Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location
A Longitudinal FDG-PET/CT Study

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Background—Arterial calcium (Ca) deposition has been identified as an active inflammatory process. We sought to test the hypothesis that local vascular inflammation predisposes to subsequent arterial calcium deposition in humans.

Methods and Results—From a hospital database, we identified 137 patients (age, 61±13 years; 48.1% men) who underwent serial positron-emission tomography/computed tomography (1–5 years apart). Focal arterial inflammation was prospectively determined by measuring 18F-fluorodeoxyglucose uptake (using baseline positron-emission tomography) within predetermined locations of the thoracic aortic wall and was reported as a standardized uptake value. A separate, blinded investigator evaluated calcium deposition (on the baseline and follow-up computed tomographic scans) along the same standardized sections of the aorta. New calcification was prospectively defined using square root–transformed difference of calcium volume score, with a cutoff value of 2.5. Accordingly, vascular segment was classified as either with or without subsequent calcification. Overall, 67 (9%) of aortic segments demonstrated subsequent calcification. Baseline median (interquartile range) standardized uptake value was higher in segments with versus without subsequent calcification (2.09 [1.84–2.44] versus 1.92 [1.72–2.20], P=0.002). This was also true in the subset of segments with Ca present at baseline (2.08 [1.81–2.40] versus 1.86 [1.66–2.09], P=0.02), as well as those without (2.17 [1.87–2.51] versus 1.93 [1.73–2.20], P=0.04). Furthermore, across all patients, subsequent Ca deposition was associated with the underlying 18F-fluorodeoxyglucose uptake (inflammatory signal), measured as standardized uptake value (odds ratio [95% confidence interval]=2.94 [1.27–6.89], P=0.01) or target-to-background ratio (2.59 [1.18–5.70], P=0.02), after adjusting for traditional cardiovascular risk factors.

Conclusions—Here, we provide first-in-man evidence that arterial inflammation precedes subsequent Ca deposition, a marker of plaque progression, within the underlying location in the artery wall. (Circ Cardiovasc Imaging. 2013;6:747-754.)

Key Words: positron-emission tomography • vascular calcification • arterial inflammation

Vascular calcification is a marker of atherosclerosis1 and is predictive of cardiovascular morbidity and mortality.2,3 Recently, arterial calcification (Ca) has been identified as an actively regulated process closely linked to atherosclerotic inflammation.4 Histological studies have shown plaque macrophages to colocalize with calcified plaques,5 and in vitro studies demonstrated the role of macrophage-monocyte–derived inflammatory mediators in the calcification process.6–8 A serial in vivo study demonstrated a real-time association of macrophage burden with early osteogenic activity in an animal model.9 Thus, the relationship between local inflammation and subsequent Ca deposition has been well outlined in both in vitro and animal studies.

The relationship between systemic markers of inflammation and Ca deposition in humans has not been well documented, with conflicting findings reported.10–12 Furthermore, the relationship between focal arterial inflammation and subsequent calcium deposition in that same location remains unknown. One obstacle to evaluating the relationship between local inflammation and Ca has been the lack of methods to measure local arterial inflammation in humans. However, during the past several years, 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) has been validated as a measure of arterial inflammation in humans. FDG is a glucose analog that enters cells through the glucose transporter protein (GLUT) and is retained within the cells at a rate that is proportional to glycolysis.13 The uptake of FDG within atherosclerotic plaques...
correlates with macrophage concentration in animals\(^\text{14}\) and humans\(^\text{15}\) and derives from the well-described phenomena of enhanced glycolysis in activated macrophages,\(^\text{16,17}\) especially macrophages activated by the classical/innate pathways.\(^\text{18}\)

Accordingly, we sought to test the hypothesis, in humans, that arterial locations that are inflamed (versus uninfamed) at baseline manifest subsequent Ca deposition and that regions within the same vessel, with different degrees of inflammation, will exhibit different rates of Ca deposition. To do so, FDG-PET was used to measure local atherosclerotic inflammation within predefined locations in the thoracic aorta at baseline. Thereafter, a separate group of investigators used serial computed tomography (CT) to quantify initial and subsequent Ca deposition within the artery wall for those same locations. Accordingly, the PET and CT imaging approach provided an opportunity to noninvasively assess whether a nidus of increased vascular inflammation is associated with subsequent vascular calcium deposition in the same location.

