EXTENDED REPORT

Cardiac dysfunction in patients with systemic lupus erythematosus and antiphospholipid syndrome

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Objective: To comparatively assess the parameters of systolic and diastolic cardiac function in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).

Methods: Consecutive patients (n=74) who were free of cardiovascular symptoms were divided into four groups: (1) SLE (n=23); (2) SLE with antiphospholipid antibodies (aPL; n=18); (3) SLE with APS (n=20); and (4) primary antiphospholipid syndrome (PAPS; n=13). Pulsed, continuous, colour Doppler echocardiography, and M-mode and B-mode studies were performed.

Results: Left ventricular end diastolic and end systolic dimensions were higher in SLE as compared with patients with PAPS (p=0.022 and 0.022, respectively), with a trend towards a lower fractional shortening in SLE (p=0.07), suggesting systolic dysfunction. Parameters of diastolic function were more impaired in patients with APS, reflected by lower left ventricular and right ventricular E wave to A wave (E:A) ratios in patients with APS (groups 3, 4) compared with those without APS (groups 1, 2; 1.15 (0.40) v 1.49 (0.43), p=0.001 and 1.19 (0.31) v 1.49 (0.41), p=0.001, respectively) and a more prolonged left ventricular isovolumic relaxation time (IVRT; 94.2 (24.6) v 84.4 (17) ms, respectively, p=0.055). Patients with APS were older than those without APS (47.12 (14.86) v 34.29 (12.6), p=0.0001). Patients with SLE were younger than those with PAPS (38.19 (14.68) v 48.53 (13.97), p=0.023).

Conclusion: Abnormal echocardiographic findings were detected frequently in asymptomatic patients with SLE or PAPS. Although patients with SLE were younger, left ventricular systolic function was more impaired in patients with SLE compared with those with PAPS, whereas left ventricular and right ventricular diastolic function, as reflected by IVRT and E:A ratios, were significantly more impaired in patients with APS.

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by disturbances in innate and adaptive immune mechanisms. Multiple systems and organs may be involved in the primary autoimmune processes. In recent years, awareness of secondary damage accumulation in patients with SLE has greatly increased the need for emphasis on and implementation of early preventive strategy.^{1–2} Early and accelerated atherosclerosis and cardiovascular disease have been clearly documented and the policy of primary and secondary prevention adopted.^{3–4} New insights into the possible role of antiphospholipid antibodies in endothelial dysfunction, vascular and valvular pathology as well as the role of inflammation in atherogenesis have been added.^{4–7}

Although the frequent and classical SLE manifestations affecting the skin, joints and kidneys, and cytopenia are commonly detected and routinely evaluated, the early lung and cardiac involvement, although not rare, is mostly subclinical and thus usually escapes detection.⁸ These manifestations may, however, evolve into life-threatening disorders in a subset of patients. Non-invasive techniques for the assessment of cardiac function are relatively simple and universally available. Many of the cardiopulmonary manifestations characteristic of SLE are seen in the antiphospholipid syndrome (APS), in both the primary and secondary syndrome.^{9–10} The primary aim of this study was to assess subclinical cardiac involvement in patients with SLE and in those with APS asymptomatic in terms of cardiovascular symptoms. The secondary aim was to compare parameters of cardiac function between SLE, SLE with antiphospholipid antibodies (aPL), SLE with APS or primary antiphospholipid syndrome (PAPS), to study the possible contribution of aPL and/or APS to these

findings. Non-invasive echocardiographic studies were used as possible tools for early diagnosis and follow-up.

METHODS

Patients

Seventy-four consecutive patients with SLE and/or APS treated at our outpatient clinic during 2001–3, who were asymptomatic with regard to cardiovascular symptoms and who gave their consent to participate in the study, were evaluated. The study was approved by the institutional ethical committee. The patients were divided into four groups: (1) SLE (n=23); (2) SLE with aPL (n=18); (3) SLE with APS (n=20); (4) PAPS (n=13). All patients with SLE fulfilled the revised criteria of the American Rheumatism Association for the classification of SLE.¹¹ All patients with APS, primary and secondary, fulfilled the Sapporo preliminary classification criteria for APS.¹² Patients considered positive for aPL had a positive test, of medium or high titre for anticardiolipin IgG or IgM, or a positive lupus anticoagulant test on at least two occasions, at least 6 weeks apart. Anticardiolipin antibody tests were prepared in different laboratories in outpatient clinics using standard commercial ELISA kits. For each patient the tests were repeated in the same initial laboratory. Lupus anticoagulant test was performed for all the patients in a single hospital-based laboratory using the activated partial thromboplastin time with a lupus anticoagulant sensitive thromboplastin, or the dilute Russell viper venom test.

