causing subsequent myocardial restriction, was not a significant feature in two recent series.^{61,62}

Radiological and Angiographic Features

Pericardial effusion is an important presenting feature in primary cardiac amyloidosis,^{46,50} although this has been somewhat neglected in previous published reports. Difficulty may well be experienced in differentiating a pericardial effusion from a thickened myocardium ('water-bottle shape' heart), especially if radio-isotopic examinations are performed only in the anteroposterior position. Thus, on account of the marked myocardial thickening, rectilinear and scintillation scanning may well demonstrate the 'halo' or 'horseshoe' deformity surrounding the cardiac blood pool, increased spacing between the heart and liver, and a reduced cardiac diameter when this is contrasted with that seen on the plain radiograph. Nevertheless, this important potential misinterpretation may be avoided by taking additional radioscan in the left anterior oblique projection, which then allows clear visualization of any thickening of the interventricular septum.⁸¹ An additional differentiating point between these two pathological presentations is that of 'snubbing' of the left ventricular blood pool seen with myocardial thickening secondary to amyloidosis, myocardial hypertrophy, and even perhaps with other infiltrative cardiomyopathies. Pericardial effusion has also been seen in isolated cases post mortem^{30,59} but usually only if there is direct amyloid infiltration of the pericardial tissues,⁸² or if the patient is in severe congestive cardiac failure.

Significant cardiomegaly may also sometimes be caused by predominant enlargement of the right atrium due to dilatation secondary to markedly elevated right heart pressures. Chew *et al.*⁴⁶ reported a similar situation. Therefore, care must be taken not to misinterpret this right atrial dilatation as a pericardial effusion.

Primary cardiac amyloidosis is often associated with amyloid deposits in the perivascular space and interstitium of the lungs; the latter may mimic and be radiologically indistinguishable from pulmonary congestion.⁸³⁻⁸⁶ The distinction between these two conditions may be further complicated by the fact that the cardiac failure of primary cardiac amyloidosis is generally refractory to therapy and thus the radiological signs of 'pulmonary congestion' may remain. Furthermore, because amyloidosis gives rise to a disseminated interstitial pulmonary picture it must be considered in the differential diagnosis of such diseases as miliary tuberculosis, eosinophilic granuloma, lymphangitic carcinoma and sarcoidosis. Calcifications and even ossification have been noted in the pulmonary interstitium infiltrated by amyloid deposits.⁸⁷ This calcification may well be missed on routine radiography but is usually detected with tomography.

However, there are no characteristic radiological appearances of amyloidosis within the lung and thus a diagnosis can be firmly established only by biopsy and microscopic examination of the tissue by special staining

techniques. Cine angiographic features of the cardiac chambers, especially the ventricles, are usually highly suggestive of amyloid infiltration. Trabeculation is, as a rule, far more coarse and the papillary muscle impressions are more marked, but cavity distortion is minimal when compared with that seen in fairly advanced constrictive pericarditis. Systolic emptying of the ventricles is also usually somewhat reduced in the absence of increase in the end-diastolic volume. Right atrial cine angiograms tend to demonstrate a moderately dilated chamber despite the heavy infiltration of the atrial wall by amyloid deposits. Calcification of the pericardium is also absent, a feature which strongly differentiates this condition from that of constrictive pericarditis, whether tuberculous or otherwise.

Haemodynamic Features

Hetzel *et al.*³⁵ were the first to realize that the haemodynamic changes seen with cardiac amyloidosis could be identical to those so well described with constrictive pericarditis,⁸⁸⁻⁹¹ they ascribed these changes to 'alterations in the distensibility characteristics of the myocardium'. This is not surprising, as the 'constriction' in amyloid heart disease is within the myocardium itself, rather than in the pericardium as in constrictive pericarditis.