## Methods

### Design and Subjects

Out of a database of patients who underwent fused PET/CT studies for clinical indications between years 2004 and 2011 at the Massachusetts General Hospital, we identified 1410 unique patients who underwent ≥2 PET/CT examinations spaced 1 to 5 years apart. Subsequently, we reviewed the medical records of all 1410 patients and excluded any patient who had ≥1 of the predefined exclusion criteria: age <35 years, presence of chronic inflammatory disease, use of anti-inflammatory medications, or presence of active malignant cancer (defined as any radiological or pathological evidence of malignant cancer disease or undergoing chemotherapy or radiation therapy within 1 year before initial PET/CT and throughout the interval). The image sets for all 137 unique patients meeting the above criteria were then prepared for blinded analysis of the PET and CT images by 2 geographically distinct investigative groups who were blinded to the clinical data.

### Imaging Acquisition and Analysis

FDG-PET imaging was performed on a hybrid PET/CT scanner (Biograph 64, Siemens, Forchheim, Germany, or similar system). Briefly, FDG was administered (\(\approx\)10 mCi) intravenously after an overnight fast, and PET images were acquired 45 to 60 minutes later. A nongated, noncontrast-enhanced CT was obtained for attenuation correction of PET images. CT imaging was performed using a pitch 1.0, tube voltage 120 kVp, tube current 40 mA, and slice thickness 5 mm. Prior studies have demonstrated that calcium scores measured on CT images obtained from a hybrid PET/CT scanner are comparable with that obtained on a dedicated CT scanner.\(^\text{19}\)

Imaging data sets were sent to 2 separate groups for analysis. The group performing analysis of vascular FDG uptake was provided the baseline fused FDG-PET/CT imaging studies, but not the subsequent PET or CT images, to ensure that they would remain blinded to changes in aortic calcification. The group measuring calcium deposition was provided the baseline and follow-up attenuation correction CT scans (but not the PET imaging data). Clinical data were not available to either group performing the image analysis. Accordingly, complete mutual blinding between the 2 groups was achieved.

### Analysis of Vascular Inflammation at Baseline

FDG uptake was measured on baseline PET/CT scans using a multimodality fusion workstation (Leonardo TrueD, Siemens). First, the thoracic aorta was identified in coronal PET-CT images. Next, axial images of the thoracic aorta were evaluated every 5 mm along the longitudinal axis of the aorta. At each axial level, a region of interest was drawn along the circumference of the aorta. In this manner, a stack of region of interests were produced, yielding consecutive segments of 5 mm thickness, which together constituted the aorta, starting at the level of the anterior border of pulmonary artery and ending at the corresponding axial segment at the descending aorta. For each region of interest, the maximum standardized uptake value (SUV) for FDG uptake was determined, and the axial location co-ordinate was recorded. In addition, the target-to-background ratio was derived from the SUV of each region of interest to the mean venous blood activity, derived from averaging of 10 SUV values obtained from the superior vena cava. This corrects for the blood compartment contribution and FDG accumulation. Of note, at locations where arterial FDG uptake could not be adequately distinguished from intense uptake from an adjacent structure (eg, lymph node, esophagus, or heart), the SUV values were not recorded.

