ECHOCARDIOGRAPHIC ABNORMALITIES IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AT KENYATTA NATIONAL HOSPITAL (KNH)

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MBCHB

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DECLARATION

This research is my original work and has not been presented for a degree at any other university.

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DEDICATION

This piece of work is dedicated to my first born Paul Sorie Conteh Jr, my ultimate legacy

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LIST OF ABBREVIATIONS

1.	**A**	Late mitral flow
2.	**A'**	Late myocardial velocity
3.	**ACL**	Anticardiolipin
4.	**ACR**	American College of Rheumatology
5.	**ANA**	Antinuclear antibody
6.	**aPL**	Antiphospholipid
7.	**CVD**	Cardiovascular disease
8.	**CW**	Continuous wave Doppler
9.	**2D**	Two dimension
10.	**Dct**	Mitral deceleration time
11.	**E**	Early Mitral flow
12.	**E'**	Early myocardial velocity
13.	**KNH**	Kenyatta National Hospital
14.	**LA**	Left atrium
15.	**LV**	Left ventricle
16.	**MV**	Mitral valve
17.	**PAH**	Pulmonary arterial hypertension
18.	**PAP**	Pulmonary arterial pressure
19.	**PH**	Pulmonary hypertension
20.	**$P_{1/2}$**	Pressure half time
21.	**SLE**	Systemic lupus erythematosus
22.	**sPAP**	Systolic pulmonary arterial pressure
23.	**TLR**	Toll like receptor

ABSTRACT

Background: The cardiovascular system is frequently affected in patients with systemic lupus erythematosus (SLE). Involvement of various constituents of the heart and pulmonary vessels has been found in several clinical and autopsy studies in patients with SLE; most of which can be detected by noninvasive two dimensional and Doppler echocardiography. More than half of SLE patients experience clinical cardiovascular manifestation during the course of the disease and cardiovascular complications are among the leading causes of morbidity and mortality in patients with SLE. The study set out to determine the prevalence and spectrum of cardiac abnormalities; determined by echocardiography in SLE patients at KNH.

Methodology: This was a cross-sectional descriptive study of SLE patients attending clinic at KNH. A total of 63 SLE patients were sampled consecutively over a period of 3 months. Clinical examination and transthoracic echocardiography were done for all participants. The echocardiogram outcome variables included; pericardial effusion, thickening and calcification, systolic and diastolic dysfunction, mitral valve thickening, stenosis and regurgitation, aortic valve thickening, stenosis and regurgitation, and pulmonary hypertension.

Results: Sixty three SLE patients participated in the study, the mean age of participants was 36.7 years, with a female to male ration of 20:1. The mean duration of disease was 36.0 (IQR 14.0 – 65.0) months and over 70% of participants were on at least 2 disease modifying medication. The over all prevalence of echocardiographic abnormalities was found to be 88.9%, the major drivers of this high prevalence being pericardial and valvular thickening. The single most common cardiac lesion in the study was pericardial thickening at 77.8%. The mitral valve was the most commonly affected valve with 69.8% and 30.2% having mitral thickening and regurgitation respectively. Diastolic dysfunction was found in 50.8% of participants and was found to be associated with older age at diagnosis. Pulmonary hypertension was found in 22.2% of participants.

Conclusion: The study demonstrates a high prevalence of cardiac abnormalities among SLE patient despite being on disease modifying medications. Even though the majority of these abnormalities comprised of clinically insignificant pericardial and valvular thickening, the prevalence of valvular insufficiency and pulmonary hypertension are substantially high.

1.0 INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder resulting in multi-systemic inflammatory damage, the epidemiology of which is still largely undetermined in Africa. The general view has prevailed that the prevalence of SLE in black Africans is low (1). However recent studies by African researchers have clearly demonstrated that SLE may be common in Black Africans living in Africa. Tikly et al described the clinical feature and antibody profile of 111 black South Africans with SLE (2). A recent survey of the clinical experience of specialists and general practitioners treating SLE in West, East and Southern Africa including Kenya, suggests that the condition is being diagnosed more often than previously thought (3). Participants estimated the number of new SLE cases they had seen in the last twelve months within five categories: None (2.4%), one to five (23.8%), five to ten (19%), ten to twenty (11.9%), twenty to fifty (13.8%) and more than fifty (19%) (3). A survey to determine the clinical spectrum and outcome of SLE in hospitalized Black African in Durban, South Africa demonstrate a high mortality rate of 29% and the commonest causes of death were renal, infection, neurological and cardiac (4).

Involvement of the pericardium, endocardium, myocardium, coronary and pulmonary vessels has been found in several clinical and autopsy studies in patients with SLE(5), most of which can be detected by noninvasive two dimensional (2D) and Doppler echocardiography.

The most characteristic cardiac abnormalities in SLE are non-infective vegetations (Libman-Sacks endocarditis); which was in the past thought to rarely result in significant valvular regurgitation or destruction (6). However more recent studies have shown valvular heart disease to be common in SLE patients and associated with substantial morbidity and mortality (7).

Myocarditis is a rare but potentially fatal manifestation of SLE. It is often subclinical in nature, but 5 - 10% of all SLE patients develop symptomatic myocarditis (8). Other forms of myocardial dysfunction also occur in SLE and present as diastolic dysfunction.

Pulmonary hypertension is another serious and potentially life threatening complication of SLE with a reported prevalence ranging from 0.5 - 14% (9, 10). The prognosis in SLE patients with pulmonary hypertension has been reported to be very poor, with a mean survival from the onset of two years (11). It is the third most common cause of death in SLE following infection and organ failure (12).

Prevention of cardiovascular disease associated morbidity and mortality among these patients depends on early detection and close follow up of patients with cardiovascular disease. Data on the prevalence and spectrum of cardiac lesions among these patients is therefore crucial to inform practice guidelines with regards initial investigation and subsequent follow up of SLE patients. However to date there are no studies documenting the prevalence and spectrum of cardiac lesions including pulmonary hypertension among SLE patients in our setting.

2.0 LITERATURE REVIEW

Cardiovascular disease (CVD) has recently been acknowledged as a major cause of morbidity and mortality in SLE. The range of CVD in SLE is broad and includes atherosclerosis, vascular inflammation, Raynaud's phenomenon, endothelial dysfunction, myocardial dysfunction and coronary artery disease. The heart specifically is very frequently involved in SLE. All cardiac structures can be involved; pericardium, coronary vessels, myocardium, endocardium and conduction tissue.

2.1 Pericardial Disease

Pericarditis is one of the most characteristic disease manifestations of SLE and is included in the American College of Rheumatology (ACR) classification of SLE (13). Pericardial effusion occurs at some point in over one half of patients with SLE and may precede the clinical signs of lupus. It is the most common echocardiographic lesion in SLE and is the most frequent cause of symptomatic cardiac disease (14).

The pericardium can be involved by acute and chronic inflammatory changes. Acute pericarditis can be sero-fibrinous or fibrinous whereas in chronic pericarditis the fibrous or fibro-fibrinous aspect prevails. In addition to pericardial inflammation, pericardial effusion can also result from fluid retention due to haemodynamic abnormalities and/or low colloid osmotic pressure in patients with SLE. Pericardial involvement appears more frequently at the onset of SLE and during relapses. The course is benign in the majority of patients with pericardial disease. However, the presence of pericardial disease is usually associated with active disease in other organs (15).

In a study done in Pakistan to detect cardiac abnormalities and determine their associations in SLE patients, Hameed et al (16) did transthoracic echocardiography in 48 patients who fulfilled the ACR criteria for diagnosis of SLE. An echocardiographic abnormality was detected in 28 patients (58.33%), and it was commoner in younger age group. Pericardial involvement with some degree of effusion was the commonest abnormality and was found in 16 (57%) of the patients with echocardiographic abnormalities.

In a similar study conducted in the lupus clinic at a Medical University in Bangladesh; Shazzad et al (17) evaluated patients fulfilling the ACR criteria for SLE and without cardiovascular symptoms, using standard transthoracic echocardiography. Out of 50 patients, 80% were found to have abnormal echocardiographic findings. Pericardial thickening was

found in 38% of patients and pericardial effusion in 20%. They found a significant relationship between disease duration and cardiac abnormalities ($p<0.01$). They also found a trend towards higher frequency of heart involvement in active disease than in remission but it was not statistically significant.

Shahin et al (18) in Egypt, did a study to evaluate the incidence of morphologic and functional cardiac abnormalities in patients with SLE. All patients were submitted to standard two-dimensional and Doppler echocardiographic evaluation of cardiac function and morphology. Cardiac abnormalities that are likely to be associated with the underlying SLE disease process were detected in 28 patients (45.2%), with 14 of them having evidence of more than one abnormality. Pericardial effusion was detected in 12 patients (19.4%), and in one patient it was severe enough to require pericardiocentesis. No difference was observed in the antibody profiles between patients with and without pericardial effusion.

