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Echocardiographic findings in patients with rheumatoid arthritis attending the rheumatology clinic at the Kenyatta National Hospital

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Abstract

Objectives: To determine the prevalence of echocardiographically detected cardiac abnormalities in patients with Rheumatoid Arthritis (RA) at Kenyatta National Hospital (KNH).

Design: Cross-sectional descriptive study.

Setting: Rheumatology clinic at Kenyatta National Hospital.

Subjects: One hundred and four rheumatoid arthritis patients who gave consent/assent.

Results: One hundred and four RA patients fulfilled the inclusion criteria with a mean age of 51 years and a female to male ratio of 25:1. The prevalence of echocardiographic abnormalities was found to be 62.5% and was unrelated to CDAI and duration of disease. The most common cardiac lesion was pericardial effusion at 39.4%. The tricuspid valve was the most commonly affected valve with 15.4% having Tricuspid Regurgitation (TR). Pulmonary hypertension was found in 5.5% of patients.

Conclusion: This study shows a high prevalence of cardiac abnormalities among RA patients despite these patients being on disease modifying medications and being diagnosed relatively earlier. Majority of the patients were in remission with duration of illness less than 5 years.

Introduction

Rheumatoid Arthritis (RA) is a progressive, systemic autoimmune disease characterized by chronic inflammation of multiple joints with associated systemic manifestations. RA is associated with many extra-articular clinical manifestations and various organ involvement including the skin, eye, heart, lung, hematopoietic tissue, renal, nervous and gastrointestinal systems¹. Extra-articular manifestations of RA occur in about 40% of patients, either at the beginning or during the course of their disease².

The disease is associated with a high risk for morbidity and premature death

secondary to the earlier development of cardiovascular diseases. Cardiac manifestations are observed in RA patients and echocardiography is the method of choice to detect pathologies in the morphology and function of heart. A wide range of spectrum of cardiac abnormalities has been described in various cohorts of RA³.

The most common cardiac involvement in RA is pericarditis and various studies have reported an increase in the prevalence in patients with seropositive RA and it is usually clinically silent⁴. A study in South Africa done by Mody⁵ using two dimensional (2D) echocardiogram to determine the presence of pericardial effusion revealed a 6% prevalence in the RA cohort that was studied. Pericardial disease was detected in 5.5% of RA patients in a study done in Turkey using standard echocardiographic findings⁶.

Myocardial disease in RA is typically clinically silent and only manifests as myocardial dysfunction after a prolonged preclinical phase⁷. Manuela di Franco *et al*⁷ studied 32 patients with RA in Italy and found left ventricular filling abnormalities characterised by a reduced transmitted flow velocity (E/A) ratio versus controls. They concluded that RA patients, in absence of clinical evidence of heart disease, show diastolic dysfunction characterised by impaired E/A and systolic/diastolic (S/D) ratio.

Cardiac tissues especially valve leaflets are extremely vulnerable to the process of inflammation and autoimmunity⁸. In a study by Beckhauser *et al*⁹, valve involvements in RA patients were investigated and 15.2% were recognized with valve disease⁹. Valve damages were more common in patients whose disease was of more than 15 years duration and the aortic valve was most commonly involved⁹. A study conducted by Guedes *et al*¹¹ revealed that the number of valves involved increased with advancing age but was unrelated to disease duration¹⁰. Regurgitation is the most common form of valve disease,

although stenosis has been reported¹¹. The mitral valve was selectively involved in the RA patients studied by Guedes *et al*¹⁰, and mitral valve disease was significantly more common in the RA group than in the control group.

Pulmonary involvement is common among patients with RA and has a variety of manifestations including pulmonary hypertension. Dawson *et al*¹² in the United Kingdom studied raised pulmonary artery pressures measured with doppler echocardiography in 146 RA patients. Twenty one percent of all the RA patients had pulmonary hypertension without significant cardiac disease or lung disease evident on pulmonary function testing.

