

# Prevalence and Risk Factors of Carotid Vessel Wall Inflammation in Coronary Artery Disease Patients

## FDG-PET and CT Imaging Study

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**OBJECTIVES** We investigated the prevalence and clinical risk factors of carotid vessel wall inflammation by means of  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) in a population consisting of coronary artery disease (CAD) patients.

**BACKGROUND** The atherosclerotic disease process is characterized by infiltration and retention of oxidized lipids in the artery wall, triggering a disproportionate inflammatory response. Efforts have been made to use noninvasive imaging to quantify this inflammatory response in the vessel wall. Recently, carotid FDG-PET has been shown to reflect the metabolic rate of glucose, a process known to be enhanced in inflamed tissue.

**METHODS** Carotid inflammation was quantified in 82 CAD patients (age  $62 \pm 10$  years) as the maximum target-to-background ratio ( $_{\text{wholevessel}}\text{TBR}_{\text{max}}$ ). Furthermore, we assessed the maximal standardized uptake value values ( $_{\text{wholevessel}}\text{SUV}_{\text{max}}$ ), the single hottest segment (SHS), and the percent active segments (PAS) of the FDG uptake in the artery wall, measured by FDG-PET.

**RESULTS** Whole-vessel  $\text{TBR}_{\text{max}} > 1.8$  was present in 67%,  $> 2.0$  in 39%,  $> 2.2$  in 23%, and  $> 2.4$  in 12% of the population. Multiple linear regression analysis with backward elimination revealed that body mass index (BMI)  $\geq 30 \text{ kg/m}^2$  ( $p < 0.0001$ ), age  $> 65$  years ( $p = 0.01$ ), smoking ( $p = 0.02$ ), and hypertension ( $p = 0.01$ ) were associated with  $_{\text{wholevessel}}\text{TBR}_{\text{max}}$ . The number of components of the metabolic syndrome was also associated with  $_{\text{wholevessel}}\text{TBR}_{\text{max}}$  ( $p = 0.02$ ). In similar analyses,  $_{\text{wholevessel}}\text{SUV}_{\text{max}}$  was associated with BMI  $\geq 30 \text{ kg/m}^2$  ( $p < 0.0001$ ), age  $> 65$  years ( $p = 0.004$ ), male gender ( $p = 0.02$ ), and hypertension ( $p = 0.04$ ); SHS with BMI  $\geq 30 \text{ kg/m}^2$  ( $p < 0.0001$ ), age  $> 65$  years ( $p = 0.02$ ), smoking ( $p = 0.04$ ), and hypertension ( $p = 0.05$ ); PAS with BMI  $\geq 30 \text{ kg/m}^2$  ( $p = 0.001$ ), smoking ( $p = 0.03$ ), and hypertension ( $p = 0.01$ ).

**CONCLUSIONS** Carotid inflammation as revealed by FDG-PET is highly prevalent in the CAD population and is associated with obesity, age over 65 years, history of hypertension, smoking, and male gender. Artery wall FDG uptake increased when components of the metabolic syndrome clustered. (J Am Coll Cardiol Img 2011;4:1195–205) © 2011 by the American College of Cardiology Foundation

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The atherosclerotic disease process is characterized by infiltration and retention of oxidized lipids in the artery wall, triggering a disproportionate inflammatory response (1). Preventive strategies have focused on controlling risk factors, such as smoking, blood pressure, and serum lipid levels, which have had partial success in reducing the incidence of atherothrombotic events (2). Nonetheless, substantial residual risk remains, even when treatment goals are fully met (3).

Increasing interest has now turned to the inflammatory component of atherogenesis. Serum biomarkers of inflammation have emerged as independent predictors of coronary artery disease (CAD). In fact, a recent study in 1,117 stable CAD patients showed that subjects with both C-reactive protein (CRP) and myeloperoxidase in the highest tertile had a 5.3-fold

increased risk of cardiovascular mortality compared with patients in the lowest tertiles (4). Moreover, the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed that identifying patients at risk by using CRP and treating them accordingly with statins can reduce cardiovascular event rates by 57% compared with placebo (5). Currently, novel pharmacotherapies that target anti-inflammatory pathways in atherosclerosis are being investigated (6).

In line with this development, efforts have been made to use noninvasive imaging to quantify vessel wall inflammation. Recently, carotid  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) has been shown to reflect the metabolic rate of glucose, a process known to be enhanced in inflamed tissue. In fact, FDG uptake is significantly associated with both the degree of macrophage infiltration and the levels of inflammatory gene expression in plaques (7–9). Furthermore, this noninvasive technique is capable of assessing

efficacy of anti-inflammatory interventions in humans (10,11).

To further validate whether carotid FDG-PET is a surrogate marker for vessel wall inflammation, it is important to investigate the relation between FDG-PET and CAD risk factors. A previous study showed that carotid inflammation was associated with several CAD risk factors (12). However, this retrospective study was limited by the fact that it only included cancer patients with a low prevalence of CAD. In a more recent study by Rudd *et al.* (13), involving 41 patients with vascular disease or multiple cardiovascular risk factors, there was significantly higher carotid FDG uptake in patients with documented CAD and in males (compared with females). A limitation of that study was the heterogeneity of the study population with respect to their cardiovascular disease burden as well as the small number of patients. Therefore, the prevalence of vessel wall inflammation and its relationship with CAD risk factors in a predefined CAD population is still not fully understood.