### Analysis of Vascular Calcium Deposition

A separate, experienced investigator evaluated Ca deposition (within the same areas of the thoracic aorta that were analyzed by PET) on baseline and follow-up attenuation correction CT using a dedicated workstation (TeraRecon AquariusWS, version 3.7.0-8). Briefly, aorta was evaluated for segmental Ca deposition (attenuation threshold of ≥130 HU in ≥3 contiguous voxels) relative to axial locations by identifying the z location of each axial image (a scanner-derived co-ordinate reference, measured in millimeter from the top of the data set). For evaluation of changes in segmental arterial calcification, the CT image sets were manually aligned, and the equivalent z locations for the 2 CT image sets were identified. Thereafter, quantification of the change in Ca was performed using previously used methods, wherein the calcium volume score (CVS) was prospectively defined as our primary measurement, based on the observation in other studies that it provides the most reliable index for change in calcification.\(^\text{20}\) New Ca deposition between baseline and follow-up CT scans was prospectively defined based on the Hokanson square root statistical method as previously reported.\(^\text{21}\) This method uses the square root–transformed difference in baseline and follow-up CVS, with a cutoff of 2.5 (the difference beyond measurement error) to define progression, and accounting for interscan variability across a range of CVS. Accordingly, arterial segments that had a square root–transformed difference in baseline and follow-up CVS ≥2.5 were classified as demonstrating subsequent calcification and <2.5 without subsequent calcification. Recently, it has been shown that the square root method is the best measure of coronary artery calcium progression for the prediction of mortality in asymptomatic individuals\(^\text{22}\) and was recommended to facilitate comparisons of calcium progression.\(^\text{23}\) To validate the process of manual matching and Ca scoring of arterial segments on serial CT, analysis was repeated on 35 segments from 20 patients with calcified segments on follow-up selected at random. Six months elapsed between first and second reads, and the reader was provided with only baseline axial locations to enable comparisons. Among 35 segments (25 without subsequent calcification and 15 with subsequent calcification), the intraclass correlation coefficient for baseline and follow-up CVS was high (intra-class correlation coefficient [95% confidence interval], 0.95 [0.90-0.97]), indicating excellent intraobserver agreement encompassing the process of manually matching the images followed by measurement of calcium deposition in the baseline and follow-up images.

### Registration of PET and CT Data

After completion of imaging analysis, the relative z locations were matched for the 3 scans: baseline PET, baseline CT, and follow-up CT. The baseline PET was registered to the baseline CT via the automatic registration of z locations (axial locations) provided in the image data (because the baseline PET and CT were performed during a single PET/CT session). The registration of baseline and follow-up CT was done during CT analysis as described above. Thus, for each vascular segment analyzed, baseline PET measures of inflammation and baseline and follow-up CT measures of Ca deposition were registered across all 3 image sets (Figure 1).
To determine the relationship between local inflammation and subsequent Ca, we prospectively defined 2 different types of analysis to be performed:

1. Per-segment analysis
   a. An across-patient analysis where all arterial segments from the entire population are compared.
   b. A within-patient analysis to abolish the between-subject factors that may affect future Ca deposition.

2. Per-patient analysis, where we studied FDG uptake in 2 patient groups: patients with segments with subsequent Ca (progressors) and patients without segments with subsequent Ca (nonprogressors).

Statistical Analysis

Descriptive data are presented as mean (SD) for continuous normally distributed variables, median (interquartile range) for continuous non-normally distributed variables, and frequency with proportions for nominal variables, as appropriate. Continuous variables were compared using independent sample $t$ test for parametric variables and Mann–Whitney $U$ test for nonparametric variables. Categorical variables were compared using $\chi^2$ test. Data for FDG uptake and demographic and clinical variables of interest were evaluated in univariate logistic regression analysis (generalized estimating equations model), and a cutoff of $P<0.05$ was used to select variables within 2 multivariate models. Within-subject correlations among vascular segments were accounted for in the regression analysis. Intraclass correlation coefficients with 95% confidence interval were calculated for intraobserver variation. Significance was determined at the 0.05 (2-sided) threshold. All analysis was performed using SAS version 9.2 and SPSS version 17.0 (SPSS Inc, Chicago, IL).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Population (n=137)</th>
<th>Progressors (n=44)</th>
<th>Nonprogressors (n=93)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (13)</td>
<td>66 (9)</td>
<td>54 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>48.1</td>
<td>50.0</td>
<td>47.3</td>
<td>0.769</td>
</tr>
<tr>
<td>Follow-up duration, y</td>
<td>1.75 (1.33)</td>
<td>1.58 (1.33)</td>
<td>1.96 (1.73)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hypertension, % (n=134)*</td>
<td>39.6</td>
<td>54.5</td>
<td>32.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic BP, † mm Hg</td>
<td>120 (22)</td>
<td>130 (19)</td>
<td>120 (20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy,* %</td>
<td>31.3</td>
<td>45.5</td>
<td>24.4</td>
<td>0.01</td>
</tr>
<tr>
<td>DM,* %</td>
<td>12.6</td>
<td>20.5</td>
<td>8.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Hyperlipidemia,* %</td>
<td>33.6</td>
<td>50.0</td>
<td>25.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Statin therapy, %</td>
<td>29.1</td>
<td>45.5</td>
<td>21.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Active smoking, ‡ %</td>
<td>7.4</td>
<td>4.5</td>
<td>8.7</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8</td>
<td>27.5 (6.7)</td>
<td>26.4 (5.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Atherosclerosis,§ %</td>
<td>9.5</td>
<td>13.7</td>
<td>7.5</td>
<td>0.3</td>
</tr>
<tr>
<td>FRS</td>
<td></td>
<td></td>
<td>7 (12)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Prior chemotheraphy, %</td>
<td>78.9</td>
<td>29.1</td>
<td>78.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Prior chest radiotherapy, %</td>
<td>16.1</td>
<td>13.6</td>
<td>86.4</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data presented as %, mean (SD), or median (interquartile range). BMI indicates body mass index; DM, diabetes mellitus; FRS, Framingham risk score; and systolic BP, systolic blood pressure.

