Different Type of Carotid Arterial Wall Remodeling in Rheumatoid Arthritis Compared with Healthy Subjects: A Case-Control Study

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ABSTRACT. ***Objective.*** Rheumatoid arthritis (RA) is associated with an increased cardiovascular (CV) risk, but mechanisms behind this increased risk have not been fully elucidated. Carotid arterial remodeling is the change of structural properties in response to hemodynamic or metabolic factors aimed at keeping wall stress within certain limits. This process might become maladaptive when stress on the arterial wall increases beyond these limits. We investigated whether maladaptive carotid arterial remodeling is present in RA compared with control subjects.

Methods. The 2 cohorts were 96 patients with RA and 274 healthy subjects, who were investigated cross-sectionally. Carotid intima-media thickness (cIMT) and interadventitial diameter (IAD) were assessed by B-mode carotid ultrasonography. Lumen diameter (LD), circumferential wall stress (CWS), and circumferential wall tension (CWT) were calculated. Linear regression analyses were used to investigate the association between presence of RA and carotid arterial remodeling.

Results. Compared with healthy subjects, RA was associated with a 0.40 mm (9.3%) greater LD, 0.41 mm (7.8%) greater IAD, 10% higher CWS, and 8% higher CWT. The groups had comparable cIMT. Associations remained similar after exclusion of patients with prior CV disease and after adjustment for demographic factors and CV risk factors.

Conclusion. RA is associated with maladaptive outward carotid arterial remodeling. These results are relevant because maladaptive outward remodeling is associated with plaque instability and rupture. These results indicate an alternative pathway, beyond the traditional CV risk factors, in RA that amplifies the CV risk. (First Release Oct 1 2012; J Rheumatol 2012;39:2261–6; doi:10.3899/jrheum.120617)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CAROTID ARTERIAL WALL REMODELING
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Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints affecting about 1% of the general population[1]. RA has been associated with an increased risk of cardiovascular (CV) disease, which is not fully accounted for by traditional CV disease risk factors[2,3]. Hence, the search for additional mechanisms linking RA to CV disease is relevant.

Because of inflammatory, metabolic, and/or hemodynamic alterations within the arterial environment, carotid arterial remodeling might develop as an adaptive mechanism aimed at keeping shear stress within certain limits[4]. Remodeling is maladaptive when changes in the vascular wall are accompanied by an elevated circumferential wall stress (CWS) and circumferential wall tension (CWT).

Arterial remodeling can be distinguished into inward and

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outward remodeling. Inward remodeling is characterized by a decrease in lumen diameter [LD, with more increased carotid intima-media thickness (cIMT) than interadventitial diameter (IAD)], and outward remodeling is characterized by an increased LD (with more increased IAD than cIMT)[4,5]. Outward remodeling is associated with degradation of subendothelial matrix by metalloproteinases, and may increase the risk of plaque rupture[5,6]. Inward remodeling results in luminal narrowing but stable atherosclerotic plaque because of more fibrous tissue and calcifications in the vessel wall.

To date, increased LD and IAD corresponding with outward remodeling have been found in a study examining female patients with RA[7]. However, whether these findings implicate a maladaptive carotid arterial remodeling is not clear. The goal of our study was to examine the type, if any, of carotid arterial wall remodeling in RA.

MATERIALS AND METHODS

CARRÉ study (RA). The CARRÉ study is a prospective cohort study investigating CV disease and its risk factors in patients with RA[8]. In 2000, a random sample was drawn of patients with RA registered at the Jan van Breemen Research Institute – Reade in Amsterdam, The Netherlands. Patients fulfilled the 1987 American College of Rheumatology classification criteria for RA, and were aged between 50 and 75 years[9]. An ultrasound study of the carotid artery was performed in 2001 in a randomly selected subgroup of 102 patients. From these, 96 nondiabetic patients with RA were selected for our study (6 participants with known diabetes mellitus or a fasting glucose level > 7 mmol/l were excluded). Data regarding health status, medical history, and medication use were assessed by questionnaires, as reported[8]. A physical examination was performed to determine the 28-joint Disease Activity Score (DAS28)[10]. In addition, to assess the functional (disability) status, the self-reported patient-oriented Health Assessment Questionnaire (HAQ) was used (a generic measure for various chronic diseases)[11]. Further, the presence or absence of erosions on radiographs of hands and feet were recorded (yes/no).