The first haemodynamic study, carried out on a patient with primary amyloidosis in 1950,⁹² demonstrated that the amyloid heart was unable to augment its diastolic volume. A few years later Gunnar *et al.*²¹ published the second case of 'primary' amyloidosis with cardiac involvement; because of a positive Mantoux test (1:10 000), the patient had been started on antituberculosis therapy in view of the strong likelihood of tuberculous constrictive pericarditis, diagnosed prior to cardiac catheterization, but the diagnosis proved to be multiple myeloma with secondary amyloidosis. Haemodynamically the patient showed severe right atrial hypertension, the contour of the pressure curves taking on an 'M' or 'W' configuration. The ventricular pressure curves had features of an 'inelastic and hypodynamic chamber'. So, although the peak systolic pressure exceeded normal, it was certainly less than anticipated with the high ventricular filling pressures (i.e. the end-diastolic pressure). The contour of the diastolic component of the ventricular pressure curve also revealed impressive characteristics in that there was a 'early diastolic dip' followed by a 'diastolic plateau'. Thus, the right atrial and ventricular pressure curves indicated that the haemodynamic disorder consisted of rapid emptying of the atria into the ventricles, especially during the phase of ventricular isometric relaxation, followed by a rapid rise in the diastolic ventricular pressure, which stabilized to a higher than normal end-diastolic value because of the limited distensibility of the ventricle.

Elevation of the pulmonary capillary wedge pressure (indirect left atrial pressure) further indicated involvement of the left side of the heart by the infiltrative amyloid deposits. A reduced peak systolic left ventricular pressure, as well as a narrow pulse pressure in the systemic circulation, was evidence of reduced cardiac output, which was further markedly reduced by exercise. Therefore all the above haemodynamic findings have

been claimed to be 'characteristics' of constrictive pericarditis.

Some authors⁸⁰ went a step further in saying that the end-diastolic pressure of the affected ventricle was greater than one-third of the systolic pressure, but many authors^{22,23} have found this claim to be inconsistent. Often there is elevated pulmonary artery diastolic pressure similar to pulmonary capillary wedge pressure, the right ventricular end-diastolic pressure, and the right atrial pressure. These are also known to occur with right ventricular infarction.⁹³⁻⁹⁷

The above haemodynamic features can be seen in a wide spectrum of diseases such as sarcoidosis, haemochromatosis, chronic myocarditis with fibrosis, endomyocardial fibrosis, and primary amyloidosis associated with Gaucher's disease.⁹⁸ All these diseases eventually result in restriction to ventricular filling (the 'stiff heart' syndrome).

The differentiation of constrictive pericarditis from the 'restrictive'⁹⁹ cardiomyopathy of primary cardiac amyloidosis on haemodynamic grounds is usually exceptionally difficult, if not impossible.^{31,100} At times there is asymmetrical involvement of the heart by amyloid infiltration, whereas there is usually symmetrical constriction by constrictive pericarditis. Also, a raised late diastolic pressure in constrictive pericarditis is usually caused by a uniform restriction of ventricular filling,²⁴ whereas with restrictive cardiac amyloidosis the raised right ventricular end-diastolic pressure usually represents the transmission of an exceptionally exaggerated 'a' wave. Therefore, a significantly prominent 'a' wave is usually absent in constrictive pericarditis and may be strikingly raised with primary cardiac amyloidosis.¹⁰¹ It has also been stated that with more myocardial involvement by a primary disease process, especially of the left ventricle, the left atrial 'a' wave is usually some 10-20 mmHg greater than the 'a' wave in the right atrium.²⁴ By contrast, the difference between the right and left atrial 'a' waves in constrictive pericarditis is usually less than 6 mmHg. Chew *et al.*⁴⁶ claimed that constrictive pericarditis and primary cardiac amyloidosis could be clearly contrasted on haemodynamic grounds. In the former there is a near-normal systolic emptying phase with a normal end-systolic volume and better preservation of stroke volume; rapid filling of the ventricles in early diastole also gives rise to an early third heart sound and there is little or no further filling late in diastole. In constrictive pericarditis there is also a low early left ventricular diastolic pressure which rises early to a plateau, with a high mid-diastolic and end-diastolic pressure and the absence of an 'atrial kick'. Rapid ventricular filling allows the patient with constriction to raise the cardiac output by a compensatory increase in heart rate. Constrictive pericarditis more often than not has similar left and right ventricular diastolic pressures,¹⁰² usually not found in primary cardiac amyloidosis. Chew *et al.*⁴⁶ went on to claim that 'restrictive cardiomyopathy' (i.e. a small group of diseases with diastolic filling disorder) can also be differentiated from 'amyloid heart', in that patients in the former group do indeed resemble patients with constrictive pericarditis but can be differentiated on the grounds of unequal involvement of the two ventricles, the disease being more often left-sided. Furthermore, patients with 'restrictive

cardiomyopathy' have normal systolic function, a normal-sized heart, an early and loud third heart sound and early filling of the left ventricle, which is rapid with reduced early diastolic pressure, but which increases abruptly with cessation of further filling during mid-diastole or late-diastole. This group of patients is also thought to have underlying endocardial disease; the relationship to Loeffler's disease of temperate zones and to endomyocardial fibrosis of the tropics awaits further clarification.