*Data available for 134 patients.

†Data available for 131 patients: 41 patients with segments with subsequent calcification and 90 patients without segments with subsequent calcification.

‡Data available for 131 patients.

§Coronary artery disease, cerebrovascular disease, peripheral artery disease.

||Data available for 70 patients: 25 patients with segments with subsequent calcification and 45 patients without segments with subsequent calcification.

Results

One hundred thirty-seven patients who underwent serial PET/CT imaging as a part of scheduled surveillance and as indicated for alteration of clinical course to rule out recurrence of malignancy (yet were free from active malignancy) were identified. Table 1 summarizes demographic and cardiovascular risk profile of the total population and also provides the profiles of the 2 patient subgroups: progressors and nonprogressors. Table 2 summarizes clinical indications for serial PET/CT and documents prior history of chemotherapy or chest radiation therapy.

Per-Segment Analysis

Across-Patient Analysis

Throughout the 137 patient image sets, baseline PET and coregistered serial CT image data were recorded for a total of 735 arterial segments. Of 735 arterial segments, 67 (9%) manifested subsequent calcification, whereas 668 (91%) did not. In an across-patient analysis that pooled all segments.
from all patients, the median baseline segment SUV was higher in segments with (versus without) subsequent calcification. This analysis was repeated to examine the relationship between initial focal arterial inflammation and subsequent focal calcium progression within 2 subgroups of arterial segments: segments with calcium already present at baseline and segments without preexisting calcium. The focal arterial inflammatory signal remained higher in both subgroups. Furthermore, the segments that demonstrated incident calcification (those without Ca on baseline scan that demonstrated subsequent calcification) had the highest SUV, whereas segments with Ca present at baseline but which did not manifest subsequent calcification had the lowest SUV. An analysis of the segmental target-to-background ratio showed similar results (Table 3). An example image demonstrating this phenomenon is shown in Figure 2.

In univariate analyses, segment SUV, segment target-to-background ratio, age, diagnosis of hyperlipidemia, statin therapy, systolic blood pressure, baseline CVS, and follow-up duration were all associated with subsequent calcification. Furthermore, segment SUV and segment target-to-background ratio remained independent predictors of CVS progression in multivariate models (Tables 4 and 5).

Within-Patient Analysis

Furthermore, we evaluated the relationship between baseline arterial inflammation and subsequent calcium deposition after further controlling for all between-subject factors. To accomplish this, we conducted a within-patient analysis where the segmental FDG uptake was expressed relative to the mean FDG uptake for the entire aorta within which that segment resides (as the percent difference between the individual segment SUV and the mean SUV of the whole aorta). The mean aortic SUV was derived from the average of evaluable segmental SUV values constituting the aorta. Within each patient, the relative baseline SUV was higher in segments that manifested subsequent calcification (mean% difference SUV±SD: 2.81±8.39 versus −0.44±8.51 segments with versus without subsequent Ca, P=0.003). This held true in subset analyses of segments with Ca present at baseline (1.44±7.35 versus −2.95±9.32, P=0.007) and segments without Ca at baseline (6.52±10.05 versus −0.16±8.37, P=0.001; Figure 3).

Per-Patient Analysis

Finally, we compared FDG uptake between nonprogressors (n=93) and progressors (n=44) in the following manner:

1. A single per-patient average SUV derived from all segments of both groups: There was no significant difference in SUV between nonprogressors and progressors (1.95±0.35 versus 2.05±0.34, P=0.12).
2. A single per-patient average SUV derived from segments with subsequent Ca in the progressors: Progressors had higher SUV uptake than nonprogressors (2.10±0.37 versus 1.95±0.35, P=0.026).

