

Non-invasive assessment of the presence and severity of cardiac amyloidosis

A study in familial amyloidosis with polyneuropathy by cross sectional echocardiography and technetium-99m pyrophosphate scintigraphy

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SUMMARY Twelve patients with familial amyloidosis with polyneuropathy were examined both by cross sectional echocardiography and by technetium-99m pyrophosphate scintigraphy to assess involvement of the heart non-invasively. All 12 patients had echocardiographic abnormalities. The most prominent findings were highly refractile myocardial echoes, thickened heart valves, and increased thickness of the heart walls. Four patients had abnormal myocardial uptake of technetium-99m pyrophosphate. The remaining eight had equivocal or no myocardial uptake and were considered to have normal scintigrams. A certain amount of amyloid is probably required to produce an abnormal scintigram, although lesions with less amyloid can evidently be identified by echocardiography. Neither the duration of polyneuropathy nor its severity showed any relation to the echocardiographic or scintigraphic findings.

It is concluded that cross sectional echocardiography is superior to technetium-99m pyrophosphate scintigraphy in detecting cardiac involvement in familial amyloidosis with polyneuropathy and that these results may also be applicable to other forms of amyloidosis.

Systemic amyloidosis commonly affects the heart, with cardiac failure and disturbances of rhythm and conduction being important manifestations.¹ Nevertheless, a definite antemortem diagnosis of cardiac amyloidosis is, of course, not possible without cardiac biopsy.^{1,2} During recent years, however, echocardiography and technetium-99m pyrophosphate scintigraphy have both been reported as valuable aids in the non-invasive diagnosis of cardiac amyloidosis.³⁻⁸ In most previous studies a high proportion of the patients had congestive heart failure, which indicated advanced cardiac involvement.

The aim of this study was to evaluate and compare

the usefulness of these non-invasive methods in determining involvement of the heart in familial amyloidosis with polyneuropathy at different degrees of severity and with varying duration of symptoms.

Patients and methods

Familial amyloidosis with polyneuropathy is a neuropathic form of hereditary systemic amyloidosis and has been reported in localised areas of several countries, including Portugal, Japan, Sweden, England, and the USA.^{9,10} Twelve patients with familial amyloidosis with polyneuropathy (five men and seven women) were included in the study after having given their informed consent. Their ages ranged from 32 to 69 (mean 54) years, and the duration of their symptoms from 2 to 16 (mean 7) years. All patients had typical progressive polyneuropathy,

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Table 1 Clinical and electrocardiographic data and radiological heart volume in 12 patients with familial amyloidosis with polyneuropathy

Case No	Age (yr) and sex	Duration of neuropathy (yr)	Degree of neuropathy	Comments	ECG	Heart volume (ml/m ² BSA)*
1	67F	5	+++	Slight aortic incompetence Heart failure	Second degree AV block (Wenckebach type)	580
2	49F	16	++++	—	First degree AV block, LAFB	450
3	54F	8	++	—	Normal	320
4	59M	6	++	Heart failure	First degree AV block, LAFB, RBBB	810
5	54F	5	++	—	First degree AV block	320
6	63F	10	+++	Heart failure	Second degree AV block (Wenckebach type)	570
7	44F	7	+++	—	Normal	270
8	42M	2	++	—	Normal	410
9	69M	4	++	Heart failure	Atrial fibrillation	520
10	49F	7	+++	Pacemaker	Pacemaker rhythm	450
11	66M	7	+++	Persistent ductus arteriosus Heart failure Pacemaker	Pacemaker rhythm	810
12	32M	2	+	—	Normal	360

+, slight; ++, moderate; +++, severe; +++++, very severe¹¹; AF, atrial fibrillation; AV, atrioventricular; BSA, body surface area; LAFB, left anterior fascicular block; RBBB, right bundle branch block.

*Normal values: men <500 ml/m²; women <450 ml/m².

and histological examination of biopsy specimens from the skin or rectal mucosa showed amyloid in all of them. There was no evidence of inflammatory disease or immunocyte dyscrasia. The degree of polyneuropathy was used as a measurement of the severity of the disease and was graded on the basis of the patients' ability to perform normal daily activities as¹¹: very severe (one patient), severe (five), moderate (five), and slight (one) (Table 1).

