


Original article

Arterial wall inflammation is increased in rheumatoid arthritis compared with osteoarthritis, as a marker of early atherosclerosis

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Abstract

Objective. RA is associated with higher risk of cardiovascular (CV) disease. Ongoing systemic inflammation is presumed to accelerate atherosclerosis by increasing inflammation in the arterial wall. However, evidence supporting this hypothesis is limited. We aimed to investigate arterial wall inflammation in RA vs OA, and its association with markers of inflammation and CV risk factors.

Methods. 18-fluorodeoxyglucose PET combined with CT (¹⁸F-FDG-PET/CT) was performed in RA ($n=61$) and OA ($n=28$) to investigate inflammatory activity in the wall of large arteries. Secondary analyses were performed in patients with early untreated RA ($n=30$), and established RA, active under DMARD treatment ($n=31$) vs OA.

Results. Patients with RA had significantly higher ¹⁸F-FDG uptake in the wall of the carotid arteries (beta 0.27, 95%CI 0.11–0.44, $P<0.01$) and the aorta (beta 0.47, 95%CI 0.17–0.76, $P<0.01$) when compared with OA, which persisted after adjustment for traditional CV risk factors. Patients with early RA had the highest ¹⁸F-FDG uptake, followed by patients with established RA and OA respectively. Higher ESR and DAS of 28 joints values were associated with higher ¹⁸F-FDG uptake in all arterial segments.

Conclusion. Patients with RA have increased ¹⁸F-FDG uptake in the arterial wall compared with patients with OA, as a possible marker of early atherosclerosis. Furthermore, a higher level of clinical disease activity and circulating inflammatory markers was associated with higher arterial ¹⁸F-FDG uptake, which may support a role of arterial wall inflammation in the pathogenesis of vascular complications in patients with RA.

Key words: RA, FDG PET/CT, atherosclerosis, inflammation

Rheumatology key messages

- Patients with RA have higher ¹⁸F-FDG uptake in the arterial wall.
- Arterial wall uptake is associated with markers of inflammation, suggesting that it is a direct method for non-invasive visualization of arterial inflammation.
- The highest arterial uptake was found in RA patients with high blood pressure and TC/HDLc-ratio, suggesting that arterial inflammation is influenced by CV risk factors during active disease.

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Submitted 17 June 2020; accepted 10 October 2020

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Introduction

RA is associated with higher cardiovascular (CV) mortality when compared with the general population [1, 2]. This is only partially explained by the increased prevalence of traditional CV risk factors [1]. Chronic systemic inflammation, a characteristic feature of RA, is assumed to further increase CV risk in these patients [1]. Notably, inflammation is also considered fundamental in the development of atherosclerosis and acute atherothrombotic occlusions [3]. In fact, inflammatory activity of an

atherosclerotic plaque (i.e. vulnerable plaque), rather than the degree of stenosis, is the major determinant of acute CV events [4].

If and how systemic inflammation interacts with local inflammation in the arterial wall is largely unknown. It has been suggested that systemic inflammation, for example by circulating pro-inflammatory cytokines, increases arterial wall inflammation, thereby accelerating plaque development and instability [4]. If this hypothesis is correct, systemic inflammation, for example induced by autoimmune disease, would be expected to be associated with increased arterial wall inflammation. In line with this, histologic evidence supports that patients with RA indeed have more vulnerable and inflamed atherosclerotic lesions than controls [5]. However, as most of these studies are of retrospective design (i.e. post-mortem) and performed in a single centre, the evidence they provide is useful for generating new hypotheses, but limited. Prospective studies exploring the effects of inflammation and anti-inflammatory medication on vascular tissue are necessary.

Fluorodeoxyglucose (FDG) PET/CT has been proposed as an imaging modality for plaque inflammation [6]. In previous studies, increased FDG uptake has been reported in the arterial wall of RA patients when compared with healthy controls [7–10]. In the current study, we compared vascular wall FDG uptake as measured with ^{18}F -FDG-PET/CT in RA patients to OA, and investigated its relationship with CV risk factors and inflammatory markers. New compared with earlier reports is that we included OA patients, which is of additional value, as their physical activity and use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) is similar to RA [10–14]. Furthermore, we performed whole body ^{18}F -FDG-PET/CT scans in patients with early untreated RA, as well as established RA, with data on all large arteries, as opposed to the majority of the other studies that only included the aorta and/or carotids.