In a South African study to describe the clinical, echocardiographic and laboratory characteristics of large pericardial effusions and cardiac tamponade (19), patients above the age of 13 presenting with large pericardial effusions requiring diagnostic and/or therapeutic pericardiocentesis were prospectively enrolled at Tygerberg Academic Hospital. A large pericardial effusion was defined as having more than 10 mm separation between the pericardium and epicardium on echocardiography. Out of a total of 258 patients, 8 cases met the ACR diagnostic criteria of SLE. Seven of these had been previously diagnosed with SLE whereas in 1 patient cardiac tamponade was the initial presentation. Common associated clinical findings included lupus nephritis (n = 5), arthralgia (n = 4) and Raynaud's phenomenon (n = 3). Echocardiographic findings included a thickened or echocardiographically bright pericardium (n = 4), left ventricular hypertrophy (n = 3) and pancarditis (n = 2).

2.2 Myocardial Dysfunction

Myocardial dysfunction in SLE may be the consequence of several factors including; myocarditis directly due to the disease process, coronary artery disease due to premature atherosclerosis, hypertension, renal failure, valvular disease and toxicity from medications such as cyclophosphamide and chloroquine (14, 20)

Myocarditis is the most characteristic feature of myocardial involvement in SLE. It is characterized by small foci of fibrinoid necrosis with infiltrates of plasma cells and

lymphocytes and small foci of myocardial fibrosis (21, 22). It is often subclinical in nature but 5 – 10% of all SLE patients develop symptomatic myocarditis (8)

Accelerated atherosclerosis with coronary artery disease is one of the causes of morbidity and premature death in SLE. The risk of development of coronary artery disease is 4-8 times higher in SLE patients than in controls and the greatest increase in relative risk is among young women who otherwise have low risk of coronary artery disease (23).

Impaired renal function is a primary culprit in the progression of SLE hypertension. Given that immune complex glomerulonephritis is estimated to affect approximately 50% of patients with SLE (24), it is tempting to conclude that SLE hypertension is simply due to nephritis. However SLE is a risk factor for hypertension in humans and can occur independent of nephritis (24, 25). Hypertension and chronic kidney disease are among the leading causes of left ventricular hypertrophy and can lead to both diastolic and systolic dysfunction if not well controlled

Cumulative doses of hydroxychloroquine ranging from 292g to 4380g can cause cardiac toxicity (26, 27). It causes vacuolation and enlargement of myocytes and accumulation of myeloid and curvilinear bodies (thought to be abnormal lysosomes) within cardiac myocytes. Morphologically there is diffuse thickening of the myocardial walls (28, 29). Bilateral enlargement and restrictive physiology are also seen (29, 30)

In a study assessing systolic and diastolic function of the left ventricle (LV) in SLE patients without clinically evident CVD, using Doppler echocardiography; Wislowska et al (31) consecutively enrolled 32 patients diagnosed with SLE and compared them with 32 healthy age matched controls. No statistically significant differences in systolic heart function between groups were observed. SLE patients demonstrated significantly higher proportion of diastolic dysfunction using various indices for diastolic dysfunction including flow velocities across the mitral valve and tissue Doppler.

Allam et al (32) studied 50 patients with SLE and 20 age and sex matched healthy controls, enrolled from the outpatient and inpatient sections of the Rheumatology and Rehabilitation Department, Cairo University Hospital. They found SLE patients to have an increased prevalence of subclinical LV diastolic dysfunction and the SLE patients with positive tissue Doppler findings were of older age, had long disease duration, high disease activity index and nephritis.

2.3 Valvular Heart Disease

Both anatomical and functional valvular abnormalities have been described in SLE. Anatomical abnormalities are generally found in the mitral and aortic valves (33). Libman-Sack endocarditis is the most characteristic lesion, though valvular thickening and regurgitation are more frequently observed. The verrucae are usually found in the recess between the ventricular wall and the valve leaflet and thus tend not to deform the fissure line even when they are large and protruding into the cardiac chambers (34). The lesions (verrucae) have been shown to be of two types: Active lesion – consisting of fibrin clumps, focal necrosis and mononuclear infiltrates, frequently observed in young patients with recent disease onset and rarely lead to haemodynamically significant valvular lesion. And healed lesion characterized by vascularized fibrinous tissue associated with calcification, found in patients with long term corticosteroid use (22).

The clinical recognition of Libman-Sack endocarditis during life is extremely difficult, because valvular distortion is usually minimal even though large vegetation may be present. In addition benign cardiac murmurs are common in SLE due to coexisting anaemia, fever, myocarditis or congestive heart failure. However the verrucae can fragment and produce systemic emboli, leading to stroke and peripheral vascular disease. Furthermore infective endocarditis can develop on already damaged valve. Haemodynamically significant valvular lesions have been reported in only 3 - 4% of SLE patients and only half of these required surgical treatment (35). Infective endocarditis has been reported in 7% of SLE patients with valvular heart disease and stroke or peripheral embolism in 13% (35).

In a study by Bourre-Tessier J. et al (36), to determine the prevalence of echocardiographic abnormalities in a large SLE cohort in Canada, transthoracic echocardiography was performed in 217 subjects. Mitral valve thickness was measured by M-mode in the parasternal long axis view; a thickness $\geq$ 3 mm qualified as abnormal. Valvular regurgitations were evaluated in all echocardiographic views by 2D, color Doppler imaging and Doppler flow interrogation. Valvular abnormalities were detected in 87 patients (40.1%). The mitral valve was the most commonly affected, being involved in 81 patients (37.3% of the entire cohort). Abnormalities of this valve included insufficiency (56 patients, 25.8%) and thickening (55 patients, 25.4%). Mitral regurgitation severity was distributed as follows: mild, 38 patients (67.8%); moderate, 17 patients (30.4%); and severe, one patient (1.8%). Aortic insufficiency was detected in eight patients (3.7%) and aortic stenosis in one (0.5%). One patient (0.5%) had pulmonary valve insufficiency.

In an Egyptian study evaluating the incidence of morphologic and functional cardiac abnormalities in SLE (20), 62 patients and 20 controls were included. All patients were submitted to standard 2D and Doppler echocardiographic evaluation. Guided with color-flow imaging, pulsed-wave Doppler was used to detect and quantitate the magnitude of mitral regurgitation according to the extent of the regurgitation jet in the left atrium as follows: grade 1+, regurgitant jet extends up to the proximal one-quarter of the left atrium; grade 2+, regurgitant jet detected half way up the left atrium; grade 3+, regurgitant jet extends up to three-quarters of the left atrium; grade 4+, regurgitant jet extends beyond three-quarters of the left atrium. Valvular lesions were detected in 19 (30.6%) patients, and mitral regurgitation was detected in 18 (94.7%) of the patients with valvular lesions; grade 1+ in 14 (77.8%) patients and grade 2+ in 4 patients (22.2%). No patients were found to have grade 3+ or 4+ lesions. Among the 19 patients with valvular lesions, mitral stenosis was detected in 2 (10.5%), tricuspid regurgitation in 2 (10.5%), aortic regurgitation in 6 (31.6%), and aortic stenosis in 6 (31.6%).

In a study done in Cape town, South Africa, to determine the prevalence of valvular heart disease in SLE, Pont K. et al (37) consecutively included 24 SLE patient and 10 controls. Clinical examination, chest radiography, ECG and standard echocardiography was done for all patients and controls. They found valvular abnormality (predominantly mitral) to be common among SLE patients and none among the controls. Valvular thickening was the most common abnormality, and was seen in more than half of the SLE group. Small valvular vegetations were present in only one patient, and these were on the anterior mitral cusp tip. Mitral regurgitation was seen in 12.5%.

2.4 Pulmonary Hypertension (PH)

Pulmonary arterial hypertension (PAH) is a complex and devastating disease. It is well recognised that patients with SLE can develop PAH at any time during the course of their disease, most often in the first five years (mean delay 4.9 ± 3.7) (38) and it can be an initial manifestation of SLE.

Although PAH is the most common cause of PH in SLE, interstitial lung disease, thromboembolism, primary cardiac involvement and pulmonary veno-occlusive disease may be implicated as the cause of PH in a minority of these patients. This suggest that all but group 5 (PH with unclear/or multifactorial mechanisms) of the updated clinical classification of PH (39) can occur in SLE.

Pulmonary hypertension is the most severe form of lupus associated pulmonary involvement, with poor long term outcome despite therapeutic intervention. In a Korean study 15% of SLE deaths were due to PH (12). PH in SLE has a 3 year survival of 45% (9, 40). Chung et al also reported 3 and 5 year survival rates of patients with SLE as 45% and 17% respectively (40).

Johnson et al (41) in a retrospective analysis investigating the prevalence of PAH and possible associations with Raynaud's phenomenon, disease activity and aPL, reviewed echocardiography report of 129 patients in University of Toronto Lupus cohort. Pulmonary arterial hypertension was defined as a right ventricular systolic pressure (RVSP) ≥ 40mmHg and normal was defined as a RVSP ‹ 30 mmHg. Sixteen patients (14%) had RVSP ≥ 40mmHg and 37% had RVSP of 30 - 39mmH. Three of the 16 patients with RVSP ≥ 40mmHg had a RVSP ≥ 90 mmHg. They found no statistically significant difference in disease activity, end organ involvement or serology, between patients with RVSP ≥ 40mmHg and those with RVSP 30 – 39 mmHg or 30 mmHg at clinic visit closest to the date of echocardiogram.

