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Pulsed tissue Doppler and strain imaging discloses early signs of infiltrative cardiac disease: A study on patients with familial amyloidotic polyneuropathy

P. Lindqvist [a,b,c,d,*], B.O. Olofsson [a], C. Backman [c], O. Suhr [a], A. Waldenström [a,b]

[a] *Department of Public Health and Clinical Medicine, Heart Centre, Umeå University, S-90185 Umeå, Sweden*
[b] *Department of Cardiology, Heart Centre, Umeå University, S-90185 Umeå, Sweden*
[c] *Department of Clinical Physiology, Heart Centre, Umeå University, S-90185 Umeå, Sweden*
[d] *Institution of Surgery and perioperative sciences, Heart Centre, Umeå University, S-90185 Umeå, Sweden*

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Abstract *Background:* Familial amyloidotic polyneuropathy (FAP) is a hereditary systemic amyloidosis with cardiac involvement. As early identification of the cardiac involvement is of major clinical interest we performed this study to test the hypothesis that tissue Doppler imaging (TDI) and strain imaging (SI) might disclose cardiac involvement in patients with early stages of FAP.
Methods: Twenty-two patients with FAP and 36 healthy controls were studied. Standard M-mode and Doppler echocardiography were performed. TDI and SI were used to assess the regional longitudinal left ventricular (LV) lateral and septal and right ventricular (RV) wall functions. All time intervals were corrected for heart rate by dividing with R–R interval and presented as percentage.
Results: We found that patients in comparison with controls had increased LV and RV wall thickness and by using TDI a prolonged isovolumic relaxation time (IVRt) at the septal segment (15.0 ± 7.0 vs $10.7 \pm 4.1\%$, $p < 0.05$) and prolonged isovolumic contraction time (IVCt) at LV lateral (12.8 ± 4.3 vs $10.1 \pm 3.3\%$, $p < 0.05$), septal (12.5 ± 3.5 vs $8.9 \pm 1.9\%$, $p < 0.001$) and RV free wall segments (12.0 ± 3.6 vs $8.3 \pm 2.1\%$, $p < 0.001$). Strain was reduced at LV lateral basal segment (-4.6 ± 14.0 vs $-20.2 + 9.1$, $p < 0.001$), RV free wall mid segment (-16.2 ± 12.8 vs

* Corresponding author. Tel.: +46 9078 56980; fax: +46 9013 7633.
E-mail address: per.lindqvist@medicin.umu.se (P. Lindqvist).

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-29.4 ± 15.2) as well as both septal segments (-4.1 ± 11.7 vs $-16.2 \pm 9.0\%$, $p < 0.001$, -8.8 ± 11.5 vs $-19.4 \pm 8.4\%$, $p < 0.001$ for septal basal and mid-segment). Even in the absence of septal hypertrophy the septal strain was reduced and the regional IVCt was prolonged.

Conclusions: This is the first clinical study using TDI and strain in patients with FAP showing functional abnormalities before any morphological echocardiographic abnormalities were present. Both the left and right heart functions are involved and the disease should therefore be regarded as biventricular.

Introduction

Amyloidosis is the denotation of a heterogeneous group of disorders, which are all characterised by extracellular tissue deposits of fibrillar proteins.[1] Amyloid cardiomyopathy occurs in various types of systemic amyloidosis, but also as isolated cardiac amyloidosis.[2,3] It is of major clinical importance in AL (light-chain associated) amyloidosis, but is of clinical significance also in other types of systemic amyloidosis.[4]

Transthyretin amyloidosis denotes systemic amyloidosis that is caused by mutated transthyretin (TTR).[5] About 100 different amyloidogenic TTR mutations are now described and the majority of these are associated with a syndrome comprising neuropathy and cardiomyopathy.[6] In the most common TTR mutation, isoleucine is substituted for valine at position 122 (ATTRVal122Ile). This is found in 4% of black Americans and is associated with late onset of cardiac amyloidosis.[7]

All patients included in this study were living in northern Sweden and had a mutation where valine is exchanged for methionine at position 30 on the transthyretin molecule (ATTRVal30Met). The corresponding phenotype is often designated familial amyloidotic polyneuropathy (FAP) Portuguese type, as it was first described in Portugal.[8]