Patients and methods

Study design and participants

Consecutive participants with active RA [i.e. disease activity score of 28 joints (DAS28) ≥ 4] of ≥ 50 years, and age- and sex-matched OA controls, were recruited from outpatient clinics of the departments of Rheumatology of Reade ($n = 86$) and Amsterdam UMC, location VUmc ($n = 3$), Amsterdam, the Netherlands. Exclusion criteria were hypersensitivity to any substance used for the ^{18}F -FDG-PET-CT scan, active tuberculosis or other severe infections, pregnancy, moderate to severe heart failure (NYHA class III/IV), cancer and limited life expectancy < 12 months. Participants were categorized into three groups: newly diagnosed RA ($n = 30$) scheduled to receive MTX treatment, established RA ($n = 31$) already on conventional DMARDs and scheduled to start a TNF- α inhibitor (TNFi, adalimumab), and knee and/or hip OA confirmed on radiographs as controls ($n = 28$). Patients

with RA had to fulfil the 1987 or 2010 ACR classification criteria. This study was approved by the medical ethics committee of the VU University in Amsterdam, The Netherlands. Informed consent was obtained from all patients participating in this study.

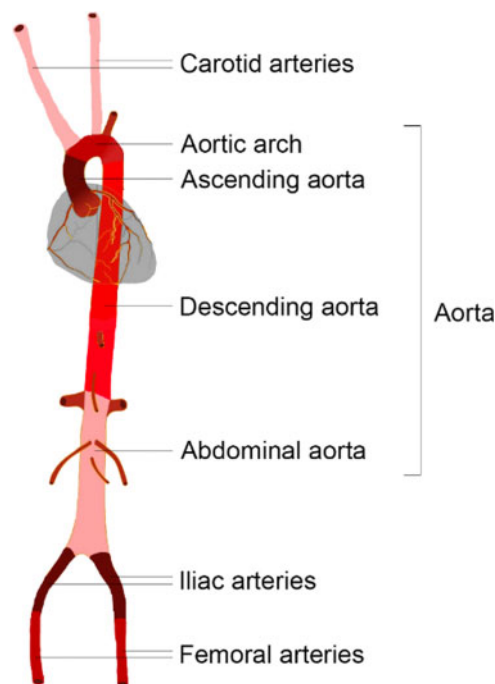
Study assessments

Demographic data, medical history, medication use, family history, disease duration, DAS28, IgM-RF, ACPA, CRP, ESR, plain-radiographic erosions in hands and/or feet, smoking status, blood pressure, BMI, weight/height² in kg/m², waist to hip ratio (WHR), total cholesterol (TC), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc) and triglycerides were assessed in all participants. Data and blood samples were collected on the same day that patients were scheduled to undergo the ^{18}F -FDG-PET/CT.

^{18}F -FDG-PET/CT image acquisition

^{18}F -FDG-PET/CT was performed according to established protocols using Gemini TF or Ingenuity TF (Philips Healthcare) PET/CT scanners at the Amsterdam UMC, location VUmc. Participants fasted for > 6 h before tracer injection. Just prior to injection, venous plasma glucose was determined and in case of glucose > 11 mmol, the scan was rescheduled. ^{18}F -FDG (7 MBq/kg per scan time per bed position in accordance with international guidelines [15]) was injected intravenously. Afterwards, the injection device was flushed with 20 mL of 0.9%

Fig. 1 Schematic overview of arterial segments used for quantification of vascular wall inflammation according to previously published predefined definitions



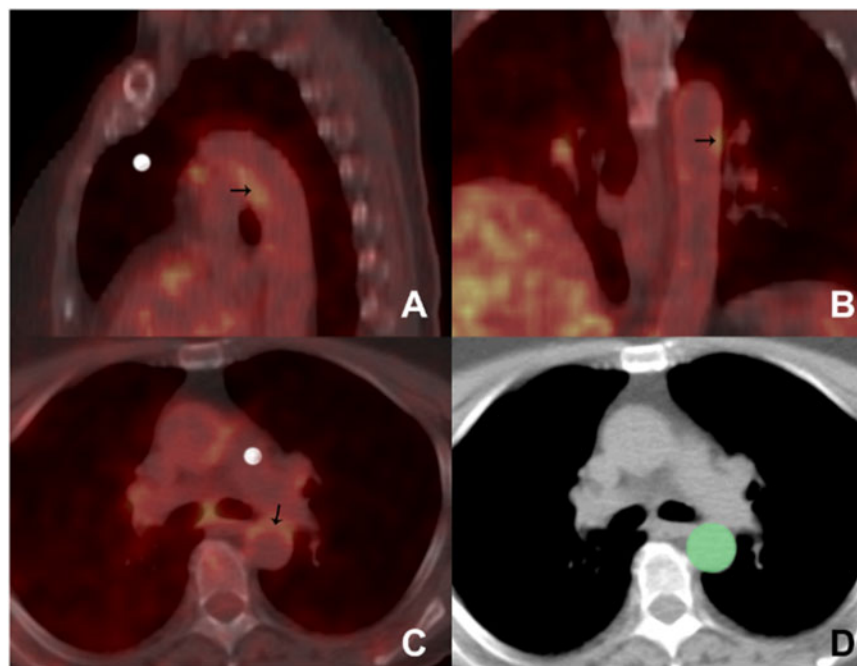
NaCl and residual activity in the administration system was measured to determine the net injected dose. After a 90 min rest period, of which 30 min full bed rest and no conversation allowed, a low-dose CT scan (120 kV, 35 mAs) was performed for localization and attenuation correction, followed by the total body PET scan (acquisition time: 2 min per bed position from head to groin and 1 min per bed position from groin to toes). PET data were normalized and corrected for attenuation, decay and scatter according to a reconstruction method based on international guidelines [15].