One patient had slight aortic incompetence and one a persistent ductus arteriosus. These two patients and a further three had symptoms and signs of heart failure and were treated with diuretics. Two patients had pacemakers implanted, one because of sinus arrest/sinoatrial block and the other because of atrial fibrilla-

tion with a slow ventricular rate. None of the patients had a history of myocardial infarction or systemic hypertension. The interval between echocardiography and scintigraphy was less than one week.

ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed with a real time wide angle (90°) mechanical scanner with three revolving 3.0 MHz transducers (ATL III, Advanced Technology Laboratories). Views of the heart were obtained in the parasternal, apical, and subcostal positions.¹² The studies were performed with different grey scale curves.¹³ Images were recorded using a Sanyo video tape recorder. M mode images were acquired from one of the transducers in the scanner

Table 2 Results of echocardiography and technetium-99m pyrophosphate scintigraphy in 12 patients with familial amyloidosis with polyneuropathy

Case No	IVS (mm)	LVPW (mm)	RVW (mm)*	Highly refractile myocardial echoes†				Thickened valves	Pericardial effusion	Scintigraphy‡
				IVS	RVW	LVPW	PM			
1	16	15	N	+++	++			Aortic, mitral	No	0
2	13	10	N	+++				—	Yes	++
3	10	10	N		+	++	++	—	No	+
4	24	22	N	+++	+			Aortic, tricuspid	Yes	++++
5	14	9	N	++			+++	—	No	+
6	16	12	N	+++	+++			Aortic	Yes	0
7	11	10	N	+				Mitral	No	0
8	11	11	N	+				—	No	0
9	20	14	6	+++	++			Aortic, mitral, tricuspid	Yes	+++
10	12	12	7	++	+++			—	Yes	0
11	19	17	N	+++				Aortic, mitral	Yes	+++
12	11	11	N	++				Aortic	No	0

IVS interventricular septum; LVPW, left ventricular posterior wall; PM, papillary muscle; RVW, right ventricular wall.

*N, normal (<5 mm).

†+, scant; ++, moderate; +++, abundant.

‡0, no; +, equivocal; ++, weak; +++, moderate; +++++, intense myocardial uptake.¹⁶

head and recorded on a fiberoptic strip recorder (ATL 100). Measurements were made in accordance with the standards of the American Society of Echocardiography,¹⁴ and the echocardiographic values obtained were compared with the normal values given by Feigenbaum.¹⁵ Highly refractile myocardial echoes were defined as distinct and very bright echoes that could be visualised in different projections or at different angulations and persisted at gain settings low enough to eliminate the echoes of the surrounding endocardium and myocardium.¹³ The distribution of the highly refractile echoes was graded as scant, moderate, or abundant.

SCINTIGRAPHY

Technetium-99m pyrophosphate scintigraphy was performed using a Portacamera IIC (General Electric) with a high resolution parallel hole collimator; 350 MBq (9.5 mCi) of the isotope was injected intravenously. Two hours later three supine views were obtained: anteroposterior, 45° left anterior oblique, and 90° left lateral. About 600 000 counts were collected over three minutes from each view. The scintigrams were recorded on polaroid and transparent films and were stored and analysed using a Digital Gamma-II computer system (Digital Equipment). Radioisotope images were graded from 0 to ++++ depending on the activity in the myocardium; 0, no activity in the region of the heart; +, faint equivocal activity believed to be in the blood pool or chest wall; ++, definite but weak activity in the myocardium but less intense than in the ribs; +++, moderate activity in the myocardium equal in intensity to the ribs but less than the sternum; ++++, intense activity in the myocardium equal to or greater in intensity than the sternum.¹⁶

Results

Table 2 summarises the echocardiographic findings. Increased thickness of the interventricular septum

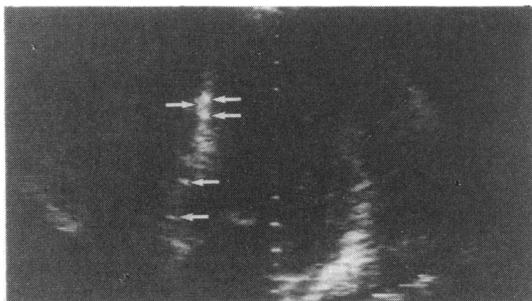


Fig. 1 Cross sectional echocardiogram in the apical four chamber view (case 4) showing highly refractile myocardial echoes (arrows).

