Echocardiogram Abnormalities in SLE Patients

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Abstract: Systemic lupus erythematosus (SLE) is associated with increased risk of cardiovascular disease. Early detection and management of cardiac disease may reduce the morbidity and improve the survival of patients with SLE. Echocardiography is a sensitive technique which has been previously demonstrated to enable assessment of subclinical myocardial dysfunction. In the setting of SLE patients, echocardiography may therefore thereby provide clinical prognostic utility, enabling risk stratification and targeted treatment. This was a retrospective cohort analysis of patients diagnosed with SLE at the King Abdulaziz University Hospital, Jiddah Saudi Arabia from 1st of January 2010 to December 2012. Demographic and biochemical data was extracted from medical records. Differences in age, disease activity and creatinine levels in relation to cardiac abnormalities were analysed using students t-test. Associations between urinary and cardiac abnormalities were analysed using chi square tests. Partial correlations were examined for association between continuous variables. The results indicated that, 123 patients met the inclusion criteria; 92.7% were female, half were of Saudi nationality and the mean age was 32.89 years. Of those patients who had had an echocardiogram, one third showed mitral regurgitation, half had evidence of tricuspid regurgitation, 38% had valve abnormalities, 16% had pericardial effusion and 19% had raised pulmonary pressure and pericardial pressure. Patients displaying tricuspid regurgitation were significantly older than those without evidence of tricuspid regurgitation (35.19 ± 12.56 vs 26.77 ± 6,70; p=0.038). Age was also negatively correlated with ejection fraction (r=-0.271, p=0.024), indicating reduced cardiac function in older patients. Anti-DNA titre was negatively correlated with haemoglobin (r=0-.379, p<0.001), vitamin D (r=-0.245, p=0.029) and calcium (r=-0.323, p=0.010) levels, and positively correlated ejection fraction (r=0.265, p=0.028). Urinary protein, creatinine and anti-DNA levels were increased in patients with pericardial effusion. The resulta concluded that Cardiac abnormalities are common in SLE patients. Early detection of cardiovascular disease would enable early intervention and thereby improve prognosis.
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1. Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease which can affect multiple organ systems, in particular the cardiovascular system. Studies have found that SLE patients are at an increased risk of developing cardiovascular disease compared to age-matched health control (Watson, et al. 2003; Solomon, et al., 2004; Asanuma, et al., 2003; Roman, et al., 2003 and Manzi, et al., 1997). Moreover, SLE patients have increased rates of atherosclerosis and significantly higher risk of hospitalization due to myocardial infarction compared to age-matched controls (Ward, 1999; Abu-Shakra, et al., 1995 and Abu-Shakra,et al., 1995). Although SLE survival rates have improved significantly over recent years, morbidity and mortality is significantly higher in patients with cardiovascular involvement (Jakes, et al., 2012). Early detection and management of cardiac disease may reduce the morbidity and improve the survival of patients with SLE.

Echocardiography is a sensitive technique which has been previously demonstrated to enable assessment of subclinical myocardial dysfunction (Jakes, et al., 2012). In the setting of SLE patients, echocardiography may therefore thereby provide clinical prognostic utility, enabling risk stratification and targeted treatment. A range of cardiac abnormalities have been reported in SLE patients, including reduced ejection fraction, impaired diastolic filling and increased LV mass (Galve, et al., 1988; Murai, et al., 1987; Crozier, et al., 1990; Leung, et al., 1990; Sasson, et al., 1992 and Paran,et al., 2004). However it is unclear whether such pathology is a disease-related effect driven by underlying inflammatory processes or whether they are associated with other predisposing conditions, such as renal disease or hypertension.

The author hypothesised that cardiac abnormalities would be more prevalent in those with active disease. Therefore the study examined cardiac abnormalities on echocardiogram in patients with SLE, and analysed the association of these with disease activity, comorbid organ disease and patient characteristics.

2. Methods

Patients and data extraction

This was a retrospective study of patients diagnosed with systemic lupus erythematosus (SLE) in Saudi Arabia. Data was extracted from the medical notes of all patients meeting the inclusion/exclusion criteria who attended the medical outpatient department of rheumatology in King Abdulaziz university, Jeddah, Saudi Arabia from January 2010 – December 2012 were included in the study, patients must have been diagnosed SLE (four or more 1997 american college of rheumatology classification criteria) and had undergone an echocardiogram.

The following data was extracted from the medical notes: age, sex, nationality. In addition the following biochemical data was extracted from the medical notes: haematological results; c-reactive protein (CRP); antinuclear factor (ANA); Anti-DNA; C 3 and 4 complement; Vitamin D, urinary protein results, creatinine, erythrocyte sedimentation rate (ESR). The following echocardiogram findings were also extracted: valve status; ejection fraction; pericardial effusion; pulmonary pressure; mitral regurgitation; mitral stenosis; aortic regurgitation; aortic stenosis; tricuspid regurgitation; tricuspid stenosis; pulmonary regurgitation; pulmonary stenosis.