¹⁸F-FDG-PET/CT image analysis

After visual inspection of the PET/CT images, the axial slice with the most intense ¹⁸F-FDG uptake was determined for every arterial segment (hotspot method [16], Figs 1 and 2). Regional arterial ¹⁸F-FDG uptake in this slice was quantified by drawing a region of interest (ROI) in this artery on the CT image, which was transferred to the PET image to determine the FDG uptake. The arterial maximal standardized uptake value (SUVmax) was calculated for each separate ROI using the maximal regional ¹⁸F-FDG uptake divided by the net injected ¹⁸F-FDG dose corrected for lean body mass and serum glucose level. SUVmax of the most-diseased segment (MDS) was calculated by also including the two slices adjacent (one proximal and one distal) to the visually determined hotspot [16]. Additionally, SUVmax values were corrected for background activity by subtracting

the mean blood SUV measured within the inferior or superior vena cava (VCI, VCS) from the arterial SUV value (cSUVmax). This method has been proposed as a new method for correcting for background FDG activity for atherosclerotic plaques compared with the maximal tissue-to-background ratio (TBRmax) [17–21]. As there is no consensus about the best way to calculate arterial FDG uptake, we have chosen to report all three values, i.e. SUVmax, cSUVmax and TBRmax. All images were analysed using an image analysis research tool for PET/CT developed in our hospital. The PET/CT images were judged by three independent observers (R.A., A.B.B., A.M.v.S.). For 10 patients, image analysis was performed by two observers, who were unaware of each other's findings. Intraclass correlation coefficients (ICCs) for all arterial segments were between 0.81 and 0.96, which represents excellent interobserver reliability according to Landis and Koch (see Supplementary Data S1, Supplementary Table S1 and Supplementary Fig. S1, available at *Rheumatology* online, for ICCs, scatter and Bland-Altman plots) [22]. The ascending aorta, aortic arch, descending aorta, abdominal aorta and left and right carotid, iliac and femoral arteries were quantified separately (Fig. 1), according to the predefined definitions that were previously published [16]. For statistical analyses, segments were combined (aorta: ascending, arch, descending and abdominal segments; carotid, femoral and iliac arteries: left and right segment) by using the segment with the highest uptake. The focal pattern and the intensity of the FDG uptake was

Fig. 2 Example of a hotspot in the descending aorta on ¹⁸F-FDG-PET/CT images



Arrows indicate hotspot in descending aorta on (A) sagittal, (B) coronal and (C) trans axial fused PET/CT images. An example of a region of interest (ROI) is depicted in green on (D) trans axial CT image.

suggestive of atherosclerosis, rather than vasculitis (Supplementary Fig. S2, available at *Rheumatology* online, and Fig. 2) [23].

Statistical analyses

Data is presented in mean (s.d.), median with interquartile range (IQR) and/or numbers (percentages). Baseline characteristics and SUVmax, cSUVmax, SUVmax MDS and TBRmax measurements between RA and OA or early RA and established RA were compared using *t* test, χ^2 test and nonparametric tests. Multivariate linear regression analyses were used to assess whether group differences remained after adjusting for CV risk factors (age, sex, BMI, pack years, hypertension, TC/HDLc-ratio) and to evaluate the influence of CV risk factors and RA-related factors (e.g. markers of inflammation) on SUVmax and cSUVmax levels in the arterial wall. Post-hoc ANOVA for trend analysis was performed to investigate whether there was a trend for increase in SUVmax, cSUVmax, SUVmax MDS and TBRmax for subsequently OA, established RA and early RA participants. Analyses were performed with SPSS, version 22 and Prism version 8.2.1 (ANOVA for trend). A *P*-value of below 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of RA and OA patients are shown in Table 1. Compared with OA, RA patients were more often current smokers, had more pack years, higher ESR and CRP and used more NSAIDs. In the subgroup analyses (Supplementary Table S2, available at *Rheumatology* online), patients with early RA had higher DAS28, ESR and CRP, and fewer erosions compared with established RA. Furthermore, they had a higher blood pressure, higher TC/HDLc ratio and lower HDL.