(>11 mm) was found in eight patients and increased thickness of the left ventricular posterior wall (>11 mm) in six patients. The interventricular septum was thickened asymmetrically (ratio of thickness of interventricular septum to left ventricular posterior wall >1.3) in two patients. Highly refractile myocardial echoes were seen in all patients (Fig. 1). The echoes were single or multiple, distinct, and very bright. Their shape was rounded or somewhat irregular, and they were usually 2 to 5 mm in diameter. The echoes emerged more clearly when a linear grey scale curve was used instead of a 45 dB logarithmic grey scale curve. The interventricular septum most often showed highly refractile echoes (11 patients), but they were also seen in the free ventricular walls (six patients) and the papillary muscles (two patients). Seven patients had thickened heart valves. In the aortic valve the thickening was usually most pronounced in the commissures, whereas the mitral and tricuspid valves were more diffusely affected. Four patients had multivalvular involvement. Decreased valvular motility was, however, found in the aortic valve of only one patient. Six patients had pericardial effusion, but the amount of fluid was considered small. All the five patients treated with diuretics for heart failure had an interventricular septal thickness exceeding 15 mm.

Table 2 also shows the scintigraphic findings. Four patients had an abnormal diffuse myocardial uptake of the isotope; in one patient it was intense (++++), (Fig. 2), in two moderate (+++), and in one weak (++) . The remaining patients either had equivocal (+) or no (0) activity in the region of the heart and were considered to have normal scintigrams. Three patients with abnormal scintigrams had advanced echocardiographic changes, and three had heart failure.

There was a relation between the thickness of the interventricular septum and an abnormal scintigram (Spearman's rank correlation coefficient $r_s=0.73$, $p<0.01$) (Fig. 3). No significant correlation was found between the duration or severity of polyneuropathy on the one hand and the thickness of the interventricular septum or of the left ventricular posterior wall, an abnormal scintigram, or heart failure on the other.

Discussion

The prevalence of involvement of the heart varies in different types of systemic amyloidosis. In primary amyloidosis and myeloma associated amyloidosis there is cardiac deposition in about 80–90% of necropsy cases, whereas involvement of the heart in secondary amyloidosis is reported less frequently, in about 60%.¹⁷ In the Swedish variant of familial amyloidosis with polyneuropathy histopathological

