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Cardiac manifestations in primary Sjögren's syndrome

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Abstract

***Objective*—To determine cardiac manifestations in primary Sjögren's syndrome (SS).**

***Methods*—Echocardiographic examination was undertaken in 64 patients (62 women, two men) with primary SS (54 definite (DSS) and 10 probable (PSS)) who had systemic symptoms. Twenty one healthy women volunteers of similar age acted as controls.**

***Results*—Acute exudative pericarditis occurred in only one patient. An echogenic pericardium was demonstrated in 21 patients (19 DSS, two PSS) (33%) who had a previous symptom free pericarditis, but in none of the controls. Pulmonary pressure was significantly greater in the patients than in the controls (31 (SD 8) mm Hg compared with 24 (7) mm Hg), but there was no significant difference between the DSS and PSS groups. Left ventricular (LV) systolic function was similar in patients and controls. Twenty two patients (20 DSS, two PSS) and one control subject were excluded from LV diastolic function evaluation because of conditions likely to influence the parameters. Of the remaining 42 patients with SS (34 DSS, eight PSS), 21 (17 DSS, four PSS) had impaired diastolic function, confirmed by several diastolic parameters. LV diastolic dysfunction and echogenic pericardium occurred independently of each other, and there was no correlation between the occurrence of these silent cardiac abnormalities and the clinical and laboratory findings.**

***Conclusion*—Obvious cardiac involvement is rare in primary SS, but clinically silent manifestations (symptom free pericarditis and LV diastolic dysfunction) are common. The clinical and prognostic significance of these changes cannot yet be defined.**

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Among the systemic manifestations of primary Sjögren's syndrome (SS), articular, lung, kidney, vascular, and gastrointestinal involvement are well known.[1–8] In contrast, cardiac manifestations are mentioned only sporadically in the literature.[4 5 9 10] This is somewhat surprising, as the other autoimmune connective tissue diseases (systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSSc), and rheumatoid arthritis (RA)) are associated with a wide range of cardiac disorders.[11] Because of the known pulmonary and vascular involvement, and the presence of various autoantibodies in primary SS, it seems improbable that these alterations do not affect the heart.

The aim of our study was to define evident or silent cardiac manifestations in primary SS.

Patients and methods

Sixty four consecutive patients (62 women, two men) with primary SS (according to the EU preliminary criteria of classification of the disease[12]) who had systemic symptoms have been examined during the period since 1992; 54 of them had definite (DSS) and 10 had probable (PSS) primary SS. The mean age of the 64 patients was 59 (SD 12) years (range 29–80 years) and the mean duration of their disease was 14 (7) years (range 3–29 years). Twenty one healthy women volunteers of similar age (mean 56 (10) years; range 27–68 years) who had no clinical or laboratory signs of an acute or chronic disease acted as controls.

All patients and control subjects were examined by echocardiography with Toshiba SSH 65A and Ultramark 9HDI equipment, using the recommendations of the American Society of Echocardiography.[13 14] The cardiologist was aware of the clinical diagnosis. Left ventricular (LV) end diastolic diameter (EDD), end systolic diameter (ESD), end diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF), and left atrial diameter were measured. Valve structures and function were examined using the colour coded and continuous wave Doppler method. Pulmonary pressure was calculated from the tricuspidal retrograde flow velocity. The pericardium was evaluated visually using two dimensional and M-mode views. An echogenic thickened pericardium was defined as a linear bright band of dense echoes behind the relatively echo free space of the posterior LV myocardium. The thickened pericardium exhibited the same amplitude of motion as the epicardium of the posterior LV wall.[13]

On line analysis of the routine echocardiogram (LV systolic function parameters, measurement of the estimated pulmonary pressure, and evaluation of the echodensity of the pericardium) was not blinded, but the evaluation was performed independently by two examiners.