Arterial ¹⁸F-FDG uptake in RA, OA and healthy controls

Patients with RA had significantly higher SUVmax, cSUVmax and TBRmax in the aorta, femoral and carotid arteries when compared with OA patients (SUVmax Fig. 3A, Supplementary Table S3, available at *Rheumatology* online). This was still significant after correction for age, sex and other traditional CV risk factors (BMI, pack years, hypertension and TC/HDLc-ratio) for the aorta (SUVmax beta 0.47, 95% CI 0.17, 0.76, *P* < 0.01; cSUVmax beta 0.35, 95% CI 0.08, 0.62, *P* = 0.01; TBRmax beta 0.60, 95% CI 0.06, 1.13, *P* = 0.03), carotid arteries (SUVmax beta 0.27, 95% CI 0.11, 0.44, *P* < 0.01; cSUVmax beta 0.13, 95% CI -0.01, 0.28, *P* = 0.06; TBRmax beta 0.32, 95% CI -0.002, 0.64, *P* = 0.05), femoral arteries (SUVmax beta 0.28, 95% CI 0.04, 0.52, *P* = 0.03; cSUVmax beta 0.20, 95% CI -0.02, 0.42, *P* = 0.07, TBRmax beta 0.29, 95%

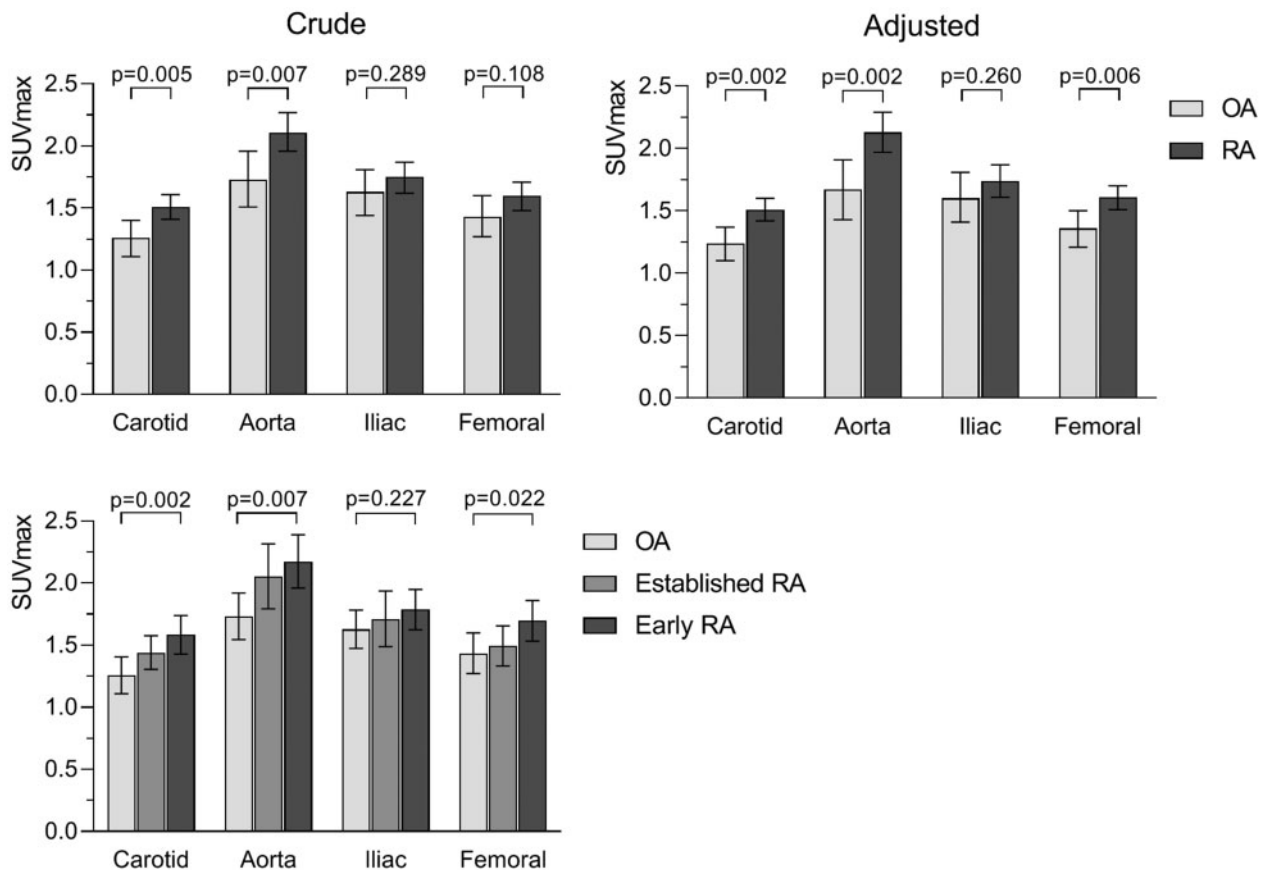
TABLE 1 Baseline characteristics of RA and OA patients