In a systematic review of literature in China by Xia et al (42), that included 642 Chinese SLE patients from 22 studies in which transthoracic echocardiography and/or right heart catheterisation were performed to diagnose PH: the prevalence of PH; defined as pulmonary arterial systolic pressure › 30mmHg ranged from 2.8 – 23.8. The three most commonly observed clinical characteristics associated with PH were Raynaud's phenomenon, arthritis and serous effusion. Among the laboratory findings, positive anti-nuclear antibodies (ANA), positive anti-cardiolipin (ACL) and positive ribonucleoprotein (RNP) were significantly higher in the lupus patients with PH.

In a cross sectional Egyptian study to screen for asymptomatic pulmonary hypertension in SLE patients using Doppler echocardiography (43), 74 patients attending the outpatient clinic of Rheumatology and Rehabilitation Department at Minia University Hospital were evaluated. PAH was detected in 8 patients (10.8%). Systolic pulmonary arterial pressure (sPAP) ranged from 34 mmHg to 61.2 mmHg (43.19 ±9.28). No significant difference was found between patients with and those without PH as regard clinical features. However, significantly higher frequencies of rheumatoid factor and ACL antibodies were found in patients with pulmonary hypertension compared to those without (P ‹ 0.02, P ‹ 0.008 respectively).

2.5 Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is the primary noninvasive imaging modality for quantitative and qualitative evaluation of cardiac anatomy and function. Echocardiography has become central to care of patients precisely because it is almost universally available, can be performed in the outpatient setting or the intensive care unit, provides usable clinical information on the vast majority of patients, is relatively inexpensive, and has significant clinical and prognostic value. A limitation of TTE is the inability to obtain high-quality images in all patients, especially those with a thick chest wall or severe lung disease, as ultrasound waves are poorly transmitted through lung parenchyma. There is also the limitation of inter and intra observer variability that can be minimized by adherence to standard echocardiography practice guidelines.

2.5.1 Pericardial Evaluation

Echocardiography is the method of choice for evaluating most pericardial diseases, given its ability to provide both anatomic and physiologic/hemodynamic information. When competently performed in patients with good acoustic windows, echocardiography accurately detects pericardial effusions and provides clinically relevant information about their size and hemodynamic importance. However echocardiography is less reliable than magnetic resonance imaging and computed tomography in detecting pericardial thickening and calcification as well as small loculated effusions, but can still be extremely useful in these conditions.

The task force of the American College of Cardiology (ACC), the American Heart Association (AHA), and the American Society of Echocardiography (ASE) gave class I recommendations for the uses of echocardiography in known or suspected pericardial disease, including effusion, constrictive pericarditis, or effusive-constrictive pericarditis (44).

2.5.2 Evaluation of Systolic and Diastolic Function

LV systolic function is usually assessed by the resting left ventricular ejection fraction (LVEF). The LVEF is expressed as the ratio of the stroke volume divided by the end-diastolic volume and is calculated as follows.

Stroke volume (SV) = LV end-diastolic volume - LV end-systolic volume

LVEF (%) = (SV ÷ LV end-diastolic volume) x 100

Although invasive methods, such as contrast left ventriculography, have been widely used and are validated for accuracy in assessing LVEF, noninvasive echocardiography can provide the same information without the associated procedural risks. Estimation of the LVEF by 2D echocardiography can be done either qualitatively by visual inspection of global and regional function or quantitatively, using geometric assumptions regarding the shape of the LV cavity. Echocardiography can generate a number of quantitative assessments of LV size and function. Quantitative measurements are available for uni-dimensional (M-mode), two-dimensional (2D), and three-dimensional (3D) techniques.

The correlation between echocardiography and left ventriculography and single photon emission computer tomography for determining left ventricular ejection fraction are reported to be 0.83 and 0.81 respectively (45).

Left ventricular diastolic function can be characterized by measurement of left ventricular relaxation and chamber stiffness. The gold standard for assessing these parameters is high fidelity LV pressure and volume measurements by cardiac catherisation. Given the invasive nature and high cost of the approach, reliable noninvasive measurements are highly desirable. Echocardiography is the most practical, routine clinical approach and represents the cornerstone for evaluating LV diastolic function (46). The comprehensive echocardiographic evaluation to assess diastolic dysfunction includes the careful acquisition and analysis of a number of 2D and Doppler parameters. Doppler data that should be acquired and analysed include mitral inflow, pulmonary venous flow and tissue Doppler mitral annulus velocities. From the mitral inflow, early (E) and late (A) velocities, deceleration time (Dct) and isovolumetric relaxation time (IVRT) are derived and used to identify and grade diastolic dysfunction.

2.5.3 Valvular Evaluation

2D echocardiography is the preferred modality for imaging valve morphology and motion. Leaflet thickness and mobility, valve calcification, and the appearance of subvalvular and supravalvular structures can also be assessed. Echocardiography is the primary non-invasive imaging method for valve stenosis assessment (47). Valve stenosis is reliably diagnosed by the thickening and decreased mobility of the valve leaflets whereas evaluation of the severity of stenosis requires Doppler echocardiography. Echocardiography with Doppler has also emerged as the method of choice for the noninvasive detection and evaluation of the severity

and etiology of valvular regurgitation (48). The diagnosis of valvular regurgitation is made by Doppler echocardiography and 2D echocardiography is valuable for determining the etiology of the regurgitation, as well as its effects on ventricular dimensions, shape, and function.

2.5.4 Assessment of Pulmonary Pressure

The gold standard investigation to diagnose PAH is right heart catheterization, with an increase in mean PAP ≥ 25mmHg at rest, pulmonary capillary wedge pressure ≤ 15mmHg and pulmonary vascular resistance › 240dynes/sec/cm being diagnostic (49). Non-invasive Doppler echocardiography is a well-established and useful screening tool for PH and should be considered particularly for patients with symptoms of PH, aPL antibodies and prior to or during pregnancy. Doppler echocardiography estimate of systolic pulmonary arterial pressure (sPAP) can be unreliable because overestimation by 10mmHg is common, as is underestimation in severe tricuspid regurgitation when calculated from tricuspid regurgitation jet alone (49). The European Society of Cardiology and European Respiratory Society guidelines have proposed arbitrary criteria for PH diagnosis by echocardiography, using tricuspid regurgitation peak velocity, Doppler calculated sPAP, assumption of right atrial pressure of 5mmHg and additional right heart variables suggestive of PH (49). The right heart variables suggestive of PH are tricuspid annular systolic plane excursion (TAPE), increased velocity of pulmonary regurgitation and short acceleration time of right ventricular ejection into pulmonary artery. Right chamber enlargement, increased right ventricular wall thickness, abnormal shape and function of interventricular septum and dilated main pulmonary artery are variable suggestive of advanced PH (50).

A recent meta-analysis on the accuracy of echocardiography for diagnosis of pulmonary hypertension reported sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85; n=12) (51). And the conclusion from this study was that; echocardiography is a useful and noninvasive modality for initial measurement of pulmonary pressures but due to limitations, right heart catheterization should be used for diagnosing and monitoring pulmonary hypertension.

3.0 STUDY JUSTIFICATION

SLE is not a rare entity in our setting and cardiac involvement represents a significant contributor to morbidity and mortality in this condition. However there is no local data documenting the prevalence and spectrum of cardiac abnormality in patients with SLE in our setting. This study was done to provide useful information to clinicians about the burden of cardiac disease among SLE patients and also to contribute to filling the information gap about SLE in Africa.

We believed the study result will provide a comprehensive frame work for documenting cardiac lesions among SLE patients in our setting. It will also contribute to the way forward with regards the detection and management of cardiovascular complications among SLE patients in our clinics.

4.0 STUDY QUESTION

What is the burden of cardiac disease in SLE patients at KNH.

5.0 OBJECTIVES

5.1 Broad Objective

To determine the prevalence and spectrum of cardiac abnormalities; determined by echocardiography in SLE patients at KNH.

5.2 Specific Objectives

1. To determine the prevalence of cardiac abnormalities detected by echocardiography in SLE patients attending clinic at KNH.
2. To describe the various types of cardiac lesions including, pericardial, myocardial and valvular, present among SLE patients attending clinic at KNH.

5.3 Secondary objective

1. To document associations between cardiac abnormalities and demographic and clinical features.

6.0 METHODOLOGY

6.1 Study Design

The study was a cross sectional descriptive study of SLE patients attending clinic at KNH.

6.2 Study Setting:

The study was conducted at KNH which is the National Referral Hospital located within an urban environment in Nairobi. It provides specialized clinical services to patients mainly from Nairobi and its environs. The Rheumatology clinic is a specialized clinic that follows out patients with rheumatological disorders. The clinic is held once a week and patients are seen by rheumatologists and internal medicine residents. Stable patients are reviewed at an interval of 1 – 3 months based on the clinicians' assessment.