Discussion

In this study, we provide initial in-human evidence that focal arterial inflammation (as quantified by FDG uptake) precedes subsequent deposition of arterial calcium within the same locations during the following 1 to 5 years. Although as expected the presence of cardiovascular disease risk factors was associated with subsequent calcification, local FDG uptake remained the strongest predictor of subsequent local calcification after adjusting for risk factors. These findings

Table 2. Clinical Indications for Serial PET/CT

<table>
<thead>
<tr>
<th>Indication for PET/CT</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>78</td>
</tr>
<tr>
<td>Gynecological cancer</td>
<td>11</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>11</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>9</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8</td>
</tr>
<tr>
<td>Follow-up pulmonary nodule</td>
<td>6</td>
</tr>
<tr>
<td>Melanoma</td>
<td>5</td>
</tr>
<tr>
<td>Other*</td>
<td>9</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>110</td>
</tr>
<tr>
<td>Prior chest radiotherapy</td>
<td>22</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; and PET, positron-emission tomography.

*Histocytosis, laryngeal cancer, leukemia, multiple myeloma, prostate cancer, sarcoma, thyroid cancer, and tonsillar cancer.

Table 3. Across-Patient Comparison of FDG Uptake in Arterial Segments With and Without Subsequent Calcification

<table>
<thead>
<tr>
<th>Arterial Segments</th>
<th>With Subsequent Calcification</th>
<th>Without Subsequent Calcification</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All segments</td>
<td>n (%)</td>
<td>67 (9%)</td>
<td>668 (91%)</td>
</tr>
<tr>
<td></td>
<td>SUV</td>
<td>2.09 (1.84–2.44)</td>
<td>1.92 (1.72–2.20)</td>
</tr>
<tr>
<td></td>
<td>TBR</td>
<td>2.06 (1.88–2.27)</td>
<td>1.98 (1.83–2.19)</td>
</tr>
<tr>
<td>Arterial segment calcification at baseline</td>
<td>Present</td>
<td>n (%)</td>
<td>49 (42%)</td>
</tr>
<tr>
<td></td>
<td>SUV</td>
<td>2.08 (1.81–2.40)</td>
<td>1.86 (1.66–2.09)</td>
</tr>
<tr>
<td></td>
<td>TBR</td>
<td>2.04 (1.87–2.23)</td>
<td>1.93 (1.78–2.13)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>n (%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td></td>
<td>SUV</td>
<td>2.17 (1.87–2.51)</td>
<td>1.93 (1.73–2.20)</td>
</tr>
<tr>
<td></td>
<td>TBR</td>
<td>2.10 (1.91–2.35)</td>
<td>2.00 (1.83–2.30)</td>
</tr>
</tbody>
</table>

Variables are presented as median (interquartile range). FDG indicates 18F-flourodeoxyglucose; SUV, standardized uptake value; and TBR, target-to-background ratio.
suggest that local vascular inflammation plays an important role in Ca deposition (an index of atherosclerotic plaque progression) and might in fact represent downstream mechanistic mediator of these systemic risk factors.

A robust relationship between focal inflammation and subsequent calcification was observed in both across- and within-patient analyses: arterial segments that manifest any subsequent calcium deposition had higher inflammatory signals at baseline. This is consistent with the findings of Aikawa et al9 in animal models, wherein they showed that macrophage infiltration precedes osteogenic activity and subsequent calcification. Similarly, a prior serial PET/CT study by Ben-Haim et al24 found that 8% of studied population had vascular areas with initial FDG uptake and subsequent Ca on follow-up using qualitative methods only. Notwithstanding, we demonstrated the prior mentioned phenomena using quantitative methods as well as strict blinding between Ca analysis and FDG uptake analysis.

In addition, we observed that the presence of preexisting calcification is associated with lower arterial inflammation. This is again consistent with previous findings that vascular inflammation is lowest in densely calcified locations.25,26 Interestingly, we also observed that vascular segments that already contained calcium at baseline but that subsequently manifested additional calcification had higher FDG uptake than the average for all arterial segments evaluated within that same patient. This observation might reflect ongoing inflammatory cellular activity, plaque expansion, and Ca deposition within the matrix adjacent to the calcium present at baseline, resulting in enlargement of the calcific focus. Thus, it is reasonable to assume that inflammation and calcification represent different phases of atherosclerosis, with inflammation being the predominant process in early stages of atherosclerosis27 promoting plaque progression and calcification, which in turn seems to prevail in more advanced stages. At some point in this spectrum, however, a dense nidus of calcium might provide little substrate for further inflammation, which might explain the fact that densely calcified locations had the lowest inflammatory signal of all in this study.