Hoorn study (healthy subjects). The Hoorn Study is a Dutch cohort study of glucose tolerance and CV risk factors[12]. For our study, data were used from a random sample of all men and women aged 50 to 75 years, drawn from the municipal population registry office of Hoorn in 1989 (n = 2484)[13]. In 2000, a followup examination including ultrasound was carried out among all surviving participants. For the present analyses, we selected a subgroup of 274 participants with a normal glucose metabolism (according to the 1999 World Health Organization criteria[14]). Subjects using antirheumatic drugs or with a verified diagnosis of RA were excluded. The local ethics committees approved both study protocols and all participants gave their written informed consent for the studies in accord with the Declaration of Helsinki.

Assessment of CV disease and risk factors in study protocols. CV disease history was based on the participant's medical records, obtained from the participant's general practitioner or hospital. CV disease consisted of coronary, cerebral, or peripheral arterial disease. In brief, coronary disease was defined as a history of myocardial infarction confirmed by a cardiologist, or a percutaneous transluminal coronary angioplasty, or surgery for ischemic heart disease. Cerebral arterial disease was defined as a history of stroke or transient ischemic attack confirmed by a neurologist or a carotid endarterectomy. Peripheral arterial disease was defined as peripheral arterial reconstructive surgery or limb amputation. In both cohorts, ascertainment of CV risk factors was done according to similar standard procedures. Body mass index was calculated as the ratio of weight and squared height. Hypertension was defined as a systolic blood pressure (SBP) over 140 mm Hg and/or a diastolic blood pressure (DBP) over 90 mm Hg and/or current use of antihypertensive medication. Mean arterial pressure (MAP) was defined as [(2 × DBP) + SBP]/3. Triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were determined from fasting blood samples by enzymatic techniques[13].

Ultrasonography. In both studies, the observers, who were unaware of the participants' clinical or laboratory characteristics, performed an ultrasound analysis of the right common carotid artery. The 2 observers were both physicians trained by the Institute for Cardiovascular Research of the Vrije Universiteit of Amsterdam. Similar protocols, standard operating procedures, and equipment were used. Each observer performed a reproducibility test with other experienced observers from the institute before starting to perform measurements. Interobserver and intraobserver variability were good, with variations < 10%. Measurements were performed with a 7.5-MHz linear probe, connected to a computer equipped with vessel wall movement detection software and an acquisition system (Wall track system, Pie Medical) that enables measurement of the IAD and cIMT. After localization of the common carotid artery, cross-sectional measurements were performed 10 mm proximal of the carotid bulb. Sites with mural atherosclerotic plaques were avoided because of difficulty in identifying carotid arterial variables in these regions[15]. The distance between the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall corresponds with cIMT, and the distance between the media adventitia interface of the near and far wall corresponds with the IAD. Measurements of IMT and IAD were triggered by echocardiogram to the R-peak of the cardiac cycle. LD was calculated with the following formula: LD = IAD – (2 × cIMT) in mm. Carotid pulse pressure (PP) was estimated by calibration of the distension waveforms[13]. Pulsatile and mean CWS and CWT were calculated as follows: pulsatile CWT (in kPa) = PP × (LD/2), pulsatile CWS (kPa) = CWT/IMT, mean CWT (kPa) = MAP × (LD/2), and mean CWS (kPa) = CWT/IMT[16].