	RA (n = 61)	OA (n = 28)
Demographics		
Age, years	63 (8)	63 (6)
Women, n (%)	34 (55.7)	16 (57.1)
Median inclusion year, n	2014	2016
Cardiovascular risk factors		
Previous CVD, n (%)	13 (21.3)	9 (32.1)
Hypertension, n (%)	34 (55.7)	19 (67.9)
Systolic BP, mmHg	135 (20) [*]	132 (19)
Diastolic BP, mmHg	82 (10)	82 (8)
Current smoking, n (%)	15 (24.6) [*]	2 (7.1) [*]
Pack years	8 (0–30) [*]	2 (0–12) [*]
DM, n (%)	10 (16.4)	3 (10.7)
Fasting glucose, mmol/L	5.7 (1.2)	5.3 (0.6)
TC/HDLc ratio	3.5 (1.3)	3.4 (1.1)
TC, mmol/L	4.9 (1.1)	4.8 (1.0)
HDLc, mmol/L	1.5 (0.7)	1.5 (0.4)
LDLc, mmol/L	2.8 (0.9)	2.7 (0.9)
Triglycerides, mmol/L	1 (0.8–1.5)	1.2 (0.9–1.6)
Waist/hip ratio, cm ^a	0.92 (0.08)	0.98 (0.18)
Body mass index, kg/m ²	28 (6)	29 (6) [*]
Medication, n (%)		
Antihypertensive drug	29 (47.5)	16 (57.1) [*]
Statin	16 (26.2)	12 (42.9)
Aspirin	12 (19.7) [*]	11 (39.3) [*]
Disease-related factors		
Disease duration, years	1 (0.4–9) [*]	5 (3–11) [*]
RF and/or ACPA positive, n (%)	43 (70.5)	—
Erosions, n (%)	21 (34.4)	—
Nodules, n (%) ^b	6 (9.8)	—
DAS28, range 0–10	4.7 (1.1)	—
ESR, mm/h	22 (12–37) [*]	7 (4–13) [*]
CRP, mg/L	8 (1–25) [*]	1 (1–3) [*]
RA medications, n (%)		
NSAID	37 (60.7) [*]	6 (21.4) [*]
COXIB	6 (9.8)	0/0
Methotrexate	27 (44.3)	—
Prednisone	14 (22.9)	—
Other DMARD	17 (27.9)	—

Continuous variables are presented as mean (s.d.) or as median (IQR). Categorical and dichotomous variables are presented as numbers and/or percentages. Missings: ^a16%, ^b23%, all other variables <3%. Student's *t* test, χ^2 test and nonparametric test were used to investigate differences between the groups at baseline. *Statistically significant. rangeBP: blood pressure; COXIB: COX-2-selective NSAID; CVD: cardiovascular disease; DAS28: disease activity score of 28 joints; DM: type 2 diabetes mellitus; HDLc: high-density lipoprotein cholesterol; IQR: interquartile; LDLc: low-density lipoprotein cholesterol; pack years: (packs smoked per day)*(years as a smoker); TC: total cholesterol.

CI -0.06, 0.64, *P* = 0.10). In the sub-analyses within the RA group (early vs established), we found that the early RA group had the highest FDG uptake measured in SUVmax and cSUVmax, followed by established RA and OA (SUVmax Fig. 3B, all SUVmax Fig. 3A, Supplementary Table S4, available at *Rheumatology* online). SUVmax MDS gave comparable results to the

Fig. 3 Arterial wall FDG uptake in RA vs OA



Crude and adjusted means with confidence intervals of arterial wall ¹⁸F-FDG uptake in RA (n=61) vs OA (n=28) and early RA vs established RA vs OA analysed with a linear regression analysis adjusted for age, sex, hypertension, TC/HDLc ratio, pack years and BMI.

SUVmax hotspot method, while TBRmax did not differ significantly between the three groups (Table 2 and Supplementary File 3, available at *Rheumatology* online). After adjustment for ESR or CRP the differences in SUVmax between the RA and OA patients were reduced or not significant anymore, suggesting that the SUVmax differences were at least partly explained by differences in systemic inflammation.

