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The heart in Portuguese amyloidosis

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Summary: **A systematic investigation was performed in patients with familial amyloidotic polyneuropathy, Portuguese type (AFp) to assess the pattern and incidence of cardiac involvement. Of 327 patients investigated, ECG abnormalities were present in 285 (87.2%). Low voltage and QS pattern in V1, V2, V3 were found in 51.3% and 35.7% patients respectively. Conduction disturbances were present in 211 (64.5%). Sinus node disease, 1st degree and Wenckebach interventricular blocks were frequent. Complete atrioventricular block was observed in only 2 patients (0.6%). Left anterior hemi-block was present in 30.8%, left bundle branch block in 3.9%, left posterior hemi-block in 2.4% and right bundle branch block in 2.1%. Holter monitoring showed a much higher incidence of conduction disturbances, most of these occurring at night.**

The mean values of septum and posterior wall thickness and mass evaluated by echocardiography in 72 patients were normal. The systolic and diastolic global and regional functions, determined in 12 patients, analysing the echo by a digitization computer technique, were normal. In 7% a trivial pericardial effusion was observed. In 16 patients with ECG changes and normal echocardiograms the technetium 99m pyrophosphate scanning was negative.

We conclude that the ECG is the most precise, sensitive and clinically useful method for detecting cardiac amyloidosis in patients with AFp. In spite of the rarity of congestive and restrictive patterns, the incidence and severity of conduction disturbances does not allow us to consider heart disease in AFp as a benign entity.

Heart involvement is a common feature in all forms of systemic amyloidosis, including the heredofamilial syndromes. The heterogeneity of the amyloid protein precursors, the genetic or acquired nature of these diseases, the different ages at which symptoms appear and their duration, make it difficult to establish a common pattern of heart manifestations in amyloidosis. There are generally five clinical presentations for amyloid heart disease: dilated (congestive) cardiomyopathy, arrhythmia and conduction disturbances, hypertrophic and restrictive cardiomyopathies and the 'stiff heart syndrome'. Familial amyloidotic polyneuropathy, Portuguese type (AFp), involves motor, sensory and autonomic nerves and is transmitted by a dominant autosomal gene. All these patients have the same protein amyloid precursor – a variant of prealbumin – and an incidence of 100% of cardiac amyloidosis at necropsy. In the course of a systematic approach to AFp, clinical, electrocardiographic (ECG), Holter monitoring, echocardiographic and technetium 99m scanning studies were performed and their utility assessed. Data from these studies are reported here to establish the general pattern and incidence of cardiac involvement in AFp.

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Methods

A nerve or skin biopsy, positive for amyloid, was the required criterion for patient selection. All the patients showed the typical neurological picture and the hereditary pattern (Andrade, 1952). A standard ECG was recorded in 327 consecutive patients. We performed 24 hour Holter monitoring using 2 leads in 100 consecutive patients aged 40.5 ± 10.2 (range 24–74) years with a mean time of symptom duration 6.7 ± 5.5 years. Semiautomatic analysis of tracings was made by a cardiologist who recorded representative parts.

M-mode echocardiograms were performed in 72 patients (40 men), with mean age 37.3 ± 9.13 years, and in 20 normals age and sex matched. Parameter determinations were performed according to Crawford *et al.* (1980) using the mean of 3 measurements. In 12 patients and 10 normals, age and sex matched, left ventricular global and regional diastolic function were assessed by digitized analysis of the left ventricle echocardiogram. Three cycles in each recording were digitized and for each cardiac cycle we acquired the continuous left ventricular dimension and its rate of change (Figure 1). Its most positive value is the filling rate. We determined the isovolumic relaxation and the rapid filling rate periods (Figure 1) (Sutton *et al.*, 1982). For the septum and posterior wall, we obtained