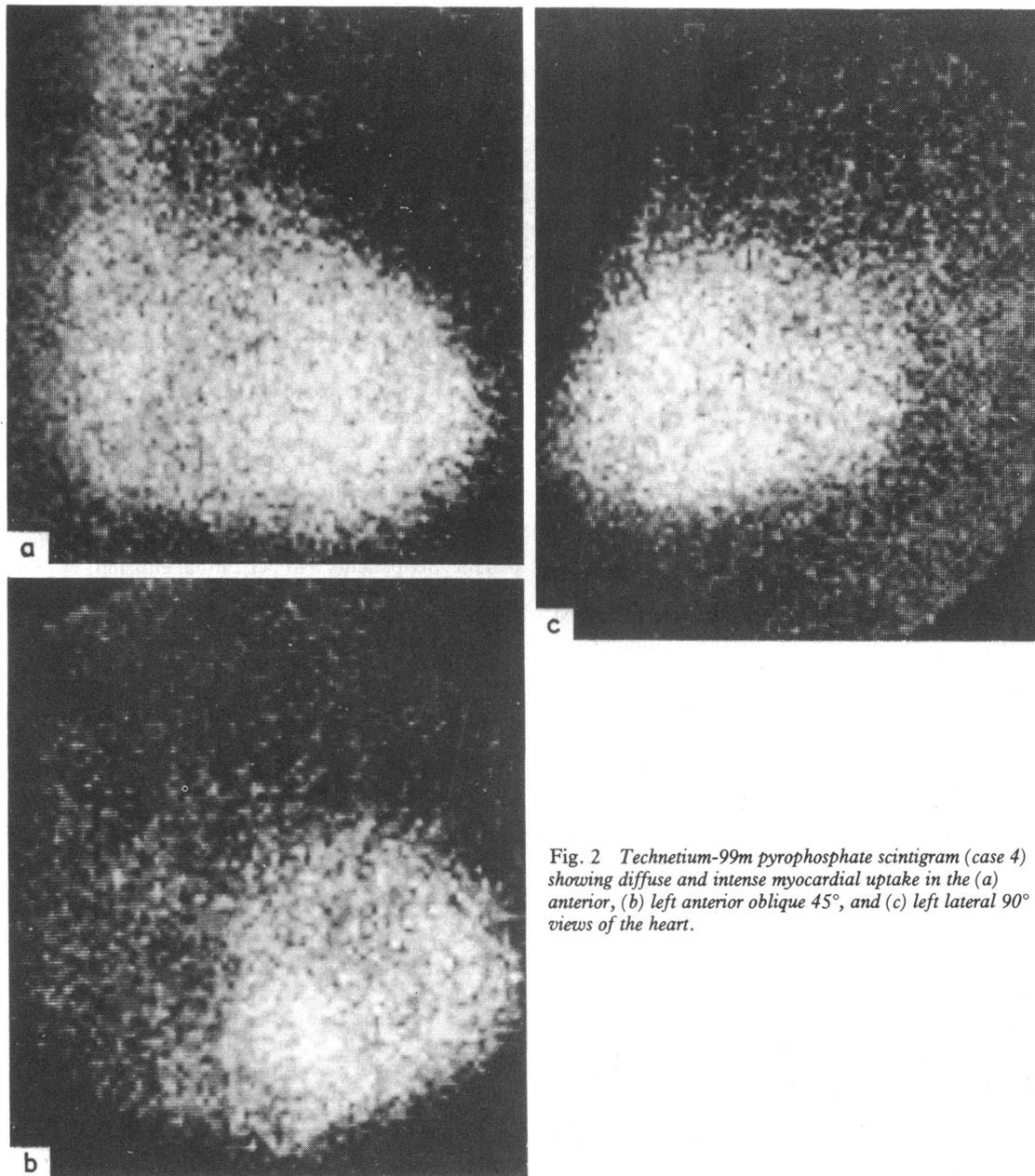


Fig. 2 Technetium-99m pyrophosphate scintigram (case 4) showing diffuse and intense myocardial uptake in the (a) anterior, (b) left anterior oblique 45°, and (c) left lateral 90° views of the heart.

examinations of the heart at necropsy have invariably shown the presence of amyloid.¹⁸⁻²⁰

Early diagnosis of familial amyloidosis with polyneuropathy is possible owing to a characteristic clinical picture and the familial occurrence, and, consequently, involvement of the heart may be studied at different stages of the disease. The most important cardiac manifestations are disturbances of rhythm and

conduction.^{21,22} Congestive heart failure, a common manifestation in other forms of amyloidosis,¹ is less frequently reported in familial amyloidosis with polyneuropathy.²³ The reasons for this are unknown, but diagnosis at an early stage, as well as differences in the biochemical composition of amyloid,^{10,24} may be important factors.

The most common echocardiographic findings

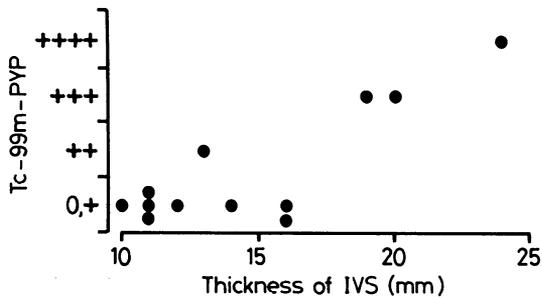


Fig. 3 Relation between the thickness of interventricular septum (IVS) and myocardial uptake of technetium-99m pyrophosphate (Tc-99m-PYP). 0, no; +, equivocal; ++, weak; +++, moderate; and +++++, intense myocardial uptake. Spearman's rank correlation coefficient $r_s=0.73$, $p<0.01$.

