Differences in Atherosclerotic Coronary Heart Disease Between Subjects with and without Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular diseases (CVD). We compared the histologic features of coronary artery disease in patients with RA and non-RA controls.

Methods. Forty-one RA patients who died and underwent autopsy between 1985 and 2003 were matched to 82 non-RA controls of the same age and sex with similar history of CVD and autopsy date. Coronary arteries were submitted for histologic evaluation. The grade of stenosis was evaluated in each artery. The numbers of vulnerable plaques and acute coronary lesions were counted. The composition of a representative stable and vulnerable plaque from each vessel was evaluated. Chi-square tests were used to compare differences between groups.

Results. Patients and controls had similar age at death (mean 79 yrs) and 61% were female in both groups. Overall, there was no significant difference in grade of stenosis or number of acute coronary lesions. Among subjects with CVD, 54% of controls had grade 3–4 lesions in left main artery versus only 7% of patients ($p = 0.023$). Vulnerable plaques in left anterior descending (LAD) artery were significantly more common in patients than controls ($p = 0.018$). Inflammation was observed more frequently in patients, in both the media of left circumflex ($p = 0.005$) and adventitia of LAD artery ($p = 0.024$). Similar trends were seen for subjects with heart failure.

Conclusion. There was less histologic evidence of atherosclerosis but greater evidence of inflammation and instability in RA patients compared to controls. These differences suggest that the mechanisms responsible for cardiovascular morbidity and mortality may be different in patients with RA. (First Release Mar 15 2007; J Rheumatol 2007;34:937–42)

Key Indexing Terms:
CORONARY DISEASE RHEUMATOID ARTHRITIS INFLAMMATION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory condition affecting roughly 1% of the adult general population. Subjects with RA have a reduced life expectancy and higher mortality rates compared with the general population. This excess mortality is generally attributed to mortality from cardiovascular disease (CVD)[1]. Patients with RA also appear to have increased morbidity from CVD when compared to non-RA subjects[2-4].

Atherosclerosis is generally recognized as an immune-mediated inflammatory disorder characterized by the presence of activated lymphocytes within atherosclerotic plaques, with inflammation playing a key role in coronary instability[5-7]. Atherosclerosis appears to share many similarities with RA, including mast cell and T cell activation, increased C-reactive protein (CRP) concentrations, and expression of adhesion molecules. Thus, it has been postulated that the systemic inflammation in RA may also have deleterious effects on the vessel wall[8,9]. Inflammatory markers, especially CRP, have been suggested to be independent risk factors for atherosclerosis[10].

We have previously shown that markers of systemic inflammation confer a statistically significant additional risk for cardiovascular death among patients with RA, even after controlling for traditional cardiovascular risk factors and comorbidities[11].

Therefore coronary artery disease is emerging as a major determinant of cardiovascular morbidity and mortality in RA[11-14]. Further, there is some evidence, at the level of the carotid arteries, of early atherosclerosis as measured by ultrasound in patients with RA[15], which correlates with high levels of CRP[16]. Together, these data suggest that RA patients may have earlier, more severe or more vulnerable coronary artery disease. Our goal was to compare the pathologic features of coronary atherosclerosis from autopsied hearts identi-

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fied from a population-based incidence cohort of RA patients compared to age- and sex-matched individuals from the same underlying population who did not have RA.

MATERIALS AND METHODS

Subjects and design. This was a retrospective population-based study of patients with RA and age- and sex-matched subjects without RA who died and underwent autopsy between 1985 and 2003 in Olmsted County, Minnesota, USA. RA patients included in this study were part of a previously described inception cohort of Rochester, Minnesota, residents aged ≥ 18 years[14,17], who were diagnosed with RA between January 1, 1955, and January 1, 1995 (based on 1987 American College of Rheumatology criteria for RA[18]). For each RA patient who died and underwent autopsy between 1985 and 2003, 2 control subjects were selected. Controls were matched on age (± 1 yr), sex, presence or absence of CVD, and autopsy date (± 1 yr). Similar history of CVD was defined as presence of heart failure (HF; Framingham Heart Study Criteria[19]) and/or ischemic heart disease, including hospitalization for myocardial infarction (MI), silent MI, revascularization procedures, and angina pectoris.

The study was approved by the Mayo Clinic Institutional Review Board.

Clinical data collection. The entire inpatient and outpatient medical records of the study subjects from all healthcare providers in Olmsted County were reviewed longitudinally starting at 18 years of age (or date of migration to Olmsted County for those who first became residents after age 18) and continuing until death. Information was collected regarding RA disease characteristics, clinically documented occurrence of cardiovascular events, cardiovascular risk factors, and the results of erythrocyte sedimentation rate (ESR) tests.