All SLE patients seen at the clinic are routinely assessed clinically for signs and symptom of active disease. Complete blood count, erythrocyte sedimentation rate and/or C-reactive protein are also routinely done to assess disease activity. Other laboratory investigations including anti-dsDNA, compliment factors, serum albumin, serum creatinine, urinary protein and creatinine are done based on recommendations by clinicians after clinical evaluations of patients. Medications are prescribed or modified based clinical and laboratory assessments. Noninvasive cardiac evaluation is not part of the routine evaluation of SLE patient at the clinic, it is only requested for patients presenting with symptoms or signs of cardiac disease.

6.3 Study Population

SLE patients on follow up at KNH.

6.4 Patient Selection

6.4.1 Case Definition

Patients fulfilling the ACR criteria (13) for diagnosis of SLE and on follow up at KNH

6.4.2 Inclusion Criteria

1. Patients 13 years of age and above
2. Willing to particpate and give written consent or ascent for those less than 18 years old

6.5 Sample Size Determination

A prevalence of cardiac abnormalities among SLE patients of 45.2% as reported by Shahin et al (18), in a similar study done in Egypt was used in the sample size calculation. A total of 69 SLE patients were on follow up at the Rheumatology clinic, KNH at the time of protocol development for the study. Based on these numbers, the accessible population was described as finite (less than 10,000) hence the sample size was calculated as per the formula:

$$n = \frac{NZ^2 \times p(1-p)}{d^2(N-1)+Z^2 p(1-p)}$$

Where; n = sample size required

N = Size of target population = 69

Z = z score for 95% confidence interval = 1.96

p = Proportion of SLE patients with cardiac abnormality = 45.2%

d = Margin of error = 5%

Thus, the minimum sample required to achieve the objectives of the study was 58.

6.6 Sampling Method

Consecutive sampling was used to recruit participants at the KNH Reumatology clinic and the medical wards untill the desired sample size was attained.

6.7 Patient Recruitment

The principal investigator and a trained research assistant went through the patients' files before the start of the Rheumatology clinic to identify SLE patients. The purpose and procedures of the study were explained to those who satisfied the inclusion criteria. After addressing any question or concern partaining to the study, participants were requested to give written consent. A thorough physical examination was performed by the principal investigator for all participants. Then each participant had an echocardigraphy study undertaken by a cardiologist at the department of cardiology KNH, with full participation of the principal investigator.

6.8 Clinical Methods

The principal investigator and the trained research assistant administered the study proforma to collect demographric data from all participants. The data included age , gender, duration of disease and current medications. Data on current clinical status of each patient was obtained through a standard and comprhensive clinical evaluation with emphasis on signs and syptoms attributible to SLE. The clinical examination focused on evaluating the following manifestaions:

Arthritis – examination of large and small joints for tenderness, deformity, soft tissue laxity of periarticular soft tissue and effusion

Musocutaneous involvement – examination of skin and mucous meembrane for alopecia malar rash, discoid rash and mouth ulcers

Raynaud's phenomenon – nail fold capilloroscopy was done to objectively assess for evidence of Raynaud's phenomenon. This was done by applying parafin oil over the nail fold and examining the capillaries with a fundoscope at a magnification of 40. In normal conditions, the microvascular pattern is characterized by a regular array of microvessels with large intra/inter individual variability (52, 53).

Serositis – examination of the abdomen for ascites and examination of the chest for pleural rub.

6.9 Clinical Variable Definition

6.9.1 Arthritis

Arthritis was defined by history and/or examination findings as follows:

- History of migratory joint pains with symetrical distribution
- Joint effusion or soft tissue laxicity at the affected joint
- Flexion deformity, ulnar deviation or swan neck deformity of the hand

6.9.2 Mucocutanous Involvement

Mucocutanous involvement was defined by any of the following findings:

- History of prominent rash on the cheek that last for more than one month in the last three months
- History of rapid loss of lots of hair in the last three months
- Butterfly rash – finding of erythema over the cheeck and nose but sparing the nasolabial folds
- Discoid rash – finding of erythematous raised patches with keratotic scaling with or without scaring
- Alopecia – hair loss with or without scaring on the scalp, eyebrows, eyelashes, beard and/or body hair

6.9.3 Raynaud's phenomenon

Raynaud's phenomenon was defined by any of the following findings:

- History of cold or emotion induced colour changes, numbness or aches of the digits of the hands and/or feet
- Loss of capillary and/or dilataion of nail fold capillaries on capilloroscopy (52)

6.9.4 Serositis

Serositis was defined by any of the following:

- Pleurisy – Chest pain on deep inspiration and/or pleural rub on auscultation
- Peritonitis – Demonstration of ascitis on clinical examination

6.10 Echocardiography Methods

Each patient underwent a comprehensive transthoracic echocardiography study performed according to the recommendations of the American Society of Echocardiography (54). We performed complete 2D, M-mode and Doppler analyses using a Phillips iE 33 ultrasound system equipped with a 2.5Hz multifrequency transducer. Standard parasternal long and short axis, apical and subcostal views were obtained.

6.10.1 Pericardial Assessment

The pericarium and pericardial space were assessed in the parasternal long axis and subcostal views and measurements made using M-mode. Pericardial thickness was measured as the width of the echogenic band around the myocardium. Pericardial efuusion was measured as the echo free separation between the visceral and parietal pericardium on M-mode. Pericardial separation that disapeared during diastole was considered trivial and not recorded.

6.10.2 Assessment of Myocardial Function

Systolic Function

M-mode and 2D measurements of left ventricular morphology were performed according to standard protocols (54). In M-mode, systolic parameters such as left ventricular(LV) diameter in end diastole and end systole, interventricular septum and LV posterior wall thickness in diastole and systole were measured. From these measurements, LV mass index and LV fractional shortening were computed. LV diastolic and sytolic volumes and LV ejection fraction were measured using the biplane Sympson's method in the convensional apical four and two chamber views.

Diastolic Function

Diastolic function indices were assessed by pulsed Doppler recording across the mitral valve; with the sample volume located between the tips of the mitral valve leaflets. The peak velocity of early (E) and late (A) mitral out flow were measured, from these measurements the E/A ratio was calculated, mitral deceleration time (Dct) and isovolumetric relaxation time (IVRT) were also measured.

6.10.3 Valve Assessment

Mitral Valve

The mitral valve (MV) was evaluated by 2D and M-mode in the parasternal and apical views to assess valve thickness, leaflet mobility and presence of vegetation. Coulour flow doppler in multiple planes was employed to detect mitral regurgitation. Pressure gradient across the mitral valve was obtained using continuous wave Doppler (CW) by placing the sample volume across the mitral orifice in the apical four chamber view. The mean gradient was then calculated from the velocity time intergral across the MV as meassured by CW doppler. The

MV pressure half time ($P_{1/2}$) was also estimated from which the MV area was calculated using the Hatle equation.

Aortic Valve

The aortic avlve was evaluated in the parasternal long and short axis views to assess opening of the cusps, number of cusps, thickness and presence of vegetation. Colour flow doppler was applied in the parasteral long axis and apical five chamber views to detect regurgitation. In instances where aortic regurgitation was detected CW Doppler was applied to the regurgitant jet in the apical five chamber view to estimate the pressure half time.

CW Doppler across the aortic valve in the apical five chamber view was aslo used to asses the gradient across the valve, from which the maximum velocity across the aortic valve was derived using the Benoulli equation. Using the continuity equation the aortic valve area was estimated from the maximum velocity across the valve.

Tricuspid and Pulmonry Valves

Two dimension and doppler assessment of the tricuspid and pulmonary valve were done in the parasternal and apical views to assess morphology and detect regurgitation.

6.10.4 Estimation of Pulmonary Arterial Pressure

The sPAP was estimated by measuring the tricuspid regurgitant peak velocity in the apical four chamber view, from which the pressure difference between the right ventricle and right atrium was estimated using the Bernoulli equation. The value obtained was then added to an estimated right atrial pressure based on the diameter of the inferior venacava, to give the sytolic pulmonary arterial pressure. Other echocardiographic variables to reinforce the diagnosis of PH were evaluated including velocity of pulmonary valve regurgitation and deceleration time of RV ejection into the pulmonary artery.

6.11 Ehcocardiogram Outcome Variable Definition

6.11.1 Pericardial Effusion: Echo free space surrounding the heart (19).

- Small Effusion: Less than 5mm in maximum dimension and visualised through out the cardiac cycle.
- Moderate Effusion: 5 to 10mm in dimension

- Large Effusion: greater than 10mm in dimension

6.11.2 Pericardial Thickening: Pericardial thickness greater 3mm (36).

6.11.3 Pericardial Calcification: Echo bright area around the heart.

6.11.4 Systolic Dysfunction: Fractional shortening less than 29% and/or ejection fraction less than 50%.

6.11.5 Diastolic Dysfunction (55):

- Grade 1: Impaired relaxation; mitral E/A ‹ 1, DT › 200msec, IVRT › 100msec
- Grade 2: Pseudonormal pattern; E/A 0.8 – 1.5, DT 150 – 200msec, IVRT 60 – 100msec
- Grade 3: Restrictive reversible; E/A › 2, DT ‹ 160msec, IVRT ‹ 60msec and reversible on valsava maneuvre
- Grade 4: Restrictive irreversible; same as Grade 3 but irreversible on valsava maneuvre

6.11.6 Mitral Valve Thickening: Mitral valve dimention greater than 3mm in the prasternal long axis in diastole measured at the mid portion of the anterior leaflet by M-mode (35).

