

# Prevalence of Silent Ischemic Heart Disease in Patients of Rheumatoid Arthritis

Swapneel P Kadrekar<sup>1</sup>, Silas Supragya Nelson<sup>2</sup>

<sup>1</sup>Post Graduate Student, Department of Medicine, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India,

<sup>2</sup>Associate Professor, Department of Medicine, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

## Abstract

**Background:** Almost half of the deaths in patients of rheumatoid arthritis (RA) are due to cardiovascular diseases. Many studies have shown that patients of RA are at increased risk of mortality and morbidity from ischemic heart disease (IHD). In half of the RA patients with confirmed IHD, the disease was clinically silent. Hence, early detection of the silent IHD is important to reduce the morbidity and mortality in patients of RA.

**Objectives:** The objectives of this study were to determine the prevalence of silent IHD in RA patients, to identify the predictors of silent IHD in patients with RA and to study the correlation between silent IHD and RA disease activity.

**Methods:** A total of 50 patients with a diagnosis of RA, attending the Medicine Outpatient Department and admitted in medicine wards of N.S.C.B. Medical College and Hospital, Jabalpur (M.P), were taken into the study determining the prevalence of silent IHD in RA. All patients fulfilled the 2010 ACR/EULAR classification criteria for RA.

**Results:** Prevalence of silent IHD in RA patients in this study is 10%. There is significantly increased the incidence of silent IHD among patients with increased duration of RA, increased disease activity, and increased total cholesterol and erythrocyte sedimentation rate.

**Conclusions:** There is a quite common prevalence of silent IHD in patients with RA. The predictors for silent IHD are prolonged disease duration, high disease activity, hypercholesterolemia, and presence of high activity markers.

**Key words:** Ischemic heart disease, Rheumatoid arthritis, Silent

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder of unknown etiology marked by a symmetric, peripheral polyarthritis, and various systemic manifestations. RA patients are more prone to heart conditions such as the thickening of the artery walls (atherosclerosis) and heart attacks.<sup>[1]</sup>

The most common cause of death in RA is cardiovascular disease, accounting for more than 50% of the mortality.<sup>[2]</sup>

The risk for myocardial infarction in female RA patients is twice that of women without RA, and in long-standing disease of at least 10 years, the risk is 3 times higher. The most likely explanation is that the inflammation associated with RA has an impact on the vasculature.<sup>[3]</sup>

The pathogenic mechanisms involved in accelerated cardiovascular complications in RA appear to be complex and multifactorial. Both traditional and non-traditional risk factors potentially contribute to the increased cardiovascular risk. There is a need for heightened awareness of the increased risk for silent ischemia, early myocardial infarction, and sudden death.<sup>[4]</sup>

The underlying cause of ischemic heart disease (IHD) appears to be accelerated in patients with RA. The reason for this may be related to clustering of classical cardiac risk factors such as dyslipidemia, a prothrombotic state, and other processes.

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**Corresponding Author:** Dr. Silas Supragya Nelson, Silver Oak Compound, Napier Town, Russel crossing, Jabalpur, Madhya Pradesh, India. Phone: +91-9826111066. E-mail: silasnelson@gmail.com

However, classical risk factors, though important, do not appear to be sufficient to explain the accelerated atherosclerosis associated with RA.<sup>[5]</sup> This is possibly due to the systemic inflammation associated with RA, which may make RA itself (like diabetes) an independent risk factor for the development of IHD.<sup>[6]</sup>

## MATERIALS AND METHODS

- A total of 50 patients with a diagnosis of RA, attending the Medicine Outpatient Department (OPD) and admitted in medicine wards of N.S.C.B. Medical College and Hospital, Jabalpur (M.P), were recruited into the study, determining the prevalence of silent IHD in RA.
- All patients fulfilled the 2010 ACR/EULAR classification criteria for RA.

### Criteria for Selection of Patients

#### Inclusion criteria

Include cases of RA.

A case of RA is defined on the basis of 2010 ACR/EULAR classification criteria for RA.