The cardiac manifestations are heterogeneous in the various syndromes with cardiac amyloidosis. Thus, the amyloid cardiomyopathy in AL amyloidosis is often associated with severe heart failure,[4] while in FAP clinical signs of cardiac involvement is restricted and comprise mainly arrhythmias and conduction disturbances.[9] This is probably due to different biochemical properties in FAP with more limited infiltration and a slower progress of the deposits. The findings reported from two-dimensional echocardiographic studies are of similar character in AL amyloidosis and FAP but the abnormalities found are more prominent in AL amyloidosis.[10,11] Typical findings comprise increased left ventricular wall thickness, normal or reduced left ventricular volume, normal or mildly reduced fractional shortening, increased left atrial dimension and a spectrum of diastolic dysfunction parameters for both the left and right ventricle.[12–15] Other common findings are pericardial effusion and hyper-refractile myocardial echoes.[14,16–18]

Koyama et al. have in recent studies used modern echocardiographic techniques, such as tissue Doppler imaging (TDI) and strain imaging (SI), in their assessment of the amyloid cardiomyopathy in patients with AL amyloidosis. These techniques seem to disclose early stages of cardiac dysfunction preceding symptoms of heart failure.[19,20]

Early identification of the cardiac involvement in various systemic amyloidosis has become of major clinical interest because its occurrence and severity may influence the choice of therapies such as bone marrow transplantation in AL amyloidosis and liver alone or combined liver and heart transplantation in FAP.[21–23]

The aim of our study was to test the hypothesis that tissue Doppler imaging and strain imaging could disclose cardiac involvement in patients with early stages of FAP.

Methods

Study population

Twenty-two patients with familial amyloidotic polyneuropathy (FAP) (11 males and 11 females, mean age 60, range 34–79 years) considered for orthotopic liver transplantation were included in the study.

In all cases, the diagnosis was based on clinical symptoms including peripheral neuropathy, amyloid demonstrated in histopathological examinations of biopsy specimens from rectal mucosa, and positive genetic testing for the ATTRVal30Met mutation. Some clinical and anthropometric data of the patients are shown in Table 1.

None of the patients showed signs of heart failure or was on medication for any cardiovascular disease and therefore the clinical consequence of

Table 1 General characteristics in patients with familial amyloidotic polyneuropathy (FAP) and controls

	Controls ($n = 36$)	FAP ($n = 22$)	p Value
Age (years)	61 ± 10	60 ± 13	ns
Female/male	21/15	11/11	ns
Systolic blood pressure (mmHg)	135 ± 16	130 ± 16	ns
Diastolic blood pressure (mmHg)	76 ± 9	78 ± 10	ns
Height (m)	1.69 ± 0.09	1.70 ± 0.11	ns
Weight (kg)	72 ± 12	71 ± 14	ns
Heart rate (bpm)	62 ± 9	76 ± 11	<0.001

these FAP patients' cardiac involvement should be considered as limited. The duration of the symptomatic disease was 3.1 ± 2.0 years (range 1–9 years). All patients had sinus rhythm, four patients had left anterior hemiblock and one had first degree AV-block. None of the patients showed low voltage on ECG. Patients with pacemaker rhythm, left or right bundle branch block were excluded. Thirteen of the patients underwent a pulmonary function test that in all cases was proved normal. A total of 36 healthy subjects (21 females) in similar ages were randomly selected from the Swedish tax bureau register and constituted the control series. Some clinical and anthropometric data of the controls are shown in Table 1.

Patients and controls had given their informed consent for participating in the study, which was approved by the local ethics committee.

Standard echocardiography

We used a Vingmed Vivid 7 digital ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with a phased array transducer (1.5–4 MHz) where standard two-dimensional and Doppler echocardiography were used as well as pulsed and colour myocardial TDI. The echocardiographic examination was performed with the subject in the left lateral decubitus position and recordings were made during expiration. Parasternal and apical projections were obtained according to the recommendations of the American Society of Echocardiography.[24] All recordings were performed with a simultaneous superimposed electrocardiogram (ECG). A phonocardiogram (PCG) was applied to display the second component of the heart sound (S_2) to define end-systole.[25] Recordings were taken at a sweep speed of 100 mm/s.