Two dimensional (2D) echocardiography is a non-invasive procedure capable of displaying a cross-sectional view of the heart, including the chambers, valves and the major blood vessels that exit from the left and right ventricle. It is particularly useful in detecting various valvular lesions, measuring the left ventricular ejection fractions, determining myocardial wall abnormalities and also measuring the pulmonary pressures and detecting the presence of pericardial effusions

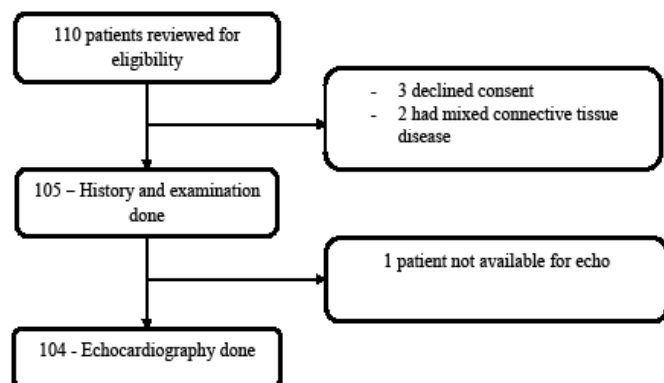
Materials and Methods

The study population was RA patients on follow up at KNH. Current hospital records show that there are 146 RA patients attending the rheumatology clinic. A sample of RA patients derived from this finite population (n=104) was subjected to a non-invasive 2D echocardiograph for the determination of cardiac abnormalities. Consecutive sampling method was used to recruit patients with RA who visited the KNH Rheumatology Clinic.

Results

Between 16th December 2015 and 17th March 2016, 110 patients being managed for RA at KNH were screened for study eligibility, of these 104 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 with 6 patients excluded. All 104 subjects had echocardiography studies done and were included in the analysis as depicted in Figure 1.

Figure 1: Flow chart of patients screening and enrolment process



A. *Demographics and duration of disease:* The mean age of the study sample was 51.0 years. The cohort in this

study as expected was predominantly female with a ratio of 25:1. Majority of the patients had RA disease duration of > 1 year (84.6%) (Table 1).

Table 1: Patients demographic characteristic and duration of disease

Variable	Frequency (%) n = 104
Age (years)	
Mean age (SD)	51.0 (16.4)
Min-Max	13-88
Gender	
Male	4 (3.8)
Female	100 (96.2)
Duration of disease	
Less than 1 year	16 (15.4)
1 to 5 years	48 (46.2)
6 to 10 years	31 (29.8)
>10 years	9 (8.6)

B. *Clinical variables:* Fifty one percent of all patients were on at least 2 combination Disease Modifying Anti Rheumatic Drugs (DMARD's) (45.2% on 2 and 5.8% on 3 DMARDs respectively). Forty nine percent of patients were on a single DMARD and the most frequently used DMARD was hydroxychloroquine. Frequency of patients on methotrexate was 22.2%. Leflunomide as the other DMARDs used by this population was 18.3% (Table 2).

Table 2: Frequency of DMARDS used by patients

Number of drugs	Frequency (%) n=104
1	51 (49.0)
2	47 (45.2)
3	6 (5.8)
DMARDS	
Hydroxychloroquine	39 (37.5)
Methotrexate	8 (7.7)
Leflunomide	4 (3.8)
Hydroxychloroquine+ Methotrexate	9 (8.7)
Hydroxychloroquine+ Leflunomide	38 (36.5)
Hydroxychloroquine+ Methotrexate+ Leflunomide	6 (5.8)

C. *Echocardiographic findings:* The overall prevalence of cardiac abnormalities detected by echocardiography was 62.5% (CI 52.9 – 72.1) with the major contributors to this high prevalence being pericardial effusion and type 1 diastolic dysfunction. However both the pericardial effusion and type 1 dysfunction were regarded to as clinically insignificant because there were no associated features or echocardiographic feature of constrictive pericarditis or tamponade associated with the pericardial effusion and all the patients with type 1 diastolic failure were at NYHA grade 1 with no other features of decompensation (Table 3).

Table 3: Frequency of cardiac abnormalities

Variable	Frequency (%)	95% CI
Cardiac abnormalities		
Abnormal	65(62.5)	52.9-72.1
Normal	39(37.5)	27.9-47.1

D. *Pericardial assessment:* Pericardial effusion was the most common abnormality detected among patients in the study with a prevalence of 39.4%. The pericardial effusion in this subset of patients was graded as mild effusion (<5mm) as it was not associated with clinical or echocardiographic feature suggestive of constrictive pericarditis. No pericardial thickening was observed in the study and none of the patients was found to have pericardial calcification on echocardiography.