#### Exclusion criteria

Include patients known to have

- IHD
- Family history of IHD (defined as a male or female first degree relative sustaining any ischemic cardiovascular disease)
- History of chronic smoking
- Diabetes mellitus (DM) (defined as fasting blood sugar (FBS) >126 mg/dl and/or symptoms of DM and random blood sugar >200 mg/dl)
- Hypertension (defined by JNC 7 criteria as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg)
- Patients with disabilities which may interfere with stress electrocardiogram (ECG) test as orthopedic or neurological disabilities.
  - All patients were subjected to full history taking including age, sex, smoking, family history of IHD, family history of RA or diabetes, RA disease duration, and presence of complications.
  - Following investigations were included in the study:
    1. Complete blood count with erythrocyte sedimentation rate (ESR)
    2. B. urea, S. creatinine
    3. Fasting lipid profile - low-density lipoprotein (LDL), high-density lipoprotein, very LDL, triglycerides, cholesterol
    4. FBS, postprandial blood sugar
    5. CRP, RA factor
    6. ECG
    7. 2D echo
    8. Treadmill test (TMT)

Disease activity in RA was measured by DAS28 score.

### Exercise TMT

- All patients were subjected to exercise treadmill stress ECG using the modified Bruce protocol.
- Heart rate, blood pressure, and a 12-lead ECG were obtained at baseline and at each stage of the exercise protocol (every 3 min)
- Target heart rate was calculated as  $220 - \text{age}$ .
- Exercise endpoints included:

Physical exhaustion, significant arrhythmia, severe hypertension (SBP >240 mmHg or DBP >110 mmHg), or severe hypotensive response (decrease >20 mmHg in SBP from baseline).

### Positive exercise ECG was defined as

- ST-segment depression of  $\geq 1$  mm which was horizontal or downsloping, lasting at least for 80 ms
- Development of sharply pointed, symmetrical, arrowhead inverted T waves
- Inversion of U waves developing after exercise
- Failure to increase or actual decrease in Q wave amplitude with exercise
- Development of LBBB with exercise.
- Lengthening of QTc interval with exercise
- Development of multiform ventricular ectopics
- Development of uniform ventricular ectopics, especially
  - If they are occurring in showers
  - If they give rise to bigeminal rhythm
  - If occurring in patient of age 40 years or more
  - If persisting for several minutes or longer
  - Silent ischemia was defined as ischemia on stress test in the absence of angina and/or ECG changes of either a bundle branch block or ST segment abnormality consistent with IHD.

## RESULTS

- Prevalence of silent IHD in RA patients in this study is 10% as shown in pie chart below [Figure 1].
- Prevalence of silent IHD in RA patients is increased with increase in disease activity [Figure 2].
- There is significant association between increased duration of RA and occurrence of silent IHD in RA patients [Figure 3].
- There is significantly increased prevalence of silent ischemic heart disease among patients with increased ESR [Figure 4].