Strain echocardiography

By convention, myocardial lengthening is given a positive strain value (positive ε) and shortening a negative value (negative ε). For one-dimensional strain (ε), $\varepsilon = \Delta L/L_0$ where ΔL is the change in length and L_0 is the starting point of change in length of a myocardial segment. The longitudinal strain was assessed from apical four-chamber view. Echocardiographic data from the two-dimensional images were transferred to a subsequent off-line analysis of scan line-based digital data. TDI and strain data from the two-dimensional images were analysed off-line using the Echopac 6.3 archiving application software. Strain distance was 12 mm and measurements were taken simultaneous from each segment with a sampling volume of 6 mm in width and 12 mm in length. The mean frame rate was 94 ± 12, range 71–137 frames/s.

Echocardiographic measurements

The following M-mode echocardiographic measurements were made: left ventricular (LV) internal diameter, inter-ventricular septal thickness, and posterior wall thickness, all measured at end-diastole (onset of the Q-wave of the ECG). LV mass was derived as proposed by Devereux and Reichek.[26] LV internal diameter was also measured at end-systole (the shortest distance between the septum and the posterior wall) and LV fractional shortening was calculated.[27] LV ejection fraction was derived from Simpson's modified biplane method.[24] The LV lateral, septal, anterior, posterior systolic atrio-ventricular (AV) plane displacements were measured and the mean value of these was calculated. RV free wall systolic AV-plane displacement was also measured.[28] Right ventricular (RV) parasternal end-diastolic inflow dimension and RV outflow tract fractional shortening were measured as previously described.[29,30] RV free wall thickness was measured at end-diastole.

Peak early (E) and late (A) diastolic velocities were measured from pulsed wave Doppler recordings of the mitral and the tricuspid flow velocities respectively, and E/A ratio was calculated.[31] LV early (E) wave deceleration time (DT) was measured from the peak to the zero velocity of the E-wave.[31] LV isovolumic relaxation time (IVRt) was measured as the time

interval between aortic valve closure (S_2) and the onset of the E-wave.

Pulsed TDI analysis from LV lateral, septal and RV free wall was made at the basal level.[32,33] Peak systolic (Sv), early (Ev) and late (Av) diastolic velocities were measured. We also measured the isovolumic contraction time (IVCt) from end of Av to onset of Sv and isovolumic relaxation time (IVRt) from end of Sv to onset of Ev. As heart rate was significantly higher in patients, all time intervals were adjusted for heart rate by dividing the time intervals with the R–R interval and were presented as percentage.

Systolic ε at basal and mid-segmental levels was obtained by measuring the total extent of myocardial shortening during ejection and expressed as the percent change from initial length. The S_2 from the PCG and/or end of T-wave from ECG was used as reference points of end-systole. This was done as peak strain might occur during early diastole, which is shown in myocardial ischemia.[34]

Statistics

A commercially available statistics program, (SPSS 11.1) was used. All data are presented as mean ± SD. Pearson's correlation and linear regression analyses were performed to display certain relations. Student's unpaired *t*-test was used to compare values between groups. Non-parametric Mann Whitney test was used when appropriate. Stepwise multiple regression analysis was performed to assess the influence of age, heart rate and septum thickness on septal systolic strain. A *p*-value less than 0.05 was considered significant.

Results

The two-dimensional echocardiography findings are shown in Table 2. Patients had lower LV end-diastolic dimension ($p < 0.01$), increased septal ($p < 0.01$) and posterior wall thickness ($p < 0.001$) and increased LV mass ($p < 0.05$) compared to controls. No differences between patients and controls were found in variables indicating LV systolic function such as radial motion (FS) and longitudinal ring motion or ejection fraction. No patient had any pericardial effusion. Among patients the LV Doppler examination showed higher *A*-velocity ($p < 0.05$) and longer IVRt ($p < 0.05$) compared to controls.

RV end-diastolic dimension was reduced ($p < 0.05$), wall thickness was increased ($p < 0.01$) and the systolic RV AV plane displacement decreased ($p < 0.01$) (Table 3).

