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# Myocardial ischemia in female patients with rheumatoid arthritis assessed with single photon emission tomography--myocardial perfusion imaging

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## Abstract

**BACKGROUND:** Non-specific cardiac symptoms in female patients with rheumatoid arthritis (RA) could indicate early cardiovascular disease.

**MATERIALS AND METHODS**: Myocardial perfusion imaging (MPI), with 99mTc tetrofosmin stress–rest single photon emission computer tomography (SPECT), in 13 RA female patients with atypical cardiac symptoms, was compared to 44 weight- and age-matched females with similar cardiac complaints (control group). Smoking, hypertension, diabetes mellitus, dyslipidemia, obesity and cardiac heredity were recorded and compared between the study and control group. MPI was assessed using 17 segment polar map and with a scale of 0 to 5 scoring.

**RESULTS:** Patients with RA demonstrated higher cardiovascular risk (46%) compared to control individuals (17%). In addition, patients with RA had more irreversible myocardial ischemic abnormalities in their MPI than the control group. Dyslipidemia and obesity was found more frequent in RA patients with MPI SSS $\geq$ 4.

**CONCLUSION:** RA patients with atypical cardiac complaints are at higher risk for cardiovascular disease; early detection and monitoring of this patient group could potentially reverse or successfully manage the consequences of the upcoming cardiovascular disease.

**KEY words: myocardial perfusion imaging, myocardial ischemia, tetrofosmin, risk factors, females, rheumatoid arthritis**

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## Introduction

Rheumatoid arthritis (RA) is an inflammatory disease involving multiple systems that predominantly cause joint destruction but also affect extra-articular organs resulting in significant functional disabilities and reduced quality of life [1–4]. Patients with either RA or other chronic inflammatory rheumatoid diseases may develop progressive cardiovascular disease [5]. These cardiovascular complications consist of increased rate of coronary artery disease and systemic atherosclerosis [6].

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Several cardiovascular imaging modalities exist, such as nuclear imaging, cardiac computed tomography and carotid ultrasonography, to evaluate patients with increased cardiovascular risk [7]. Myocardial perfusion imaging (MPI), employing single photon emission tomography (SPECT), is a highly reliable imaging method to assess myocardial ischemia. Its sensitivity has been reported to reach 85%, specificity of 83%, positive predictive value of 66%, negative predictive value of 94% and accuracy of 84% [8]. Myocardial perfusion imaging with pharmacologic stress may represent the imaging test of choice in female patients with reduced exercise capability such as the RA patients, reaching sensitivity of 80–85% and specificity of 84–93% [9].

Several risk factors have been linked to coronary-artery disease in RA patients. Metabolic syndrome seems to exist in a higher rate in patients with RA, consisted of 31% in patients with early RA and 42% in patients with long-standing RA, compared to only 11% in

**Table 1.** Characteristics of the patients (median, min-max), information concerning cardiac risk factors and myocardial perfusion imaging

| Characteristics | Patients (#13) | Control group (#44) | P |
|---|---|---|---|
| Age (median, ± SD) | 67.8 ± 8.34 | 67.5 ± 7.53 | NS |
| Weight | 71.85 (53–90) | 70.98 (54–93) | NS |
| Smoking | 3 (23.1%) | 4 (9.1%) | 0.038 |
| Hypertension | 10 (76.9%) | 34 (77.3%) | NS |
| Diabetes Mellitus | 2 (15.4%) | 10 (22.7%) | NS |
| Dyslipidemia | 9 (69.2%) | 29 (65.9%) | NS |
| Obesity | 3 (23.1%) | 11 (25.0%) | NS |
| Cardiac Heredity | 5 (38.5%) | 16 (36.4%) | NS |
| MPI SSS < 4 | 7 (53.8%) | 37 (84.1%) | 0.022* |
| MPI SSS ≥ 4 | 6 (46.2%) | 7 (15.9%) | 0.004* |

MPI: myocardial perfusion imaging; b. SSS: summed stress score; c. NS: non-significant; d. SD: standard deviation; e. * $p \leq 0.05$ was considered to be statistically significant

matched control individuals [10]. Thus, early detection of metabolic syndrome and control of risk factors such as smoking, dyslipidemia, hypertension, and obesity is warranted in RA patients [6]. Traditional risk factors for cardiovascular disease seem to confer the same risk for either RA or non-RA patients [11, 12].

In this retrospective study, we evaluated the rate of myocardial ischemia and the role of cardiac risk factors, after using –99mTc-TF-SPECT MPI in female patients with rheumatoid arthritis and compared them to an age and weight matched control group.