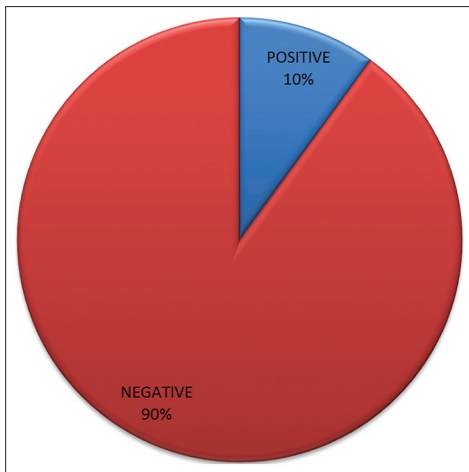


Figure 1: Silent ischemic heart disease in rheumatoid arthritis patients

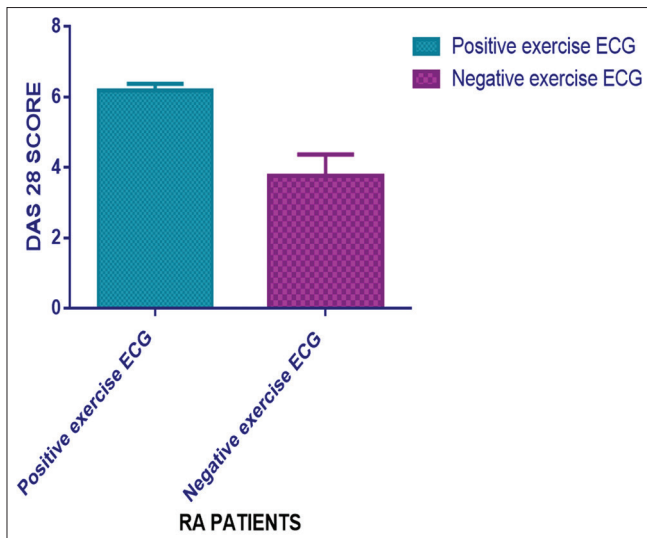


Figure 2: DAS28 score and positive exercise electrocardiogram relation

- Prevalence of silent IHD in RA patients is increased in patients with high total cholesterol.

There was no significant correlation of silent IHD in RA patients with LDL, HDL or triglycerides [Figure 5].

## DISCUSSION

- In the current study, we studied a total of 50 patients who were diagnosed as cases of RA. These patients were attending the medicine OPD and were admitted in medicine wards of N.S.C.B. Medical College and Hospital, Jabalpur (M.P) [Table 1]
- In all 50 patients studied, we did not find any evidence of IHD on ECG and 2D echo
- All these patients were subjected to undergo TMT to detect silent IHD.

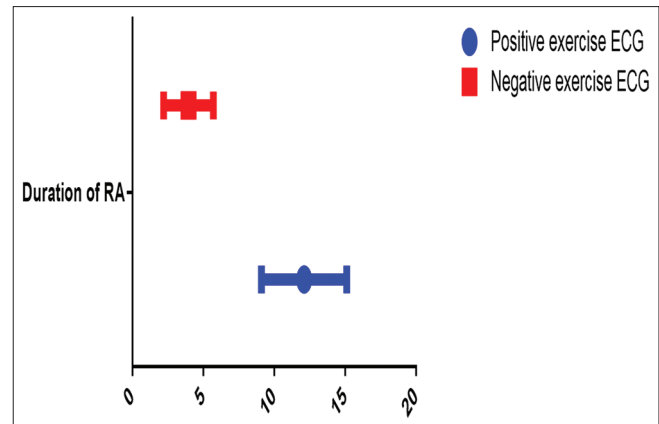


Figure 3: Duration of rheumatoid arthritis and positive exercise electrocardiogram relation