Table 2 Echocardiographic indices of left ventricular function in patients with familial amyloidotic polyneuropathy (FAP) and controls

	Controls ($n = 36$)	FAP ($n = 22$)	*p* Value
2D/M-mode			
LA diameter (mm)	37.9 ± 5.3	36.8 ± 7.1	ns
LV end-diastolic dimension (mm)	49.4 ± 5.3	45.4 ± 4.8	<0.01
LV end-systolic dimension (mm)	29.5 ± 4.8	27.0 ± 5.3	ns
LV fractional shortening (%)	40 ± 7	41 ± 9	ns
Septal end-diastolic thickness (mm)	9.3 ± 1.7	12.3 ± 4.6	<0.01
PW end-diastolic thickness (mm)	8.2 ± 1.6	11.2 ± 3.4	<0.001
LVEF (%)	58 ± 8	60 ± 13	ns
AV-plane displacement, mean (mm)	12.8 ± 2.0	11.4 ± 2.6	ns
LV mass (g)	179 ± 53	250 ± 128	<0.05
Doppler			
Mitral *E*-velocity (cm/s)	63 ± 15	64 ± 15	ns
Mitral *A*-velocity (cm/s)	65 ± 15	75 ± 18	<0.05
Mitral *E/A* ratio	1.0 ± 0.3	0.9 ± 0.2	ns
Mitral *E*-deceleration (ms)	210 ± 60	201 ± 56	ns
LV IVRt/RR (%)	9.0 ± 2.5	12.0 ± 3.7	<0.01

LV = Left ventricular; PW = posterior wall; LA = left atrial; *E* = peak early diastolic velocity; *A* = peak late atrial diastolic velocity; IVRt = isovolumic relaxation time; RR = R–R time interval; EF = ejection fraction; AV = atrio-ventricular.

Peak systolic and diastolic myocardial velocities at all LV and RV segments were not different between groups. However, in patients the isovolumic periods were found to be prolonged; IVCt at LV lateral ($p < 0.05$), septal ($p < 0.001$) and RV free wall ($p < 0.001$) and IVRt at the septal segment ($p < 0.05$), Table 4.

Systolic strain was reduced at the basal LV lateral and both septal segments ($p < 0.001$, respectively), and the RV free wall mid-segment ($p < 0.05$), Table 5. There was a significant linear relationship between mid-septal strain and septal thickness in patients and controls ($r = 0.66$, $p < 0.001$) (Fig. 2). After performing multiple regression analysis including heart rate, age and septal thickness as independent factors and systolic mid-segmental strain as dependent factor, septum thickness was the only factor that correlated to strain.

Table 3 Echocardiographic indices of right ventricular function in patients with familial amyloidotic polyneuropathy (FAP) and controls

	Controls ($n = 36$)	FAP ($n = 22$)	p Value
2D/M-mode			
RV end-diastolic dimension (mm)	24.3 ± 6.7	20.5 ± 6.6	<0.05
RVOT fractional shortening (%)	65 ± 14	65 ± 18	ns
RVOT end-diastolic wall thickness (mm)	3.3 ± 1.0	4.8 ± 2.1	<0.05
RV AV-plane displacement (mm)	25.5 ± 4.7	21.5 ± 3.9	<0.01
Doppler			
Tricuspid *E*-velocity (cm/s)	43 ± 11	55 ± 12	<0.001
Tricuspid *A*-velocity (cm/s)	36 ± 8	52 ± 14	<0.001
Tricuspid *E*/*A* ratio (cm/s)	1.2 ± 0.3	1.1 ± 0.3	ns

RV = Right ventricular; OT = outflow tract; RA = right atrial; *E* = early diastolic velocity; *A* = late atrial diastolic velocity.

Table 4 Regional longitudinal myocardial function in patients with familial amyloidotic polyneuropathy (FAP) and healthy controls assessed with pulsed Doppler tissue imaging

	Controls ($n = 36$)	FAP ($n = 22$)	p Value
LV lateral wall			
Sv (cm/s)	7.5 ± 1.8	8.4 ± 2.3	ns
Ev (cm/s)	8.5 ± 3.0	7.5 ± 3.4	ns
Av (cm/s)	9.0 ± 2.4	8.4 ± 2.4	ns
IVRt/RR (%)	9.2 ± 3.4	9.7 ± 5.4	ns
IVCt/RR (%)	10.1 ± 3.3	12.8 ± 4.3	<0.05
Septal wall			
Sv (cm/s)	6.4 ± 1.3	6.6 ± 1.7	ns
Ev (cm/s)	6.6 ± 1.8	6.1 ± 3.5	ns
Av (cm/s)	8.9 ± 1.8	8.0 ± 2.2	ns
IVRt/RR (%)	10.7 ± 4.1	15.0 ± 7.0	<0.05
IVCt/RR (%)	8.9 ± 1.9	12.5 ± 3.5	<0.001
RV free wall			
Sv (cm/s)	12.4 ± 2.6	12.6 ± 3.7	ns
Ev (cm/s)	11.0 ± 3.1	8.9 ± 2.4	<0.001
Av (cm/s)	13.8 ± 3.5	14.6 ± 3.3	ns
IVRt/RR (%)	4.6 ± 3.1	7.7 ± 6.0	ns
IVCt/RR (%)	8.3 ± 2.1	12.0 ± 3.6	<0.001