The aim of the current study was to assess the prevalence of carotid vessel wall inflammation as assessed by FDG-PET and to identify which clinical risk factors are associated with carotid inflammation in a population consisting of patients with documented CAD.

## METHODS

**Study design.** This was a cross-sectional study, investigating the prevalence of carotid vessel wall inflammation and the relation between clinical risk factors and carotid inflammation as assessed by FDG-PET. The study was conducted at the Mount Sinai School of Medicine, New York. The study protocol was reviewed and approved by the institutional review board, and all subjects gave written informed consent. Inclusion criteria were males and females with a diagnosis of CAD. CAD was defined as a history of myocardial infarction, percutaneous

## ABBREVIATIONS AND ACRONYMS

<b>BMI</b>	= body mass index
<b>CAD</b>	= coronary artery disease
<b>CT</b>	= computed tomography
<b>FDG-PET</b>	= $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography
<b>HDL</b>	= high-density lipoprotein cholesterol
<b>PAS</b>	= percent active segments
<b>ROI</b>	= region of interest
<b>SHS</b>	= single hottest segment
<b>SUV</b>	= standardized uptake value
<b>TBR</b>	= target-to-background ratio

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transluminal coronary intervention or coronary artery bypass surgery. Subjects with previous carotid surgery or fasting glucose levels  $\geq 11.1$  mmol/l were excluded (14).

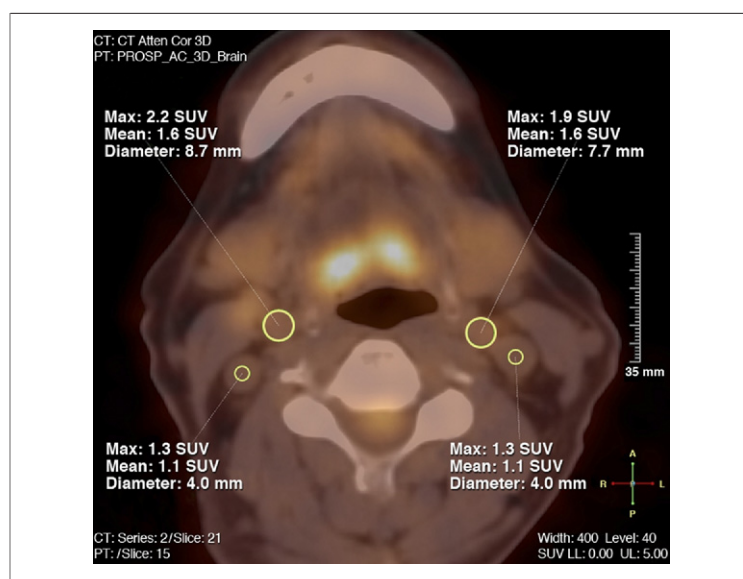
**Questionnaire, and biometric and biochemical measurements.** Presence of cardiovascular risk factors, use of medication, and family history of CAD were assessed by a questionnaire. Presence of hypertension was defined as a history systolic blood pressure  $>140$  mm Hg, or a diastolic blood pressure  $>90$  mm Hg. Diabetes was defined as use of an antidiabetic treatment (diet, oral, parenteral). Weight and height were measured to calculate body mass index (BMI). Fasting glucose levels were obtained by fingerstick blood glucose measurements (Accu-Chek Advantage, Roche Diagnostics, Indianapolis, Indiana) prior to FDG administration.

**FDG-PET/computed tomography imaging.** FDG-PET/computed tomography (CT) was performed after an overnight fast using a GE Healthcare (Milwaukee, Wisconsin) LightSpeed Discovery ST PET/CT scanner (14,15). FDG was administered intravenously ( $562.4 \pm 81.4$  MBq), and patients rested comfortably for 99 to 193 min before the scan of the neck was started. A low-dose CT scan (140 kV, 80 mA, and 4.25-mm slice thickness) was performed for attenuation correction and co-registration. No CT contrast agent was administered. Head and neck were placed into a head holder for imaging of the carotids. Images from 1 bed position (15.5 cm) with coverage extending inferior to the internal auditory meatus were acquired in 3-dimensional mode for 15 min.

**Image analysis.** Image analysis was performed on a dedicated, commercially available workstation (Extended Brilliance Workspace V4.0.0.3206, Philips Medical Systems Inc., Cleveland, Ohio). An experienced reader (J.B.) analyzed all scans. To assess intraobserver agreement, a subset of 15 randomly assigned scans were analyzed twice by the same reader, with a minimum of 14 days between the first and second reading to avoid recall bias.

After loading the PET and CT images, the general imaging quality was reviewed, and as applicable, the following parameters were also reviewed: optimal counts, coverage, and image reconstruction of both carotids, and co-registration of the PET and CT images. Data were excluded from the analysis if significant motion artifact, as assessed by blurring edges of the CT and/or movement between the PET and CT co-registered images was present. In general, each slice of the fused PET/CT was judged as 1 segment of the carotids. The

carotid artery was divided anatomically into common, internal, and external carotid arteries, respectively. Only the common carotid artery up to the bifurcation was analyzed on both sides of the neck in order to ensure a correct identification of the vessel anatomy and to minimize the impact of FDG uptake in surrounding structures. Slices where the anatomy of the artery could not be identified with certainty or those slices with a high FDG uptake in the surrounding tissue/structures (affecting the FDG uptake within the vessel) were excluded from further analysis. Arterial FDG uptake was quantified by drawing a region of interest (ROI) around each artery on every slice of the co-registered transaxial PET/CT images (Fig. 1). Next, the maximal arterial standardized uptake value ( $SUV_{max}$ ) was calculated as the maximal pixel activity within the ROI of every slice of the vessel. The SUV is the decay-corrected tissue concentration of FDG in kilobecquerels per milliliter, adjusted for the injected FDG dose and the body weight of the patient, and is a well-recognized method for quantification of FDG-PET data (16). By averaging the maximum SUV values of all arterial slices of the left and right carotid arteries, a wholevessel  $SUV_{max}$  value was derived for the carotid arteries. The maximal arterial target-to-background ratio ( $TBR_{max}$ ) was then calculated by correcting



