Exercise Echocardiography in Rheumatoid Arthritis: A Case-Control Study

Mohammed K. Saghir, MD, Christine Attenhofer Jost, MD, Kenneth J. Warrington, MD, Stephen S. Cha, MS, and Patricia A. Pellikka, MD, FASE, *Rochester, Minnesota*

Background: Rheumatoid arthritis (RA) is associated with increased cardiovascular risk.

Methods: To assess the role of exercise echocardiography (EE) in the evaluation of patients with RA, follow-up (mean, 6.7 ± 3.7 years) was retrospectively obtained in 159 patients with RA who underwent EE. Patients were matched for age, gender, and cardiovascular risk factors with 454 controls who underwent EE.

Results: Patients with RA were more likely to have positive results for ischemia on EE (odds ratio, 2.32; 95% confidence interval, 1.48-3.64; $P = .0003$). Rest and exercise wall motion score indexes were higher in the RA group (1.14 ± 0.33 and 1.22 ± 0.39, respectively, vs 1.06 ± 0.18 and 1.10 ± 0.24 in controls; $P < .005$ for each). Logistic regression adjusted for age revealed an increased odds ratio for myocardial ischemia of 1.06 (95% confidence interval, 1.02-1.11; $P = .005$) per year of RA. Five-year all-cause mortality in subjects with RA with myocardial ischemia on EE was 14.9%, compared with 4.3% in RA subjects without ischemia ($P = .028$).

Conclusion: RA was associated with a 2-fold increased risk for myocardial ischemia on EE; risk increased with the duration of RA. Mortality was increased in patients with RA with ischemia on EE. (J Am Soc Echocardiogr 2009;22:1228-31.)

Keywords: Rheumatoid arthritis, Exercise echocardiography, Coronary artery disease, Collagen vascular disease, Stress echocardiography, Ischemia, Autoimmune

Rheumatoid arthritis (RA) is a common autoimmune disorder that affects 1% to 2% of the population.[1] Patients with RA are at increased risk for coronary artery disease (CAD) and myocardial infarction.[2,3] The mechanism behind this increased risk is not entirely understood, although inflammation may play a role in the pathogenesis of CAD. Among patients presenting for coronary angiography, patients with RA have an increased incidence of multivessel CAD.[4] Increased coronary artery calcification is seen in patients with long-term RA compared with early RA.[5] RA is associated with increased carotid medial thickness and plaque score.[6] There is evidence that the increased risk is related to the overall burden of inflammatory disease in RA, established cardiovascular risk factors, and female gender.[3,6-8]

Exercise echocardiography (EE) is frequently used for the assessment of patients with known or suspected CAD, especially in the presence of repolarization abnormalities on resting electrocardiography.[9] EE accurately predicts cardiac morbidity, mortality, and outcomes in CAD.[10-13] However, there are no data on the diagnostic accuracy of stress testing, with or without imaging, in patients with RA, nor are there data on the capacity of these modalities to predict outcomes in these patients.

We sought to determine whether an increased incidence of CAD exists in patients with RA compared with matched controls, using EE to detect CAD. We also sought to identify clinical characteristics associated with CAD and whether the presence of myocardial ischemia on EE affected survival in patients with RA.

METHODS

Patients

This retrospective case-control study was approved by the institutional review board; all participants agreed that their records could be accessed for research. From 1990 to 2007, 17,152 patients were seen at the Mayo Clinic with the diagnosis of RA. Of these, 909 patients underwent stress echocardiography. Selecting only those who underwent EE, 296 patients were identified. Medical records were reviewed to identify patients in whom the diagnosis of RA was confirmed by a rheumatologist. The diagnosis was confirmed in 159 patients; these constituted the RA group. The time from RA diagnosis to EE was recorded. To facilitate data collection, a 1:3 matched case-control study was planned rather than attempting to include the entire population of >70,000 patients who underwent stress echocardiography during this time period. Thus, an attempt was made to find 3 control patients without RA per patient with RA who underwent EE for each patient in the RA group while

From the Department of Medicine (M.K.S.), the Division of Cardiovascular Diseases (C.A.J., P.A.P.), the Division of Rheumatology (K.J.W.), and the Division of Biomedical Statistics and Informatics (S.S.C.), Mayo Clinic, Rochester, Minnesota.