LV = Left ventricular; RV = right ventricular; Sv = systolic velocity; Ev = early diastolic velocity; Av = atrial velocity; IVRt = isovolumic relaxation time; IVCt = isovolumic contraction time; RR = R–R time interval.

To further test the hypothesis that strain echocardiography discloses very early signs of infiltration even in FAP patients without echocardiographic morphologic abnormalities we compared a subgroup of 14 patients and 34 controls with septal thickness less than 12 mm. The IVCt was still statistically significantly prolonged at the septal segment ($p < 0.05$) and RV free wall ($p < 0.01$) and strain reduced at LV lateral basal, mid-septal, and RV free wall mid-segments among the patients ($p < 0.05$) (Table 6).

Discussion

In the present study we showed that tissue Doppler imaging and systolic strain imaging are useful techniques detecting wall motion disturbances even in patients with limited cardiac involvement due to FAP. Amyloid cardiomyopathy is an integral part of the various systemic amyloidosis but depending on the biochemical composition of the amyloid deposits and their extent, amyloid cardiomyopathy may range from asymptomatic to be the cause of severe congestive heart failure.[35] The most severe form of amyloid cardiomyopathy is generally found in patients with AL (light-chain associated) amyloidosis where intractable heart failure is a common cause of death.[18] Right ventricular dilatation with restrictive filling pattern seem to occur only in AL amyloidosis and is associated with adverse outcome.[13,15,36] In this study we have included only patients with FAP, which is a type of systemic amyloidosis where both the clinical picture and the natural course of the disease are entirely different from what is observed in AL amyloidosis. Thus, the salient clinical

Table 5 Longitudinal strain imaging (ε) in patients with familial amyloidotic polyneuropathy (FAP) and healthy controls

	Controls ($n = 36$)	FAP ($n = 22$)	p Value
LV lateral wall			
Basal ε (%)	−20.2 ± 9.1	−4.6 ± 14.0	<0.001
Mid ε (%)	−13.9 ± 7.8	−8.3 ± 10.4	ns
Septal wall			
Basal ε (%)	−16.2 ± 9.0	−4.1 ± 11.7	<0.001
Mid ε (%)	−19.4 ± 8.4	−8.8 ± 11.5	<0.001
RV free wall			
Basal ε (%)	−27.7 ± 11.2	−23.7 ± 13.7	ns
Mid ε (%)	−29.4 ± 15.2	−16.2 ± 12.8	<0.05

LV = Left ventricular; RV = right ventricular.

Table 6 Longitudinal strain (ε) and TDI derived time intervals in patients with familial amyloidotic polyneuropathy (FAP) and healthy controls with septal thickness below 12 mm

	Controls ($n = 34$)	FAP ($n = 14$)	p Value
Septal end-diastolic thickness (mm)	9.1 ± 1.4	9.5 ± 1.5	ns
Septal wall IVCt/RR (%)	9.0 ± 1.7	11.0 ± 2.6	<0.05
RV free wall IVCt/RR (%)	8.3 ± 2.1	11.4 ± 3.4	<0.01
LV lateral basal ε (%)	-19.4 ± 8.5	-8.7 ± 13.0	<0.05
Septal wall mid ε (%)	-19.7 ± 8.6	-13.3 ± 4.8	<0.05
RV free wall mid ε (%)	-28.5 ± 14.5	-17.4 ± 12.0	<0.05

LV = Left ventricular; RV = right ventricular.

feature of FAP is a sensimotor polyneuropathy while the cardiac involvement mainly manifests as electrocardiographic disturbances. Clinical signs of heart failure are very uncommon even in advanced stages of this disease. FAP patients generally succumb to complications of their polyneuropathy and not to heart failure.

In our study, patients with FAP were found to have significantly higher heart rate than the controls. The reason for this is unclear, but in the absence of clinical and echocardiographical signs of congestive heart failure or abnormal filling patterns we believe that an autonomic neuropathy in FAP might be the cause. The increased heart rate was taken into account as we corrected the time intervals to R—R intervals in our evaluation.