**Figure 1. FDG-PET Image Analysis**

This figure shows 1 slice of the fused positron emission tomography/computed tomography (PET/CT) images of the neck in transaxial view. Regions of interest (ROIs) (yellow) drawn around the outer border of the vessel walls of the left and right common carotid arteries, as well as, for evaluation of the 18F-fluorodeoxyglucose (FDG) blood pool activity, within the lumen of both jugular veins ( $SUV_{max}$ ,  $SUV_{mean}$ , and diameter of the ROIs). SUV = standardized uptake value.

the  $SUV_{max}$  for blood activity. This was done by dividing the  $SUV_{max}$  values in the artery by the average blood  $SUV_{mean}$ , estimated from both jugular veins to produce a blood-corrected artery SUV. This is considered to be a reflection of arterial FDG uptake (17). For evaluation of the mean FDG blood pool uptake, as depicted by the mean  $SUV_{mean}$ , at least six 3- to 4-mm ROIs were placed in consecutive slices of both jugular veins and averaged. Corrected  $SUV_{max}$  values were then averaged in order to derive a  $^{wholevessel}TBR_{max}$  for both carotid arteries. Additionally, we identified the single hottest segment (SHS), defined as the highest  $TBR_{max}$  value of the carotid arteries, as well as the percent active segments (PAS) of each common carotid artery. PAS reflects the percentage of all segments of either the left or right carotid artery above a pre-defined threshold, namely  $TBR_{max} > 1.9$ . This threshold was determined by calculating the median of all  $^{wholevessel}TBR_{max}$  values ( $TBR_{max} > 1.9$ ) of the included patients.

In order to provide information about the prevalence of different degrees of FDG uptake in both common carotid arteries, we defined 4 different potential cutoff values for vessel wall inflammation, namely  $^{wholevessel}TBR_{max} > 1.8$ ,  $> 2.0$ ,  $> 2.2$ , and  $> 2.4$  based on the results of a previously published study by Tawakol et al. (7).

**Statistical analysis.** All continuous variables are expressed as mean  $\pm$  SD, and categorical data as absolute numbers and percentages throughout this paper.

Multiple linear regression analysis with backward elimination was used to assess the association between CAD risk factors and  $^{wholevessel}TBR_{max}$ ,  $^{wholevessel}SUV_{max}$ , SHS, and PAS. Whole-vessel  $TBR_{max}$ ,  $^{wholevessel}SUV_{max}$ , SHS, and PAS were the response variables, and CAD risk factors the explanatory variables. The explanatory variables included were age  $> 65$  years, male gender, BMI  $\geq 30$  kg/m<sup>2</sup>, smoking, hypertension, alcohol use, exercising, diabetes, fasting glucose levels, and family history of cardiovascular disease. Variables were retained if  $p < 0.10$ . Multiple linear regression analyses were also performed to assess the association between each of these retained individual CAD risk factors and  $^{wholevessel}TBR_{max}$ ,  $^{wholevessel}SUV_{max}$ , and SHS, as well as PAS. The  $^{wholevessel}TBR_{max}$ ,  $^{wholevessel}SUV_{max}$ , SHS, and PAS were taken as the response variables, and each of the aforementioned CAD risk factors as the explanatory variable, adjusting for the other risk factors (BMI  $\geq 30$  kg/m<sup>2</sup>, age  $> 65$  years, hypertension,

smoking, male gender) as potential confounders. To assess the relation between the number of components of the metabolic syndrome and  $^{wholevessel}TBR_{max}$ , a 1-way analysis of variance was performed to test for between-group differences. To assess the intraobserver agreement of the image analysis, intraclass correlation coefficients with 95% confidence intervals were calculated in a subgroup of patients who underwent vascular FDG-PET imaging at our institution (18). Depending on normal distribution, the Pearson or Spearman rho correlation coefficients (r) were calculated to assess the relation between FDG circulation time (i.e., the time interval between FDG injection and starting time of the carotid data acquisition), acquired counts in the carotids, injected FDG dose, and  $^{wholevessel}TBR_{max}$ , as well as between the different FDG uptake parameters. All statistical analyses were performed using SPSS statistical package 16.0 (SPSS Inc., Chicago, Illinois).

## RESULTS

**Population characteristics.** A total of 82 patients were included in the study, of which all underwent FDG-PET/CT imaging. In 3 of the 82 patients, FDG-PET analysis could not be performed due to high FDG uptake in the thyroid, affecting the visualization and analysis of FDG uptake within the carotid arteries, leaving 79 eligible patients for image analysis. Patient characteristics are shown in Table 1.

**FDG-PET imaging and CAD risk factors.** Values for  $^{wholevessel}TBR_{max}$ ,  $^{wholevessel}SUV_{max}$ , SHS, and PAS, as well as prevalence of different cutoff values for  $^{wholevessel}TBR_{max}$ , are shown in Table 1. Comparison of the 4 different FDG uptake parameters showed highly significant positive correlations between all FDG uptake values ( $r > 0.64$ ;  $p < 0.0001$  for all comparisons).