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; IVRT, isovolumic relaxation time; PAP, pulmonary arterial pressure; PAPS, primary antiphospholipid syndrome; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index

Table 1 Demographic and disease characteristics of the study groups

	Group 1 SLE	Group 2 SLE+αPL	Group 3 SLE+APS	Group 4 PAPS
Age (years)	35.76 (12.7)	32.3 (12.5)	46.2 (15.7)	48.5 (13.9)
Disease duration (years)	8.23 (7.5)	7.44 (3.3)	8.58 (5.14)	10.36 (10.42)
Activity Index (SLEDAI)	8.2 (6.9)	7.3 (5.25)	6 (6.18)	Not relevant
Damage Index (SLICC)	0.91 (1.44)	0.5 (0.98)	1.47 (1.5)	1.85 (1.62)

αPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; PAPS, primary antiphospholipid syndrome; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics.

Exclusion criteria for all patients were: cardiorespiratory symptoms, history of ischaemic heart disease, cardiomyopathy or clinically significant valvular heart disease.

Demographic data, disease duration, current drugs, SLE disease activity and damage indices, the presence of risk factors for cardiovascular disease (hypertension, hyperlipidaemia, diabetes mellitus and cigarette smoking) and antiphospholipid antibody test results for all patients were obtained from the patients' charts. A full physical examination and laboratory tests for the assessment of disease activity were performed at study entry.

Echocardiographic evaluation

M-mode and B-mode echocardiography, and pulsed, continuous, colour Doppler examination were performed for all patients with a Hewlett Packard 5500 ultrasound system (Hewlett Packard, Andover, Massachusetts, USA) using a 3.5-MHz transducer. Those performing and evaluating the echocardiograms were unaware of the clinical diagnosis of the patients. The echocardiograms were evaluated independently by three echocardiologists. Long axis, short axis and four chamber views were obtained. Left ventricle end systolic and end diastolic diameters were measured for calculation of the fractional shortening. The fractional shortening measures and ratios depict the change in diameter of the left ventricle between the contracted and relaxed states, reflecting left ventricular systolic performance. A fractional shortening of <29% was considered as left ventricular systolic dysfunction.^{13, 14} Calculation of the left ventricular ejection fraction was performed using the modified Simpson's method of disc calculation from an apical four-chamber view at end systole and end diastole. Endocardial tracing was performed manually to obtain left ventricular end-systolic volumes, left ventricular end-diastolic volumes and left ventricular ejection fraction.¹³ Right ventricular systolic function was evaluated qualitatively as normal or abnormal by visualisation in different planes, and evaluated independently by three echocardiologists. Diastole is divided into four phases: isovolumetric relaxation, rapid filling, slow filling and atrial contraction. The mitral and tricuspid inflow velocity curve obtained by pulsed Doppler was used to calculate the following diastolic variables: E wave (peak early velocity occurring during the rapid filling phase), A wave (peak velocity at the time of atrial contraction), E:A ratio (a marker of

diastolic function, normal E:A values: 1–2) and DT (deceleration time of the peak early velocity). Left ventricular isovolumic relaxation time (IVRT) was obtained with simultaneous recording of the left ventricular inflow and outflow velocities. The right ventricular IVRT was calculated by subtracting the time interval between the peak of the R wave on the electrocardiogram and the end of the pulmonic systolic flow profile from the time interval between the peak of the R wave and the onset of the tricuspid valve opening. Pulmonary artery systolic pressure was estimated by continuous wave echocardiography recorded in the apical four-chamber view as the peak systolic pressure gradient across the tricuspid valve and the estimated right atrial pressure. Valvular anatomical and functional lesions were assessed and the severity of any valvular regurgitation (mitral, aortic and tricuspid) was graded as mild, moderate or severe.

Disease duration, disease activity and accrued damage

In all patients with SLE, disease duration was calculated from the time of diagnosis to the time of study entry. Disease activity was scored using the systemic lupus erythematosus disease activity index (SLEDAI),¹⁵ and disease damage was scored using the Systemic Lupus International Collaborating Clinics damage index, which was used for the scoring of patients with PAPS as well.¹⁶

Cardiovascular risk factors

Data regarding the presence of hypertension, diabetes mellitus, hyperlipidaemia and cigarette smoking were collected and recorded.