Arterial ¹⁸F-FDG uptake association with markers of inflammation and CV risk factors

In RA, higher ESR was associated with a higher ¹⁸F-FDG uptake in the arterial wall of all arterial segments (i.e. carotid, aorta, iliac and femoral arteries) after correction for age, sex, hypertension, TC/HDLc ratio, pack years and BMI (Table 3). Pack years, NSAID use, hypertension, TC/HDLc-ratio, BMI, and WHR were not statically significantly associated with increased arterial ¹⁸F-FDG uptake for both RA and OA participants (data not shown). For RA participants, in some arterial segments higher CRP and DAS28 were significantly associated with a higher ¹⁸F-FDG uptake. In nearly all arterial

segments, diabetes was associated with a significant increase in SUVmax in the arterial wall. Furthermore, in RA patients, cSUVmax and TBRmax values for the carotid arteries, aorta, iliac and femoral arteries were also associated with serological inflammatory markers (Supplementary Tables S5 and S6, available at *Rheumatology* online). For OA participants, CRP, ESR and diabetes were not associated with the SUVmax values in the arterial segments. The cSUVmax and TBRmax values were not associated with any of these values in OA (Supplementary Tables S5 and S6, available at *Rheumatology* online).

Discussion

The results of this study show that patients with RA have an increased ¹⁸F-FDG uptake in the wall of several arterial vessels compared with OA patients. This finding remained significant after adjustment for traditional CV risk factors. Furthermore, the ¹⁸F-FDG uptake was associated with serological and clinical markers of inflammation such as CRP, ESR and DAS28. Higher levels

TABLE 2 Arterial wall ¹⁸F-FDG uptake in early RA and established RA vs OA

		Beta	95% CI	P-value
SUVmax				
Carotid	Early RA	0.242	-0.01, 0.50	0.06
	Established RA	0.328	0.74, 0.58	0.01
Aorta	Early RA	0.368	-0.07, 0.81	0.10
	Established RA	0.473	0.04, 0.91	0.03
Iliac	Early RA	0.095	-0.29, 0.48	0.63
	Established RA	0.082	-0.30, 0.46	0.67
Femoral	Early RA	0.323	0.05, 0.59	0.02
	Established RA	0.223	-0.06, 0.50	0.12
SUVmaxMDS				
Carotid	Early RA	0.199	-0.01, 0.41	0.06
	Established RA	0.196	-0.01, 0.40	0.06
Aorta	Early RA	0.199	-0.10, 0.50	0.18
	Established RA	0.130	-0.17, 0.43	0.38
Iliac	Early RA	0.030	-0.23, 0.29	0.81
	Established RA	0.043	-0.21, 0.30	0.73
Femoral	Early RA	0.243	-0.003, 0.49	0.05
	Established RA	0.223	-0.03, 0.48	0.08
cSUVmax				
Carotid	Early RA	0.220	-0.02, 0.46	0.07
	Established RA	0.218	-0.02, 0.45	0.07
Aorta	Early RA	0.375	-0.05, 0.80	0.08
	Established RA	0.390	-0.03, 0.80	0.07
Iliac	Early RA	0.042	-0.36, 0.44	0.84
	Established RA	-0.040	-0.43, 0.35	0.84
Femoral	Early RA	0.299	0.06, 0.54	0.02
	Established RA	0.097	-0.15, 0.34	0.43
TBRmax				
Carotid	Early RA	0.397	-0.02, 0.82	0.06
	Established RA	0.286	-0.13, 0.70	0.17
Aorta	Early RA	0.560	-0.16, 1.28	0.12
	Established RA	0.374	-0.33, 1.08	0.29
Iliac	Early RA	-0.013	-0.68, 0.66	0.97
	Established RA	-0.119	-0.77, 0.53	0.72
Femoral	Early RA	0.516	0.06, 0.97	0.03*
	Established RA	0.102	-0.37, 0.57	0.66

Linear regression analyses adjusted for age, sex, hypertension, TC/HDLc ratio, pack years and BMI. cSUVmax: corrected SUVmax; SUVmax: maximum standardized uptake value; TBRmax: maximum tissue to background ratio. Reference = OA.