Statistical analyses. Characteristics of both study populations are presented as means ± SD, median (interquartile range) in case of skewed variables, or percentages in case of categorical data. Student's t test, Mann-Whitney U test, and Pearson's chi-square test were used to compare baseline characteristics between patients with RA and healthy subjects. Linear regression analyses were performed to assess the association between carotid arterial wall variables and RA. Additional adjustment was performed for demographic factors, blood pressure variables (MAP and carotid PP), use of cardioprotective medication (antihypertensives and statins), and CV risk factors (total cholesterol, smoking, prior CV disease, and hypertension).

Analyses were repeated after exclusion of subjects with prior CV disease (n = 27) and with exclusion of patients with RA who had an impaired fasting glucose (n = 6). Additional regression analyses were performed among patients with RA to investigate whether RA-related factors [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), DAS28, HAQ, bone erosions, disease duration, rheumatoid factor positivity, and use of antiinflammatory treatment] were associated with the various carotid arterial wall variables. Analyses were carried out using SPSS 17.0 software (SPSS Inc.) and p values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics. Baseline characteristics of patients with RA and healthy subjects are shown in Table 1. Patients with RA were more often hypertensive and smokers, but were also younger. The majority of patients with RA were immunoglobulin (Ig) M rheumatoid factor-positive and had erosions on radiographs. Patients with RA had average disease duration > 8 years and moderately active disease with mean DAS28 of almost 3.4. Most patients with RA used a disease-modifying antirheumatic drug (DMARD) at baseline (66% methotrexate, 23% sulfasalazine, and 14% pred-

Table 1. Baseline characteristics. Data are mean ± SD, median (interquartile range), or percentage, as appropriate.

Characteristic	Healthy Subjects, n = 274	Patients with RA, n = 96
Demographics		
Age, yrs	69 ± 6	63 ± 7*
Sex, % males	49	40
Cardiovascular risk factors		
Systolic blood pressure, mm Hg	137 ± 20	142 ± 18*
Diastolic blood pressure, mm Hg	74 ± 9	78 ± 9*
Mean arterial pressure, mm Hg	95 ± 12	99 ± 11*
Carotid pulse pressure, mm Hg	59 ± 17	53 ± 14*
Antihypertensives, %	25	24
Hypertension, %	55	59*
Total cholesterol, mmol/l	5.80 ± 1.02	5.69 ± 1.01
LDL cholesterol, mmol/l	3.7 (3.1–4.2)	3.6 (3.0–4.4)
HDL cholesterol, mmol/l	1.51 ± 0.43	1.47 ± 0.48
Triglycerides, mmol/l	1.2 (0.9–1.6)	1.3 (1.0–1.7)
Statin use, %	13	12
Prior CV events, %	8	15
Body mass index, kg/m^2	26.1 ± 3.2	26.0 ± 4.3
Waist-hip ratio	0.91 (0.83–0.97)	0.89 (0.83–0.96)
Current smoking, %	15	31*
Pack-yrs	22 (9–34)	28 (18–42)
RA-related factors		
ESR, mm/h	—	18 (8–27)
CRP, mg/l	—	6 (3–15)
DAS28	—	3.44 ± 1.23
HAQ	—	0.63 (0.13–1.00)
Bone erosions, %	—	81
RA disease duration, yrs	—	8.7 ± 3.3
RF positivity, %	—	70
Current NSAID use, %	—	66
Current methotrexate use, %	—	64
Current sulfasalazine use, %	—	23
Current prednisone use, %	—	14

* $p < 0.05$. HAQ: Health Assessment Questionnaire; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NSAID: nonsteroidal anti-inflammatory drugs; CV: cardiovascular; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; RA: rheumatoid arthritis; RF: rheumatoid factor.

nisone). None of the participants used a biologic DMARD. Figure 1 shows the mean values of carotid properties according to the presence or absence of RA.