6.11.7 Mitral Regurgitation: Backward flow into the LA on colour flow doppler across the mitral valve (56).

- Grade 1+: Regurgitant jet extending upto the proximal ¼ of the left atrium (LA)
- Grade 2+: Regurgitant jet detected half way up the LA
- Grade 3+: Regurgitant jet detected upto ¾ of the LA
- Grade 4+: Regurgitant jet extending beyond ¾ of the LA

6.11.8 Mitral Stenosis: Mitral valve area less than $2cm^2$ (56)

6.11.9 Aortic Valve thickening: Thickness greater than 2mm measured at the tip by M-mode in the parasternal long axis view during systole (35).

6.11.10 Aortic Regurgitation: Back flow into the LV on colour flow doppler through the aortic valve (56). Severity of aortic regurgitation was defined as follows:

Severity	**Pressure Half time (msec)**
Mild	› 500
Moderate	200 – 500
Severe	‹ 200

6.11.11 Aortic Stenosis: Aortic valve area less than $2cm^2$ (56)

6.11.12 Pulmonary Hypertension

Pulmonary hypertension was defined according to the ESC guidelines for the diagnosis and treatment of pulmonary hypertension (49) as follows:

Possible Pulmonary Hypertension: sPAP ≤ 36 but presence of additional echocardiographic variables suggestive of PH or sPAP 37 – 50mmHg with or without additional echocardiographic variables suggestive of PH

Likely Pulmonary Hypertension: sPAP › 50mmHg with or without additional echocardiographic variable suggestive of PH.

7.0 QUALITY ASSURANCE

Echocardiography studies were carried out by a qualified cardiologist; Dr BM Gitura together with the principal investigator, at the Department of cardiology KNH. Echocardiography images were downloaded to a compact disc and independently reviewed by a second cardiologist; Prof. EN Ogola. In cases of discrepancies, the two cardiologist reviewed the echocardiography studies together to arrived at a consensus.

8.0 ETHICAL CONSIDERATION

The study proposal was reviewed and approved by the department of Clinical Medicine and therapeutics, University of Nairobi and the KNH/UON joint ethics committee. Only patients who gave written consent were included in the study. Patients had the liberty to wtihdraw from the study at any time they so desire, without any concequence regarding their managemnet. Patient confidenciality was maintained through out the study. Echocardiography findings were communicated to patients at the time of the procedure and reports made availabe in their files for use by their attending physicians. Cases found to have cardiac abnormality that require treatment, were referred to the cardiac clinic.

9.0 DATA MANAGEMENT AND STATISICAL ANALYSIS

All data from study proforma and echocariography study were coded, entered and managed in statistical parkage for social sciences, version 21.0 data entry sheet. Data cleaning and verification was performed at the end of data collection and statistical analysis was performed using the same programme.

The study population was described using demographic and clinical characteristics. Continuous data (age, duration of disease) was analysed into means and medians while categorical data was analysed using percentages. Prevalence of cardiac abnormality was analyzed as the proportion participants with any echocardiographic abnormality out of the total number of participants recruited, with corresponding 95% confidence interval. Furthermore, various types of cardiac lesions were analyzed and presented as proportions. Associations between various cardiac lesions and demographic and clinical factors were analysed, using Student's t test to compare means and chi square test for categorical data associations. Criteria for statistical significance was set as a p value of less than or equal to 0.05.

10.0 RESULTS

Between 22nd January 2015 and 23rd April 2015 78 patients being managed for SLE at KNH were screened for study eligibility, of these 71 subjects underwent a targeted history and examination and were booked for echocardiography either the same day or another day during the course of the week. Priority was given to subject residing out of Nairobi to have their echocardiography done the same day they were seen at the Rheumatology clinic. Sixty three subjects had echocardiography studies done and were included in the analysis as depicted in the flow chart below.

10.1 Demographics

The study population as expected was predominantly female, with 60 females and 3 males. The mean age of the population was 36.7 (SD ±9.8) years. The mean age at diagnosis was 32.8 years and the mean duration of diseases was 36.0 (IQR 14.0 – 65.0) months as shown in table 1.

Table 1: Patients' demographic characteristics

Variable	Frequency (%)
Sex	
Male	3 (4.8)
Female	60 (95.2)
Current age in years	
Mean (SD)	36.7 (9.8)
Min-Max	17.0-59.0
Categories	
<30	14 (22.2)
30-39	25 (39.7)
40-49	14 (22.2)
>=50	10 (15.9)
Age at diagnosis in years	
Mean (SD)	32.8 (9.6)
Duration since diagnosis in months	
Median (IQR)	36.0 (14.0-65.0)

10.2 Clinical Variables

10.2.1 Clinical Manifestation

The predominant clinical manifestation observed during the study was arthritis with 55.6% having symptom and /or sign of arthritis, followed by Raynaud's phenomenon at 28% as depicted in figures 1. Only 6 (9.5%) participants had none of the clinical manifestation evaluated for in the study.

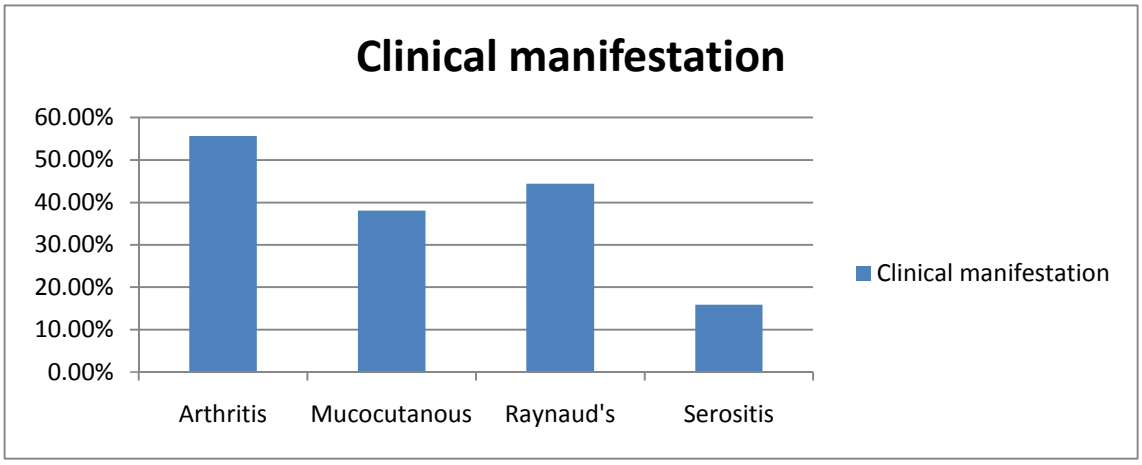

Figure 1: Frequency of clinical manifestations

10.2.2 Disease Modifying Medications

As out lined in figures 2 A and B, over 70% of the study population was on at least two disease modifying medication and about 45% on three different disease modifying medication. Hydroxychloroquine, was the most frequently used disease modifying drug (73%), followed by steroid (65.1%). Only 6.3% of participants were not on disease modifying medication.