## Patients and methods

### Study Participants

An extensive request in the medical records of the Nuclear Medicine Department of our University Hospital between 2011 and 2016 has been achieved summing up patients with RA who were subjected to myocardial perfusion imaging with 99m Tc tetrofosmin in stress–rest single photon emission computer tomography (MPI – 99mTc-TF-SPECT). For retrieving specific data, inclusion criteria were applied such as no other disease existed than RA, atypical cardiac complaints such as chest wall pain, palpitations, without known cardiac disease, and negative electrocardiograph (ECG). We found 16 patients with RA who underwent the test, 13 females and 3 males. All patients followed one day protocol. The stress protocol was either pharmacological or Bruce treadmill exercise test. Patients when subjected to 99mTc-TF-SPECT MPI were routinely recorded with ECG at the beginning and continuously monitored during stress time. Any changes in ECG were noted in the medical charts. The imaging protocol used for 99mTc-TF-SPECT MPI has been described in our previous studies [13, 14] and performed according to published guidelines [15]. According to our search, only three male patients were found and finally excluded from the study due to their minimal contribution to the whole dataset, and thus, only the 13 females were evaluated. For the selection of the healthy individuals, 120 female patients that underwent the same test without positive RA diagnosis were initially selected to form the control group. These females had the test for atypical cardiac complaints such as nonspecific chest pain or palpitations with no medical disease, negative history for cardiac disease, negative clinical evaluation and negative ECG prior to MPI. Among these females, 44 were age- and weight-matched with the RA patients and finally selected to form the control group. In both groups, major cardiovascular risk factors were recorded, including smoking when either active or ceased within the last 3 months prior to the test, hypertension and/or diabetes mellitus and/or dyslipidemia, obesity and family history of cardiovascular disease.

This retrospective study was performed after approval by the Hospital's Clinical Research Committee. As a retrospective analysis of MPI data, prior written patients consent was not obtained since it was not required by our Hospital's Clinical Research Committee. All subjects were blinded during statistical analysis.

### MPI evaluation

For MPI evaluation, two nuclear medicine physicians independently evaluated the images, and a third nuclear medicine physician participated when a difference in MPI scoring among the two nuclear medicine physicians existed. Scoring was evaluated with a 17-segment polar map, [16] with a scale of 0 to 5, according to the severity of the myocardial perfusion deficit. Thus, when there was normal isotope uptake by the total area of myocardium. the score was 0. When there was a mild decreased activity, the score recorded as 1. Mild to moderate decreased activity had a score of 2. Moderately decreased myocardial activity was rated as 3. Score 4 denoted a severely compromised myocardial isotope uptake, and score 5 characterized the lack of myocardial tracer activity. All segments were scored according to the grade of the defect seen and these individual scores were then summed to offer a measurement of abnormality of the entire myocardium. Thus, stress and rest MPI was evaluated as the summed stress score (SSS) and the summed rest scores (SRS) of the 17-segment polar map. Myocardial perfusion imaging scan was evaluated as abnormal when SSS was ≥ 4, with mild ischemia when SSS was graded from 4 to 8, moderate from 9 to 13, and severe when summed score was > 13. [17] The difference between the summed stress and summed rest scores (SSS-SRS) were reflective of the burden and non-reversible nature of the existing ischemia [18].

### Statistical Analysis

For statistical analysis and MPI evaluation, we used SPSS version 20 for windows (SPSS, Chicago, IL), and Microsoft Excel version 2013 (© Microsoft). Rheumatoid arthritis patients and control group were separately analyzed after splitting into two subgroups (one with SSS $< 4$ and another with SSS $\geq 4$). Risk factors were evaluated in each group and each subgroup. Baseline characteristics were described using median and frequencies for categorical variables (using a 2 test for comparisons of discrete variables). $P < 0.05$ was considered significant. Furthermore, due to the small number of RA patients, we evaluated the summed segments (basal, mid and apical segments) of anterior, anteroseptal, inferoseptal, inferior, inferolateral, anterolateral and apical cardiac wall.

## Results

The characteristics and MPI of the 13 RA patients and 44 control females are shown in Table 1. Comparison of patients with RA and control females demonstrated a statistically significantly higher number of patients in the RA group with a MPI value of SSS $\geq 4$, (6/13, 46%) compared to control females 7/44 (16%) ($P = 0.004$), (Tab. 1). Among the RA patients, one had mild ischemia (1/6, 16%), four had moderate ischemia (4/6, 68%) and one had severe ischemia (1/6, 16%). All patients with abnormal MPI test in the control group had only mild ischemia.