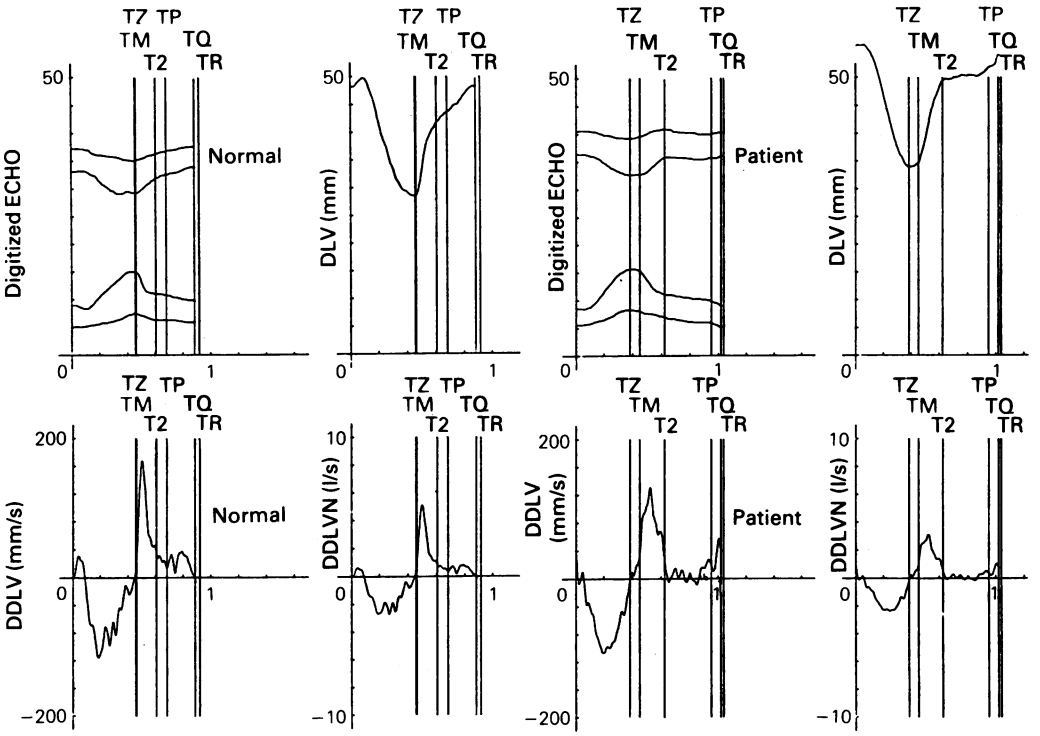

Figure 1 DLV – left ventricle dimension during the cycle. DDLV – rate of change of LV dimension. DDLVN – plots of normalized rate of change of LV dimension. TZ – minimum diameter; TM – opening of mitral valve; T2 – end of the rapid filling period; TP – start of the P wave; TQ – start of QRS. (Note: all X axes are time axes in seconds).

the thickness variation during the digitized cardiac cycle and the rate of change normalized by the instantaneous thickness. The most negative value corresponds to the normalized peak rate of diastolic thinning of the wall (Figure 2). In 16 patients, 9 women and 7 men, mean age 40.5 (range 28–55) years, technetium 99m pyrophosphate scintigraphy was performed. Three hours after 925 MBq of the isotope was injected intravenously, 2,500,000 counts were collected from antero-posterior, 45° left anterior and 90° left lateral views. All these patients had electrocardiographic changes and normal echocardiograms.

Results

In 327 patients observed in the last 25 years, cardiac failure was very rarely seen (0.1%). Syncopal attacks were a frequent complaint, mostly due to hypoadrenergic postural hypotension and to conduction disturbances. Electrocardiographic changes were present in 285 (87.2%) patients (Table I). Low voltage and a QS pattern in V1 to V3 were found in 51.3% and 35.7% of patients respectively. Conduction disturbances – the most frequent finding – were present in 64.5% patients. Sinoatrial block was found in 8.5%. At atrioventricular level, partial blocks of 1st degree and Wenckebach type were commonly found. Complete heart block was found in only 2 patients. The interventricular conduction disturbances were characterized by a marked difference between left and right bundle branch involvement. Left bundle branch disease was present in 122 patients (36.1%) with a high incidence of left anterior fascicular block (30.8%). Complete right bundle branch block was present in 7 patients (2.1%), less than those with left posterior fascicular block (2.4%). Associate blocks, at different levels, were present in 111 patients. The comparison in the same patient between standard ECG and Holter monitoring findings showed a higher incidence of conduction disturbances in the latter, especially sinoatrial block (22:9%) and the Wenckebach type of atrioventricular block (26:7%). In all Holter recordings the higher degree of these disturbances occurred at night. This method enabled us to detect arrhythmias rarely found on standard ECG with special reference to ventricular tachycardia runs (6%). Thirty patients had conduction disturbances or arrhythmia only in