Transmitral flow velocities were recorded by pulsatile Doppler methods, with the sample volume located at the tips of the mitral leaflets from the apical four chamber view.[15] Peak early

diastolic (E wave) and atrial contraction (A wave) velocities were measured by averaging five cardiac cycles to avoid ventilatory influence on LV filling dynamics. Velocity time integrals of early (VTIE) and atrial (VTIA) filling were obtained by digitising the contours of at least five velocity curves. The following LV diastolic parameters were calculated in a blind manner using the Microsoft Vega Computer System (off line analysis):

peak early diastolic filling (E wave, peak E) (cm/s)
peak late diastolic filling (A wave, peak A) (cm/s)
E:A ratio
acceleration time of the E wave (AT) (cm/s^2)
deceleration time of the E wave (DT) (cm/s^2)
diastolic filling time (DFT) (ms)
velocity time integral of the E wave (VTIE) (cm)
velocity time integral of the A wave (VTIA) (cm)
total velocity time integral (VTItot) (cm)
VTIE:VTIA
LV filling fraction (FFlv) (%)
atrial filling fraction (FFa) (%)
heart rate (beats/min)
cardiac output (CO) (ml/min)

In addition to routine laboratory tests, immunological variables were determined in all patients with primary SS: antinuclear antibodies, IgM rheumatoid factor, antibodies to native DNA, SS-A, SS-B, Sm, and RNP, lupus erythematosus cell phenomenon, circulating immunocomplexes, complement C3 concentrations, and serum immunoglobulins.

STATISTICS

The data are expressed as mean (SD). Statistical analysis was by Student's *t* test for comparison of the systolic LV function between SS patients and controls, and by analysis of variance for evaluation of LV diastolic parameters. Statistical significance, established by the χ^2 test, was defined as $p < 0.05$.

Table 1 Clinical manifestations and findings in patients with primary Sjögren's syndrome (SS)

Manifestations and examinations	*Frequency of occurrence*		
	DSS (n = 54)	*PSS (n = 10)*	*Total (n = 64)*
Articular	51	9	60
Arthralgia	8	3	11
Arthritis	43	6	49
Vascular	24	4	28
Vasculitis	8	0	8
Purpura	8	0	8
Raynaud's syndrome	18	4	22
Renal	13	4	17
Complete RTA	10*†	0	10
Incomplete RTA	3	4	7
Upper airway	37	8	45
Lower airway	20	4	24
Bronchitis	10	2	12
PFT: Obstructive signs	5	0	5
Restrictive signs	2	0	2
Obstructive + restrictive	0	0	0
Normal	1	1	2
ND	2‡	1	3
Lung fibrosis (radiographic)	10	2	12
PFT: Obstructive signs	2	0	2
Restrictive signs	2	1	3
Obstructive + restrictive	1§	0	1
Normal	2	1	3
ND	3	0	3
Antibody positivity			
SS-A	39¶	0	39
SS-B	17¶	0	17
SS-A and/or SS-B	41¶	0	41

DSS = Definite SS; PSS = probable SS; RTA = renal tubular acidosis; PFT = pulmonary function test; ND = not done.
*Chronic tubulointerstitial nephritis histologically and renal stones in one patient; †renal stones in one patient; ‡ = interstitial pneumonitis in one patient; §histologically proved recurring lymphocytic interstitial pneumonitis; ¶not determined in one patient.

Table 2 Echocardiographic findings in patients with primary Sjögren's syndrome (SS) (n = 64)

Echocardiographic finding	*Frequency of occurrence*			
	DSS	*PSS*	*DSS + PSS*	*(%)*
Moderately dilated left ventricle	3/54	1/10	4/64	6
Diffuse myocardial lesion	2/54	0/10	2/64	3
Segmental wall motion disturbance	1/54	0/10	1/64	2
Concentric left ventricular hypertrophy	7/54	0/10	7/64	11
Mitral insufficiency (more than grade I)	2/54	1/10	3/64	5
Aortic insufficiency (more than grade I)	1/54	1/10	2/64	3
Mitral prolapse	2/54	1/10	3/64	5
Asymmetric septal hypertrophy	1/54	0/10	1/64	2
Echogenic pericardium	19/54	2/10	21/64	33
Increased estimated pulmonary pressure	21/54	3/10	24/64	37
Abnormal LV diastolic function*	17/34	4/8	21/42*	

DSS = Definite SS; PSS = probable SS; LV = left ventricular.
*22 (20 DSS and two PSS) of the 64 patients excluded from evaluation.