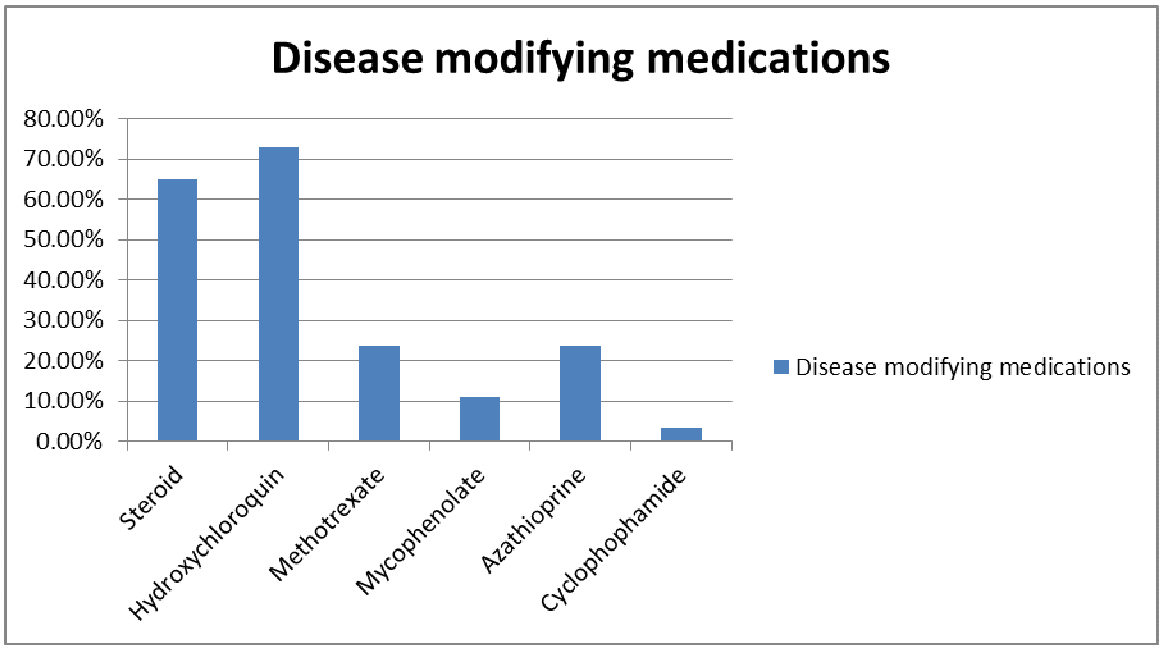

Figure 2A: Disease modifying medications used by participants

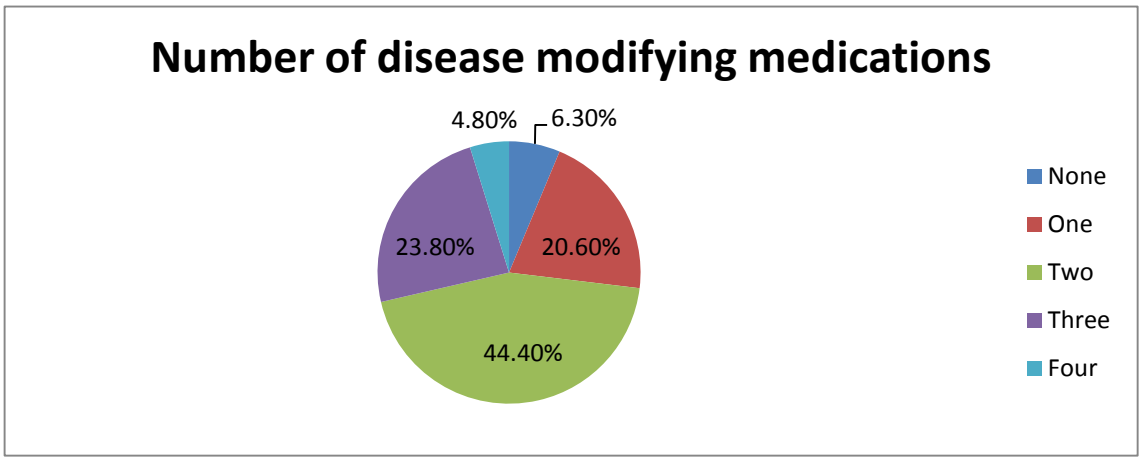

Figure 2B: Number of disease modifying medications used by participants

10.3 Echocardiography Findings

The overall prevalence of cardiac abnormalities detected by echocardiography was 88.9% (CI 81.5 - 95.6) with the major contributors to this high prevalence being clinically insignificant pericardial thickening and valvular thickening. The pericardial and valvular thickening were referred to as clinically insignificant because there was no associated clinical or echocardiographic feature of constrictive pericarditis associated with the pericardial thickening and only a third of the thickened valves had concomitant insufficiency.

10.3.1 Pericardial Assessment

Pericardial thickening was the most common abnormality detected among participants in the study with a prevalence of 77.8%. The pericardial thickening was not associated with clinical or echocardiographic feature suggestive of constrictive pericarditis. Significant pericardial effusion was detected in only one participant and was not associated with any clinical or echocardiographic feature of tamponade. None of the participants was found to have pericardial calcification on echocardiography.

10.3.2 Myocardial Function

There was generally good systolic function among participants with only 11.1% of participants having systolic dysfunction. Diastolic dysfunction on the other hand was more prevalent in this population of SLE patients, with a prevalence of 50.8% and the most prevalent type being type I diastolic dysfunction, making up 50% of all diastolic dysfunction, followed by type II making up 37.5%. Details of systolic and diastolic dysfunction are outlined in table 2.

Table 2: Systolic and diastolic dysfunction

Variable		**Frequency (%)**
Systolic dysfunction		7 (11.1)
	Fractional shortening ‹29% Mean fractional shortening (SD	7 (11.1) 34.7 (4.4)
	Ejection fraction ‹ 50% Mean ejection fraction (SD)	1 (1.6) 64.4 (4.4)
Diastolic dysfunction		32 (50.8)
Type (n = 32)	Type I	16 (50)
	Type II	12 (37.5)
	Type III	4 (12.5)

10.3.3 Valvular Assessment

The overall prevalence of valvular abnormalities detected in the study population was 88.9% (table 3). The valvular abnormalities found in this cohort of SLE patients were valvular

thickening and regurgitation, the mitral valve being the most commonly affected. Mitral valve thickening was found in 69.8% and mitral regurgitation in 30.2% of study participants. Among participant with mitral insufficiency, 94.7% had grade I mitral insufficiency. All patients found to have tricuspid regurgitation had associated high pulmonary pressure and therefore considered not to be due to the direct effect of SLE on the valves. No participant was found to have vegetation or stenosis of any valve. 6.3% were found to have aortic regurgitation.

Table 3: Valvular abnormalities

Variable	**Frequency (%)**
Valvular abnormalities	56 (88.9%)
Mitral valve thickening	44 (69.8)
Mitral regurgitation	19 (30.2)
Mitral stenosis	0
Mitral vegetation	0
Aortic valve thickening	16 (25.4)
Aortic regurgitation	4 (6.3)
Aortic stenosis	0
Aortic vegetation	0
Tricuspid stenosis	0
Tricuspid Vegetation	0
Pulmonary regurgitation	1(1.6)
Pulmonary stenosis	0
Pulmonary vegetation	0

10.3.4 Pulmonary Pressure

Of the 63 participants in the study, 14 (22%) were found to have pulmonary hypertension and 2 (3.2%) had likely pulmonary hypertension (figure 3). One of the participants with likely pulmonary hypertension had clinical and echocardiographic features of right ventricular dysfunction at the time of evaluation.

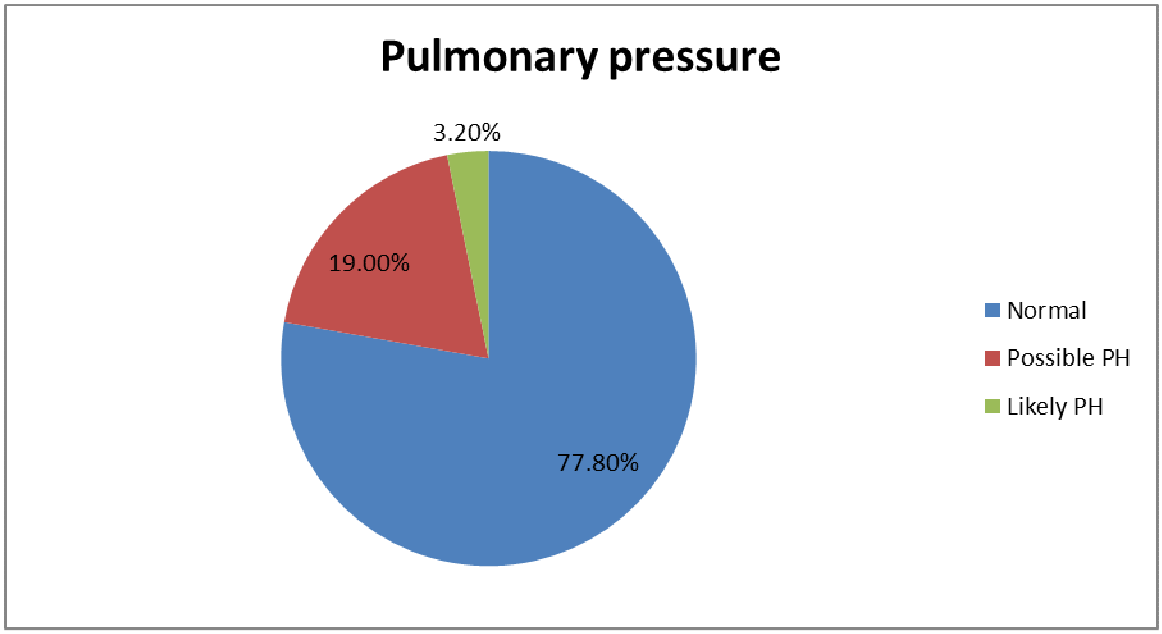

Figure 3: Pulmonary pressure

10.4 Associations

A positive association was found between age at diagnosis and diastolic dysfunction, with the mean ages for participants with and without diastolic dysfunction being 36.7 and 28.7 (p value 0.001). There was no association between diastolic dysfunction and the other demographic and clinical features including use of hydroxychloroquine, as depicted in table 4. Similarly no association was found between either valvular abnormalities or pulmonary hypertension and any of the demographic or clinical features evaluated in the study.