Multivariate linear regression analysis with backward elimination, showing the relation between CAD risk factors and the various FDG-PET parameters, are shown in Table 2. BMI  $\geq 30$  kg/m<sup>2</sup>, age  $> 65$  years, hypertension, smoking, and male gender are shown to be strong determinants of the FDG uptake in the carotid artery walls.

Furthermore, multivariate linear regression analysis showed that BMI  $\geq 30$  kg/m<sup>2</sup>, age  $> 65$  years, hypertension, and smoking were independent risk factors for carotid inflammation as depicted by  $^{wholevessel}TBR_{max}$  (Fig. 2). Further analysis revealed



**Table 1. Characteristics of the CAD Population**

Characteristics	n = 82
Age, yrs	62.0 ± 9.7
>65	33 (40.2)
Gender	
Male	67 (81.7)
Female	15 (18.3)
BMI, kg/m <sup>2</sup>	27.8 ± 4.1
BMI <25	21 (25.6)
BMI ≥25 to <30	40 (48.8)
BMI ≥30	21 (25.6)
Lifestyle	
Smoking	
Never	37 (45.1)
Former	38 (46.3)
Current	7 (8.6)
Alcohol users	32 (39.0)
Exercisers	50 (61.0)
Medical history	
Cardiovascular disease	
Myocardial infarction	32 (39.0)
Percutaneous transluminal coronary intervention	61 (74.4)
Coronary artery bypass surgery	23 (28.4)
Stroke/transient ischemic attack	3 (3.7)
Peripheral artery disease	4 (4.9)
Family history of cardiovascular disease	48 (58.5)
Hypertension	59 (72.0)
Duration of hypertension, months	133.9 ± 119.4
Diabetes	31 (37.8)
Type I diabetes	3 (3.7)
Type II diabetes	28 (34.1)
Duration of diabetes, yrs	12.5 ± 15.0
Fasting glucose, mmol/l	6.0 ± 1.5
Medication	
Statin	78 (95.1)
Duration, months	55.5 ± 73.5
Beta-blocker	50 (61.0)
Calcium-channel blockers	13 (15.9)
ACE inhibitors	32 (39.0)
AT II blockers	10 (12.2)
Nitrates	9 (11.0)
Diuretics	13 (15.9)
Aspirin	75 (91.5)
Clopidogrel	60 (73.2)
Insulin	6 (7.3)
Oral antidiabetics (metformin and/or others)	26 (31.7)

*Continued*

**Table 1. Continued**

FDG-PET/CT	n = 79
Blood pool activity (left and right jugular vein; SUV <sub>mean</sub> )	1.08 ± 0.1
wholevessel TBR <sub>max</sub>	2.0 ± 0.3
wholevessel TBR <sub>max</sub> >1.8	55 (69.6)
wholevessel TBR <sub>max</sub> >2.0	32 (40.5)
wholevessel TBR <sub>max</sub> >2.2	19 (24.1)
wholevessel TBR <sub>max</sub> >2.4	10 (12.7)
wholevessel SUV <sub>max</sub>	2.14 ± 0.4
Single hottest segment	2.32 ± 0.4
Percent active segments	56.3 ± 37.7
0%	10 (12.7)
1%–30%	16 (20.2)
31%–60%	18 (22.8)
61%–90%	8 (10.2)
91%–100%	27 (34.2)

Values are mean ± SD or n (%). Percent active segments is defined as the percentage of segments with TBR<sub>max</sub> >1.9.

ACE = angiotensin-converting enzyme; AT II = angiotensin II; BMI = body mass index; CAD = coronary artery disease; FDG-PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; SUV<sub>max</sub> = maximum standardized uptake value; TBR<sub>max</sub> = maximum target-to-background ratio.

**FDG-PET methodology.** Concerning the intraobserver variability, intraclass correlation coefficient values for wholevessel TBR<sub>max</sub> were 0.98 (0.94 to 0.99) for the left and 0.97 (0.90 to 0.99) for the right carotid, indicating excellent agreement. The mean time difference between first and second reading was 29.1 days, with a range of 14 to 55 days.

No correlation was observed between wholevessel TBR<sub>max</sub> and FDG circulation time ( $r = 0.20$ ,  $p = 0.08$ ), acquired counts in the carotids ( $r = -0.07$ ,  $p = 0.57$ ), or injected FDG dose ( $r = 0.15$ ,  $p = 0.18$ ).

## DISCUSSION

The aim of our study was to determine the prevalence of carotid vessel wall inflammation, quantified by FDG-PET, in a CAD population and to identify which cardiovascular risk factors are related to carotid inflammation. We demonstrate that low-grade vessel wall inflammation is frequent in the CAD population. In addition, we show that BMI ≥30 kg/m<sup>2</sup>, age >65 years, history of hypertension, smoking, and male gender are important clinical risk factors for carotid FDG uptake. Moreover, FDG uptake in the vessel wall showed a high correlation with the number of components of the metabolic syndrome. These findings may be important since histology studies have shown that plaque inflammation is associated with plaque rupture and

that the number of components of the metabolic syndrome was significantly associated with wholevessel TBR<sub>max</sub> (Fig. 3). Independent predictors for wholevessel SUV<sub>max</sub>, SHS, and PAS values are shown in Figure 4.