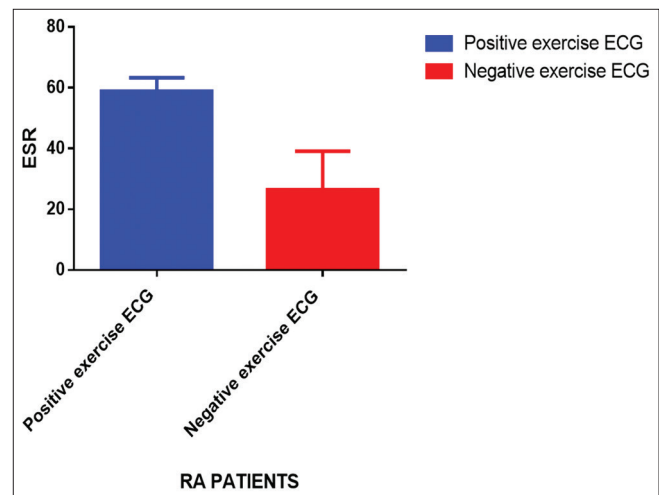
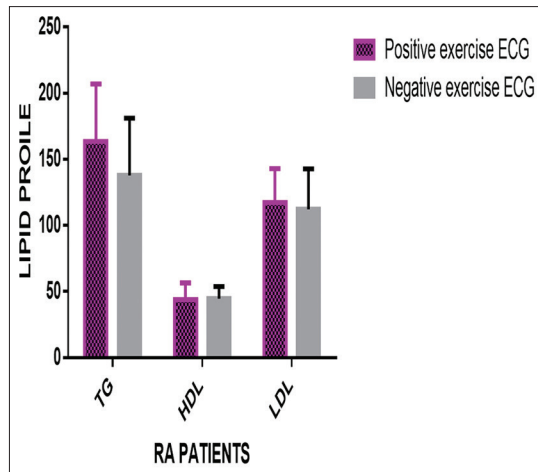
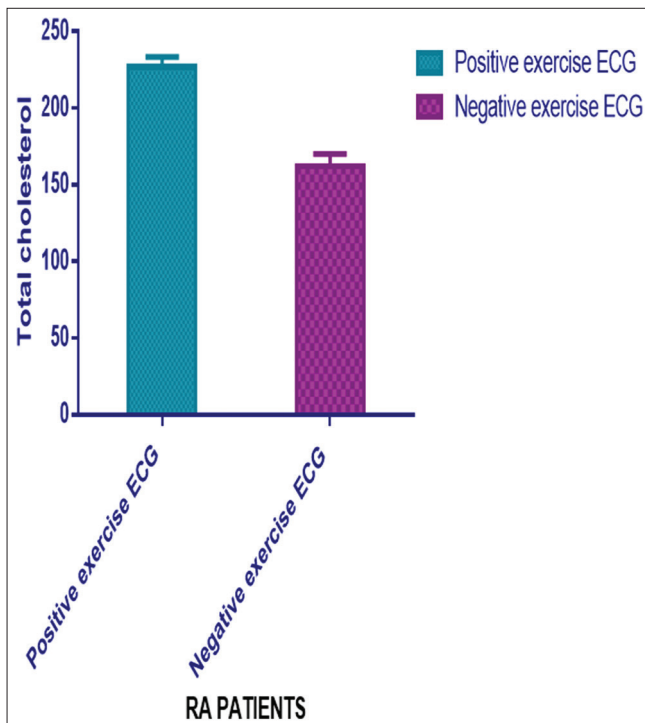


Figure 4: Erythrocyte sedimentation rate and positive exercise electrocardiogram relation

- In 5 patients, we found the TMT to be abnormal. In 4 patients, we found multifocal VPCs, and in 1 patient, we found significant ST depression. Of 5 patients who showed abnormal TMT, 4 were females and 1 was male
- Hence, in our study, we found silent IHD in 10% of the patients. These were consistent with the results of Dala *et al.*, 2012 [Figure 6].<sup>[7]</sup> They had found silent IHD in 10.6% of the patients. Maradit-Kremers *et al.*, 2005,<sup>[8]</sup> concluded that patients with RA have a significantly higher risk of CHD when compared with non-RA subjects. RA patients are less likely to report symptoms of angina and more likely to experience unrecognized MI and sudden cardiac death. RA has a greater burden of coronary atherosclerosis at their first angiogram that is independent of traditional CV risk factors. This may be due, at least in part, to the expansion of number of classic CD4+ T cells that have previously been implicated in the pathogenesis of IHD<sup>[9]</sup>
- In the present study, the frequency of stable IHD (SIHD) increased in RA patients with prolonged



**Figure 5: LIPID profile and positive exercise electrocardiogram relation**



**Figure 6: Total cholesterol and positive exercise electrocardiogram relation**

duration, and this goes hand-to-hand with the study of Fietta *et al.*, 2009,<sup>[10]</sup> who reported that atherosclerosis is an early and common finding in RA patients, positively correlating to the disease duration and severity. This was also consistent with Dala *et al.*, 2012, Menoufiya University Hospitals, Egypt<sup>[7]</sup>