Ultrasonography and carotid arterial wall variables. The association of carotid arterial wall variables and presence of RA is shown in Table 2. Compared with healthy subjects, LD and IAD were higher in RA (6.43 mm and 8.04 mm vs 6.13 mm and 7.79 mm; $p = 0.03$, $p = 0.08$, respectively). There was no difference in cIMT between patients with RA and healthy subjects (0.81 mm vs 0.83 mm; $p = 0.08$). While mean and pulsatile CWS was not different between groups, patients with RA did have significantly higher mean CWS and CWT (509 kPa and 319 kPa vs 452 kPa and 295 kPa; $p = 0.004$, $p = 0.004$, respectively). These differences remained statistically significant after adjustment for important confounders (Table 2). Adjustment for demographics, blood pressure variables (local carotid PP), and CV risk factors did not essentially change the results. Results were similar when patients with prior CV disease and/or RA patients with impaired fasting glucose level were excluded from analyses.

Carotid arterial wall measurements and markers of inflammation. Additional regression analyses were performed to investigate the association between several RA-related factors and carotid arterial wall variables (Table 3). Only the HAQ, CRP, and current use of prednisone were associated with a lower IMT.

DISCUSSION

Our study shows that RA is associated with maladaptive outward carotid arterial remodeling, demonstrated by a higher mean circumferential wall stress and tension. These findings are relevant because this might contribute to plaque instability and rupture[17].

The increased CV burden in RA is thought to be due to the chronic inflammatory process inherent to RA, as inflammation also seems to play a pivotal role in the atherosclerotic process[18,19]. Traditional surrogate markers of CV risk, such as cIMT, do not convey the CV risk in RA accurately[20,21]. Studies into the atherosclerotic process have shown that the fibrous cap of an atherosclerotic plaque becomes thinner (and thus more vulnerable) when the inflammatory process within the plaque intensifies[22,23]. These vascular changes may result in plaque rupture and lead to myocardial infarction or stroke.

Inflammation may play a role in this process by causing outward carotid arterial remodeling, because inflammatory cells produce damaging metalloproteinases, which in turn inhibit proliferation and promote apoptosis of smooth muscle cells in the arterial walls, leading to outward remodeling and medial thinning[5]. The initial reactive process of outward remodeling becomes maladaptive when circumferential wall stress and tension are not compensated and thus remain elevated. Increased mean CWS (calculated using MAP) as well as pulsatile CWS (calculated using local PP) are implicated in large-artery remodeling[24]. Although pulsatile CWS is best known for enhancing atherogenesis[25], mean CWS can cause rupture of load-bearing elastin fibers in response to the fatiguing effect of tensile stress[24,26].

As a consequence, elevated mean CWS and CWT will increase the risk for rupture of underlying structures, such as the fibrous cap of the atherosclerotic plaques. Hence, one may hypothesize that patients with an inflammatory disease, such as RA, are more prone for plaque rupture because of a more outward process of remodeling and with increased mean CWS.

There are few studies of the structural differences of carotid arterial wall variables between patients with RA and healthy individuals. Schott and colleagues described an increased LD and IAD in female patients with RA and