**Table 2. Multiple Linear Regression Analyses With Backward Elimination to Identify Clinical Risk Factors of Carotid Vessel Wall Inflammation**

	B	95% Confidence Interval	p Value
<b>wholevesselTBR<sub>max</sub></b>			
BMI ≥30 kg/m <sup>2</sup>	0.29	0.15 to 0.44	<0.0001
Age >65 yrs	0.16	0.04 to 0.28	0.01
Hypertension	0.18	0.04 to 0.33	0.01
Smoking	0.27	0.04 to 0.51	0.02
Male	0.14	−0.02 to 0.30	0.09
<b>wholevesselSUV<sub>max</sub></b>			
BMI ≥30 kg/m <sup>2</sup>	0.38	0.22 to 0.55	<0.0001
Age >65 yrs	0.22	0.07 to 0.36	0.004
Male	0.23	0.04 to 0.41	0.02
Hypertension	0.16	0.008 to 0.32	0.04
<b>Single hottest segment</b>			
BMI ≥30 kg/m <sup>2</sup>	0.4	0.21 to 0.59	<0.0001
Age >65 yrs	0.2	0.03 to 0.36	0.018
Smoking	0.32	0.012 to 0.62	0.042
Hypertension	0.18	0.000 to 0.36	0.05
<b>Percent active segments</b>			
BMI ≥30 kg/m <sup>2</sup>	30.8	12.58 to 49.0	0.001
Hypertension	21.9	4.57 to 39.22	0.014
Smoking	32.9	3.75 to 62.13	0.028

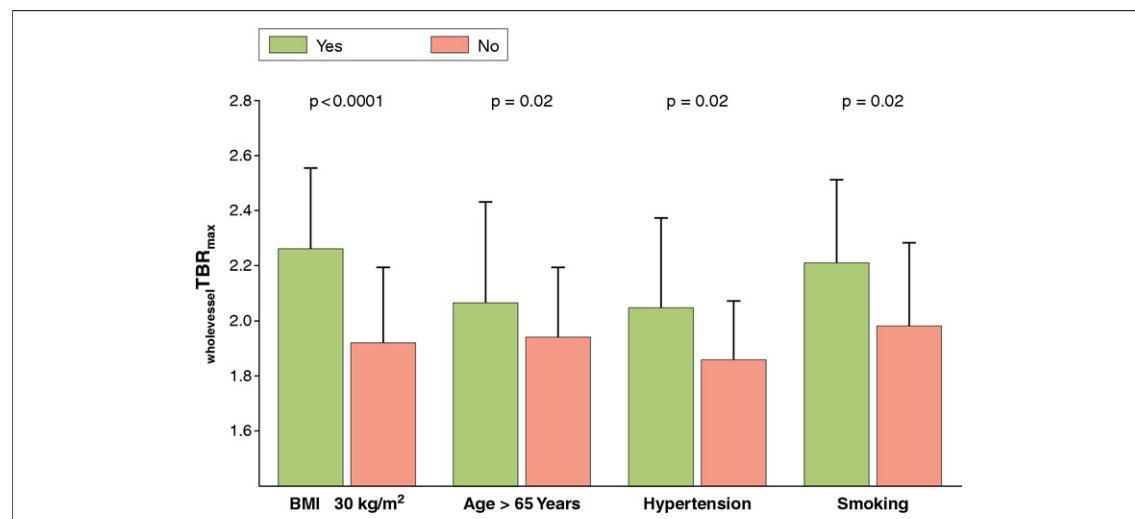
Whole-vessel target-to-background ratio (*wholevesselTBR<sub>max</sub>*), whole-vessel maximum standardized uptake value (*wholevesselSUV<sub>max</sub>*), single hottest segment, and percent active segments were the response variables, and the coronary artery disease risk factors age >65 years, male gender, body mass index (BMI) ≥30 kg/m<sup>2</sup>, smoking, alcohol use, exercise, hypertension, diabetes, fasting glucose levels, and family history of cardiovascular disease were the explanatory variables. Variables were retained in the model when *p* < 0.10. The best model is shown. B is the regression coefficient. Percent active segments is defined as the percentage of segments with *TBR<sub>max</sub>* >1.9.

atherothrombotic events (19). Our results imply that vessel wall inflammation may persist despite medical therapy, even at the highest *wholevesselTBR<sub>max</sub>* cutoff value.

Whether vessel wall inflammation measured by FDG-PET is related to the occurrence of future cardiovascular events is currently being investigated in large longitudinal follow-up studies (20). The determination of the prevalence of low-grade carotid inflammation depends on the choice of the cutoff *TBR<sub>max</sub>* value. It remains a matter of debate as to whether the vessel wall is considered “inflamed.” Histological studies of plaques obtained after carotid endarterectomy have shown that symptomatic plaques have higher macrophage content than asymptomatic plaques (21–23). Jander et al. (22) revealed that the percentage of macrophage-rich area of the plaque was 18 ± 10% in recently symptomatic patients versus 11 ± 4% in asymptomatic patients with carotid stenosis (*p* = 0.005). Obviously, there is some overlap between these groups, so pinpointing an exact number of macrophages to determine inflammation is difficult. However, it does provide an order of magnitude in which macrophage content is clinically relevant. To

translate this into meaningful FDG-PET–related cutoff values poses another challenge. Tawakol et al. (7) performed in vivo FDG-PET imaging in 17 patients that subsequently underwent carotid endarterectomy. These authors showed that plaque macrophage content was related to a gradual increase in plaque FDG uptake. Most plaques with TBR values under 1.8 had macrophage areas in the range of 0% to 5%, lesions with TBRs between 1.8 and 2.8 had 5% to 15% macrophages, and plaques with TBRs above 2.8 had macrophage areas >15% (7). For our study, in order to provide an estimate about the different degrees of FDG uptake in our study population, we felt it reasonable to set TBR cut points between 1.8 and 2.4 on the basis of the aforementioned pathologically derived values.