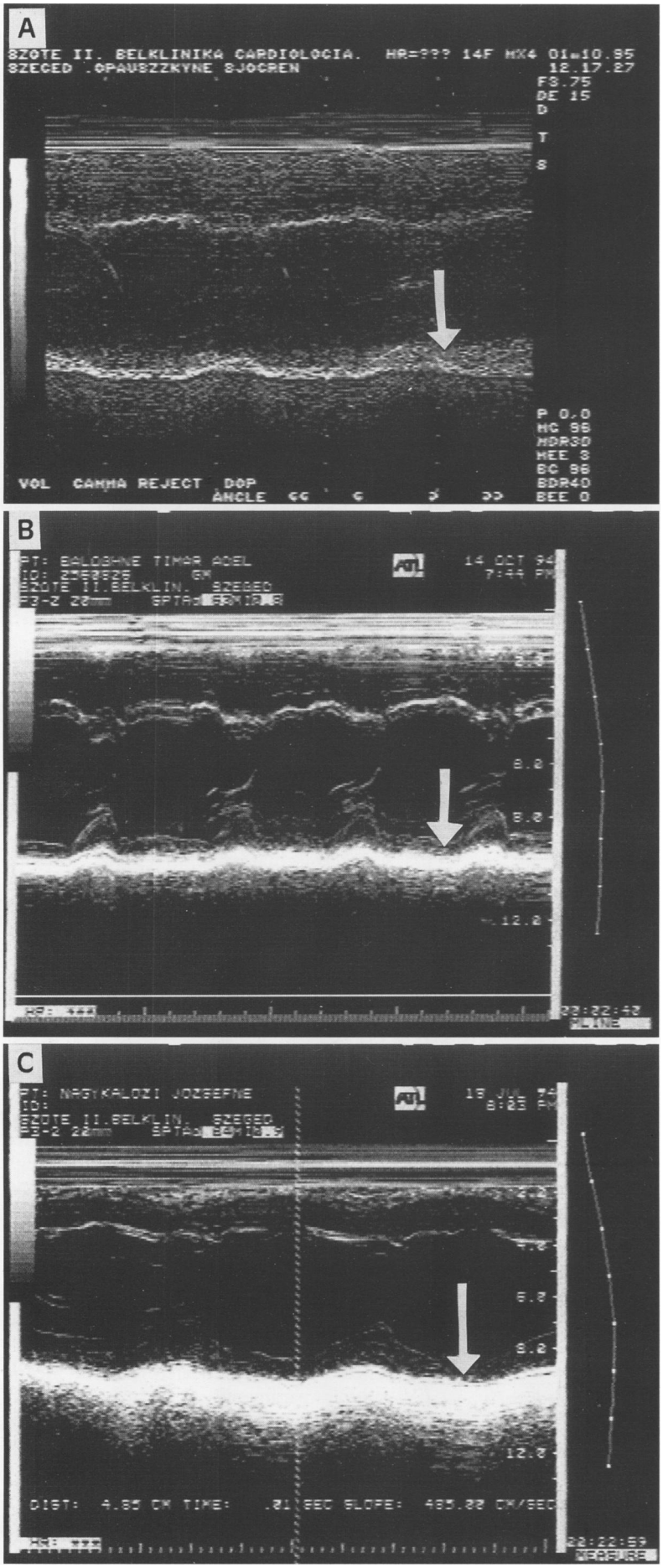
Results

Table 1 lists the clinical findings. Articular involvement (arthritis and arthralgia) was the most common systemic manifestation of SS in our patients (94%), followed by, in order of frequency, involvement of the upper airways (70%; rhinitis, pharyngolaryngitis, and tracheitis sicca), vascular changes (44%; vasculitis 13%, purpura 13%, and Raynaud's phenomenon 34%), lower airway disease (38%; bronchitis sicca, interstitial pneumonitis, and lung fibrosis), renal manifestations (27%; renal tubular acidosis and chronic tubulointerstitial nephritis), and acute exudative pericarditis (one patient).

Table 2 and the figure show the abnormalities, other than the last, obviously cardiac, manifestation listed above, that were revealed by echocardiography. An echogenic pericardium was observed in 21 (19 DSS and two PSS) of the 64 SS patients, but even though the pericardium was echogenic, there were no clinical signs of pericardial constriction, and the chest radiograph did not show pericardial calcifications in these patients. There were no pericardial changes in the control subjects.

Reproducibility of measurement of LV parameters calculated by analysis of variance was good: there were no statistically significant differences between repeated measurements. LV systolic parameters (EDD, ESD, EDV, ESV, and EF) and left atrial diameter did not differ between the SS patients and the controls, but the estimated pulmonary pressure was significantly greater in the SS group (without significant differences between DSS and PSS patients) than in the control subjects (31 (8) mm Hg compared with 24 (7) mm Hg) ($p < 0.05$).