Among all patients with RA, a total of 221 segments (17 x 13) were evaluated in MPI SSS and 221 segments in SRS. Of them, 23 segments in SSS and 18 segments in SRS had at least a mildly decreased activity scored with 1. Total score in those segments were 69 in SSS and 34 in SRS. The difference SSS-SRS was 5 segments with total score of 35. Control females had 748 segments (17 x 44) evaluated with 46 segments exhibiting decreased activity in SSS and 15 in SRS. Total score in those segments were74 in SSS and 26 in SRS. The difference SSS-SRS was 31 segments with total score of 48. Assessment of MPI in all 102 segments of the 6 RA patients with SSS $\geq 4$ revealed 16 segments that exhibited score1 in SSS and 14 segments with score 1 in SRS. Total score was 57 and 29 respectively. The difference SSS-SRS was 2 segments with total score of 28. Among the 119 segments of the 7 control females with SSS $\geq 4$, 14 segments scored 1 in SSS and 5 segments similarly scored 1 in SRS. Total score was 35 in SSS and 8 in SRS. The difference SSS-SRS was 9 segments with total score of 27 (Table 2).

Thus, among the RA patients, there were 5/23 (22%) myocardial segments having 51% reversible abnormalities assessed by the SSS-SRS MPI. In the contrary, the control females had milder abnormalities consisting of 31/46 segments with 67% reversible abnormalities in their SSS-SRS MPI. Among those RA patients with a SSS $\geq 4$, only 2/16 (13%) segments demonstrated changes in SSS-SRS MPI consisting with 49% reversibility. In the contrary, control females had 9/14 (64%) myocardial segments with 77% reversible lesions. These results suggest that patients with RA had more irreversible myocardial ischemic abnormalities in their MPI than the control group.

An additional analysis has been performed based on the different cardiac segments. As shown in Table 3, although the anterolateral segment may be the most affected part of the myocardium in patients with RA, the results could be noted with skepticism due to the small number of RA patients. In the rest of myocardium, the number of segments with ischemia showed only a minor increase in the RA compared with the control group. However, this minor increase could be due to statistically insignificant variations secondary to small size of patients' dataset. The cardiovascular risk factors in RA and control patients are shown in Table 4. It appears that more RA patients with SSS $\geq 4$ compared to those with SSS $< 4$ had hypertension, dyslipidemia and obesity. In addition, more RA patients than control females with SSS $\geq 4$ had dyslipidemia and obesity.

**Table 2.** Number of segments and total score evaluated in MPI (summed stress score, summed rest score and their difference) in RA patients and control females

| Individuals | | Segments/MPI | Summed scores |
|---|---|---|---|
| Control all | Total | 748/44 | |
| | SSS | 46/44 | 74 |
| | SRS | 15/44 | 26 |
| | Difference SSS-RSS | 31/44 | 48 |
| RA all | Total | 221/13 | |
| | SSS | 23/13 | 69 |
| | SRS | 18/13 | 34 |
| | Difference SSS-RSS | 5/13 | 35 |
| Control SSS ≥ 4 | Total | 119/7 | |
| | SSS | 14/7 | 35 |
| | SRS | 5/7 | 8 |
| | Difference SSS-RSS | 9/7 | 27 |
| RA SSS ≥ 4 | Total | 102/6 | |
| | SSS | 16/6 | 57 |
| | SRS | 14/6 | 9 |
| | Difference SSS-RSS | 2/6 | 28 |

a. RA: patients with rheumatoid arthritis; b. MPI: myocardial perfusion imaging; c. SSS: Summed stress score; d. SRS: Summed rest score

**Table 3:** Evaluation of the segments in MPI in patients and controls with SSS ≥ 4

| | Segments SSS ≥ 4/Segments SRS | |
|---|---|---|
| MPI | RA | Controls |
| anterior | 8/4 | 8/2 |
| anteroseptal | 2/1 | 0/0 |
| inferoseptal | 8/3 | 3/1 |
| inferior | 11/8 | 4/1 |
| inferolateral | 0/0 | 3/0 |
| anterolateral | 20/8 | 10/5 |
| Apex | 8/5 | 0/0 |

a. MPI: myocardial perfusion imaging; b. SSS: summed stress score; c. SRS: summed rest score; d. RA: patients with rheumatoid arthritis

### Limitations of the study

The limitations of the study included its retrospective nature and the small number of RA patients. In addition, limited data was available concerning disease activity and the anti-inflammatory