**Clinical risk factors and vessel wall inflammation.** We observed that obesity, aging, history of hypertension, smoking, and male gender were independent predictors of carotid inflammation as depicted by FDG-PET. By far the strongest determinant for all different FDG uptake parameters was increased BMI. Furthermore, we found a significant relation between the metabolic syndrome and vessel wall inflammation. Our findings are in line with previous publications. In a retrospective study in patients that underwent FDG-PET imaging for cancer screening, Tahara et al. (12) showed that carotid inflammation was associated with waist circumference, hypertension, glucose intolerance, and the metabolic syndrome. The similarities with our findings are striking, considering the fact that very different populations were investigated. We investigated a CAD population, whereas only 12.5% of their population had a history of CAD. Moreover, compared with our study, the number of men (68% vs. 82%), BMI (24 ± 3 kg/m<sup>2</sup> vs. 28 ± 4 kg/m<sup>2</sup>), history of hypertension (42% vs. 72%), and the number of diabetic patients (7% vs. 38%) were all markedly lower. Furthermore, in contrast to the current report, their study was performed on a standalone PET scanner only, and they did not apply a vascular-tailored imaging protocol. Despite these differences, both studies revealed that obesity and the number of components of the metabolic syndrome were strong determinants of carotid inflammation (12). In a more recent prospective trial in patients with known CAD or multiple cardiovascular risk factors, Rudd et al. (13) found carotid FDG uptake to be significantly higher in patients with known CAD and in males versus females. Their results are in broad agreement, not only with the study by Tahara et al. (12) mentioned in the



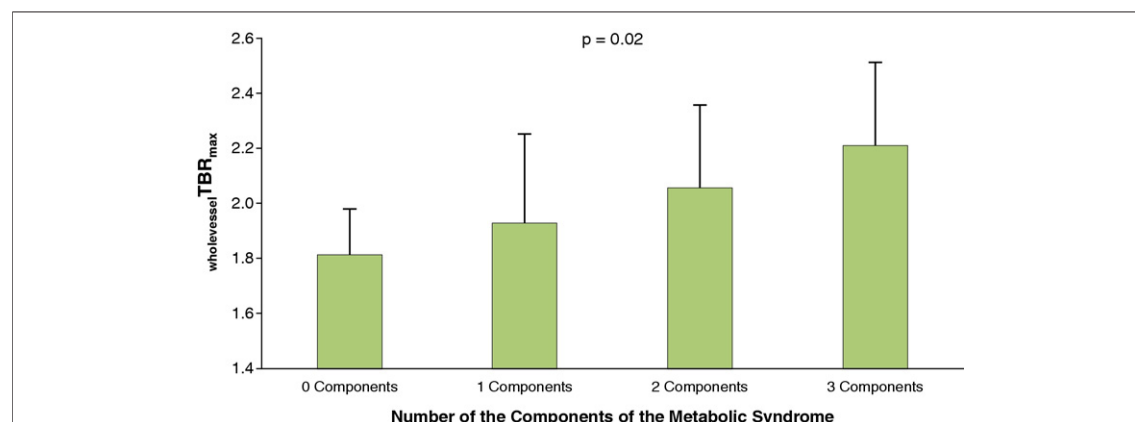
**Figure 2. Clinical Risk Factors of Carotid Vessel Wall Inflammation in CAD Patients**

This figure shows that body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, age >65 years, hypertension, and smoking are independent predictors for carotid wall inflammation as depicted by the whole-vessel target-to-background ratio (whole-vessel TBR<sub>max</sub>). Bars represent standard deviations. p Values are adjusted for the other 4 predictors given in Table 2. CAD = coronary artery disease.

previous text, but also with the results of our study, all indicating higher FDG uptake in the carotids of men compared with women (12,13). This observation suggests that atherosclerotic plaques in men may be more highly inflamed, perhaps providing a pathological link for their higher rate of cardiovascular events. However, the number of patients in our study was twice that of the study by Rudd *et al.* (13), providing greater statistical power. Furthermore, similar to the study population by Tahara *et al.* (12), the number of men (73% vs. 82%), BMI ( $26 \pm 5$  kg/m<sup>2</sup> vs.  $28 \pm 4$  kg/m<sup>2</sup>), history of hypertension (61% vs. 72%), and the number of