Because of factors influencing LV diastolic function, 22 patients with SS (20 DSS, two PSS) (17 older than 60 years, one with valvular



M-mode echocardiograms of patients with primary Sjögren's syndrome. ***A:*** *Normal pericardium of a 39 year old patient.* ***B:*** *Moderately echogenic pericardium of a 38 year old patient.* ***C:*** *Markedly echogenic pericardium of a 49 year old patient. White arrow indicates pericardium.*

heart disease, three with LV hypertrophy, one with diabetes mellitus), and one 68 year old control subject were excluded from evaluation of diastolic function of the heart. The LV diastolic function was examined in the remaining 42 patients with SS (34 DSS and eight PSS) and in 20 age matched controls (table 3). Of the diastolic parameters, only the E:A ratio (regarded as the principal Doppler index) was significantly smaller in the 42 patients than in the control subjects (0·98 (0·2) compared with 1·15 (0·3)) ($p < 0·05$). E:A was abnormal (<1) in 21 of the 42 patients with SS (17 DSS and four PSS). In the 17 DSS patients, besides the reduced E:A, the values of other diastolic parameters (peak E, DFT, VTI_E, VTI_E:VTI_A, FFlv, and FFa) were also abnormal, differing significantly from those in control subjects. In the four patients with PSS who had an abnormal E:A ratio, the values of most of these diastolic variables also differed from those in the controls, but significance was not calculated because of the small numbers (table 3). In the remaining 21 patients with SS who had a normal E:A ratio (≥1), these parameters were also normal, and their values did not differ significantly from those in the controls.

No correlation was found between the LV diastolic function and the presence of an echogenic pericardium. Both the LV diastolic function and the morphology of the pericardium were assessed in parallel in 34 DSS and eight PSS patients. Of the 12 patients with DSS who had an echogenic pericardium, five (42%) had an abnormal and seven (58%) had a normal LV diastolic function. Among the 22 patients with DSS who had a normal pericardium, the LV diastolic function was abnormal in 12 (55%) and normal in 10 (45%). Among the eight patients with PSS, two had an echogenic pericardium without LV diastolic dysfunction. Of the remaining six patients with a normal pericardium, two had a normal and four had an abnormal diastolic function.

Comparison of the echocardiographic diastolic parameters against the age of the patient, duration of the disease, presence of different clinical manifestations, and type of treatment (non-steroidal anti-inflammatory drugs, chloroquine, or corticosteroid) did not reveal any significant correlation.

The immunological data revealed that only SS-B antibody positivity occurred more commonly in the patients with DSS who had an LV diastolic dysfunction (nine of 17) than in those without a diastolic disturbance (three of 16; in one patient SS-A and SS-B antibodies were not measured). The pericardial characteristics were not significantly correlated with any of the clinical and laboratory findings.

Discussion

Involvement of the heart is a common finding in most connective tissue diseases, pericarditis being mentioned most often in the literature.[11] Clinical experience and the literature both indicate that primary SS differs from SLE,

Table 3 Left ventricular (LV) diastolic parameters in patients with primary Sjögren's syndrome (SS) and in normal control subjects

LV diastolic parameters	*SS patients with E:A <1*			*Controls (n = 20)*
	DSS + PSS (n = 21)	*DSS (n = 17)*	*PSS (n = 4)*	
Age (yr)	50 (8)	48 (8)	54 (8)	55 (10)
peak E (cm/s)	42 (13)*	41 (10)*	46 (13)	58 (20)
peak A (cm/s)	58 (16)	60 (15)	50 (15)	53 (20)
E:A ratio	0·75 (0·15)*	0·70 (0·12)*	0·94 (0·13)	1·15 (0·3)
DT (cm/s²)	180 (59)	184 (58)	163 (59)	211 (59)
AT (cm/s²)	78 (30)	80 (31)	70 (31)	77 (22)
DFT (ms)	398 (116)*	395 (117)*	411 (117)	488 (91)
VTItot (cm)	12 (4)	12 (4)	12 (5)	14 (5)
VTIE (cm)	5·4 (2·4)*	5·4 (2·3)*	5·4 (2·4)	8·1 (2·9)
VTIA (cm)	6·1 (2·2)	6·5 (2·1)	5·8 (2·3)	5·7 (2·3)
VTIE:VTIA ratio	0·9 (0·5)*	0·9 (0·5)*	0·9 (0·5)	1·4 (0·6)
FFlv (%)	35 (7)*	32 (5)*	38 (8)	41 (8)
FFa (%)	52 (13)*	54 (12)*	46 (13)	40 (9)
HR (beats/min)	80 (13)	80 (11)	79 (13)	75 (12)

Values are mean (SD).
DSS = Definite SS; PSS = probable SS; peak E, peak A = peak early and late diastolic filling; DT, AT = deceleration and acceleration times of the E wave; DFT = diastolic filling time; VTItot, VTIE, VTIA = total, F wave, and A wave velocity integrals; FFlv, FFa = left ventricular and atrial filling fractions; HR = heart rate.
*$p < 0.05$ compared with controls.