It is worth noting that the findings of this study conflict with those of a prior study. Meirelles et al26 failed to find an association between FDG uptake at baseline and Ca deposition at follow-up. However, in contrast to our study, Meirelles et al26 did not use quantitative methods for the assessment of FDG uptake and Ca deposition, relying only on subjective evaluation of the images. In addition, prior investigators included individuals who were being treated with chemotherapeutic agents and radiation therapy, which might impact the biology of the arterial wall and, in turn, might have confounded their findings.
It is well accepted that calcium deposition is a clinically relevant manifestation of atherosclerotic plaque progression. Accordingly, the findings of this study, by showing that inflammation precedes calcification, support the hypothesis that inflammation is an important driver of plaque progression. This finding extends the observation of Fayad et al.,28 wherein changes in carotid inflammation (between 6 months and baseline) correlated with changes in carotid artery remodeling. However, in that study, the observed vascular changes were confounded by drug treatment, and the relationship between initial arterial inflammation and subsequent plaque progression was not reported. Hence, the current study provides the first such relationship between index inflammatory imaging and subsequent local plaque progression.

Prior animal studies have shown that areas with high FDG uptake were associated with plaque thrombosis,29,30 whereas human studies have shown that high aortic and carotid FDG uptake is related to subsequent risk of plaque rupture and clinical events.31–33 However, in those studies, the relationship between location of inflammation and the location (or vessel bed) of the subsequent atherothrombotic event was not reported. Although those studies serve to demonstrate that FDG uptake provides a systemic index of increased risk, they do not provide any insights about the local consequences of focal arterial inflammation. Accordingly, the current study provides a plausible explanation for those prior reports, wherein a nidus of plaque inflammation may contribute to local atherosclerotic progression. These findings make obvious the need to evaluate the relationship prospectively between initial plaque inflammation and subsequent plaque progression and plaque rupture (manifested by a local or downstream atherothrombotic event). Such a prospective study could establish focal arterial inflammation by FDG-PET/CT as a useful clinical risk factor or possibly as a surrogate marker for use in clinical investigations. A conceivable clinical scenario where local plaque progression may be important is in the assessment of carotid stenosis, especially in patients with asymptomatic moderate-to-severe stenosis. In this population, if this imaging approach was validated prospectively, a low PET signal may encourage conservative therapy, whereas a high signal might prompt more aggressive interventions. Accordingly, future prospective studies should evaluate the significance of local PET signal in more

### Table 5. Factors Associated With Subsequent Segmental Calcification: Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1: SUV and Covariates</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Model 2: TBR and Covariates</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental SUV</td>
<td>2.94 (1.27–6.89)</td>
<td>0.01</td>
<td></td>
<td>Segmental TBR</td>
<td>2.59 (1.18–5.70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.004–1.06)</td>
<td>0.03</td>
<td></td>
<td>Age</td>
<td>1.04 (1.01–1.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.03 (1.01–1.05)</td>
<td>0.005</td>
<td></td>
<td>Systolic blood pressure</td>
<td>1.02 (1.004–1.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.84 (0.50–16.10)</td>
<td>0.24</td>
<td></td>
<td>Hyperlipidemia</td>
<td>1.38 (0.49–3.87)</td>
<td>0.54</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>0.57 (0.10–3.32)</td>
<td>0.53</td>
<td></td>
<td>Statin therapy</td>
<td>1.42 (0.45–4.49)</td>
<td>0.55</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>1.002 (1.001–1.003)</td>
<td>&lt;0.001</td>
<td></td>
<td>Follow-up duration</td>
<td>1.002 (1.001–1.003)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline CVS</td>
<td>1.002 (1.001–1.004)</td>
<td>0.01</td>
<td></td>
<td>Baseline CVS</td>
<td>1.002 (1.001–1.004)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CI, confidence interval; CVS, calcium volume score; DM, diabetes mellitus; OR, odds ratio; SUV, standardized uptake value; and TBR, target-to-background ratio.