Statistical analysis

Continuous parameters were shown as mean (standard deviation (SD)). To analyse statistically significant differences in mean continuous parameters between two groups of patients, Student's t test was used, and between >2 groups of patients, analysis of variance was applied using the Duncan multiple comparison option.¹⁷ For categorical variables, the χ^2 test or Fisher's exact test was used as appropriate. To analyse the data in a multivariate context, a series of logistic regression models was fitted to the data. A p value of ≤ 0.05 was considered significant.

Table 2 Distribution of drugs currently used

Drugs	Group 1 SLE, n (%)	Group 2 SLE+αPL, n (%)	Group 3 SLE+APS, n (%)	Group 4 PAPS, n (%)
ASA	5 (21.7)	11 (61.1)	11 (55)	7 (53)
HCQ	20 (85.9)	15 (83.3)	19 (95)	4 (30.7)
Prednisone	16 (69)	11 (61)	10 (50)	0
AZA	4 (17.3)	5 (27.7)	4 (20)	0
MTX	2 (9.6)	4 (22.2)	1 (5)	0
CTX	1 (4.3)	0	2 (10)	0

ASA, low-dose aspirin; AZA, azathioprine; CTX, cyclophosphamide; HCQ, hydroxychloroquine; MTX, methotrexate.

Table 3 Comparison of systolic parameters in systemic lupus erythematosus and primary antiphospholipid syndrome

Group	SLE (groups 1–3)	PAPS (group 4)	p Value
Age (years)	38.19 (14.68)	48.53 (13.97)	0.023
LVESD (mm)	29.34 (3.5)	28.98 (5.7)	0.022
LVEDD (mm)	47.18 (3.9)	46.09 (4.7)	0.022
FS (%)	42.3 (7.69)	51.5 (10.95)	0.07

FS, fractional shortening; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; PAPS, primary antiphospholipid syndrome.

RESULTS

We evaluated 74 patients who were divided into four groups. Table 1 presents the mean ages of the patients in the four groups. Patients with SLE in groups 1, 2 and 3 were younger than those with PAPS (mean (SD) age 38.19 (14.68) ν 48.53 (13.97) years, $p = 0.023$). Patients with APS (groups 3 and 4) were significantly older than those without APS (groups 1 and 2; mean (SD) age 47.12 (14.86) ν 34.29 (12.6) years, $p = 0.001$).

Disease activity, disease duration and damage

No significant difference was found in disease activity between the three groups of patients with SLE according to SLEDAI scores. Similarly, no significant difference was observed in disease duration between the four groups of patients. Damage indices were significantly higher in patients with APS (groups 3 and 4) as compared with those in patients without APS (groups 1 and 2; Systemic Lupus International Collaborating Clinics damage index 1.62 (1.54) ν 0.73 (1.26); $p = 0.008$). This significant difference was maintained when comparing the patients with PAPS with those in the three SLE groups (1.85 (1.62) ν 0.97 (1.38); $p = 0.047$).

Cardiovascular risk factors

Most of the patients did not have hypertension. There were three cases in group 1, two cases in group 2, five in group 3 and six in group 4, leading to more patients with hypertension among those with APS versus those without APS ($p = 0.023$). None of the study patients had diabetes mellitus, and only a small number of patients in each group had hyperlipidaemia, with no significant difference between the groups.

Most of the patients did not smoke. There were six smokers in group 1; nine in group 2; five in group 3; and two in group 4.

Drugs

Table 2 shows the distribution of drugs currently used by the study patients.

Echocardiography

Left ventricular end diastolic and end systolic dimensions were significantly higher in the three groups of patients with SLE as compared with those with PAPS ($p = 0.022$ and 0.022 ,

Table 4 Comparison of diastolic parameters in patients with and without APS

Group	Non-APS (group 1, 2)	APS (group 3, 4)	p-value
Age (years)	34.29 (12.6)	47.12 (14.86)	0.0001
LV E:A	1.49 (0.43)	1.15 (0.40)	0.001
LV IVRT (ms)	84.4 (17.08)	94.2 (24.6)	0.055
RV E:A	1.49 (0.41)	1.19 (0.31)	0.0012

APS, antiphospholipid syndrome; E:A, ratio of E wave to A wave; IVRT, isovolumic relaxation time; LV, left ventricle; RV, right ventricle.

respectively; table 3). There was a trend towards a lower fractional shortening in the three groups of patients with SLE as compared with those with PAPS ($p = 0.07$; table 3).