**Table 4.** Risk factors in patients with rheumatoid arthritis and control individuals according to MPI summed stress score

| | Patients with Rheumatoid arthritis | | Control Group |
|---|---|---|---|
| Risk factors | SSS < 4 | SSS ≥ 4 | SSS ≥ 4 |
| Total risk factors | 12 | 16 | 18 |
| Smoking | 3/7 (43%) | 0/6 (0%) | 0/7 (0%) |
| Hypertension | 4/7 (57%) | 5/6 (83%) | 6/7 (86%) |
| Diabetes Mellitus | 1/7 (14%) | 1/6 (17%) | 3/7 (43%) |
| Dyslipidemia | 4/7 (57%) | 5/6 (83%) | 3/7 (43%) |
| Obesity | 0/7 (0%) | 3/6 (50%) | 2/7 (29%) |
| Cardiac Heredity | 2/7 (28%) | 2/6 (33%) | 4/7 (57%) |
| With 1 risk factor | 2/7(28%) | 0/6 (0%) | 2/7 (28%) |
| With 2 risk factors | 3/7 (44%) | 3/6 (50%) | 1/7 (16%) |
| With 3 risk factors | 2/7 (28%) | 0/6 (0%) | 2/7 (28%) |
| With 4 risk factors | 0/7 (0%) | 3/6 (50%) | 2/7 (28%) |

a. MPI: myocardial perfusion imaging; b. SSS: summed stress score

drugs used for management. Furthermore, no body mass index could be calculated since only weight but not height was recorded in the medical charts of the patients.

## Discussion

In the present study, higher cardiovascular risk was found in RA patients with nonspecific cardiac symptoms compared to controls with similar symptoms. Specifically, in our study, 58% of RA patients had myocardial abnormalities in MPI, indicating ischemia. In accordance with our results, another study in 18 RA patients without a known cardiac disease reported a rate of myocardial abnormalities of 45% [19]. However, in that study, only 78% were females, and the imaging method performed was MRI. Asymptomatic RA patients may display myocardial ischemia at similar levels to DM patients [20]. In a study of 106 females with RA the incidence of coronary heart disease has been reported as 7 per 1000 patients-years [20]. Right and left ventricular diastolic dysfunction is diagnosed more frequently in patients with early stage RA, with left ventricular diastolic dysfunction linked to coronary heart disease [22].

This high rate of cardiac abnormalities in RA patients even without any clinical symptoms or ECG changes may be due to microvasculitic abnormalities [23]. When a systemic inflammation is present in RA patients, the cardiac disease may be manifested with more clinical findings and atherosclerosis might lead to increased cardiovascular morbidity [24]. Thus, apart from traditional risk factors, atherosclerosis in RA patients may be aggravated by disease activity, such as polymorphonuclear cell counts, radiographic evidence of cumulative inflammation, serum uric acid increased levels, hypothyroidism [25], and increased erythrocyte sedimentation rate [26]. However, another study reported no correlation of coronary artery disease in RA patients with the titers of rheumatoid factor, body mass index and hypercholesterolemia [27]. In our study due to lack of detailed information about the disease activity of RA patients and mode of treatment we were not able to assess these parameters in relation to cardiovascular risk.

Overall in our study, the traditional cardiovascular risk factors were not significantly different between patients and control females even though RA that exhibited an abnormal MPI had a higher rate of dyslipidemia and obesity compared to control individuals. However, diabetes mellitus and cardiac heredity were attributes seen at higher rates in controls than in RA patients in our study. In accordance with our study, previously published results indicate that the traditional cardiovascular risk factors in RA patients cannot entirely explain their increased incidence of coronary heart disease [28]. Although the traditional cardiovascular risk factors were similar in a group of 68 RA patients compared to 64 controls, RA patients had the propensity to develop coronary artery disease twice as frequently as the control individuals [11]. In addition, another study indicated that RA patients develop cardiovascular disease almost ten years earlier than their age- and sex-matched individuals and tend to suffer twice as frequently myocardial infarction compared to their counterparts [29]. Apart from myocardial infarction, heart failure due to left ventricular diastolic dysfunction is linked to increased cardiovascular mortality in patients with RA. Thus, diagnosis of heart failure in early asymptomatic stages is more likely to be treatable in RA patients [30, 31]. A study in 144 RA women, exhibiting low risk of cardiovascular disease as assessed by the Systematic COronary Risk Evaluation (SCORE), showed that one-third of them, experience high-risk atherosclerosis when age older than 49.5 years and/or cholesterol levels over 5.4 mmol/l suggest that they should be managed appropriately [32]. Similar conclusions of increased subclinical atherosclerosis were made in another prospective study in 71 RA patients ≤ 60 years old compared to 40 age- and sex-matched controls [33].

In conclusion, our results corroborate other studies that show increased incidence of cardiovascular risk in RA female patients compared to control individuals. The presence of increased risk even in patients with minimal or atypical cardiac symptoms indicates that early detection of the increased risk in RA patients is warranted in order to monitor or pharmaceutically reverse the indolent cardiovascular disease.

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## Conflict of interest

None

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N/A

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