Table 4: Associations with Diastolic dysfunction

Variable	Diastolic dysfunction		OR (95% CI)	P value
	Yes (n=32) n (%)	No (n=31) n (%)		
Age at diagnosis Mean (SD)	36.7 (9.1)	28.7 (8.5)	-	0.001
Duration since diagnosis Median (IQR)	42.0 (16.5-66.0)	33.0 (14.0-65.0)	-	0.767
Arthritis				
Yes	19 (54.3)	16 (45.7)	1.4 (0.5-3.7)	0.535
No	13 (46.4)	15 (53.6)	1.0	
Mucocutanous involvement				
Yes	12 (50.0)	12 (50.0)	1.0 (0.3-2.6)	0.921
No	20 (51.3)	19 (48.7)	1.0	
Raynaud's phenomenon				
Yes	15 (53.6)	13 (46.4)	1.2 (0.5-3.3)	0.693
No	17 (48.6)	18 (51.4)	1.0	
Serositis				
Yes	8 (80.0)	2 (20.0)	4.8 (0.9-25.0)	0.082
No	24 (45.3)	29 (54.7)	1.0	
Hydroxychloroquin				
Yes	23 (50.0)	23 (50.0)	0.9 (0.3-2.7)	0.836
No	9 (52.9)	8 (47.1)	1.0	

11.0 DISCUSSION

We found an overall prevalence of echocardiographic abnormalities in this population of SLE patient to be 88.6%. This represents a composite of pericardial, myocardial and valvular abnormalities as well as pulmonary hypertension. We included the whole spectrum of cardiac abnormalities that could be evaluated by echocardiography, to provide base line data that could serve as a frame work from which further studies on specific cardiac abnormalities could spring forth. The high prevalence was mostly driven by clinically insignificant pericardial thickening and valve thickening. The pericardial and valvular thickening are described as clinically insignificant because none of the participants with pericardial thickening had any clinical or echocardiographic finding of constrictive pericarditis and only about a third of participants with valvular thickening had concomitant valvular regurgitation. The overall prevalence of cardiac abnormalities in this study is similar to a study by Shazzad et al (17) that reported a prevalence of echocardiographic abnormalities among SLE patient of 80%, using similar echocardiographic modalities and covering a similar spectrum of cardiac abnormalities.

The pericardium is the most commonly affected cardiac constituent in SLE, with over half of patients having an episode of pericarditis during the course of their illness (14). Being a sequel of pericarditis, it is not surprising that we found pericardial thickening in 77.8% of participants in this study. The pericardial thickening found in this cohort of SLE patient was not associated with any clinical or echocardiographic feature of constrictive pericarditis. This is in keeping with the natural history of pericarditis in SLE, which is usually acute, occurs during flairs and rarely progress to constrictive pericarditis (57). Significant pericardial effusion was found in only 1.6% of the study participants, which is indicative of active pericarditis. This low prevalence of pericardial effusion could probably be explained by the fact that majority of the participants were on two or more disease modifying agents, with only 6.3% not on any disease modifying medication at the time of the study. In a study done in Egypt, Shahin et al (18) found pericardial effusion in 19% of SLE patients which is relative high, however the medication profile of the participants was not reported.

Myocardial dysfunction in SLE is a consequence of several factors including direct effect of SLE on the myocardium, premature atherosclerosis and side effects of some of the medications used to treat the condition, specifically hydroxychloroquine and cyclophosphamide. Myocardial dysfunction in SLE patients presents majorly as diastolic

dysfunction and in the majority of patients it is asymptomatic. In our study we found a generally good systolic function among SLE patient with only 11.1% with mild systolic dysfunction. Most of the systolic dysfunction was accounted for by subtle reduction in fractional shortening. This is comparable to a similar study in Bangladesh that reported systolic dysfunction in 8% (17) of SLE patients. Shahin et al (18) found an even lower prevalence of systolic dysfunction at 4.8% among of SLE patient at a university clinic in Cairo. With regards to diastolic function we found a higher proportion of diastolic dysfunction at 50.8%. Diastolic dysfunction was found to be associated with older age at diagnosis of SLE. Even though the study was not adequately powered to assess association, this finding is consistent with the natural course of diastolic function, which is known to deteriorate with advancing age. However no association was found between diastolic dysfunction and use of hydroxychloroquine. The high proportion of diastolic dysfunction was not surprising considering the multiple risks for myocardial dysfunction associated with SLE including direct inflammation, hypertension and premature atherosclerosis. Shiruli et al (58) in a Master of Medicine thesis looked at cardiovascular risk factors in this same cohort of patients and found a high prevalence of cardiovascular risk factors, namely; hypertension (42.5%), dyslipidemia (74.2%) and carotid plaque (22.9%). Thus the high proportion of diastolic dysfunction may represent a preclinical consequence of these multiple cardiovascular risk factor in this cohort of SLE patients.

To further explain the high proportion of diastolic dysfunction, we used E wave deceleration time and isovolumetric relaxation time in addition to E and A velocities across the mitral valve to assess diastolic function, resulting in a high sensitivity for picking up diastolic dysfunction. Shazzad et al in a similar study in Bangladesh, using similar parameters found diastolic dysfunction in 72%. Other studies using only E and A velocities across the mitral valve have reported lower frequencies of diastolic dysfunction. The high prevalence of diastolic dysfunction should be a cause for concern because of the potential to progress to diastolic heart failure. Diastolic heart failure preferably referred to as heart failure with preserved ejection fraction is frequently encountered in elderly patients with multiple comorbidities and associated with similar mortality rates as heart failure with reduced ejection fraction. However, to date no medical therapy has been shown to confer survival benefit to patients with heart failure with preserved ejection fraction. Thus long term prospective studies are needed determine the course of diastolic dysfunction and evaluate interventions to prevent the development of diastolic dysfunction in SLE patients.

The most characteristic cardiac lesion in SLE as described by earlier studies in this condition is Libman-Sack endocarditis. However with the wide spread use of disease modifying medications in SLE the verrucous vegetations of Libman-sack endocarditis are rarely seen. The predominant valvular lesions seen among SLE patients in the era of disease modifying drugs are valvular thickening and regurgitation. In this study we found valvular lesions in 88.9% which was relatively high. The majority of these valvular lesions were valvular thickening with no associated valvular regurgitation. We used similar cut offs for valvular thickening as was used in a study done in Canada by Bourre-tessier et al (36) that found valvular abnormalities in only 40.1%. From our study we cannot determine the exact reason for this high prevalence of valvular thickening in this population. However, a plausible explanation would be subclinical rheumatic heart disease contributing to the high prevalence of valvular thickening, since this condition is prevalent in our setting and also predominantly affects the valves on the left side of the heart. There is no local data documenting the prevalence of subclinical rheumatic heart disease in Kenya. However worldwide estimates demonstrate the highest prevalence of rheumatic heart disease in Sub-Saharan Africa, at a rate of 5 to 7 per thousand (59). Okello et al (60) in a study done in Uganda to determine the burden, risk factors and outcome of rheumatic heart disease, found a prevalence of 14.6 per thousand which is twice the estimate for Sub-Saharan Africa.

The most commonly affected valve in our study was the mitral valve with 69.8% having mitral thickening and 30.2% having mitral regurgitation. Bourre-Tessier et al (36) also found the mitral valve to be the most commonly affected valve with mitral valve thickening found in 25.4% and mitral regurgitation in 25.8%. We did not find any association between valvular abnormality and disease duration, age at diagnosis or clinical features, however our study is not adequately powered to assess the associations. Also, with regards to the disease modifying medications, we only documented the medications the patient were taking at the time they were being evaluated for the study and therefore cannot assess how long they have been on the medications and their adherence to the medications. Bourre-Tessier et al (36) found use of corticosteroid for the last one year to be associated with valvular insufficiency. Other studies have also demonstrated association between valvular abnormalities and level of ant-Ro/SS-A and anti-La/SS-B antibodies (18)

Pulmonary hypertension was found in 22.2% of participants in our study. This is similar to the proportion of PH found by Bourre-Tessier et al (36) among SLE patients in Canada, but

significantly higher than the 0.5 – 14% (9, 10) generally reported in literature. Though majority of them (85%) are classified as possible pulmonary hypertension, this is a significant finding because of the substantial morbidity and mortality associated with pulmonary hypertension in patients with SLE. Pulmonary hypertension is the most severe form of lupus associated pulmonary involvement, with poor long term outcome despite a number of therapeutic interventions. The mean survival from onset of pulmonary hypertension is two years (11). We did not find any association between raised pulmonary pressure and any of the demographic or clinical factors evaluated. Though our study is not adequately powered, pulmonary hypertension is known to occur at any time during the course of SLE and can in some cases be the initial presentation of the disease condition. It has also been shown not be associated with disease activity or extra pulmonary manifestations (61).