Reprint requests: Patricia A. Pellikka, MD, Mayo Clinic, Division of Cardiovascular Diseases, 200 First Street SW, Rochester, MN 55905 (E-mail: *pellikka.patricia@mayo.edu*).

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matching for age, gender, dyslipidemia, diabetes mellitus, hypertension, and smoking status. These controls were chosen to minimize variance from prior conditions between the two groups while maximizing possible differences due to RA status. A total of 454 patients without RA were obtained and constituted the control group.

Cardiovascular Risk Factors

Hypertension was defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, and/or the use of antihypertensive medications. Subjects were considered to have dyslipidemia if their total cholesterol levels were >200 mg/dL and/or if they were receiving lipid-lowering medications. Diabetes mellitus was defined according to American Diabetes Association criteria.

Exercise Echocardiography

All patients underwent symptom-limited treadmill EE according to previously defined methods.[14] Exercise was performed according to the Bruce protocol in 590 patients, the Naughton protocol in 4 patients, and the modified Bruce protocol in 19 patients. There were no significant differences in exercise protocol between controls and patients with RA ($P = .12$).

Wall motion was scored according to a 16-segment model, in which 1 = normal or hyperdynamic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, and 5 = aneurysm.[15] Wall motion score index (WMSI) was calculated at rest and with exercise as the sum of segmental scores divided by the number of segments. New or worsening wall motion with exercise was considered indicative of myocardial ischemia. Wall motion abnormalities that were present at rest and unchanged with exercise were classified as fixed. The results of EE were considered abnormal if there were fixed and/or new wall motion abnormalities with stress. By side-by-side comparison of images, left ventricular end-systolic volume with exercise was compared with left ventricular end-systolic volume at rest and classified as decreased (normal response), unchanged, or increased.

Coronary Angiography

Coronary angiographic records were obtained on all subjects in the RA group if the angiography occurred <6 months after the EE. The sensitivity and specificity of exercise WMSI > 1 in predicting coronary artery stenosis ≥ 50% diameter on angiography was calculated.

Follow-Up

Follow-up was obtained by December 1, 2007. The Social Security Death Index and chart review were used to ascertain survival status. The endpoint was all-cause mortality, and no censoring was performed.

Statistical Analysis

Continuous variables are expressed as mean ± SD. Nonparametric comparisons between groups were based on Wilcoxon's rank-sum test. Parametric comparisons between the two groups were based on a two-sample Student's *t* test. A *P* value < .05 was considered statistically significant. Conditional logistic regression was used to investigate the relationship between RA and the prognostic factor, myocardial ischemia on EE, in 1:3 matched case-control studies. The relationship between age and number of years of RA was evaluated, as was the association with ischemia. The 95% confidence interval (CI) for each odds ratio was calculated using logistic regression analysis and was considered statistically significant if it did not cross unity. Kaplan-Meier curve analysis was performed to assess survival in patients with RA stratified according to the presence of myocardial ischemia on EE. All statistical analyses were performed using SAS/STAT version 9.1.3 (SAS Institute Inc, Cary, NC), and the SAS MCSTRAT macro was used to perform the conditional logistic regression analysis.[16]

RESULTS

Study Group

There were 159 patients in the RA group and 454 patients in the control group. Among patients with RA, 95 (64%) were aged ≥65 years and 54 (36%) were aged <65 years at the time of EE; the mean duration between the diagnosis of RA and EE was 10.0 ± 8.3 years. The most common indications for EE in the RA and control groups were evaluation of chest pain and/or dyspnea (52% vs 57%, $P = .29$) and evaluation of known CAD (8% vs 13%, $P = .11$). Clinical characteristics are presented in Table 1. There were no significant differences between the groups in age, gender, dyslipidemia, diabetes mellitus, hypertension, smoking status, prior myocardial infarction, prior percutaneous coronary intervention, and prior coronary artery bypass grafting (all *P* values > .10).