- We also found that the occurrence of SIHD is significantly increased in patients with RA in association with the high markers of inflammation and activity as high ESR and this agrees with other studies as that of Dala *et al.*, 2012.<sup>[7]</sup> It is also consistent with Chung *et al.*,

**Table 1: Comparison between ischemic and non-ischemic group regarding history, clinical and laboratory data in RA patients**

Data	Mean±SD		P value
	Positive exercise ECG	Negative exercise ECG	
Age	56.6±14.95	47.82±9.87	0.079
Hemoglobin	10.32±2.65	11.84±1.98	0.121
ESR	58.8±4.54	26.4±12.79	0.000
RA duration	12.1±6.74	3.97±1.76	0.000
Das 28 score	6.18±0.20	3.76±0.61	0.000
Total cholesterol	226.8±6.57	161.84±8.35	0.001
Triglycerides	163.4±43.49	137.82±43.32	0.217
HDL	43.98±12.48	44.71±9.05	0.869
LDL	117.42±25.62	112.14±30.60	0.713

ECG: Electrocardiogram, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, HDL: High-density lipoprotein

2005, who reported that the prevalence and severity of coronary calcification is increased in established RA and is related, in part, to elevated inflammatory markers.<sup>[11]</sup> Galiutina and Bychak, 2011, also found that silent myocardial ischemia in patients with the RA was associated with high activity of inflammatory process. CV morbidity and mortality strongly correlate with disease activity, whereas the successful pharmacological control of the chronic inflammation decreases the risk of CV complications<sup>[12]</sup>

- Myasoedova *et al.*, 2011, also reported that their findings underscore the importance of systemic inflammation as a key player in the development of CVD in RA by demonstrating independent associations of ESR and CRP with cardiovascular outcomes and mortality. This is concordant with the concept of acceleration of cardiovascular risk and mortality with increasing inflammatory burden and suggests the need for minimization of cumulative inflammation in RA<sup>[13]</sup>
- In our study, age was found not to have significant association with SIHD in patients with RA. This is inconsistent with the results of Chung *et al.*, 2006,<sup>[14]</sup> and Dala *et al.*, 2012<sup>[7]</sup>
- We also found that the occurrence of silent IHD is significantly increased in patients with RA in association with the high disease activity. We had measured disease activity using DAS 28 score.
- In our study, we found the incidence of silent IHD is increased in patients with hypercholesterolemia. This finding was consistent with findings of Dala *et al.*, 2012,<sup>[7]</sup> who also showed significant association between increased silent IHD in RA patients and increased cholesterol.

#### Limitations of the Study

- RA factor and CRP are also important markers of systemic inflammation. We did not find their



**Table 2: Comparison between ischemic and non-ischemic group regarding gender, seropositivity and CRP in RA patients**

Data	Gender		RF		CRP	
	Male (%)	Female (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)
Positive exercise ECG	1 (20)	4 (80)	5 (100)	0 (0)	5 (100)	0 (0)
Negative exercise ECG	24 (53.3)	21 (46.7)	39 (86.7)	6 (13.3)	40 (88.9)	5 (11.1)
Total	25 (50)	25 (50)	44 (88)	6 (12)	45 (90)	5 (10)
Fisher's exact	0.349		1.000		1.000	

ECG: Electrocardiogram, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, HDL: High-density lipoprotein

significant association with silent IHD in patients with RA [Table 2]. Because we recorded only qualitative measurements of RA factor and CRP. Their quantitative measurements were not available at our study center.

- Study sample is small constituting 50 patients total because patients who had developed disabilities that interfered with walking and running on treadmill machine were excluded from the study.

## CONCLUSIONS

- Silent IHD is a quite common incidence in RA patients (10%).
- The predictors for SIHD are prolonged disease duration, high disease activity, hyperlipidemia, and presence of high activity markers.

“Targeting these risk factors in RA patients could help in lowering incidence of IHD and its complications.”

## Recommendation

TMT is recommended as a good screening method for silent IHD, especially in the presence of its predictors in patients with RA.

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