Left ventricular ejection fractions were within the normal range in all groups, with no significant difference between the groups: group 1, 62% (4); group 2, 64% (4); group 3, 63% (6); and group 4, 61% (4). When looking at absolute left ventricular E:A ratios, the majority were within the normal range, but the left ventricular E:A ratio was significantly lower in patients with APS (groups 3 and 4) as compared with those without APS (groups 1 and 2; 1.15 (0.4) ν 1.49 (0.43), respectively; $p = 0.001$; table 4). When looking within the SLE patient groups, we found similar findings, the left ventricular E:A ratio being significantly lower in patients with SLE with APS as compared with patients with SLE with aPL (1.12 (0.44) ν 1.71 (0.01), respectively; $p = 0.0002$). As E:A ratios are affected by age, the absolute number of patients with abnormal E:A ratios of <1 and corresponding age are shown (table 5; 13 patients in the APS groups ν 3 patients in the non-APS groups had a left ventricular E:A <1). The left ventricular isovolumic relaxation time (IVRT) was significantly more prolonged in patients with APS (groups 3 and 4) as compared with those without APS (groups 1 and 2; 94.2 (24.6) ν 84.4 (17) ms, respectively; $p = 0.055$; table 4).

When looking at absolute right ventricular E:A ratios, most were within the normal range, but the ratio was also significantly lower in patients with APS (groups 3 and 4) as compared with those without APS (groups 1 and 2; 1.19 (0.31) ν 1.49 (0.41), respectively; $p = 0.001$; table 4). Similar to the findings for the left ventricle, for the right ventricle we found that the E:A ratio was significantly lower in patients with SLE with APS as compared with those with SLE with aPL (1.21 (0.32) ν 1.7 (0.47), respectively; $p = 0.0009$) and that more patients with APS had abnormal right ventricular E:A ratios (<1) as compared with those without APS (10 ν 3 patients; table 5).

No correlation was found between impaired systolic or diastolic function and disease activity of SLE, as measured by SLEDAI.

Raised pulmonary arterial pressure (PAP >30 mm Hg) was observed in four patients with SLE. Pulmonary arterial pressures were within normal range in the PAPS group. Three patients had a history of pulmonary embolism, in one patient the PAP was 31 mm Hg and in two the PAP could not be measured in the absence of tricuspid regurgitation. All three patients had both SLE and APS. No structural valvular

Table 5 Distribution of E:A ratios according to group and age

	LV E/A <1		LV E/A ≥ 1	
	Number of patients	Age (yrs)	Number of patients	Age (yrs)
Group 1	2	33; 56	19	34.8 $\pm$ 12.3
Group 2	1	67	17	30.3 $\pm$ 9.3
Group 3	9	55.8 $\pm$ 14.1	11	35.2 $\pm$ 10.7
Group 4	4	59.2 $\pm$ 10.2	9	43.7 $\pm$ 13

	RV E/A <1		RV E/A ≥ 1	
	Number of patients	Age (yrs)	Number of patients	Age (yrs)
Group 1	2	33; 50	19	36.0 $\pm$ 13.2
Group 2	1	67	17	30.3 $\pm$ 9.3
Group 3	5	62.4 $\pm$ 11.7	15	39.2 $\pm$ 13.8
Group 4	5	58.4 $\pm$ 9	8	42.3 $\pm$ 13.2

abnormalities or vegetations were detected. Functional valvular abnormalities (mitral, tricuspid and aortic valve regurgitation), mostly mild, were evenly distributed among the four groups of patients. In one patient with SLE and APS who was well controlled with warfarin international normalized ratio (INR = 2.9), a large asymptomatic thrombus of the right atrium was found, which required surgical removal.

DISCUSSION

SLE and APS are autoimmune diseases, which often coexist and may involve multiple systems and organs. Tissue damage and dysfunction in active SLE are mediated by autoantibodies and immune complex formation, whereas APS has been traditionally thought to cause damage by thrombosis, vasculopathy and ischaemia. Manifestations may range from subclinical abnormalities to life-threatening disorders. Despite different pathogenetic mechanisms, many of the cardiopulmonary manifestations characteristic of SLE are seen in APS as well, in both the primary and secondary syndrome, including pulmonary hypertension, pulmonary embolism, pulmonary haemorrhage, valvular disease, coronary artery disease and myocardial dysfunction.⁹⁻¹⁰