reported in amyloidosis include a peculiar hyper-refractile myocardial appearance, thickened heart valves, increased thickness of the ventricular walls and interventricular septum, and pericardial effusion.³⁻⁵ In our series of 12 patients all had echocardiographic abnormalities consistent with cardiac amyloidosis. All five patients with heart failure had advanced echocardiographic changes, including an interventricular septum exceeding 15 mm. This may indicate that the reduced cardiac function is caused by amyloid infiltration or fibrosis with muscular hypertrophy or both. In general, the highly refractile myocardial echoes were more abundant and widespread in patients with thicker cardiac walls.²⁵ Thus the extent of the echocardiographic changes seems to parallel the reduction in myocardial function.

Diffuse and intense myocardial uptake of technetium-99m pyrophosphate has been reported in a large proportion of patients with systemic amyloidosis. Wizenberg *et al* reported that all of 10 patients showed intense myocardial uptake.⁷ The types of amyloidosis studied were not, however, stated. All these patients had moderate to severe ventricular hypertrophy, and seven patients had congestive heart failure. Falk *et al* examined 20 consecutive patients with amyloidosis associated with plasma cell dyscrasia.⁸ Of these, 11 patients had positive scintigrams, of whom eight had heart failure. One patient with heart failure had a normal scintigram. Most other reports of cardiac scintigraphy in amyloidosis concern single or a few cases with abnormal scans,^{6 26 27} and thus little is known about the occurrence of negative scans in amyloidosis.

In contrast to our results, previous reports included a larger proportion of patients with abnormal scans. We think this difference may be partly because several of our patients were examined at an earlier stage of involvement of the heart than those in the previous

studies. Differences in the biochemical composition of amyloid protein may also contribute to the differences observed.^{10 24} Falk *et al* also reported that technetium-99m pyrophosphate scintigraphy does not appear to be a sensitive indicator of early myocardial involvement in primary amyloidosis.⁸ The cause of the abnormal uptake of radiotracer in amyloidosis is not well understood. Direct binding to amyloid, possibly via a calcium dependent mechanism, has been suggested^{6 8} as well as transchelation of technetium-99m atoms from technetium pyrophosphate to amyloid proteins.²⁸ It should also be pointed out that abnormal scans with this infarct avid radiotracer are not specific for cardiac amyloidosis but have been reported in patients with various disorders besides myocardial infarction.²⁹ As with the results obtained by echocardiography, the outcome of scintigraphy was not related to the severity or duration of familial amyloidosis polyneuropathy.

Bhandari and Nanda recently reported cross sectional echocardiographic findings in a variety of myocardial disorders.¹³ They stated that in adult patients widespread and extensive myocardial involvement with highly refractile echoes was seen only in amyloidosis and, rarely, in hypertrophic cardiomyopathy. Furthermore, Weyman has pointed out that thickened heart valves may be useful in distinguishing cardiac amyloidosis from other cardiac disorders.³⁰ The combination of thickened heart valves and highly refractile echoes affecting more than one ventricular wall or papillary muscle thus seems to be diagnostic of cardiac involvement in systemic amyloidosis. The presence of less abundant or less widespread echoes also appears to indicate cardiac amyloidosis, especially in conjunction with thickened valves and thickened interventricular septum or ventricular walls. Discrete echocardiographic changes in familial amyloidosis with polyneuropathy may be identified at an early stage, and also when there is no other evidence of involvement of the heart.

In familial amyloidosis with polyneuropathy the outcome of technetium-99m pyrophosphate scintigraphy is more unpredictable. Abnormal myocardial uptake seems to indicate advanced cardiac involvement. The findings of both Wizenberg *et al*⁷ and Falk *et al*⁸ imply that this may also be valid for other forms of systemic amyloidosis. In familial amyloidosis with polyneuropathy, however, a normal scintigram does not exclude advanced echocardiographic changes, and patients with heart failure may show normal scintigrams. This may also be true for other forms of amyloidosis, although this needs further confirmation.

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