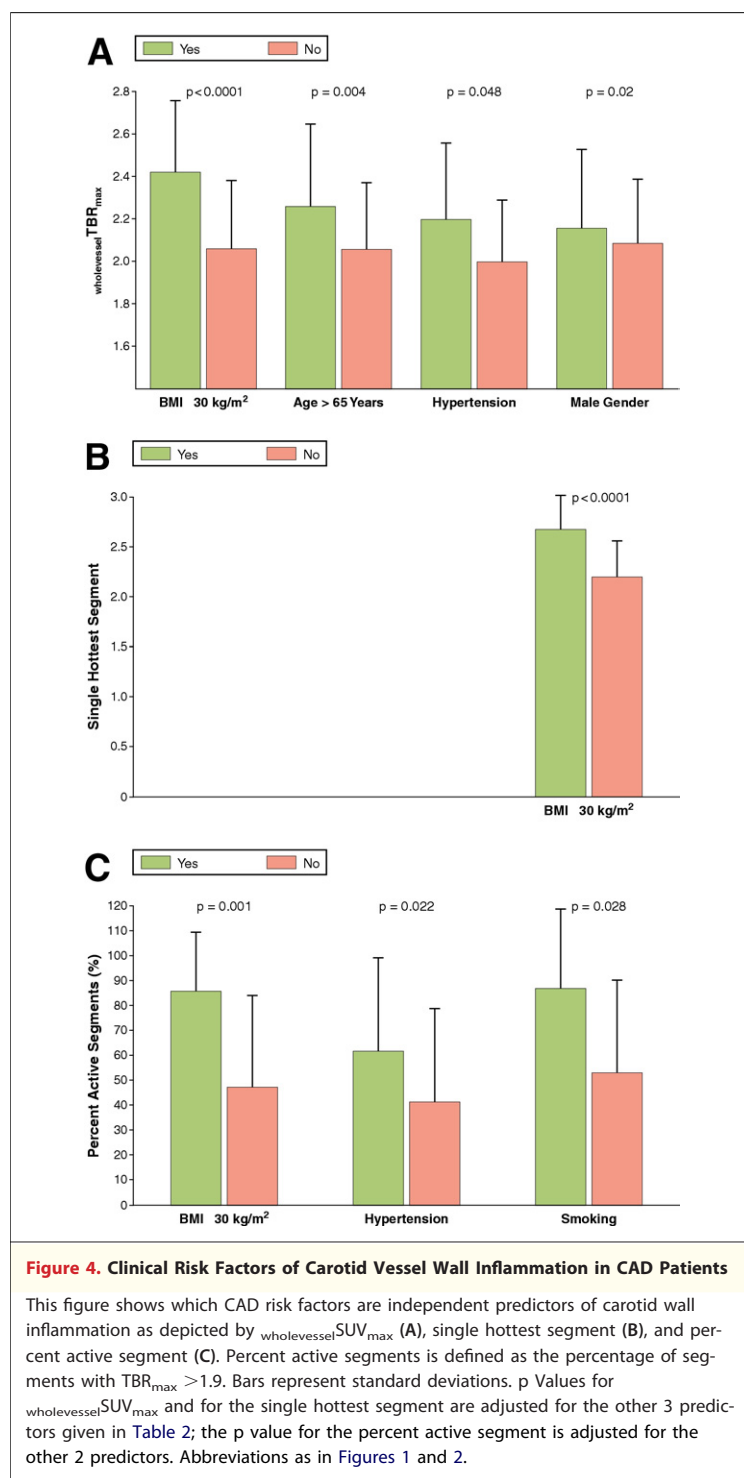
smokers and ex-smokers (49% vs. 55%) were again all markedly lower in their study, whereas the number of diabetic subjects were similar to that of our study (37% vs. 38%). Additionally, as with the study by Tahara *et al.* (12), the study population by Rudd *et al.* (13) was more heterogeneous compared with that in the current trial, which only includes patients with documented CAD.

The results of the present study have important clinical implications. Patients with the aforementioned characteristics might benefit most from anti-inflammatory pharmacotherapy. A currently widely available therapy known to exhibit anti-inflammatory



**Figure 3. Relation Between the Metabolic Syndrome and Carotid Vessel Wall Inflammation**

Whole-vessel TBR<sub>max</sub> is whole-vessel maximum target-to-background ratio. Bars represent standard deviations. A 1-way analysis of variance was performed to test for between-group differences (p = 0.02).



properties in addition to serum lipid lowering is 3-hydroxy-3-methyl-glutaryl-CoA reductase (statins) (5). Novel anti-inflammatory drugs being investigated as potential antiatherosclerotic therapies are compounds such as inhibitors of lipoprotein-associated phospholipase A2, anti-

integrin and anticytokine therapies, and mycophenolate mofetil, as well as vaccination with lipoprotein peptides (6,24). Furthermore, high-density lipoprotein cholesterol (HDL) is known to have anti-inflammatory properties, and drugs that increase HDL by cholesteryl ester transfer protein inhibition are currently being investigated in phase II and phase III trials (25,26).

To assess the efficacy and safety of these novel compounds, longitudinal follow-up studies assessing clinical endpoints will need to be performed. However, such studies are expensive and time consuming, and expose many patients to a drug of which the benefit or potential harm is unknown. Therefore, prior to embarking on such studies, efficacy can be investigated by use of surrogate imaging markers (27). Imaging FDG uptake by the vessel wall has emerged as a valuable surrogate marker of vessel wall inflammation (28). The results of our current study suggest that assessing the efficacy of novel cardiovascular drugs with anti-inflammatory properties might best be performed in obese or metabolic syndrome patients.