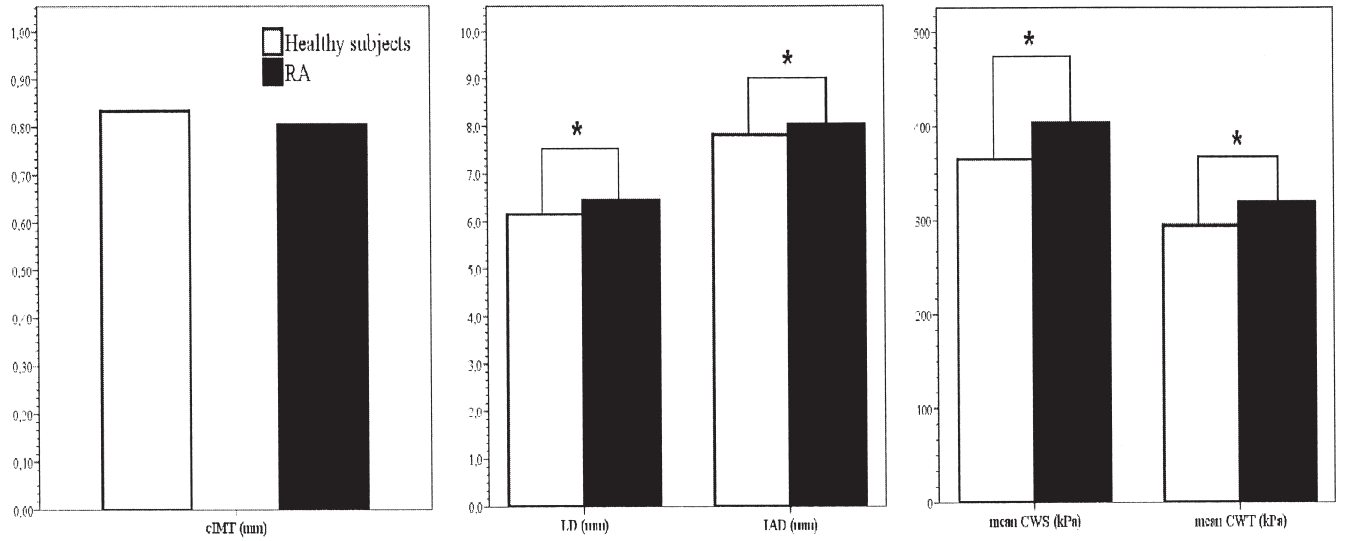

Figure 1. Mean values of carotid intima-media thickness (cIMT), lumen diameter (LD), interadventitial diameter (IAD), circumferential wall stress (CWS), and circumferential wall tension (CWT), comparing healthy subjects and patients with rheumatoid arthritis (RA). * $p < 0.05$.

Table 2. Linear regression analyses addressing rheumatoid arthritis (RA) as a predictor of various carotid artery wall characteristics. Results are presented as regression coefficients (95% CI) reflecting differences (in mm) of carotid arterial wall variables between patients with RA and healthy subjects.

Model	LD	cIMT	IAD	Mean CWS	Mean CWT
1	0.55 (0.32; 0.78)*	0.02 (–0.02; 0.05)	0.59 (0.34; 0.83)*	41.9 (14.9; 69.9)*	44.8 (28.8; 60.7)*
2a	0.42 (0.19; 0.65)*	0.01 (–0.03; 0.05)	0.45 (0.21; 0.69)*	—	—
2b	0.59 (0.37; 0.81)*	0.02 (–0.02; 0.06)	0.63 (0.41; 0.86)*	45.3 (19.5; 71.1)*	48.7 (35.1; 62.3)*
3	0.42 (0.19; 0.65)*	0.01 (–0.03; 0.05)	0.44 (0.21; 0.68)*	43.7 (18.1; 69.4)*	47.5 (34.0; 60.9)*
4	0.40 (0.16; 0.64)*	0.003 (–0.04; 0.04)	0.41 (0.16; 0.66)*	35.9 (8.6; 63.1)*	38.3 (24.6; 52.0)*

* $p < 0.05$. Model 1: age + sex. Model 2a: model 1 + mean arterial pressure. Model 2b: model 1 + carotid pulse pressure. Model 3: model 2a + use of antihypertensives + use of statins. Model 4: model 3 + hypertension + total cholesterol + smoking + prior CV disease. LD: lumen diameter; cIMT: carotid intima-media thickness; IAD: interadventitial diameter; CWS: circumferential wall stress; CWT: circumferential wall tension.

Table 3. Inflammatory measures and carotid artery remodeling in patients with rheumatoid arthritis (RA). Results are presented as regression coefficients (95% CI). Analyses were adjusted for age, sex, and carotid pulse pressure.