Details of data collection and definitions have been described[14,17]. In brief, hospitalization for MI was defined using standardized epidemiological criteria, based on cardiac pain, biomarker levels, and Minnesota coding of the electrocardiogram (ECG)[20]. Silent MI was considered at the date of first documentation of characteristic ECG or recorded physician diagnosis in a subject with no documented history of previous MI. Cardiovascular risk factors were ascertained throughout followup and defined according to established diagnostic criteria, as described[14,17]. RA disease activity during the 2 year period prior to death was defined as elevated ESR of ≥ 39 mm/h or any change in drug therapy during the same 2 year period.

Histopathologic data. Hearts were available from all patients who had undergone autopsy. The left main artery (LMA), left anterior descending (LAD), left circumflex (LCX), and right (RCA) coronary arteries were dissected from the epicardium and decalcified either at the time of autopsy or for the purpose of the study. They were then cross-sectioned at 3-mm intervals and entirely submitted for microscopic examination. Histologic slides were stained with hematoxylin-eosin and Verhoeff-van Gieson and reviewed by 2 pathologists (MCA and WDE).

An overall grade of stenosis was assessed in each artery according to the most severe obstruction in cross-sectional area (grade 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4, > 75% stenosis)[21]. Extent of coronary atherosclerosis was defined as the total number of vessels with severe disease defined as grade 4 (of 4) stenosis in LAD, LCX, and RCA and grade 3 or 4 in the LMA[22]. Multiple vessel disease was defined as 2 or more coronary arteries with grade 4 (of 4) stenosis and/or LMA with grade 3 or 4 stenosis.

A plaque was considered vulnerable if it had a fibrous cap < 65 μm thick and contained > 25 inflammatory cells per high-power (x40) field[23]. All other plaques were classified as stable. The numbers of stable and vulnerable plaques were counted in each vessel. Acute lesions (plaque rupture or erosion, luminal thrombus, plaque hemorrhage, or post-angioplasty dissection) were documented, if present.

Composition of one representative stable and vulnerable plaque was assessed using a semiquantitative evaluation of plaque components. Components of plaque included dense fibrous tissue/collagen, calcifications, cellular tissue/smooth muscle cells, lipid/foam cells, elastic tissue, and inflammation (other than foam cells). These components were expressed as a percentage of the total plaque area for a sum of 100%. Inflammation of media and adventitia was semiquantitatively assessed as none, mild, moderate, and severe.

Presence of MI, along with location and extent, was noted and classified as acute or old based on histologic features.

Statistical analysis. Descriptive statistics (means, proportions, etc.) were used to summarize the data. Chi-square and Fisher's exact tests were used to evaluate differences between groups (RA and non-RA) for categorical and dichotomous variables. The rank-sum test was used to examine differences between groups for continuous variables. In order to determine whether RA patients who died and underwent autopsy were representative of patients who died and did not undergo autopsy, presence of CVD and cardiovascular risk factors were compared.

RESULTS

The mean age at death among the 41 patients with RA was 79.2 years and 61% were women. The age/sex-matched control group comprised 82 subjects without RA; their mean age at death was 79.3 years and 61% were women. There were no statistically significant differences in prevalence of traditional risk factors for CVD between patients and non-RA subjects (Table 1). Twenty-five patients (61%) with RA and 51 subjects (62%) without RA had a clinical history of CVD, including 18 patients and 34 non-RA controls diagnosed with HF.

In the overall group of 41 patients with RA and 82 controls without RA, no significant differences were noted for severity and extent of atherosclerosis, proportion of subjects with infarcts, number of acute coronary lesions, type of plaques (stable vs vulnerable), or composition of plaque. However, more RA patients (32% vs 11%) had medial inflammation of the LCX (p = 0.005) and adventitial inflammation of LAD (90% vs 72%; p = 0.024).

In the subset of subjects with CVD, significant differences were noted between patients (n = 25) and non-RA subjects (n = 51). Indeed, only 32% of RA patients with CVD had multiple vessel disease, in contrast to 61% of non-RA subjects with CVD (p = 0.018). RA patients with CVD had less severe coronary artery disease, as expressed by extent of atherosclerosis (Figure 1A) and overall grade of stenosis (Figure 1B) compared to non-RA subjects with CVD. Extent of atherosclerosis was less severe in RA patients, with 32% showing a score > 2 in contrast to 61% of non-RA subjects (p = 0.011;

Table 1. Demographic and clinical characteristics of 41 patients with RA and 82 controls who died between 1985 and 2003 and underwent autopsy.