Exercise Echocardiography

Exercise echocardiographic parameters are summarized in Table 2. Patients with RA had lower ejection fractions and achieved lower workloads. Patients with RA also had higher WMSI values at rest and with exercise, more often had increases in end-systolic volume with exercise, and were more likely to have ischemia on EE.

Coronary Angiography

Of the 26 patients in the RA group who underwent coronary angiography, CAD was present in 18 (69%) and included single-vessel disease in 7 (27%), 2-vessel disease in 5 (19%), and 3-vessel disease in 6 (23%). The sensitivity and specificity of EE for predicting angiographic stenosis were 85% (95% CI, 58%-96%) and 88% (95% CI, 47%-99%), respectively.

RA and Ischemia

Comparing patients with RA with controls, the diagnosis of RA had an odds ratio of 2.32 (95% CI, 1.48-3.64; $P = .0003$) for myocardial ischemia on EE. Among patients with RA with myocardial ischemia on EE, the duration between diagnosis of RA and EE was 13.0 ± 9.0 years. This was significantly higher than in patients with RA without myocardial ischemia (8.6 ± 7.7 years) ($P = .003$). Among patients with RA, age and the duration of RA were not correlated (Spearman's $\rho = 0.05$, $P = .52$). In a multivariate logistic regression setting applying stepwise elimination method, both age and the duration of RA were associated with ischemia in patients with RA: the odds ratios for myocardial ischemia were 1.05 (95% CI, 1.01-1.09; $P = .0248$) per year of age and 1.06 (95% CI, 1.02-1.11; $P = .005$) for each year of RA prior to EE. Among patients with duration of RA < 10 years, a patient aged ≥65 years had an odds ratio for myocardial ischemia of 3.59 (95% CI, 1.32-9.78; $P = .012$) compared with a patient aged <65 years. Among patients aged <65 years, a patient with RA duration ≥ 10 years had an odds ratio for ischemia of 5.84 (95% CI, 1.91-17.82; $P = .002$) compared with a patient with RA duration < 10 years. Finally, a patient aged ≥65 years with RA

Table 1 Clinical characteristics

	Subjects with RA	Controls	
Variable	(n = 159)	(n = 454)	*P*
Age (y)	64 ± 10	64 ± 9	.82
Men	69 (43%)	198 (44%)	.96
BMI (kg/m^2)	27.3 ± 5.0	27.8 ± 4.7	.81
BSA (m^2)	1.87 ± 0.22	1.88 ± 0.24	.39
Dyspnea	43 (27%)	153 (34%)	.12
Angina	76 (48%)	202 (44%)	.33
Hypertension	72 (45%)	201 (44%)	.83
Dyslipidemia	69 (43%)	201 (44%)	.85
Diabetes mellitus	10 (6%)	21 (5%)	.41
Current smoking	18 (11%)	39 (9%)	.31
β-blocker	47 (30%)	137 (30%)	.88
ACE inhibitor/ARB	9 (6%)	23 (5%)	.77
CCB	25 (16%)	60 (13%)	.43
Prior MI	19 (12%)	38 (8%)	.18
Prior PCI	19 (12%)	37 (8%)	.15
Prior CABG	15 (9%)	31 (7%)	.28

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *BSA*, body surface area; *CABG*, coronary artery bypass grafting; *CCB*, calcium channel blocker; *MI*, myocardial infarction, *PCI*, percutaneous coronary intervention.
Data are expressed as mean ± SD or as number (percentage).