Tissue Doppler imaging (TDI) represents in comparison with two-dimensional echocardiography a significant advantage in the non-invasive assessment of myocardial function. However, TDI velocities represent the net effect of the contractile and elastic properties of the area under investigation. Traction and tethering effects from other regions and cardiac translational artefacts influence the measured velocities and limits the method.[37]

Evaluation of myocardial deformation, which reflects local myocardial function, might therefore be preferable.

Myocardial strain is a dimensionless index of change in myocardial length from the original or unstressed dimension in response to an applied force and is expressed as fractional or percentage change (Fig. 1).[37] Echocardiographically determined strain has shown excellent correlation to sonomicrometry data.[38]

In our study 22 consecutive patients with FAP were examined. They are all living in the same geographic region in northern Sweden, and having the same transthyretin mutation (ATTRVal30Met). Furthermore, only patients without clinical signs of congestive heart failure were included. All echocardigraphic findings were compared with those in age and sex matched healthy controls. Our main finding was that FAP patients had subtle biventricular hypertrophy, smaller ventricular cavities, significantly reduced strain and prolonged isovolumic contraction phase in comparison with healthy controls in all three LV and RV segments, but most pronounced at the septal segment (Tables 4 and 5). Concerning systolic strain, some patterns were even reversed (lengthening during systole, Fig. 1C) and a linear relation between septal thickness and strain was found (Fig. 2). This has previously been described in patients with hypertrophic cardiomyopathy.[39]

Interestingly, abnormal strain occurred in patients without clinical symptoms and signs of CHF and even in a subgroup with normal septal thickness. Thus, measurements of systolic strain and isovolumic contraction time intervals seem to be sensitive techniques for early identification of cardiac involvement in FAP. The prolongation of isovolumic contraction time might be due to conduction disturbance, common in FAP, whereas increased isovolumic relaxation time is likely to be due to myocardial infiltration. This was evident even among patients with similar septal wall thickness. The findings might be relevant in other forms of amyloidosis and even other cardiomyopathies. There is no other study of strain echocardiography in FAP patients published with which our findings could be directly compared. Koyama et al.[19,20] have examined patients with amyloid cardiomyopathy due to AL amyloidosis. This is, however, an entirely different disease with much more severe cardiac involvement in comparison to FAP.

The common denominator is amyloid deposits within the heart — but of different origin and biochemical composition.

Despite that FAP and AL amyloidosis being two different amyloid diseases our findings should be compared with those of Koyama et al. In a study with tissue Doppler imaging (TDI) they assessed subgroups of patients with AL amyloidosis but with normal fractional shortening.[19] They found a reduced LV systolic function among patients with clinical CHF in comparison with patients without CHF.