Variable	RA, n = 41	Controls, n = 82	p
Age at death, yrs, mean ± SD	79.2 ± 9.2	79.3 ± 9.3	0.96
Women, n (%)	25 (61)	50 (61)	1.00
Cardiovascular disease, n (%)	25 (61)	51 (62)	0.90
Heart failure, n (%)	18 (44)	34 (41)	0.80
Risk factors			
Diabetes mellitus, n (%)	13 (32)	20 (24)	0.39
Dyslipidemia, n (%)	22 (59)	55 (76)	0.07
Smoker, n (%)	24 (62)	41 (52)	0.32
Hypertension, n (%)	35 (85)	77 (94)	0.12
Body Mass Index ≥ 30 kg/m^2, n (%)	9 (22)	22 (28)	0.46

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Figure 1A). Overall grades of stenosis were significantly lower in the LMA (p = 0.023) and LCX (p = 0.029) of RA patients with CVD compared to non-RA subjects with CVD (Figure 1B). Grade 3–4 lesions in LMA were present in 54% of non-RA subjects and only 7% of patients. Although it did not reach statistical significance, a similar trend was also seen in the LAD and RCA.

RA patients with CVD had significantly more vulnerable plaques in the LAD (48% vs 22% in non-RA subjects; p = 0.018) compared to non-RA subjects with CVD (Figure 2). Also, 30% of RA patients with CVD had medial inflammation of LCX compared to 9% in non-RA subjects with CVD (p = 0.024). Plaque composition, proportion of subjects with infarcts, and number of acute lesions were similar in both groups.

Similar comparative findings were observed in the subset of subjects with HF. Indeed, only 6 (33%) of 18 RA patients with HF had multiple vessel disease in comparison to 20 (59%) of 34 non-RA subjects with HF (p = 0.08). Similarly, the extent of disease and grade of stenosis were less severe in RA patients compared to non-RA subjects (Figure 3B). The comparisons did not always reach statistical significance, likely due to the smaller number of subjects in this subset.

The potential bias of undergoing an autopsy was evaluated

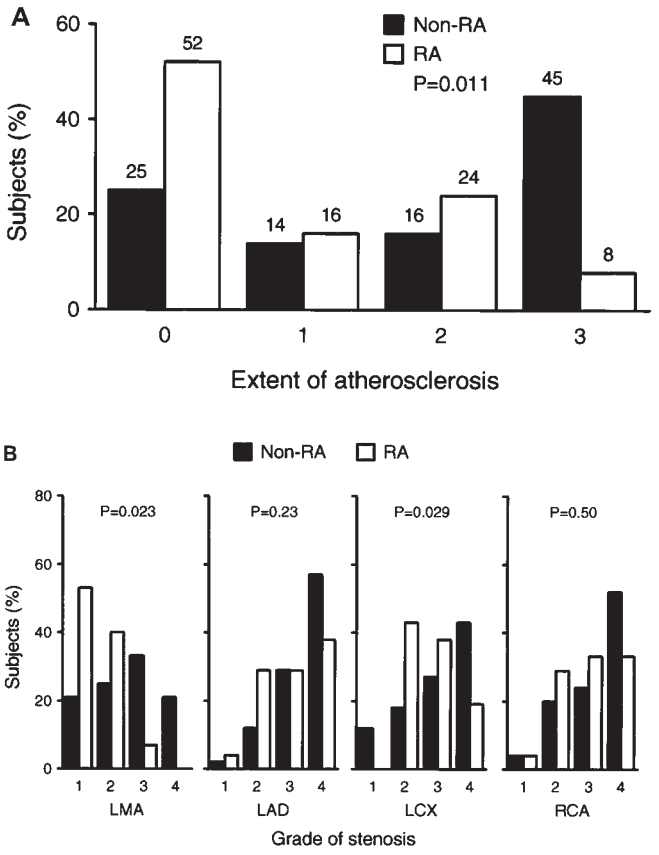

Figure 1. Proportion of study subjects with extent of atherosclerosis (A) and overall grade of stenosis in LMA, LAD, LCX, and RCA (B) among 25 RA patients with CVD and 51 controls with CVD.

