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

PETER ERIKSSON, CHRISTER BACKMAN, PER BJERLE, ANDERS ERIKSSON, SONJA HOLM, BERT-OVE OLOFSSON

From the Departments of Internal Medicine and Clinical Physiology, and the Institute of Forensic Medicine, University of Umeå, Umeå, Sweden

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. Nevertheless, a definite antemortem diagnosis of cardiac amyloidosis is, of course, not possible without cardiac biopsy. 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. 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 heredofamilial systemic amyloidosis and has been reported in localised areas of several countries, including Portugal, Japan, Sweden, England, and the USA. 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,
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 as:11 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 fibrillation 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.

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<th>IVS (mm)</th>
<th>LVPW (mm)</th>
<th>RVW (mm)</th>
<th>Highly refraclile myocardial echo†</th>
<th>Thickened valves</th>
<th>Pericardial effusion</th>
<th>Scintigraphy‡</th>
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1. IVS: Interventricular septum; LVPW: Left ventricular posterior wall; PM: Papillary muscle; RVW: Right ventricular wall.
2. *N: normal (<5 mm).
3. †+, scant; ++, moderate; ++++, abundant.
4. ‡0, no; +, equivocal; ++, weak; ++++, moderate; ++++, intense myocardial uptake.16
Cardiac amyloidosis: non-invasive assessment

head and recorded on a fibreoptic strip recorder (ATL 100). Measurements were made in accordance with the standards of the American Society of Echocardiography, and the echocardiographic values obtained were compared with the normal values given by Feigenbaum. 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. 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 images 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.

Results
Table 2 summarises the echocardiographic findings. Increased thickness of the interventricular septum (>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 multi-valvular involvement. Decreased valvular mobility 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 up take 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 rs=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%. In the Swedish variant of familial amyloidosis with polyneuropathy histopathological
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
reported in amyloidosis include a peculiar hyper-
refractile myocardial appearance, thickened heart val-
ves, 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 echocar-
diographic changes, including an interventricular sep-
tum exceeding 15 mm. This may indicate that the
reduced cardiac function is caused by amyloid infiltra-
tion 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.24 Thus the extent of the echocardiographic changes seems to parallel the
reduction in myocardial function.
Diffuse and intense myocardial uptake of tech-
netium-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,
reported. All these patients had moderate to severe ven-
tricular 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 scti-
grams, of whom eight had heart failure. One patient
with heart failure had a normal scintigram. Most
other reports of cardiac scintigraphy in amyloidosis
discuss 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 sev-
eral 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 differ-
ences 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, poss-
ibly via a calcium dependent mechanism, has been
suggested6,8 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 sec-
tional 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 card-
emyopathy. Furthermore, Weyman has pointed out
that thickened heart valves may be useful in distin-
guishing cardiac amyloidosis from other cardiac disor-
ders.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 ven-
tricular 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 scintig-
raphy is more unpredictable. Abnormal myocardial
uptake seems to indicate advanced cardiac involve-
m. The findings of both Wizenberg et al7 and
Falk et a8 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 confirma-
tion.

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References

1 Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: Analysis of 54 necropsy patients. Am J Cardiol 1983; 52: 137–46.
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P Eriksson, C Backman, P Bjerle, A Eriksson, S Holm and B O Olofsson

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