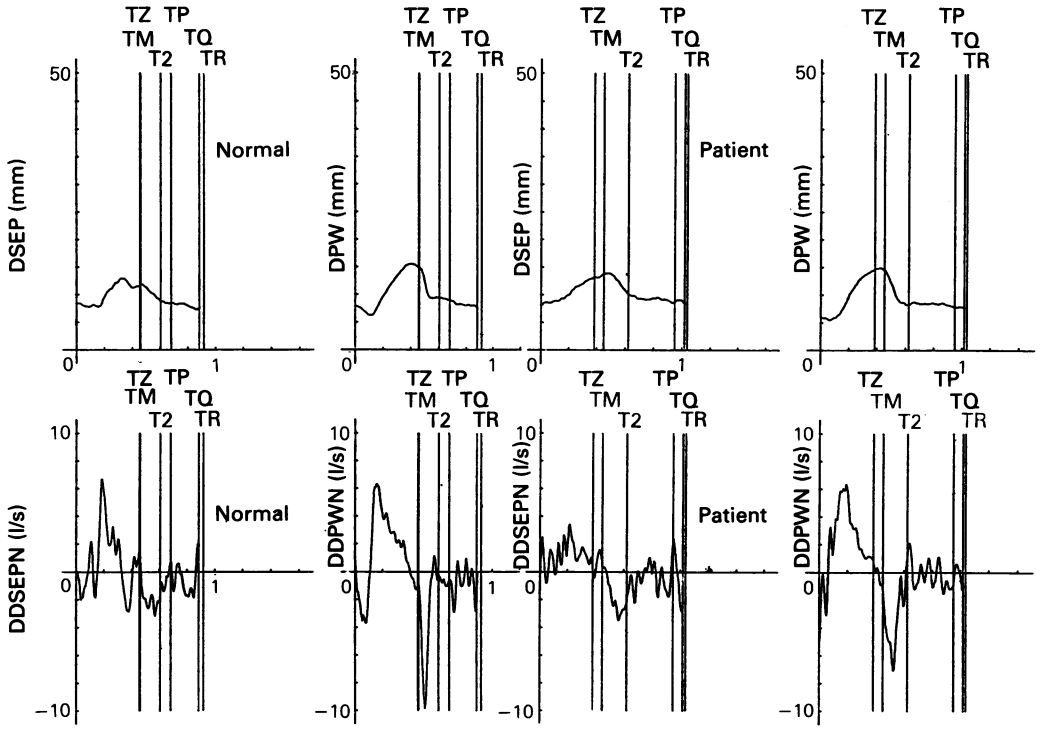

Figure 2 DSEP – septal thickness; DPW – posterior wall thickness; DDSEPN – normalized rate of change of septal thickness; DDPWN – normalized rate of change of posterior wall thickness. (Note: all X axes are time axes in seconds).

Holter monitoring. Mean values of septal diastolic thickness, posterior wall diastolic thickness, the ratio of septum/left posterior wall thickness and cross-sectional area of the left ventricle were identical in both groups. Nevertheless, increases of septal diastolic and

Table I Electrocardiographic findings in 327 patients with Portuguese amyloidosis

	N	(%)
Sinoatrial block	28	8.5
A-V block 1st degree	121	37.0
A-V block 2nd degree type I	36	11.0
A-V block 3rd degree	2	0.6
Right bundle branch block	7	2.1
Left anterior hemiblock	101	30.8
Left posterior hemiblock	8	2.4
Left bundle branch block	13	3.9
Low voltage	168	51.3
QS pattern on V1–V3	117	35.7
Normal ECG pattern	42	12.8

Table II Ambulatory ECG compared to routine ECG in 100 patients with AFp

	Routine ECG	*Ambulatory ECG*
Sinoatrial block	9	22
APBs (<30/h)	3	21
Frequent APBs (>30/h)	–	30
Ectopic supraventricular rhythm	0	8
Supraventricular tachycardia	0	6
Atrial flutter	1	2
Frequent VPBs (>30/h)	–	5
Multifocal VPBs	0	6
Paired VPBs	1	19
Ventricular tachycardia	0	6
1st degree A-V block	29	36
2nd degree A-V block (type I)	7	26
2nd degree A-V block (type II)	0	1
3rd degree A-V block	2	3
No rhythm disturbances	45	1

APB = atrial premature beat;
VPB = ventricular premature beat.

left posterior wall thickness were observed in 6 and 9 patients, respectively, at a 95% confidence level. We could not find any correlation between these abnormalities and the patients' age, duration and intensity of symptoms or ECG alterations. All the patients presented with a normal left ventricular mass and left ventricular diastolic diameter at a 95% confidence level.

Left ventricular function was decreased in 16 patients but the mean values of ejection and shortening fraction were not different from normals. All the patients had a normal filling rate. The mean values of isovolumic relaxation period and rapid filling period were normal. Septal diastolic thinning peak rate and posterior wall thinning peak rate mean values were normal. In 5 of the 72 patients, a trivial pericardial effusion was observed. The echocardiographic study in patients with AFp showed normal left ventricular mass, normal diastolic regional and global function, small increases of thickness of both walls in less than 10% and slight decrease of systolic left ventricular function in 22%. None of the patients had myocardial uptake of the isotope after technetium 99m pyrophosphate injection.