Variables	LD	cIMT	IAD	CWS	CWT
Antiinflammatory medication					
Current NSAID use, yes/no	–0.089 (–0.421; 0.243)	0.014 (–0.038; 0.065)	–0.062 (–0.410; 0.286)	–14.6 (–50.8; 21.5)	–5.0 (–25.8; 15.9)
Current MTX use, yes/no	–0.160 (–0.483; 0.163)	0.001 (–0.050; 0.051)	–0.159 (–0.498; 0.180)	–18.2 (–53.4; 17.1)	–12.0 (–32.3; 8.2)
Current SSZ use, yes/no	0.202 (–0.168; 0.572)	0.031 (–0.026; 0.088)	0.264 (–0.123; 0.650)	14.9 (–25.6; 55.5)	19.7 (–3.3; 42.7)
Current prednisone use, yes/no	0.279 (–0.187; 0.744)	–0.073 (–0.144; –0.002)*	0.133 (–0.358; 0.624)	34,8 (–15.9; 85.5)	–1.3 (–30.7; 28.1)
RA-related variables					
RF positivity, yes/no	0.149 (–0.194; 0.492)	0.030 (–0.023; 0.082)	0.208 (–0.150; 0.566)	8.5 (–29.1; 46.0)	14.8 (–6.6; 36.2)
Erosive disease, yes/no	0.187 (–0.207; 0.581)	–0.019 (–0.080; 0.042)	0.149 (–0.264; 0.563)	14.9 (–28.2; 58.0)	3.4 (–21.5; 28.2)
ESR, mm/h	0.001 (–0.010; 0.011)	–0.001 (0.002; 0.001)	0.001 (–0.011; 0.011)	0.04 (–1.10; 1.18)	0.01 (–0.7; 0.7)
CRP, mg/l	–0.006 (–0.015; 0.004)	–0.002 (–0.003; –0.001)*	–0.001 (–0.019; 0.001)	0.4 (–0.7; 1.4)	–0.3 (–0.9; 0.4)
DAS28	–0.024 (–0.151; 0.103)	–0.006 (–0.026; 0.014)	–0.035 (–0.169; 0.098)	–4.0 (–17.9; 9.9)	–3.7 (–11.6; 4.2)
DAS28 < 2.6, yes/no	–0.212 (–0.564; 0.130)	0.017 (–0.036; 0.071)	–0.181 (–0.540; 0.181)	–11.5 (–49.5; 26.4)	–8.9 (–30.6; 12.8)
HAQ-DI	0.057 (–0.276; 0.390)	–0.052 (–0.102; –0.001)*	–0.047 (–0.399; 0.306)	15.6 (–20.6; 51.9)	–3.4 (–24.5; 17.7)
RA duration, yrs	0.006 (–0.042; 0.053)	–0.003 (–0.010; 0.005)	0.001 (–0.049; 0.051)	3.4 (–1.7; 8.5)	1.8 (–1.2; 4.7)

* $p < 0.05$. NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; SSZ: sulfasalazine; RF: rheumatoid factor; DAS28: Disease Activity Score of 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index.

age-matched healthy female subjects, without any difference in cIMT[7]. We found an increased LD and IAD in both male and female patients, without concomitant increase in cIMT, indicating similar results (Figure 2). In our study, RA was independently associated with outward remodeling, with a higher circumferential wall stress and tension, even after adjustment for hemodynamic factors (MAP and local PP), which suggests that the chronic inflammatory process inherent to RA might play an additive role in the maladaptive remodeling process in these patients. To investigate this hypothesis, we studied the associations between inflammatory markers and RA-related factors with carotid arterial wall variables in patients with RA. We found an association only between a lower IMT and current use of prednisone, CRP, and HAQ, which all reflect the cumulative inflammatory burden over time. Because a stable or lower IMT is one of the characteristics of outward arterial remodeling, one might hypothesize that these variables might specifically explain this type of remodeling in RA. Previous research from our group showed in a metaanalysis that while IMT was higher in patients with RA compared to controls[21], it was still lower than expected when extrapolating the actual CV risk in RA. Concomitantly, the lack of association between other carotid arterial wall variables and inflammatory markers might be because most inflammatory markers, such as ESR and DAS28, vary over time and might not reflect the cumulative inflammatory burden in cross-sectional studies as well as do HAQ or use of prednisone. One previous study showed a significant improvement in IAD following the use of a tumor necrosis factor (TNF) blocking agent[27], a strong immunosuppressive drug. That result supports the principle that inflammation and arterial remodeling are highly interrelated. Schott and colleagues also showed that LD and IAD were positively associated with use of prednisone and methotrexate. The latter has both immunosuppressive and cardioprotective effects[28,29,30]. This might be explained by the fact that pharmacological treatment with prednisone can be seen as a marker for RA severity because patients with RA who have more severe disease tend to need more prednisone to reduce disease activity.