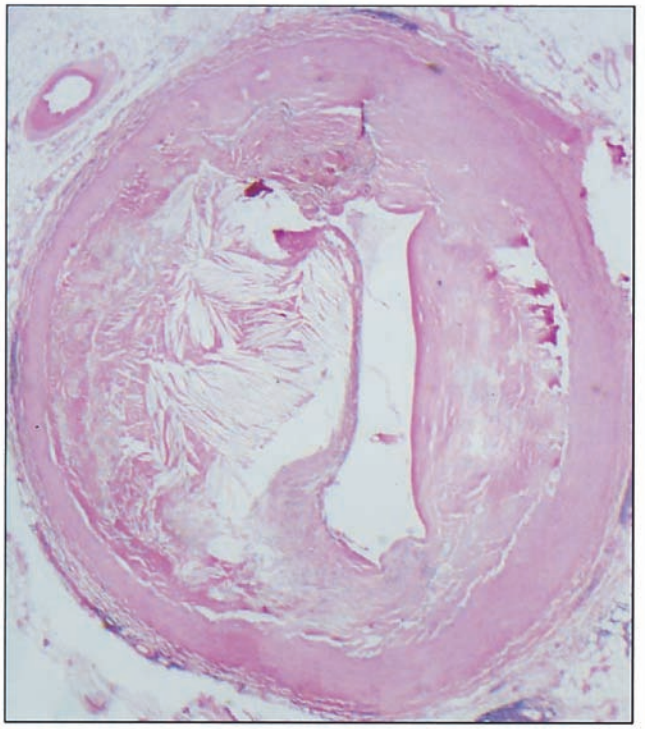

Figure 2. Low-power photomicrograph of vulnerable plaque (H&E, 20x). RA patients had more vulnerable plaques in the left anterior descending artery (48% in RA vs 22% in controls; p = 0.018).

by comparing the characteristics of the 41 RA patients who died and underwent autopsy with 163 patients who died and did not undergo autopsy. No significant differences were found in CVD and cardiovascular risk factors (Table 2).

We also assessed the relationship of RA disease activity at time of death and the morphology of coronary arteries. Twenty-six RA patients did not have active disease during the period of 3 months to 2 years prior to death, whereas 15 did. No significant differences were found in the severity and extent of atherosclerosis or in the type and composition of plaques, according to RA disease activity.

DISCUSSION

RA, inflammation, and coronary artery disease. Our findings of increased inflammation in the walls of coronary arteries combined with an increased frequency of vulnerable plaques in RA patients suggest a role for inflammation in the development of coronary atherosclerosis and CVD in these subjects. Since numerous investigators have described the importance of inflammation in the pathogenesis of atherosclerosis and its increased presence in vulnerable plaques[5-7,24], it is possible that systemic inflammation acts independently or in synergy with traditional risk factors in the development of atherosclerosis in patients with RA.

We previously showed that RA patients with persistently elevated ESR values and RA complications have a significantly higher risk of cardiovascular death[11], even after adjust-

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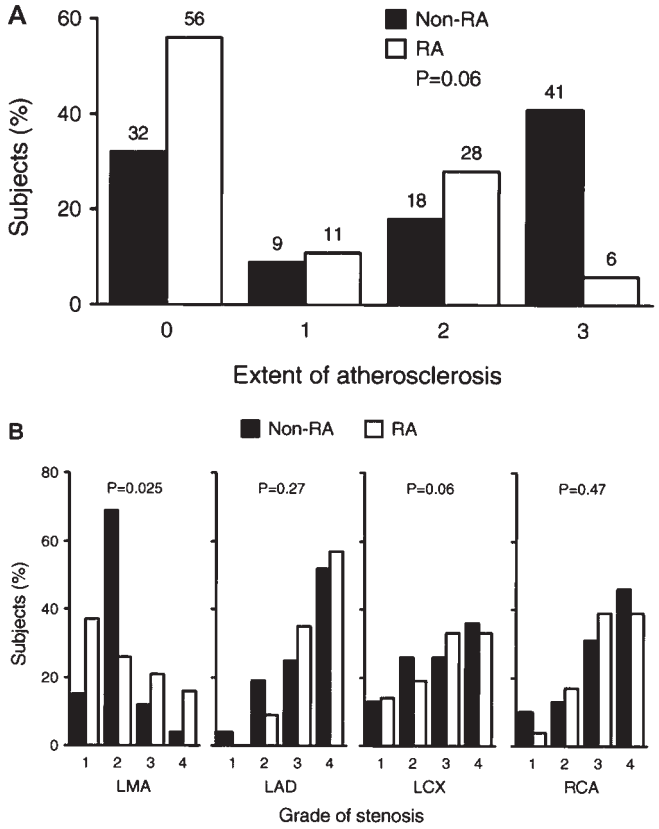

Figure 3. Extent of atherosclerosis (A) and overall grade of stenosis in LMA, LAD, LCX, and RCA (B) among 18 RA patients with heart failure and 34 controls with heart failure.