In this study, we have shown that relatively simple, non-invasive tests may detect frequent, subclinical cardiac dysfunction in patients with SLE and those with APS who are asymptomatic with regard to cardiac symptoms. None of the patients evaluated in this study had clinically significant right ventricular or left ventricular systolic dysfunction, but when comparing the three groups of patients with SLE with the group of patients with PAPS, those with SLE had more left ventricular systolic dysfunction, shown by significantly higher left ventricular end diastolic dimension and left ventricular end systolic dimension values. Cacciapuoti *et al*¹⁸ studied left ventricular function in SLE using tissue Doppler echocardiography and found impaired left ventricular function as well, but attributed this to diastolic dysfunction as opposed to our findings of a trend towards systolic dysfunction in this group of patients. This discrepancy might be explained by the fact that we conducted a comparison between SLE and PAPS. When compared with normal values, the systolic dysfunction in our patients with SLE was indeed mild, but was more marked in SLE as compared with PAPS. On the other hand, both left ventricular and right ventricular diastolic dysfunction were significantly more frequent in patients with APS (SLE with APS and PAPS), as shown by lower left ventricular and right ventricular E:A ratios and a prolonged left ventricular IVRT. Systolic dysfunction may result from severe valvular disease, or diffuse cardiomyopathy, which were not seen in this cohort of patients, or from coronary artery disease. As we excluded patients with a history of known ischaemic heart disease or any other significant heart disease, our findings may suggest subclinical coronary artery disease due to the accelerated atherosclerosis seen in patients with SLE and/or subclinical cardiomyopathy due to myocarditis. Regarding cigarette smoking as a risk factor for atherosclerosis, the percentage of smokers was higher in group 2, but, despite this risk factor, cardiac dysfunction was not significantly more impaired in this group when comparing the four groups (data not shown). Indeed, left ventricular systolic dysfunction has been shown previously in asymptomatic patients with SLE, including studies on childhood SLE, using myocardial perfusion scans, radionuclide ventriculography and echocardiography.⁹⁻¹⁹⁻²² The presence of aPL has been reported in some studies, but the small numbers did not allow for conclusions regarding their role in the pathogenesis of left ventricular systolic dysfunction. Giunta *et al*²³ performed echocardiography in 75 consecutive patients with SLE and investigated anticardiolipin antibodies in

50 of 75 patients. They were able to conclude that disease duration affects both endocardial and myocardial involvement; however, anticardiolipin antibodies seemed to be related to endocardial, but not to myocardial damage.²³ Our results support this conclusion, showing that in the group of patients with PAPS systolic myocardial function was less impaired, underlining the role of SLE itself in systolic myocardial dysfunction. Left ventricular diastolic dysfunction has been reported in SLE as well, but has been shown to be progressive over time only in patients with underlying hypertension or coronary artery disease.²² In our study, diastolic dysfunction of the right and left ventricles was more impaired in patients with APS or PAPS as compared with SLE without APS. Similarly, Tektonidou *et al*¹⁴ have shown that diastolic dysfunction, in particular of the right ventricle, is a prominent feature of APS. In this study, they were able to show a gradation of increasing diastolic dysfunction across the groups of patients with SLE without anticardiolipin, SLE with anticardiolipin, secondary APS and primary APS. Left ventricular diastolic function was impaired as well, although no similar gradation between patient groups was seen.¹⁴

Thus, although patients with SLE in our study were younger than those with PAPS, it seems that lupus itself may lead to subclinical systolic dysfunction of the myocardium, whereas the presence of APS (primary or secondary) possibly contributes to diastolic dysfunction. APS is known to cause small vessel vasculopathy/microvascular thrombosis, which may lead to myocardial ischaemia that may affect myocardial compliance.²⁴ Alternatively, the more frequent diastolic dysfunction in patients with APS found in our study may be due to the older age of these patients and the higher prevalence of hypertension, although the number of hypertensive cases was small.

Analysis showed no significant difference in disease duration between the four groups of patients, precluding analysis of the effect of disease duration on cardiac dysfunction in this study.

Interestingly, patients with APS had accrued significantly more damage as compared with those without APS, an observation which cannot be explained by differences in disease duration and supports findings in previous studies, where the presence of aPL predict early damage in SLE²⁵ and the presence of both SLE and APS increases morbidity and mortality.²⁶

In conclusion, non-invasive methods detect subclinical cardiac dysfunction in asymptomatic patients with SLE and APS. Ventricular systolic dysfunction was more common among patients with SLE, whereas diastolic dysfunction was more common in APS. Older age, the presence of hypertension, and the presence of aPL and APS were associated with more significant ventricular diastolic impairment. The potential predictive value of periodic assessments and therapeutic intervention in these patients should be evaluated in long-term studies. At present, we suggest that patients with SLE, especially those with aPL and APS as well as PAPS, undergo a baseline echocardiographic evaluation, and, according to the findings, should be followed periodically, as suggested in other connective tissue diseases in which cardiopulmonary involvement may occur.

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