Discussion

The electrocardiographic study, the largest ever performed in any form of amyloidosis as far as we know, showed a higher prevalence of conduction disturbances of the left bundle branch compared to right bundle branch disease and relative rarity of advanced forms of atrioventricular block. These findings suggest that interventricular blocks are predominantly determined by the effects of amyloid in the Purkinje network. If conduction disturbances were caused by truncular or A-V lesions we should find a higher incidence of right bundle branch disease and complete heart block. The more frequent appearance of sinoatrial disease and partial atrioventricular block, in Holter recordings, usually more severe at night, in all patients in which they were detected suggests that autonomic nerve dysfunction could be an important factor in their genesis. The echocardiographic findings explain the rarity of congestive restrictive heart failure and of the 'stiff heart syndrome'. The scintigraphic study, claimed to be an early, specific and sensitive test for diagnosing amyloid heart disease was negative in all the patients. In comparison to other forms of amyloidosis, heart manifestations in AFp are characterized by the higher frequency of ECG changes and the rarity of cardiac failure, echocardiographic abnormalities, and absence of technetium 99m pyrophosphate cardiac uptake. This discrepancy is unlikely to be related to the type of amyloid. It was recently found that cardiac senile amyloidosis (Westermark *et al.*, 1979), the hereditary amyloid heart disease described by Frederiksen *et al.* (1962), and hereditary polyneuropathic amyloidosis (Olofsson, 1982; Eriksson, 1984) all with marked cardiac impairment are, like AFp, related to prealbumin. David *et al.* (1984) studied the hearts of 11 patients with amyloidosis, 4 of which had AFp, 5 reactive amyloidosis and 2 myeloma. The amyloid deposition was much less and more unevenly distributed in the hearts and intramyocardial vessels of patients with AFp and reactive amyloid, with predominance at subendocardium and atria, than in those with myeloma. The cardiac autonomic nerves were severely affected in AFp and reactive amyloid but were spared in myeloma patients.

These pathological findings offer a possible explanation of the differences between clinical manifestations of heart disease in patients with AFp and other types of amyloidosis and of the pattern of interventricular conduction disturbances. It seems important to emphasize that, in contrast to other studies, in which amyloidosis was diagnosed after clinical heart syndromes, the population in this study has an hereditary pattern and early typical neurological picture that enables us to diagnose amyloid disease probably a long time before we can see the haemodynamic consequences of amyloid deposition in the heart. In addition, our patients have a mean age at which other detrimental influences on the heart, unrelated to amyloid, are much less probable than they are in older patients, like those with hereditary polyneuropathic amyloidosis described by Olofsson (1982) and Eriksson (1984). Finally we conclude that the ECG is the earliest, most sensitive and clinically useful method for detecting cardiac amyloidosis in patients with AFp and, in spite of the rarity of myocardial congestive, infiltrative or restrictive patterns, the incidence and severity of conduction disturbances do not allow us to consider heart disease in AFp as a benign entity.

References

ANDRADE, C. (1952). A peculiar form of peripheral neuropathy: familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain*, **95**, 408.

CRAWFORD, M.M., GRANT, D., O'ROURKE, R.A., STARLING, M.R., & GROVES, B.M. (1980). Accuracy and reproducibility of M-mode echocardiographic recommendations for measuring left ventricular dimensions. *Circulation*, **60**, 137.

DAVID, L.S., MACIEL, L., FALCAO DE FREITAS, A. &

SOBRINHO-SIMOES, M. (1984). Envolvimento cardiaco nas amiloidoses sistemicas adquiridas – Revisao de 11 casos. Communication to the 7th Reunion Hispano-Portuguesa de Anatomia Patologica. Madrid.

ERIKSSON, P. (1984). Cardiac involvement in familial amyloidosis with polyneuropathy. *Thesis*, Umea University, Umea.

FREDERIKSEN, T., GOTZSCHE, H., HARBOE, N., KIAER, W. & MELLEMGAARD, K. (1962). Familial primary amyloidosis with severe amyloid heart disease. *American Journal of Medicine*, **33**, 328.

OLOFSSON, B.O. (1982). Cardiopulmonary function in familial amyloidosis with polyneuropathy. *Thesis*, Umea University, Umea.

SUTTON, M.G.S.Y., REICHECK, N., KASTOR, J.A. & GUILIANI, E.R. (1982). Computerized M-mode echocardiographic analysis of left ventricular dysfunction in cardiac amyloid. *Circulation*, **64**, 790.

WESTERMARK, P., JOHANSSON, B. & NATVIG, J.B. (1979). Senile cardiac amyloidosis: evidence of two different amyloid substances in the ageing heart. *Scandinavian Journal of Immunology*, **10**, 303.