Table 2. Demographic and clinical characteristics of 41 RA patients who died between 1985 and 2003 and underwent autopsy and 163 patients who died between 1985 and 2003 and did not undergo autopsy.

Variable	RA Autopsy, n = 41	RA Non-autopsy, n =163	p
Age at death, yrs, mean ± SD	79.2 ± 9.2	79.8 ± 11	0.74
Women, n (%)	25 (61)	117 (72)	0.18
Cardiovascular disease, n (%)	25 (61)	98 (60)	0.92
Heart failure, n (%)	18 (44)	81 (50)	0.51
Risk factors			
Diabetes mellitus, n (%)	13 (32)	38 (23)	0.27
Dyslipidemia, n (%)	22 (59)	102 (70)	0.23
Smoker, n (%)	24 (62)	100 (62)	0.95
Hypertension, n (%)	35 (85)	151 (93)	0.14
Body Mass Index ≥ 30 kg/m^2, n (%)	9 (22)	31 (19)	0.73

ment for cardiovascular risk factors and comorbidities. This result is consistent with a study by Wallberg-Jonsson, *et al* that found a correlation between elevated ESR and cardiovascular events in patients with RA[25]. Elevated concentrations of serum CRP have also been described in the general population of subjects dying of severe coronary artery disease, and their levels correlated with the numbers of vulnerable plaques[23]. Similarly, a correlation between high levels of CRP and increased intima-media thickness (IMT) of the carotid artery, used as a surrogate marker of generalized atherosclerosis, was reported in subjects with RA[16]. Taken together these findings suggest that active systemic inflammation is a predictor of atherosclerotic coronary heart disease in RA.

Notably, the increased inflammation observed in RA patients in our study was not generalized but rather was confined to only a few vessels. This could be explained in part by the absence of active disease at the time of death in most patients. Indeed, findings at autopsy reflect the degree of inflammation at the time of death, and may not accurately reflect the degree of inflammation occurring during a lifetime or the course of the illness. However, we could not determine an association between coronary artery atherosclerosis and activity of disease at time of death in the patients with RA. There are several potential explanations for this. First, disease activity can be estimated only imprecisely in this study due to our reliance on information recorded in the medical records. Another potential explanation for this apparent discrepancy is that the majority of RA patients did not die of an acute coronary event.

Indeed, inflammation is thought to play a key role not only in the formation of plaques but most importantly in their rupture, leading to acute coronary syndromes[7]. This has been corroborated by several studies showing differences in the amount of chronic inflammation in atherosclerotic plaque at autopsy in subjects dying of acute MI compared to subjects with old MI and stable angina and subjects without ischemic heart disease[24,26]. Subjects dying of acute MI have significantly more inflammation in their plaques than subjects with old MI or stable angina, who in turn have more inflammation than subjects without ischemic heart disease. Therefore, even though patients with RA might have experienced more acute coronary events over the course of their disease, perhaps reflecting increased systemic inflammation and disease activity, this may not necessarily be evident, pathologically, at the time of autopsy, especially if the cause of death was unrelated to an acute coronary event.

RA and severity of atherosclerosis. Our results showed that RA patients had less severe coronary artery disease compared to our control subjects. This appears to be in contrast to several vascular imaging studies, which suggested increased coronary artery disease in RA patients. One study examined extent of calcium in coronary arteries as measured by electron-beam computed tomography, a marker for coronary atherosclerosis[12]. The authors described increased prevalence and severity of coronary calcification in patients with established RA, suggesting increased early coronary artery disease. However, coronary calcification does not tend to reveal vulnerable plaques, which are associated with increased inflammation, are prone to rupture, and lead to acute coronary events. The presence of inflammatory cells and vulnerable plaques in our RA patients suggests that the atherosclerotic plaques in RA have unique morphology that renders them

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more prone to rupture despite no significant atherosclerotic burden. This is consistent with the atypical clinical presentation of atherosclerotic heart disease in RA patients with lower likelihood of angina symptoms and more unrecognized MI and sudden deaths[2,3,14]. Indeed, although the site of rupture with secondary thrombosis leading to acute MI often occurs on severely stenotic plaques (> 90% stenosis)[27], several investigators have demonstrated that in sudden death, the culprit plaques are more often vulnerable and show < 75% stenosis or < 50% diameter reduction[28,29]. Therefore, it is possible that our population of RA patients had less severe atherosclerosis that was associated with more inflammatory changes still capable of resulting in significant cardiovascular morbidity and mortality.