Table 4: Pericardial abnormalities

Variable	Frequency (%) n=104	95% CI
Pericardial effusion	41 (39.4)	34.0-53.2
Pericardial effusion size		
<5mm	102 (98.1)	95.2-100.0
>10mm	2 (1.9)	0-4.8

E. *Myocardial function:* There was generally good systolic function among patients with only 2.9% of patients having systolic dysfunction characterized by an ejection fraction of less than 50%. Diastolic dysfunction on the other hand was more prevalent in this population of RA patients, with a prevalence of 22.1%, of which type 1 diastolic dysfunction was predominant (20.2%).

F. *Valvular assessment:* The overall prevalence of valvular abnormalities detected in the study population was 30.8%. The valvular abnormalities found in this cohort of RA patients were predominantly tricuspid valve regurgitation at 15.4%. All patients found to have tricuspid regurgitation had a mild regurgitation as it was not necessarily associated high pulmonary pressure. Mitral valve regurgitation was found in 5.8% and mitral stenosis in 1.9% of study patients. Among patients with mitral insufficiency, 66.7% had grade I mitral insufficiency and 33.3% had grade 2 insufficiency. 6.7% of patients were found to have aortic valve regurgitation and all were graded as mild regurgitation as it was not associated with LV dilatation (Table 5).

Table 5: Valvular abnormalities

Variable	n =28
Valvular abnormalities	28
Mitral regurgitation	6
Grade I	4
Grade II	2
Mitral stenosis	2
Mild	2
Aortic regurgitation	7
Mild	7
Aortic stenosis	0
Tricuspid regurgitation	12
Mild	9
Moderate	3
Stenosis	0
Pulmonary regurgitation	1
Mild	1
Pulmonary stenosis	0

G. *Pulmonary pressure:* Of the 104 patients in the study, 5.5% had pulmonary hypertension of which only one patient was associated with pulmonary regurgitation.

H. *Number of cardiac lesions:* Fifty five point four percent of patients with cardiac abnormalities were found to have more than one abnormality (35.4% with 2 cardiac abnormalities and 13.0% with 3 cardiac abnormalities). Forty four point six percent of the patients had only one abnormality detected on echocardiograph.

Table 6: Number of cardiac abnormalities

Number of cardiac abnormalities	Frequency (%) n = 65
1	29 (44.6)
2	23 (35.4)
3	13 (20.0)

I. *Clinical Disease Activity Index (CDAI):* Using the tool to determine the clinical activity 60.5% of all patients were in remission, 30.8% had low activity and only 8.7% had moderate activity.

J. *Associations:* The mean age at diagnosis was comparable between those who had cardiac abnormalities and those who do not have any cardiac abnormality at 51.5 and 50.2 respectively. This explorative study was not powered to make any associations between cardiac abnormalities, CDAI and duration of disease due to a small sample size. There was no association of overall cardiac abnormalities with the other variables in this study.

Patients with RA less than 1 year had cardiac abnormalities that are comparable to the general population (Table 7). The results of this study also did not show any association between cardiac abnormalities and the various drug combinations used in this cohort. Mild pericardial effusion being the most common abnormality detected in this cohort had no significant associations with both demographic and clinical variables.

Table 7: Associations of demographic and clinical variables with cardiac abnormalities

Variable	Cardiac abnormality		OR (95% CI)	P value
	Abnormal	Normal		
Age at diagnosis, mean (SD)	51.5 (16.7)	50.2 (15.1)	-	0.701
CDAI				
Remission	39 (61.9)	24 (38.1)	1.0	0.811
Low activity	19 (59.4)	13 (40.6)	0.9(0.4-2.1)	0.354
Moderate activity	7 (77.8)	2 (22.2)	2.2(0.4-11.2)	
Duration of disease				
< 1 year	11 (68.8)	5 (31.2)	1.0	0.551
1 to 5 years	29 (60.4)	19 (39.6)	0.7 (0.2-2.3)	0.475
6 to 10 years	18 (58.1)	13 (41.9)	0.6 (0.2-2.3)	0.629
>10 years	7 (77.8)	2 (22.2)	1.6 (0.2-10.6)	