PSSc, and RA as regards cardiac manifestations. The cardiac involvement in SS was described in detail by Shearn in his monograph, but the cases reported corresponded to secondary SS, in most cases associated with SLE.[16] In comprehensive studies of the clinical profile of primary SS, cardiac involvement is not mentioned, or there is only reference to the possibility of pericarditis.[1–6 9 10 16] In contrast, there is an obvious relationship between primary SS and congenital heart block, the most important clinical manifestation of neonatal lupus syndrome[17]—a model of passively acquired autoimmunity in which maternal antibodies to SS-A cross the placenta and damage the fetal myocardium and the conducting system.[18 19]

One patient exhibiting acute exudative pericarditis was the inspiration for our prospective evaluation of cardiac manifestations in primary SS.

Echocardiography demonstrated an echodense pericardium in 33% of our patients with primary SS. We believe that such an echogenic pericardium is a consequence of a symptom free pericarditis, primarily associated with the basic disease. An echogenic pericardium could also suggest a pericardial constriction,[11] but in our patients there were no clinical or radiological signs of this condition. Naturally, in some subjects the echogenic pericardium might be explained by an intercurrent virus infection, but the proportion of the patients affected appears too great for them all to be consequences of simple infections. The increased calculated pulmonary pressure observed in about one third of our patients may have been a result of diffuse interstitial lung disease.

LV diastolic dysfunction is an important cause of cardiac morbidity and appears to be one of the earliest detectable abnormalities in a number of disorders, for example hypertension, diabetes mellitus, and ischaemic heart disease.[20] Abnormal diastolic performance has been observed both in conjunction with and in the absence of a systolic dysfunction. Among the diastolic function parameters, the ratio E:A is regarded as the principal Doppler index of diastolic function, because it is the most reproducible and is relatively independent of the preload and afterload conditions.[15] E:A is ≥ 1 in a normal subject, and <1 in the event of an impaired LV relaxation. A diastolic relaxation impairment of the LV in connective tissue disorders (SLE, RA, PSSc, and seronegative spondylarthritides) has been described previously.[11 21]

LV function was investigated by Cornec *et al* in a limited number of patients with primary SS.[22] They found an impairment of diastolic relaxation in six patients aged 63 to 73 years. In the elderly, however, a decreased E:A ratio need by no means be considered pathological. This was the reason why we originally excluded these patients from the diastolic function evaluation. In our examinations, a finding of LV diastolic function impairment was also common in patients with primary SS, in spite of the fact that we excluded from the evaluation any patient with a condition that itself would influence the value of E:A. In subjects with a diastolic dysfunction, not only was E:A decreased, but other parameters (for example the diastolic filling time) also reflected the disturbance in relaxation. The mechanism of this impaired LV relaxation remains unknown. One explanation may be myocardial Raynaud's phenomenon, described in patients with PSSc,[23 24] while a small intramyocardial vessel or vasa vasorum vasculitis is also possible, but could have been confirmed only by myocardial biopsy. Although the positivity to SS-B antibody that occurred only in DSS was more frequent in patients with an LV diastolic dysfunction than in those without one, it cannot be concluded that this antibody has a direct pathological role in the development of this cardiac change.

As we could not establish any correlation between the LV diastolic dysfunction and the presence of the echogenic pericardium, it seems likely that these cardiac abnormalities can develop independently of each other in primary SS. Though both silent cardiac abnormalities were common findings in our patients with SS, without significant differences in incidence between the DSS and PSS groups, the differences between the data obtained in the patients with SS and in the control subjects might be slightly exaggerated, as our control group might be healthier than the average population.

In summary, it may be concluded that obvious heart involvement is rare, but clinically silent changes are common in primary SS. Although the latter probably do not exert any serious influence on the disease outcome, and though at present their clinical significance cannot be defined, they nevertheless form part of the clinical picture of primary SS. For this reason, further study of their prognostic significance may be indicated.

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