Table 2 Echocardiographic characteristics

	Subjects with RA	Controls	
Variable	(n = 159)	(n = 454)	*P*
Peak heart rate (beats/min)	142 ± 23	145 ± 24	.82
Workload (METs)	6.5 ± 2.2	8.0 ± 2.6	.001
Results of EE			
Positive	24 (15%)	57 (13%)	.42
Negative	121 (76%)	331 (73%)	.35
Nondiagnostic	14 (9%)	66 (15%)	.10
Ejection fraction (%)	58 ± 8	60 ± 6	.007
WMSI (rest)	1.14 ± 0.33	1.06 ± 0.18	.001
WMSI (exercise)	1.22 ± 0.39	1.10 ± 0.24	.0005
Stress end-systolic volume			
Increased	5 (3%)	12 (3%)	.60
Unchanged	25 (16%)	29 (6%)	.001
Decreased	125 (79%)	413 (91%)	.001
Exercise RPP	24,027 ± 5985	24,569 ± 5850	.39
Abnormal results on EE	65 (41%)	110 (24%)	.0005
Ischemia on EE	47 (30%)	77 (17%)	.0005
Resting WMA	45 (28%)	68 (15%)	.0005

RPP, Rate-pressure product; *WMA*, wall motion abnormality.
Data are expressed as mean ± SD or as number (percentage).

duration ≥ 10 years had an odds ratio of 7.96 (95% CI, 2.72-23.28; *P* = .0002) compared with a patient aged <65 years with RA duration < 10 years.

RA and Survival

During a mean follow-up period of 6.7 ± 3.7 years following EE, 22 patients with RA (14%) died. Figure 1 displays a Kaplan-Meier curve that represents survival data in patients with RA stratified by the presence of myocardial ischemia on EE. Five-year all-cause mortality in patients with RA with myocardial ischemia on EE was 14.9%, compared with 4.3% in patients with RA without myocardial ischemia on

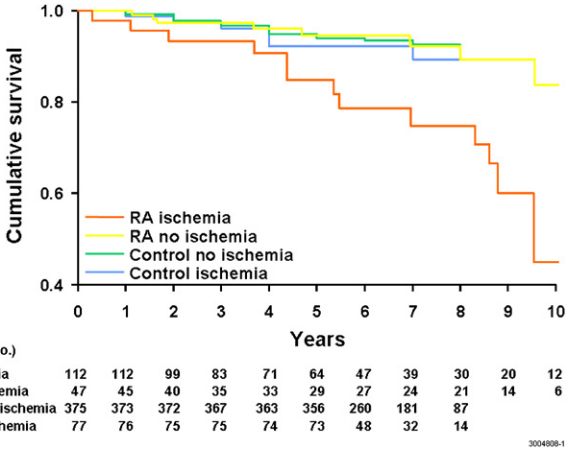

Figure 1 Cumulative survival of patients with RA according to the presence or absence of ischemia by EE.

EE (*P* = .028). Curves for the control population are also included. There was no difference between the RA and control populations without ischemia on EE (*P* = .78). Among those with ischemia on EE, there was a nonsignificant trend (*P* = .12) toward increased mortality in patients with RA with ischemia compared with controls with ischemia.

DISCUSSION

In our study, patients with RA had a higher risk for myocardial ischemia as detected by EE compared with controls matched for age, gender, and cardiovascular risk factors. This is consistent with a prior study suggesting that the Framingham risk score underestimates the cardiovascular risk of individuals with RA.[4] Furthermore, we found that the duration of RA prior to EE was associated with increased risk for myocardial ischemia on EE. In patients with RA, age and the duration of RA were independently additive in increasing the likelihood of ischemia. Finally, the presence of myocardial ischemia on EE in patients with RA had a significant negative impact on 5-year survival.