Discussion

The overall prevalence of echocardiographic abnormalities amongst 104 RA patients was 62.5%. This represents a composite of pericardial, myocardial, valvular abnormalities and pulmonary hypertension. The whole spectrum of structural and functional cardiac abnormalities that could be evaluated by echocardiography was included in the study, as to provide data that could serve as the basis for future research on cardiac abnormalities in this cohort. The prevalence of cardiac abnormalities in our study is similar to a study done in South Africa by Schorn *et al*¹³, who performed echocardiograph in 44 rheumatoid arthritis patients and showed a 73% overall cardiac abnormalities. A large number of patients in this study (55.4%) had more than one cardiac abnormality and this is also in keeping with the natural history of the chronic inflammatory state of the disease affecting all structures of the heart and the combination DMARD's used amongst these patients.

The high prevalence was mostly driven by clinically insignificant pericardial effusion and type 1 diastolic dysfunction. The pericardial effusion was graded as mild effusion as the size was less than 5mm. Type 1 diastolic dysfunction is a nonspecific echocardiographic finding 20.2% of the study population with no associated clinical features suggestive of overt heart failure. Schorn *et al*¹³ found pericardial effusion in 32% in RA patients studying a similar spectrum of structural and functional cardiac abnormalities. Macdonald *et al*¹⁴ in California performed echocardiographic studies on 51 RA patients in a cross

sectional study and reported 31% mild pericardial effusion. Pericardial disease was detected in 5.5% of RA patients in a study done in Turkey using standard echocardiographic findings. Our study reports a high prevalence of subclinical pericardial effusion at 39.4% which could be explained by both the natural history of the disease and the various combinations of disease modifying agents used for these patients (Hydroxychloroquine, Methotrexate, etc). No pericardial thickening or calcification was noted in any of the patients.

Myocardial dysfunction in RA is a consequence of several factors including direct inflammatory process of RA on the myocardium, premature atherosclerosis and side effects of some of the medications used to treat the condition, specifically cardiotoxicity related to hydroxychloroquine use. Literature suggests that myocardial dysfunction in RA patients presents predominantly as diastolic dysfunction and in the majority of patients it is asymptomatic. In our study a generally good LV function among RA patients is reported with only 2.9% having mild LV dysfunction. 20.2% of RA patients at KNH had a type 1 diastolic dysfunction and this is much lower compared to a study done by Gabriel *et al*¹⁵ in USA who did a cross sectional community based study comparing adults with and without RA and without clinical evidence of heart failure using 2D echocardiography. Their study included 244 subjects with RA with a mean age of 60.5 years wherein they reported a 31% diastolic dysfunction which had a positive association with duration of disease¹⁵. Diastolic dysfunction in our study was not found to be associated with a prolonged duration of RA even though the natural course of diastolic function is known to deteriorate with time. Furthermore, there are no associations found between diastolic dysfunction and use of disease modifying drugs. In this study confounders such as hypertension were not assessed for but the relatively high prevalence of diastolic dysfunction should be a cause for concern because of the potential to progress to overt diastolic heart failure. Diastolic heart failure preferably denoted as heart failure with preserved ejection fraction is frequently encountered in the older patients with multiple comorbidities and associated with similar mortality rates as heart failure with reduced ejection fraction.

In a study by Beckhauser *et al*⁹, valve involvements in RA patients were investigated and 15.2% were recognized with valve disease. Valve damages were more common in patients whose disease was of more than 15 years duration and the aortic valve was most commonly involved. Valvular involvement reflects the chronic inflammatory state of the disease. There was no relationship between valve involvement and gender, age, exposure to tobacco, positive RF, presence of ANA, rheumatoid nodules, and anti-cardiolipin antibodies. Our study found a high prevalence of valvular involvement compared to other studies at 30.8%. The valvular abnormalities found in this cohort of RA patients were predominantly tricuspid valve regurgitation at 15%. Tricuspid regurgitation in this cohort was mild as determined by the echo criteria it was not

associated with pulmonary hypertension hence it may be considered to be due to the effect of RA on the valves. From our study we cannot determine the exact reason for this high prevalence of tricuspid valvular regurgitation in this population. We did not find any association between valvular abnormality and disease duration, age at diagnosis or clinical features; however our study was not powered to assess for these associations.