Carotid IMT is frequently used as a surrogate measure of generalized atherosclerosis, and of coronary artery disease in particular[30]. Unfortunately, studies that compared IMT in RA patients and controls have adopted vastly divergent methodologies, and consequently reported conflicting results[15,31-38]. Indeed, findings have been inconsistent regarding the role of disease-specific factors such as disease duration, inflammatory markers, and contribution of cardiovascular risk factors. These inconsistent findings are due in part to small sample sizes (mostly ~50 patients) and in part to differences in inclusion, exclusion, and matching criteria. Although the majority of studies matched for age, sex, and race, and some for menopausal status, the inclusion/exclusion criteria of subjects with history of clinical CHD and presence of cardiovascular risk factors were different in each study. As well, the aim of the studies often was to investigate the presence of early atherosclerosis before the onset of significant CVD. Interestingly, 2 studies with large cohorts of patients failed to detect increased IMT in RA patients[37,38]. Roman and colleagues indeed showed that IMT was significantly less in RA patients compared to controls, although the percentage of atherosclerotic plaques was higher[38]. The investigators contended that atherosclerotic plaques are a better surrogate than IMT, and that IMT likely reflects blood pressure and not atherosclerosis, with similar findings shown in patients with lupus erythematosus. This is further supported by a large autopsy study that compared the morphology of atherosclerosis in carotids to that of coronary arteries, and did not find a good correlation[39].

Our study population was significantly different than the subjects included in the carotid IMT studies in patients with RA. We included subjects irrespective of presence of traditional cardiovascular risk factors or CVD. Yet we stratified our analyses according to presence of CVD and HF. Therefore, nearly all RA patients had established CVD, with an equal distribution of subjects with HF, with acute and old myocardial infarcts, and equal distribution of traditional risk factors. Thus, in the clinical context of established CVD, our RA patients showed not only less severe coronary artery disease but a different morphology, with more vulnerable plaques and more inflammation. These morphologic findings are consistent with our clinical observations that RA patients have twice the risk of developing HF, independently of traditional cardiovascular risk factors and clinical evidence of ischemic heart disease, suggesting mechanisms other than coronary artery disease are likely implicated in CVD of patients with RA[17,40].

An alternative explanation for our findings is that atherosclerosis involving the microvasculature, instead of major epicardial vessels, as described by Raza, *et al*[41], may play a significant role in RA, in a fashion similar to that described in diabetic patients[42]. However, the microcirculation was not evaluated in our study.

Our study is the first morphologic comparison of coronary arteries in a representative population of RA patients compared to non-RA subjects; however, it has a number of potential limitations. Because our observations were based on autopsied subjects, the findings may not be generalizable across all individuals in the population. Indeed, in Olmsted County, the rate of autopsy has declined over the years and the odds of having an autopsy appear to be related to male sex, hospital death, and antemortem diagnosis of CVD[43]. Nonetheless, we identified no significant differences between the RA patients who underwent autopsy and patients who did not (Table 2). As noted above, the pathologic findings at autopsy may not reflect inflammation and disease activity during the lifespan of RA patients. Our study was also limited by small sample size, which reduced the power to detect potentially important differences. Although we worked diligently to achieve comparability of RA and non-RA subjects by matching for age, sex, autopsy date, and presence or absence of CVD, which had not been done in most RA studies looking at coronary disease, we were capable of comparing only one specific subgroup of the subjects — those with heart failure. This subgroup contained a sufficient number of cases to give it power, and interestingly, the findings were similar to the overall group. Another important subgroup for analysis would have been subjects who died of an acute MI, but since only 5 out of the 41 RA patients (and 9 out of 82 controls) were in this category, the study did not have enough power to examine plaque histopathology in this subset.

Finally, because our population consisted of Olmsted County residents, a community that is 90% Caucasian, our findings cannot be generalized to non-Caucasian subjects.

The histologic findings of increased vulnerable plaques and inflammation in a subpopulation of RA patients support the role of inflammation in the development of CVD in these subjects. Moreover, the observation of less severe coronary artery disease grade suggests that alternative mechanisms (besides ischemia) explain the excess risk of cardiovascular disease and heart failure in this population.

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