Statistical methods

Data was entered in excel and analysed using SPSS v19.0 for Windows (SPSS, Chicago, IL, USA). Demographic characteristics are presented for continuous variables as means and standard deviations and categorical variables as frequencies and percentages. Differences in age, disease activity and creatinine levels in relation to cardiac abnormalities were analysed using students t-test. Associations between urinary and cardiac abnormalities were analysed using chi square tests. Partial correlations were examined for association between continuous variables. Significance was set at the 0.05 level.

3. Results

Patient demographics

123 patients met the inclusion criteria and were included in the study population. The demographic characteristics of the study population are presented in Table 1. The study population were predominantly female (n=114; 92.7%), approximately half were of Saudi nationality (n=69; 56.1%) and the mean (standard deviation [s.d.]) age was 32.89 years ± 11.30. Approximately one third of patients showed mitral regurgitation and half of patients had evidence of tricuspid regurgitation (Table 2). Valve abnormalities were detected in 38%, pericardial effusion in 16%, pericardial pressure in 19% and pulmonary pressure was raised in 19%.

Relationship between cardiac abnormalities and patient characteristics

Patients displaying tricuspid regurgitation were significantly older than those without evidence of tricuspid regurgitation (35.19 ± 12.56 vs 26.77 ± 6,70; p=0.038; Table 3). Age was also negatively correlated with ejection fraction (r=-0.271, p=0.024), indicating reduced cardiac function in older patients. No correlations with age and other echocardiogram findings were observed. Saudi and non-Saudi nationals were equally likely to show abnormal echocardiogram results. Due to the predominant female population within this cohort, relationship between gender and cardiac abnormalities in SLE patients could not be examined.

Table 1: Patient characteristics

	All
Total	123
Female	114
Male	7
Age, mean ± s.d.	32.89 ± 11.30
Nationality Saudi Non Saudi	 69 50
Anti-DNA, mean ± s.d.	549 ± 515
CRP, mean ± s.d.	8.47 ± 64
ESR, mean ± s.d.	44 ± 65.41

*Unless stated. ANA – Anti-nuclear antibody; RF – Rheumatoid Factor; CRP – C-reactive Protein; ESR – erythrocyte sedimentation rate

Table 2: Echocardiogram findings in the total population

	Frequency of abnormality in study population
Mitral Regurgitation	12/30
Mitral Stenosis	0/30
Aortic Regurgitation	1/29
Aortic Stenosis	0/29
Tricuspid Regurgitation	16/30
Tricuspid Stenosis	0/28
Pulmonary Regurgitation	1/28
Pulmonary Stenosis	0/28
Pericardial Effusion	12/73
Pulmonary Pressure	14/73

Table 3: Relationship between cardiac abnormalities and age

	Age Mean ± s.d.		p
	Abnormal	Normal	
Mitral Regurgitation	27.09 ± 8.02	34.06 ± 11.88	0.098
Tricuspid Regurgitation	35.19 ± 12.56	26.77 ± 6.70	0.038
Pericardial Effusion	27.42 ± 11.37	32.31 ± 11.06	0.169
Pulmonary Pressure	34.50 ± 12.33	30.84 ± 10.92	0.277

Relationship between disease activity and cardiac abnormalities

The association of disease activity with biochemical measures and cardiac abnormalities was analysed in all patients. Anti-DNA titre was negatively correlated with haemoglobin (r=0-.379, p<0.001), vitamin D (r=-0.245, p=0.029) and calcium (r=-0.323, p=0.010) levels, and positively correlated with antinuclear factor (r=0.443, p<0.001) and ejection fraction (r=0.265, p=0.028). There were no significant differences in the anti-DNA titres for patients with and without cardiac abnormalities, although there was a trend towards higher titres in patients with abnormal echocardiogram findings (Table 4). ESR levels were also negatively correlated with haemoglobin levels (r=-0.373, p<0.001) and positively correlated with creatinine (r=0.304, p=0.003) and 24 hour protein levels (r=0.394, p=0.016). ANA was negatively correlated with white blood cell count (r=-0.241, p=0.010). No correlations were observed for CRP.

Relationship between urinary abnormalities and cardiac abnormalities

Pericardial effusion was more likely in patients with abnormal urinary protein (77.8%, p=0.035), however there was no association between urinary protein results and pulmonary pressure, mitral regurgitation or tricuspid regurgitation. Urinary red blood cell count was also associated with pericardial effusion (75.0%, p=0.017), but not with the other cardiac abnormalities. No associations were found with either urinary white blood cells counts or urinary casts with any of the echocardiogram findings. Abnormal C4 levels were significantly associated with mitral regurgitation (91.7%, p=0.02), however there was no association between C3 and echocardiogram abnormalities. Creatinine levels were found to be significantly increased in patients with pericardial effusion; however no relationship was observed between creatinine and other echocardiogram findings (Table 5).