Past studies have shown that the mortality rate in people with RA has not markedly decreased over the past 40 years.[17] The explanation for this finding is not entirely understood, but increased cardiovascular morbidity has been suggested as a cause. In a large-scale epidemiologic prospective cohort study, women with RA were found to be at significantly increased risk for myocardial infarction.[3] In a case-control study using coronary angiography, increased multivessel CAD was found to be associated with RA.[4] Coronary artery calcium scores were significantly elevated in people with RA, and the severity of calcification was proportionally related to the erythrocyte sedimentation rate.[5] Coronary flow reserve was also significantly decreased in RA.[18] In all, the literature suggests a relationship between accelerated coronary atherosclerosis and RA. Whether this may be secondary to the chronic inflammatory state imposed by RA or medications used to treat RA is uncertain, although at least one study has shown that disease-modifying antirheumatic drug therapy reduces cardiovascular death in RA.[19]

To our knowledge, this is the first study that has evaluated the association between CAD and RA using stress testing. Moreover, the data suggest that even when adjusted for age, each year of having the diagnosis of RA increased the risk for myocardial ischemia on EE by 1.9% to 10.9%, with an average of 6.3%. This finding is consistent with past studies that have examined adverse cardiovascular

outcomes among people with RA. The Nurses' Health Study revealed a 2-fold relative risk for myocardial infarction in women with RA. This risk increased to 3-fold among women with RA for >10 years.[3]

The presence of myocardial ischemia in the background of RA was associated with a 3-fold increase in all-cause mortality over 5 years compared with patients with RA without myocardial ischemia on EE. Previous predictors of increased cardiovascular mortality in RA include an elevated blood sedimentation rate of ≥60 mm/h[8] and a C-reactive protein level ≥ 5 mg/L.[7] Patients with RA identified to be at risk for myocardial ischemia could conceivably benefit from increased monitoring and aggressive treatment for CAD and cardiovascular risk factors. Moreover, EE would be an easily accessible and relatively inexpensive means to stratify CAD risk in people with RA. Further research is necessary to determine whether aggressive treatment of RA and treatment of RA as a CAD risk factor leads to a decrease in mortality.

Limitations

Our study had limitations inherent in a retrospective study. Of the approximately 17,000 patients presenting to the Mayo Clinic with the diagnosis of RA, only 159 were included in this study, because we included only patients who had undergone EE. Consequentially, the conclusions of this study are limited to patients with RA with the functional capacity to complete an exercise stress test. Many patients with RA have significant functional disability secondary to their disease; our findings may not be applicable to this group. However, we believe that our conclusions carry significance regarding the long-term outcomes of patients with RA without functional limitations.

The sensitivity and specificity of EE for detecting CAD on angiography were based on a small number of patients. Given the retrospective design of this study, the possibility exists that the results of EE influenced the decision to perform coronary angiography. Available information was insufficient to accurately gauge the disease activity of RA over time. We included only patients in whom the diagnosis of RA was confirmed by a rheumatologist, thus ensuring that the diagnosis was correct. We cannot exclude the possibility that disease-modifying antirheumatic drug therapy influenced the results of our study. However, current literature suggests that such therapy would have resulted in underestimation of the true risk for CAD in RA. The RA group included fairly small proportions of patients with diabetes, smoking, and prior CAD. Although the control group was matched to account for these factors, mortality and positive results on EE in the study's RA and control groups may have been lower than what could be expected in the general population. Insufficient information was available to ascertain the cause of death, and all-cause death was measured instead.[20] A referral bias may exist, because this study was performed at a tertiary-care facility. Finally, patient recruitment occurred over an extended time period, during which advancements in the treatment of CAD and RA may have influenced patient outcomes.

CONCLUSION

Although the number of patients undergoing coronary angiography was small, EE was a sensitive and specific method for diagnosing CAD in patients with RA. Overall, patients with RA had a 2-fold increased risk for myocardial ischemia on EE compared with matched controls. This risk increased with increased duration of RA. Among patients with RA, the presence of myocardial ischemia on EE significantly decreased 5-year survival.

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