The finding of pulmonary hypertension in 22% has significant implication on the long term outcome of this cohort of patients, considering the morbidity and mortality associated with this complication of SLE. Even though valvular insufficiency and diastolic dysfunction in this cohort of patients were subclinical, there is the potential for progression of valvular insufficiency and deterioration of diastolic dysfunction to diastolic heart failure. These findings underscore the usefulness of screening SLE patients for cardiovascular involvement. They also offer an opportunity for interventions to prevent or forestall cardiovascular disease associated morbidity and mortality among SLE patients.

12.0 CONCLUSION

The study demonstrates a high prevalence of cardiac abnormalities among SLE patient despite being on disease modifying medications. Even though the majority of these abnormalities comprised of clinically insignificant pericardial and valvular thickening, the prevalence of valvular insufficiency and pulmonary hypertension are substantially high and relatively higher than the prevalence seen in other studies in the case of pulmonary hypertension.

13.0 RECOMMENDATIONS

We recommend base line cardiovascular assessment including echocardiographic evaluations for all SLE patients and regular follow up evaluations for those found to have significant valvular lesions and/or pulmonary hypertension.

We also recommend further studies to describe clinical and laboratory parameters associated with various cardiac abnormalities in SLE.

Finally we recommend studies be undertaken to determine the progression and outcome of cardiac abnormalities seen SLE patients in our setting.

14.0 LIMITATIONS

Echocardiography is generally not the preferred imaging modality to assess pericardial or valvular thickness because of its inherent inaccuracy for measurements less than 5mm, variable image quality and inter and intra observer variability.

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16.0 APPENDICES

16.1 Appendix 1: American College of Rheumatology Diagnostic Criteria for SLE

The diagnosis of lupus is based on both clinical features and laboratory findings. The diagnosis of SLE is satisfied when 4 of 11 of these criteria are present.

Cutaneous	1. Malar rash: fixed malar erythema, flat or raised
	2. Discoid rash: erythematous raised patches with keratic scaling and follicular plugging; atrophic scarring may occur
	3. Photosensitivity: skin rash as an unusual reaction to sunlight; diagnosed by patient history or physician observation
	4. Oral ulcers: oral or nasopharyngeal ulcers, usually painless; observed by physician
Systemic	1. Arthritis: nonerosive, involving ≥ 2 peripheral joints; characterized by tenderness, swelling, effusion
	2. Serositis: pleuritis (convincing history of pleuritic pain or rub heard by physician, or evidence of pleural effusion) or pericarditis (documented by electrocardiogram, rub, or evidence of pericardial effusion)
	3. Renal disorder: persistent proteinuria (> 0.5 g/d or > 3+) or cellular casts of any type
	4. Neurologic disorder: seizures or psychosis in the absence of other causes
Laboratory	1. Hematologic disorder: hemolytic anemia or leukopenia (< 4000/mm^3 on 2 occasions), lymphopenia (< 1500/mm^3 on 2 occasions), or thrombocytopenia (< 100,000/µL in the absence of offending drugs)
	2. Immunologic disorder: anti-dsDNA or anti-SM, or antiphospholipid antibodies (abnormal IgM or IgGanticardiolipin antibody, lupus anticoagulant, or false-positive syphilis serology)
	3. ANA in the absence of drugs known to be associated with the “drug-induced lupus syndrome”

ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded DNA; anti-SM = anti-Smith antibody; IgG = immunoglobulin

If 4 of these criteria are present or well documented at any time in a patient’s history, the diagnosis is likely to be SLE. Specificity is 95%; sensitivity is 75%.

16.2 Appendix 2: Statement of Information and Consent Form

Statement of Information for Patients Participating In the Study

Introduction

I, Dr. Sorie Conteh, a post graduate student in Internal Medicine at the University of Nairobi, would like to introduce you to a study that I will be undertaking entitled Echocardiographic abnormalities in systemic lupus erythematosus (SLE) patients at Kenyatta National Hospital.

SLE is a multisystem inflammatory disease that affects almost every organ system in the body. The heart is among the organs affected by SLE and is responsible for significant disability and death. Early diagnosis will help doctors initiate treatment and institute preventive measures to halt or delay progression of heart disease.

What is the study about?

The study seeks to document the prevalence of heart involvement among SLE patients in our population.

What does the study entails?

You will be required to give history about your condition and undergo a physical examination. Thereafter you will undergo an echocardiography study by a cardiologist, which will help identify abnormalities caused by SLE. All findings will be explained to you by the cardiologist after the study. In case of any detected abnormality requiring immediate intervention, you will be referred to the appropriate clinic.

What will I benefit from the study?

The information gathered from the study will help your doctors institute measures to treat or prevent progression of any diagnosed heart disease. The cost of the echocardiogram will be incurred by the principal investigator.

Are there any risks involved?

There is no risk involved; echocardiography is a routine non-invasive heart assessment. It is painless and has no short or long term harmful effects on your body.

Voluntary participation

Your participation in this study will be voluntary. If you choose to participate, you will be required to sign a consent form to give us permission to include you in the study. You are free to withdraw from the study and this shall not affect your care or treatment.

Confidentiality

All information gathered during the study will be kept confidential. A report of the echocardiography will be made available to your attending physician to aid in your management.

You are free to ask questions before signing the consent form.

For any further queries that you or your health care giver have, you can contact the principal investigator on 0715179843. OR

The Chairman of Ethical and Review Committee

Kenyatta National Hospital

Tel:254 020 2726300, Ext 44355, 726300-9

CONSENT FORM

I……
Age…….Tel……

Has been requested to take part in the study evaluating cardiac abnormalities in systemic lupus erythematosus patients attending Kenyatta National Hospital.

This will involve taking a history, doing a physical examination and heart evaluation by echocardiography. I also understand that my consent is voluntary and that I can withdraw from the study at any time without any penalty.

I therefore consent to be recruited into the study

Sign…… Date……

INVESTIGATOR'S STATEMENT

I the investigator have educated the research participant on the purpose and applications of this study.

Signed…… Date……

For further enquiries during the course of the study, contact the following:

Principal Investigator

Dr. Sorie Conteh

Mobile: 0715179834

Lead Supervisor

Prof. E.N. Ogola

Dept. of Clinical Medicine, UON

Mobile: 0722737944

The Secretary

KNH/UON Ethics and Review Committee

Tel: 2726300, Ext: 44102

16.3 Appendix 3: Clinical Data Collection Form

1.
2. **DEMOGRAPHIC** **Study No…….**

i) Date of birth……. ii) Gender: M F

v) Date of SLE diagnosis……. vi) Age at diagnosis……

Vii) Duration of Illness……

3. **MEDICATIONS**

Prednisone

Methyl-prednisone

NSAID

Hydroxychloroquine

Methotrexate

Cyclosporine

Balimumab

Mycophenolate

Azathioprine

4. **CLINICAL FEATURES**

Feature	**History**	**Examination**
Arthritis		
Mucocutanous involvement		
Raynaud's phenomenon		
Serositis		

16.4 Appendix 4: Echocardiography Report Form

PERICARDIAL ASSESSMENT

Pericardial Effusion

‹ 5mm

5 – 10mm

› 10mm

Pericardial thickness

‹ 3mm

› 3mm

Pericardial Calcification

Yes No

SYSTOLIC FUNCTION

Fractional Shortening……%

Ejection Fraction……%

DIASTOLIC FUNCTION

E velocity……....m/s

A velocity……m/s

E/A Ratio……

Dct…….sec

IVRT……..sec

E' velocity……m/s

A' velocity……m/s

VALVULAR ASSESSMENT

Mitral Valve

Valve thickness……mm

Vegetation: No Yes

Regurgitation: No Yes

Grade……

Stenosis: No Yes

Orifice area……..cm^2

Mean Gradient……..mmHg

Aortic Valve

Valve thickness……..mm

Vegetation: No Yes

Regurgitation: No Yes

Pressure half time……..

Stenosis: No Yes

Peak gradient……mmHg

Max Velocity……..m/s

Pressure half time……sec

Tricuspid Valve

Vegetation: No Yes

Regurgitation: No Yes

Stenosis: No Yes

Pulmonary valve

Vegetation: No Yes

Regurgitation: No Yes

Stenosis: No Yes

PULMONARY PRESSURE

Peak tricuspid regurgitant velocity……m/s

Pressure gradient between RV & RA……mmHg

Systolic pulmonary arterial pressure……..mmHg

Pulmonary Regurgitation velocity……..m/s

Deceleration time of RV ejection……sec

KNH/UON-ERC APPROVAL

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Ref: KNH-ERC/A/400 Link:www.uonbi.ac.ke/activities/KNHUoN 23rd December 2014

Dr. Sorie Conteh
Dept.of Clinical Medicine & Therapeutics
School of Medicine
University of Nairobi

Dear Dr. Conteh

Research proposal: Echocardiographic abnormalities in Systemic Lupus Erythematosus Patients at Kenyatta National Hospital (KNH) (P500/08/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 23rd December 2014 to 22nd December 2015.

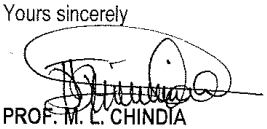
This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

"Protect to Discover"

Yours sincerely



PROF. M. L. CHINDIA
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