Table 4: Relationship between cardiac abnormalities and disease activity

	Anti-DNA titre Mean ± s.d.		p
	Abnormal	Normal	
Mitral Regurgitation	782.58 ± 599.79	448.22 ± 428.66	0.088
Tricuspid Regurgitation	598.81 ± 632.83	562.71 ± 393.80	0.855
Pericardial Effusion	926.42 ± 841.06	582.05 ± 500.81	0.060
Pulmonary Pressure	711.14 ± 662.76	566.43 ± 473.71	0.348

Table 5: Relationship between cardiac abnormalities and renal function

	Creatinine titre Mean ± s.d.		p
	Abnormal	Normal	
Mitral Regurgitation	69.75 ± 26.18	61.71 ± 17.57	0.330
Tricuspid Regurgitation	63.13 ± 18.90	67.07 ± 24.53	0.631
Pericardial Effusion	123.33 ± 33.23	70.51 ± 47.49	0.011
Pulmonary Pressure	78.64 ± 82.24	79.89 ± 62.11	0.950

4. Discussion

There is a paucity of published data concerning cardiac abnormalities in SLE patients in Saudi Arabia. This study found that cardiac abnormalities, detected by echocardiogram, are common in SLE patients. Using a retrospective cohort study design, we have demonstrated that patients with cardiac abnormalities are likely to be older and to have raised levels of both disease specific markers and urinary protein markers.

In line with previous studies, valvular involvement was the most common form of heart disease detected in our patient cohort (Galve, et al., 1988). Mitral and tricuspid regurgitation were detected in approximately one third of patients with echocardiogram results whilst, as may have been anticipated from previous studies, stenosis was rarely seen. Valve regurgitation has been postulated to be a result of immunoglobulin and complement deposition in the valvular structure which leads to valve thickening and consequently to valvular regurgitation (Khamashta, et al., 1990; Nihoyannopoulos, et al., 1990 and Roldan, et al., 1992). This theory is supported by our data which demonstrates a significant association between abnormal C4 levels and the presence of mitral regurgitation. Although immunoglobulin levels were not analysed in this study, this may be the topic of future studies to further understand the pathogenesis of valvular disease in SLE patients.

Although there was no significant relationship between anti-DNA titre and cardiac disease, there was a strong trend towards increased anti-DNA levels in patients with detectable cardiac abnormalities. These findings support previous data of a relationship between disease activity and damage to the heart (Yip, et al., 2009). Previous studies have also suggested that there may be a relationship between duration of SLE and valvular disease (Yip, et al., 2009). However, these results are controversial with other groups finding no relationship between duration, activity or severity of SLE with cardiac disease (Roldan, et al., 1996). Similarly, whilst we found a significant correlation between increased age and increased incidence of valvular damage and reduced ejection fraction, other studies have failed to demonstrate such a relationship (Yip, et al., 2009 and Roldan, et al., 1996). It is evident from the conflicting data in the literature that the pathogenesis of SLE is highly complex, with progression and disease phenotypes dependent on multiple and varied factors.

A significant relationship was found between increased creatinine levels and pericardial effusion. However, as overall creatinine levels were normal in most patients we cannot establish a causal link between renal dysfunction and cardiac abnormalities, as has been suggested in studies of patients with chronic renal failure (Amann and Ritz, 1997; Foleyet al., 1998; Foley, et al., 1998 and Ritz, et al., 1997). Indeed, these results support the argument that cardiac disease in SLE patients may be driven by underlying inflammatory disease-associated process, given that the majority of those with cardiac disease had normal renal function. importantly these results further demonstrate the multi-organ pathology often observed in SLE patients, which can make interpretation of causal effects complex in such patients.

There are a number of limitations of this study. Due to the retrospective nature of the study the author is unable to draw any causal relationships between serological and urinary markers and the presence of cardiac abnormalities. Therefore the author cannot definitely address our hypothesis that cardiac abnormalities are driven by the inflammatory SLE disease process, rather than by predisposing conditions such as renal dysfunction. Prospective studies with long-term follow-up are needed to further understand these relationships. Moreover, the study only included patients diagnosed with active disease and it would be useful to include a control population of non-disease patients in future studies. As in any retrospective analysis, we were only able to use data contained in medical notes to determine disease diagnosis. There are discrepancies within the correlative data and this may be a result of our relatively small sample size and missing data for some patients. Most notably the subset of patients with complete echocardiogram results was low and this may have compromised our ability to draw statistically significant correlations from our dataset. Further studies with larger cohorts would strengthen the preliminary conclusions of this study.

In conclusion, our study demonstrated the prevalence of cardiac abnormalities in SLE and strengthens the needs for early detection and intervention to improve the prognosis of such patients. Further work is needed to fully understand the pathogenesis of cardiovascular disease in SLE; identifying the mechanistic drivers may reveal novel treatment targets and prognostic markers to aid in the optimal management of such patients.

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