of inflammatory markers were associated with higher FDG uptake in the arteries independent of traditional CV risk factors. This indicates that patients with RA have increased inflammation in the arterial wall during active disease, which may translate into a higher CVD risk. Our results are in line with previous studies in which a higher FDG uptake was found in RA in the carotid arteries [24] and the aorta [7, 9, 10, 13]. However, in these studies, analyses on FDG vessel wall uptake was not complete with respect to uptake assessment in all arterial segments, inclusion of a control group and/or association with inflammatory markers. The newly diagnosed (early) RA group, not yet being treated with DMARDs and/or prednisone, had higher CRP, ESR and DAS28, as well

as the highest ¹⁸F-FDG uptake in all arterial segments. In contrast, the established RA group had slightly lower arterial ¹⁸F-FDG uptake (in SUVmax) compared with early RA patients. These observed lower SUVmax values in patients with established RA indicate less inflammation in the arterial wall during active disease in comparison with early RA, which is most likely explained by the fact that the established RA patients have been treated with DMARDs for a median of eight years already since diagnosis. In addition, the early RA group with the highest inflammatory burden on ¹⁸F-FDG-PET/CT had higher blood pressure, higher TC/HDLc ratio and lower HDLc, suggesting that ¹⁸F-FDG vessel wall uptake is also influenced by traditional CV risk factors during active disease. This finding is also in line with previous publications in which the lipid paradox in RA has been described extensively [25–27].

In our study, RA patients with DM had a significantly higher FDG uptake in the arterial wall than RA patients without DM, suggesting an even further increased risk in these patients. Insulin is known to alter ¹⁸F-FDG uptake in brain and muscle but not the heart, even when serum blood glucose levels (which we corrected for when calculating SUV) are comparable [28, 29]. This would suggest that, even though insulin could influence the availability of FDG in the blood pool, for example by increased uptake in muscle tissue, this would only strengthen our results, as FDG uptake in the arterial wall of RA patients with DM should then be even higher. This association between DM and SUVmax was only observed in RA, but not in the OA group, which is in line with other studies that show that DM increases the CVD risk in RA patients [30, 31]. In addition, there was a trend for a protective effect of statins on arterial inflammation, which is in line with previously published trials showing reduced arterial ¹⁸F-FDG uptake in participants after using statin therapy [32–38].

In this study, we used the visually detected single-hottest-slice for quantification of the ¹⁸F-FDG uptake (hotspot method) which is less time-consuming and potentially holds the same results as drawing ROIs on all slices of an arterial segment, because the SUVmax is calculated using the hottest voxel in the arterial wall. A previous study from our group concluded that ‘the hotspot method is equally sensitive and can be used without the risk of missing inflamed lesions’. However, that study also concluded that interobserver agreement was not optimal in the segments other than the aortic arch and abdominal aorta. In our current study, the highest interobserver agreement was also found in the aorta, indicating that the results in the aorta are possibly more reliable than the results in the other segments.

Currently, there is no consensus about the best way to calculate arterial FDG uptake and therefore we have chosen to report four metrics, i.e. SUVmax, SUVmax MDS, cSUVmax and TBRmax. For all analyses, SUVmax MDS gave comparable results to SUVmax, so incorporating information of adjacent slices to the hotspot is

TABLE 3 Association between arterial wall ¹⁸F-FDG uptake in SUVmax, inflammatory markers and medication

	RA			OA		
	Beta	95% CI	P-value	Beta	% CI	P-value
Carotid arteries						
CRP	0.003	-0.020, 0.008	0.29	0.004	-0.043, 0.051	0.86
ESR	0.006	0.002, 0.010	<0.01	0.001	-0.010, 0.012	0.82
DAS28	0.060	-0.020, 0.150	0.12	n.a.	n.a.	n.a.
Diabetes	0.350	0.110, 0.60	<0.01	-0.029	-0.550, 0.490	0.91
Statin	0.050	-0.180, 0.280	0.66	-0.183	-0.520, 0.150	0.26
Antihypertensives	0.101	-0.103, 0.304	0.33	-0.075	-0.377, 0.226	0.61
Aspirin	-0.019	-0.283, 0.245	0.88	0.091	-0.214, 0.396	0.55
Pack years	0.002	-0.001, 0.006	0.20	-0.003	-0.015, 0.009	0.62
Aorta						
CRP	0.007	-0.003, 0.017	0.16	0.009	-0.056, 0.075	0.77
ESR	0.015	0.008, 0.020	<0.01	0.008	-0.007, 0.022	0.28
DAS28	0.190	0.040, 0.340	<0.01	n.a.	n.a.	n.a.
Diabetes	0.470	-0.010, 0.950	0.055	-0.024	-0.760, 0.710	0.95
Statin	0.095	-0.340, 0.530	0.66	-0.281	-0.750, 0.190	0.22
Anithypertensives	0.138	-0.194, 0.470	0.41	-0.140	-0.523, 0.243	0.46
Aspirin	-0.221	-0.637, 0.194	0.29	0.279	-0.096, 0.655	0.14
Pack years	0.001	-0.004, 0.007	0.65	0.005	-0.011, 0.021	0.54
Iliac arteries						
CRP	0.018	0.010, 0.025	<0.01	0.022	-0.022, 0.066	0.30
ESR	0.010	0.004, 0.020	<0.01	0.004	-0.006, 0.015	0.37
DAS28	0.110	-0.020, 0.240	0.097	n.a.	n.a.	n.a.
Diabetes	0.280	-0.130, 0.70	0.18	-0.20	-0.698, 0.292	0.40
Statin	0.150	-0.220, 0.510	0.41	-0.20	-0.520, -0.120	0.20
Antihypertensives	-0.072	-0.347, 0.202	0.60	0.039	-0.280, 0.358	0.81
Aspirin	-0.091	-0.434, 0.252	0.60	0.176	-0.139, 0.492	0.26
Pack years	0.003	-0.002, 0.008	0.22	0.001	-0.011, 0.014	0.82
Femoral arteries						
CRP	0.004	-0.002, 0.009	0.199	-0.009	-0.057, 0.040	0.71
ESR	0.006	0.002, 0.011	<0.01	-0.004	-0.015, 0.007	0.48
DAS28	0.10	0.022, 0.187	<0.01	n.a.	n.a.	n.a.
Diabetes	0.48	0.250, 0.720	<0.01	-0.21	-0.770, 0.340	0.44
Statin	0.21	-0.022, 0.45	0.075	-0.20	-0.560, 0.160	0.26
Antihypertensives	0.175	-0.053, 0.403	0.13	-0.032	-0.370, 0.305	0.85
Aspirin	0.072	-0.236, 0.380	0.64	0.244	-0.083, 0.572	0.14
Pack years	0.002	-0.002, 0.006	0.35	-0.001	-0.013, 0.011	0.87