The fact that obesity and the metabolic syndrome show such a strong relation with FDG uptake in the vessel wall is intriguing. The metabolic syndrome is characterized by the clustering of obesity, insulin resistance, dyslipidemia, and hypertension (29). A meta-analysis in data from 172,573 patients showed that the metabolic syndrome increases the risk for atherothrombotic events and death, with a relative risk of 1.78 (95% confidence interval: 1.58 to 2.00) (30). Chronic low-grade inflammation, as reflected by serum biomarkers, is known to accompany the occurrence of obesity and the metabolic syndrome. In fact, epidemiological studies have shown a clear relation between obesity, metabolic syndrome, and increased levels of inflammatory markers such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), and CRP (31). A growing body of evidence supports a common pathological mechanism linking obesity to inflammation, insulin resistance, and cardiovascular disease. Adipose tissue, in addition to storing fat, is known to produce numerous cytokines and hormones (31). Studies have shown that adipocytes in obese subjects recruit macrophages, a process mediated by monocytes chemoattractant protein-1 (MCP-1) (31). Activation of the innate immune system occurs via toll-like receptors and receptors for advanced glycation end products that affect intracellular transcription pathways such as the nuclear factor  $\kappa$ B (NF- $\kappa$ B) and the c-Jun N-terminal kinase (JNK) pathways (32). In the



presence of inflammatory cells, adipocytes increase their secretion of adipokines such as adiponectin and TNF- $\alpha$ , which are known to directly instigate endothelial dysfunction (31). TNF- $\alpha$ , IL-6, and adiponectin also cause insulin resistance that induces oxidative stress and endothelial dysfunction (32,33). Kim *et al.* (34) observed a positive correlation between insulin resistance and adiponectin levels but a negative correlation between the maximum TBR levels and adiponectin. This finding is confirmed by 2 recently published studies (35,36), which also found an inverse relationship between adiponectin and arterial inflammation as assessed by FDG uptake. Since adiponectin is known to act as a brake on inflammation, and is therefore vascular protective, in both healthy individuals and those with vascular disease, it is intriguing that in those with the highest levels of this hormone, there were the lowest degrees of FDG arterial uptake (13,34–37). In addition to the pro-atherogenic inflammatory state, obesity is also associated with hypertension and increased very low-density lipoprotein cholesterol, triglycerides, and decreased HDL cholesterol (38), which might indirectly stimulate invasion of the vessel wall by monocytes. Together, these data indicate there is a direct pathophysiological link between obesity, inflammation, and atherosclerosis. Our data support the concept that obesity and the metabolic syndrome are related to vessel wall inflammation.

Of further interest is that we found a relation between smoking and carotid inflammation. Similar to obesity, smoking has shown to induce a proinflammatory state mediated by similar mechanisms as previously discussed, with elevated levels of TNF- $\alpha$ , IL-6, adiponectin and CRP, insulin resistance, oxidative stress, and endothelial dysfunction (33).

**FDG-PET/CT methodology-related issues.** In the present study, image analyses were performed by 1 experienced reader. This might reduce statistical noise related to interobserver variation, but concerns might arise about intraobserver bias. However, the blinded and randomized intraobserver agreement measurements revealed very favorable results, indicating that image analyses by 1 reader can be sufficient for the analysis being performed.

For all trials with FDG-PET imaging, concerns may arise about the impact of methodologically related variables, such as FDG circulation time, injected FDG dose, and the acquired counts. Although minimized by the use of standardized im-

aging protocols, such variations inevitably occur. Therefore, we investigated whether FDG circulation time, injected FDG dose, and the acquired counts were associated with  ${}_{\text{wholevessel}}\text{TBR}_{\text{max}}$ , and observed that none of the methodologically related variables significantly impacted the FDG uptake. Therefore, it seems unlikely this could have introduced bias in our study. Furthermore, as we did not observe a clear difference in results between those patients given high FDG doses and those given low doses, our results suggest that lower FDG doses could be used in future imaging studies.

Evaluation of cardiovascular risk factors for vessel wall inflammation yielded quite consistent results for  ${}_{\text{wholevessel}}\text{TBR}_{\text{max}}$ ,  ${}_{\text{wholevessel}}\text{SUV}_{\text{max}}$ , SHS, and PAS values. Because of these consistent results among the FDG uptake parameters, we do not believe that the results of the present study have been overly influenced by methodological issues related to the chosen way of image analysis. Furthermore, our work might add to the current discussion regarding the most appropriate way of assessing vessel wall inflammation, including the pros and cons of using the corrected TBR or the uncorrected SUV FDG uptake values.

**Study limitations.** There are some limitations of our study. First, we did not obtain serum lipid levels, markers of glucose metabolism, or serum inflammatory markers. This would have provided more complete information and more accurate determination of the metabolic syndrome. Second, this is a cross-sectional study. Therefore, we could not address whether there was a causal relationship between the presence of risk factors and vessel wall inflammation. Third, we cannot provide more detailed information about structural features of the carotid walls (calcification, lipid core) because we performed a non-contrast-enhanced CT as part of the PET/CT in order to reduce radiation exposure to patients. Furthermore, as we did not perform magnetic resonance imaging to avoid additional scanning time for the patients, morphological data from a second imaging method are also not available. Future studies, focusing on new combined imaging methods such as PET/magnetic resonance imaging, should allow this. Finally, it is unknown whether vessel wall inflammation measured by FDG-PET/CT is predictive of future cardiovascular events. Longitudinal, prospective studies testing this possibility are underway, although preliminary retrospective reports are supportive of the hypothesis (39,40).

## CONCLUSIONS

In the current study, we show that vessel wall inflammation as quantified by FDG-PET/CT is highly prevalent in the CAD population. Obesity, age over 65 years, a history of hypertension, and smoking seem to be important risk factors for carotid inflammation. Clustering of components of the metabolic syndrome also showed a strong relation with vessel wall inflammation. The results were consistent across several FDG measured endpoints that correlate with underlying inflammation. Finally, the administered activity of FDG did not

affect the results, suggesting that future studies might use lower doses than previously, thereby reducing the radiation exposure to each subject.

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**Key Words:** atherosclerosis ■  
 FDG-PET ■ inflammation ■  
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