Strengths of our study include the recording of CV-related and RA-related factors, by physicians using the same protocol. Our study has several limitations. First, pathophysiological pathways can only be investigated to a limited extent in cross-sectional epidemiological studies. Second, a single-point measuring technique was used to determine carotid arterial wall variables. Thus, results may have been influenced by local variability in the investigated arterial segment. However, by using the same ultrasound protocol, we did define the exact location on the carotid artery where measurements were made in all participants. Third, readers and observers were not masked to patient characteristics, because it is difficult to conceal disability and deformity caused by longstanding RA.

Our investigation shows that patients with RA, compared with healthy subjects, display a pattern of maladaptive outward remodeling (i.e., widening of carotid arterial diameter with elevated circumferential wall stress and tension). These

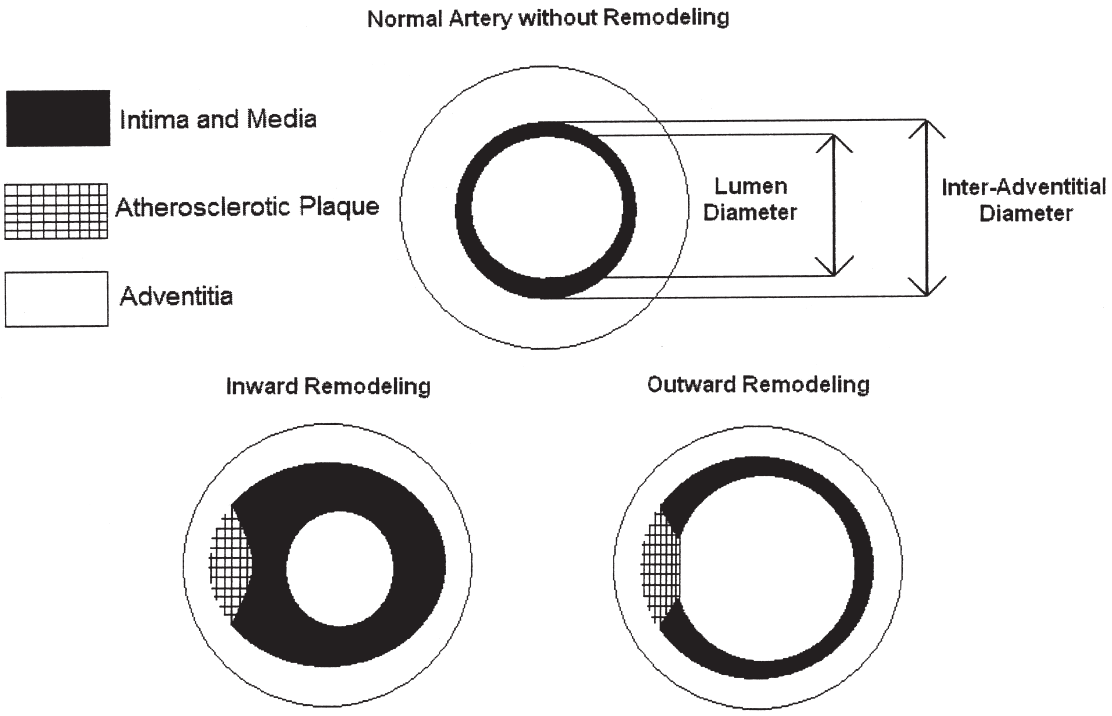

Figure 2. Arterial wall characteristics in compensatory remodeling.

findings might explain the increased CV disease burden in patients with RA and carry important implications in how subclinical CV risk is assessed in this high-risk group.

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