Finally, Shabetai and Meaney¹⁰³ reported that in both cardiac amyloidosis and constrictive pericarditis, ejection and isovolumic contraction were variable and thus did not differentiate myocardial from pericardial restriction; comparison of the left and right heart filling pressures remained the most useful haemodynamic parameter with which to distinguish between them.

Endomyocardial Biopsy in Diagnosis

Definite pathological diagnosis of myocardial disease has, until fairly recently, been possible only by means of open myocardial biopsy at thoracotomy^{26,58,104} with a percutaneous needle technique,¹⁰⁵⁻¹⁰⁷ or post mortem.^{108,109} The introduction of the revolutionary Biopome,^{110,111} adapted to the intracardiac catheter, has allowed safer acquisition of larger endomyocardial specimens and thus led to more frequent use in investigative centres,¹¹²⁻¹¹⁴ especially in heart disease of obscure origin. Modifications have been described which allow simpler percutaneous insertion, especially into peripheral arteries.¹¹⁵⁻¹¹⁷

The safety of the percutaneous Biopome catheter procedure for endomyocardial biopsy compares most favourably with that of other techniques. Cases of pericardial tamponade, haemothorax and pneumothorax secondary to cardiac perforation have been described in the literature, but these complications are rare in experienced hands. The only other significant complication is arrhythmia, which can be largely prevented by careful manipulation of the catheter.

Hedner *et al.*¹¹⁸ were the first to publish a case of primary cardiac amyloidosis diagnosed by right ventricular endomyocardial biopsy. Schroeder *et al.*¹¹⁹ then published 2 cases of secondary amyloidosis diagnosed by the same procedure; Chew *et al.*⁴⁶ diagnosed secondary amyloidosis by left ventricular endomyocardial biopsy, while Chan and Ikram¹²⁰ diagnosed a case of primary amyloidosis by the same method. The present authors subsequently published³⁵ the second case of primary cardiac amyloidosis in the world literature diagnosed by endomyocardial biopsy of the right ventricle.

Differential Diagnosis

Perhaps the most important condition which needs to be differentiated from primary cardiac amyloidosis is chronic constrictive pericarditis, which is usually tuberculous^{121,122} and initially gives rise to a pericardial effusion, followed by constriction and tamponade. This diagnosis is aided by positive skin tests and is definitive with a positive pericardial biopsy.

The connective tissue abnormalities are known to cause cardiomyopathy. Rheumatoid arthritis usually presents with its peripheral manifestations and seldom involves

the heart from the outset. In contrast, systemic lupus erythematosus (SLE) may present with cardiac involvement, the most common being Libman-Sacks endocarditis. In an autopsy series¹²³ of SLE 60-70% of cases had pericarditis as a complication. Polyarteritis nodosa may give rise to a diffuse myocarditis, but more commonly local coronary arteritis causes areas of ischaemic fibrosis; there have been various reports^{20,124} of endomyocardial fibrosis in association with this disease. Scleroderma is also known to cause a pericardial effusion as well as give rise to a 'restrictive' picture. Cardiac haemochromatosis simulating constrictive pericarditis may well be confused with amyloid infiltration of the heart. Sarcoidosis may also cause some difficulty, especially as it may also affect the conduction system, a known but unusual complication of cardiac amyloidosis. Of interest is the odd condition termed 'seroconstrictive pericarditis',¹²⁵ which may well be due to a system disease or even a viral infection, i.e. 'relapsing viral pericarditis'. This is characterized by recurrent pericardial effusions accompanied by a low-grade pyrexia. Treatment with repeated pericardiocentesis is usually effective.

Idiopathic cardiomegaly may simulate primary cardiac amyloidosis; both are characterized by cardiomegaly and cardiac failure, usually without chest pain. In the former condition intracardiac mural thrombi, with systemic and pulmonary emboli, are common.