Linear regression analyses were performed adjusted for age, sex, BMI, hypertension, packyears and TC/HDLc ratio as appropriate. DAS28: disease activity score of 28 joints; PWV: pulse wave velocity; SUVmax: maximum standardized uptake value.

probably not necessary. We did not find any statistically significant difference in TBRmax, a metric where SUVmax is divided by the mean venous blood ¹⁸F-FDG uptake to correct for the availability of ¹⁸F-FDG from the blood. It is known that TBRmax is less stable for measuring arterial wall inflammation as its variance is composed of both the variance observed in the arterial wall and the variance in the blood pool, making TBR less reproducible than SUV [19–21]. A new method proposed for correction for background activity is subtracting the mean blood SUV from SUVmax (cSUVmax), as blood activity adds to arterial wall activity [18–21]. However, this method only corrects for the partial volume effect and not for differences in availability of ¹⁸F-FDG from the blood (which is done with TBR). Both cSUVmax and

TBR have major limitations and therefore (for cross-sectional data) SUVmax might be the most appropriate metric.

Several limitations need to be discussed. As mentioned above, the OA patients might not have been the right group to compare the RA group with. Recent literature suggests that low grade inflammation also exists in OA, and this might have led to a less pronounced SUVmax difference between the groups. We did determine ¹⁸F-FDG uptake in five age- and sex-matched healthy individuals to acquire some idea about the ¹⁸F-FDG uptake in the arterial vessel wall in this group. For the aorta, the SUVmax values of the healthy controls were lower when compared with the RA and OA patients. Unfortunately, due to the low numbers we

could not perform any statistical analyses to compare the arterial FDG uptake in this group to that of the RA or OA patients. Ideally, we would have included a healthy control group with enough statistical power to perform additional analyses.

In conclusion, our study demonstrates that patients with RA have ^{18}F -FDG uptake in the arterial wall that is associated with markers of inflammation (i.e. CRP, ESR, DAS28), suggesting that it is a direct method for non-invasive visualization of inflammation in arteries. Furthermore, this finding strengthens the notion that high inflammatory burden accelerates atherosclerosis and plaque instability, thereby increasing the risk of acute CV events. In this light, optimal anti-inflammatory therapy is necessary in these patients to reduce CV risk. However, further studies are needed to investigate the direct effects of anti-inflammatory therapy on the vascular wall as measured by methods such as an ^{18}F -FDG-PET/CT.

Acknowledgements

We would like to thank all the patients of the outpatient clinics of Reade and Amsterdam UMC, location VUmc who participated in this study. All authors substantially contributed to the following points of this manuscript: conception or design of the work; or the acquisition, analysis or interpretation of data for the work; drafting the paper or revising it critically for important intellectual content; final approval of the version to be published. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

Funding: This study was partly financially supported by Abbvie.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Data, including deidentified participant data, is available upon reasonable request from the principal investigator Prof. Dr M.T. Nurmohamed by contacting the corresponding author of this manuscript.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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