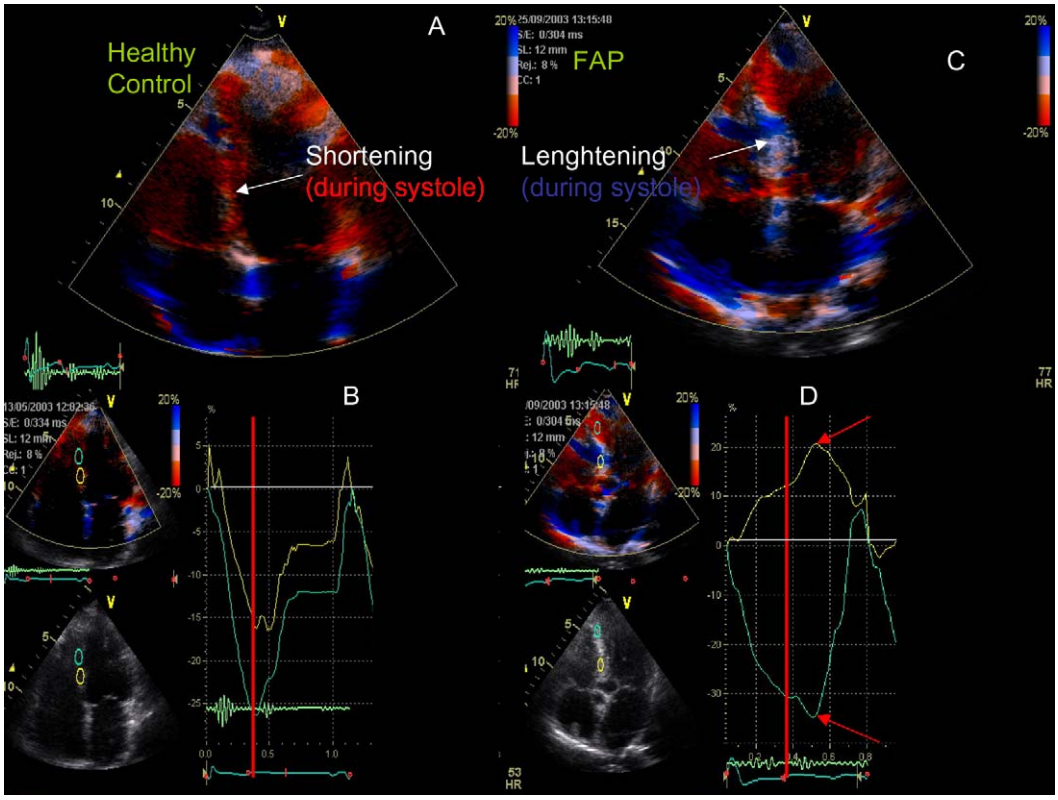

Figure 1 Different septal strain (ε) patterns in control (A and B) and patient with FAP (C and D). Yellow signal shows the basal ε whereas green reflects the mid-segmental signal. The red vertical line shows the time point for end-systole. In contrast to healthy controls, systolic ε of mid-septum was reversed (lengthening during systole) in patients with FAP (C and D).

Regarding the LV diastolic function they found a more restrictive filling pattern among patients with CHF. In another study on patients with AL amyloidosis Koyama et al. used new echocardiographic techniques such as myocardial strain and strain rate measurements.[20] They compared subgroups as in the previous study and showed that the impairment in systolic function, measured as reduced fractional shortening, occurred even in patients without CHF but with other signs of cardiac involvement. However, no healthy controls were included in these studies.

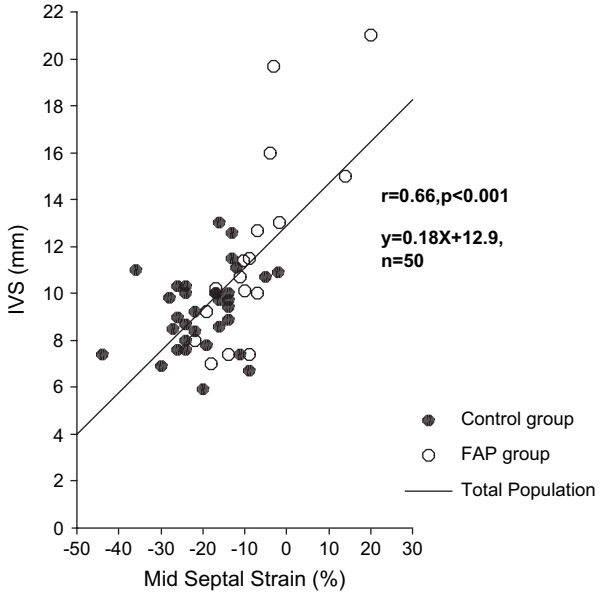

Figure 2 The correlation between mid-septal strain (ε) and septal thickness in controls and patients with FAP.

The cardiac engagement seems to be considerably less severe in our series of patients with FAP than in those studied by Koyama et al.

Thus, no patient in our study had CHF and about half of the patients had an entirely normal echocardiogram. However, even among those strain echocardiography showed a decreased systolic function in comparison with healthy controls. Our study also included an assessment of the right ventricular function, and we found a reduced strain in the mid-segment. Therefore, cardiac amyloidosis should be considered a biventricular disease.

Study limitations

Heart biopsies are for ethical reasons not possible to perform in clinical studies on cardiac amyloidosis and therefore cardiac involvement has not

been unequivocally proven in our patients. There is, however, little reason to believe that any other condition than the systemic amyloid disease should have caused the observed abnormalities.

Conclusion

Myocardial tissue Doppler imaging TDI and strain echocardiography discloses functional abnormalities due to infiltration early in the course of FAP even before any morphological abnormalities are present. Both the left and right heart is involved and the disease should be regarded as biventricular. The findings might be relevant in other types of cardiomyopathy.

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