'Constrictive endocarditis' resembles cardiac amyloidosis, which in turn can mimic constrictive pericarditis.^{17,31,99,126} Therefore, conditions such as Loeffler's endocarditis ('parietal fibroplastic endocarditis'), endomyocardial fibrosis, endocardial fibro-elastosis, and Becker's subendocardial fibro-elastosis ('South African cardiomyopathy'),¹²⁷ must be entertained in differential diagnosis. All these diseases can give rise to a 'restrictive' clinical picture³⁷ or 'stiff heart' syndrome.²⁶

In some cardiomyopathies (especially idiopathic hypertrophic subaortic stenosis) there is often gross left ventricular hypertrophy. The situation may give rise to a 'Bernheim effect' (bulging of the interventricular septum into the right ventricular cavity with transmission of intraventricular pressure from the left side), which presents as large 'a' waves in the neck veins in the presence of right-sided cardiac failure but usually in the absence of dyspnoea. However, with idiopathic hypertrophic subaortic stenosis the functional disorder differs from that caused by amyloid infiltration in that there is preservation of ejectile capacity (except in some of pre-terminal cases).

Treatment

To date there is no specific effective therapy for primary cardiac amyloidosis. Since the most common clinical presentation of this disease is congestive cardiac failure, initial medical management consists of standard diuretics with the addition of digitalis preparations. However, the cardiac failure is more often than not refractory to therapy and death usually results from it or renal failure or sometimes acute pulmonary embolism or coronary embolism.

Treatment is further complicated by the fact that these patients appear to be specifically sensitive to digitalis compounds. The first 2 cases of digitalis toxicity were

reported by Cassidy.⁵⁸ Subsequent reports⁵⁹ have emphasized this peculiarity and underlined the importance of being cautious in prescribing these preparations. This unusual sensitivity may partly be due to infiltration of the conduction system by amyloid deposits,³⁶ thus potentiating the chronotropic and dromotropic effects of digitalis.

Another manifestation of conduction system involvement is the sick sinus syndrome.⁵⁰⁻⁵⁶ Because of symptoms of this complication permanent pacemakers have been inserted without success.^{57,119}

Since a further complication of primary cardiac amyloidosis is systemic embolization originating from the atrial or ventricular mural thrombi, antiplatelet agents and anticoagulants should also be considered in management.

More recently, cardiac transplantation has been entertained. Schroeder *et al.*¹¹⁹ would have performed a transplantation on their first patient if the rectal biopsy had been negative, but unfortunately the latter indicated that the patient had systemic involvement. The chance that this operation would help is uncertain, while a heterotopic ('piggy-back') transplant would not ensure a return to normal of a diseased heart, which would almost certainly become more 'restrictive' with further amyloid infiltration. On the other hand, with an orthotopic transplant there would be the risk of organ rejection, leaving the patient without any functioning heart.

If myocardial biopsy were to be used more frequently in myocardial disease of uncertain origin (or the 'non-coronary cardiomyopathies'),²⁰ the early stages of the disease could be detected without much harm to the patient. Hopefully, the future will produce specific therapeutic regimens to counteract this uniformly fatal albeit rare condition.

Prognosis

The outlook is uniformly poor, and death usually results from congestive cardiac failure despite energetic treatment. Some authors¹⁹ have reported a survival time following the onset of symptoms of 14 months to 5 years, with an average of 32 months.³⁶ The patient may die of an acute pulmonary embolism, renal failure or, more rarely, coronary embolism. In one series,³⁹ 29% (8 patients) died suddenly and inexplicably. Three of these had myeloma-associated amyloidosis, 4 had primary amyloidosis, and 1 had secondary amyloidosis. Digitalis-induced arrhythmias were thought to have been the cause of death. The poor prognosis in primary amyloidosis associated with multiple myelomatosis was thought to be an indication of the underlying malignancy *per se*. Kyle and Bayrd¹ divided their group of 193 patients into those with primary amyloidosis (132 cases) and amyloidosis associated with multiple myeloma (61 cases). Patients in the former group had a median (50%) survival of 14.7 months, while those in the latter group had a survival of 4 months after histological diagnosis of amyloidosis. The major cause of death in this series was congestive cardiac failure in 30%.

Generally speaking, primary cardiac amyloidosis progresses more slowly than the secondary form, but the former displays no regression, whereas the latter may become reversible once the primary cause has been effectively treated.

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