Dawson *et al*¹² in the United Kingdom studied raised pulmonary artery pressures measured with doppler echocardiography in 146 RA patients and 21% of all the RA patients had pulmonary hypertension without significant cardiac disease or lung disease evident on pulmonary function testing. We report a much lower prevalence of pulmonary hypertension at 5.5% with no significant association between raised pulmonary pressure and any of the demographic or clinical variables evaluated. This was graded as mild pulmonary hypertension as it was not associated with echocardiographic and clinical evidence of an associated right ventricular enlargement or right valvular lesions. Our study population was recruited at an outpatient basis and may therefore have been skewed toward the less severe end of the disease spectrum as compared with the overall population of RA patients thus explaining the above mild and clinically insignificant findings.

References

1. Cojocaru M, Cojocaru IM, *et al*. Extra-articular manifestations in rheumatoid arthritis. *Mædica*. 2010; **5**(4):286–291.
2. Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. *Curr Med Res Opin*. 2008; **24**(2):469–480.
3. Cronstein BN. Interleukin-6-a key mediator of systemic and local symptoms in rheumatoid arthritis. *Bull NYU Hosp Jt Dis*. 2007; **65** (Suppl 1):S11–15.
4. Harada T, Aoyagi T, Endo Y, Uno K, *et al*. Effusive constrictive pericarditis due to rheumatoid arthritis revealed by pericardiocentesis with simultaneous pressure recording--a case report. *Angiology*. 2002; **53**(1):105–108.
5. Mody GM. Rheumatoid arthritis and connective tissue disorders: sub-Saharan Africa. *Baillières Clin Rheumatol*. 1995; **9**(1):31–44.
6. Hakala M, Pettersson T, Tarkka M, *et al*. Rheumatoid arthritis as a cause of cardiac compression. Favourable long-term outcome of pericardiectomy. *Clin Rheumatol*. 1993; **12**(2):199–203.
7. Di Franco M, Paradiso M, *et al*. Diastolic function abnormalities in rheumatoid arthritis. Evaluation by echo Doppler transmitral flow and pulmonary venous flow: relation with duration of disease. *Ann Rheum Dis*. 2000; **59**(3):227–229.
8. Kamiński G, Makowski K, *et al*. Degenerative valvular and left ventricle structural changes in echocardiography in patients with rheumatoid arthritis. *Pol Merkur Lek Organ Pol Tow Lek*. 2005; **107**:496–498.
9. Beckhauser AP, Vallin L, Burkievcz CJ, Perreto S, Silva MB, Skare TL. Valvular involvement in patients with rheumatoid arthritis. *Acta Rheumatol Port*. 2009; **34**(1):52–56.
10. Guedes C, Bianchi-Fior P, *et al*. Cardiac manifestations of rheumatoid arthritis: A case-control transesophageal echocardiography study in 30 patients. *Arthritis Care Res*. 2001; **45**(2):129–135.
11. Beauvais C, Kaplan G. Heart valve lesions in rheumatoid polyarthritis. Apropos of 2 cases. *Rev Rhum Mal Ostéo-Articul*. 1991; **58**(1):47–51.
12. Dawson JK, Goodson NG, Graham DR, Lynch MP. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology*. 2000; **39**(12):1320–5.
13. Schorn D, Hough IP, Anderson IF. The heart in rheumatoid arthritis: an echocardiographic study. *South Afr Med J Suid-Afr Tydskr Vir Geneesk*. 1976; **50**(1):8-10.
14. MacDonald WJ, Crawford MH, Klippel JH, Zvaifler NJ, O'Rourke RA. Echocardiographic assessment of cardiac structure and function in patients with rheumatoid arthritis. *Am J Med*. 1977; **63**(6):890-896.
15. Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. *J Rheumatol*. 1999; **26**(11):2475-9.