**Clinical Implications**

It is well accepted that calcium deposition is a clinically relevant manifestation of atherosclerotic plaque progression. Accordingly, the findings of this study, by showing that inflammation precedes calcification, support the hypothesis that inflammation is an important driver of plaque progression. This finding extends the observation of Fayad et al.,28 wherein changes in carotid inflammation (between 6 months and baseline) correlated with changes in carotid artery remodeling. However, in that study, the observed vascular changes were confounded by drug treatment, and the relationship between initial arterial inflammation and subsequent plaque progression was not reported. Hence, the current study provides the first such relationship between index inflammatory imaging and subsequent local plaque progression.

Prior animal studies have shown that areas with high FDG uptake were associated with plaque thrombosis,29,30 whereas human studies have shown that high aortic and carotid FDG uptake is related to subsequent risk of plaque rupture and clinical events.31–33 However, in those studies, the relationship between location of inflammation and the location (or vessel bed) of the subsequent atherothrombotic event was not reported. Although those studies serve to demonstrate that FDG uptake provides a systemic index of increased risk, they do not provide any insights about the local consequences of focal arterial inflammation. Accordingly, the current study provides a plausible explanation for those prior reports, wherein a nidus of plaque inflammation may contribute to local atherosclerotic progression. These findings make obvious the need to evaluate the relationship prospectively between initial plaque inflammation and subsequent plaque progression and plaque rupture (manifested by a local or downstream atherothrombotic event). Such a prospective study could establish focal arterial inflammation by FDG-PET/CT as a useful clinical risk factor or possibly as a surrogate marker for use in clinical investigations. A conceivable clinical scenario where local plaque progression may be important is in the assessment of carotid stenosis, especially in patients with asymptomatic moderate-to-severe stenosis. In this population, if this imaging approach was validated prospectively, a low PET signal may encourage conservative therapy, whereas a high signal might prompt more aggressive interventions. Accordingly, future prospective studies should evaluate the significance of local PET signal in more

**Figure 3.** Within-patient segmental arterial 18F-fluorodeoxyglucose (FDG) uptake. *Percent difference between segment standardized uptake value (SUV) and mean SUV of the whole aorta. CI indicates confidence interval.
clinically relevant vascular beds, such as coronary and carotid vasculature, and using different markers of plaque progression in addition to calcification.

**Limitations**

Our study has several limitations. First, our study included patients with prior history of malignancy and chemo/radiation therapy with a possible prolonged effect on vascular pathobiology, which in turn might confound our findings. Furthermore, measures of systemic inflammatory biomarkers, such as C-reactive protein, were not routinely acquired for cancer patients with prior history of malignancy and chemo/radiation therapy in addition to calcification.

Herein, we observe that locations within the arterial wall that manifest high inflammatory signals are more likely to manifest subsequent calcium deposition. Accordingly, we provide further evidence for the role of local inflammation as an effect of adverse local plaque behavior. Furthermore, imaging plaque inflammation may prove useful as a tool to study the mechanisms associated with local arterial calcium deposition, a well-validated index of atherothrombotic risk.

**Disclosures**

None.

**References**


CLINICAL PERSPECTIVE

It is well accepted that arterial calcification is a clinically relevant manifestation of atherosclerosis progression. Vascular inflammation has been shown to be associated with initiation, progression, and complications of atherosclerosis. Prior studies have established the relationship between inflammation and plaque thrombosis using systemic indices, such as inflammatory biomarkers and whole-vessel molecular imaging. Our study is the first in-human longitudinal study to demonstrate association between initial local plaque inflammation and subsequent plaque progression, providing a plausible explanation for those prior reports. These findings make obvious the need to prospectively evaluate the relationship between initial plaque inflammation and subsequent plaque progression and plaque rupture (manifested by a local or downstream atherothrombotic event). Such a prospective study could establish focal arterial inflammation by 18F-fluorodeoxyglucose-positron-emission tomography/computed tomography as a useful clinical risk factor or possibly as a surrogate marker for use in clinical investigations. A conceivable clinical scenario where local plaque progression may be important is in the assessment of carotid stenosis, especially in patients with asymptomatic moderate-to-severe stenosis. In this population, if this imaging approach was validated prospectively, a low positron-emission tomography signal may encourage conservative therapy, whereas a high signal might prompt more aggressive interventions.
Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study
Amr Abdelbaky, Erin Corsini, Amparo L. Figueroa, Sara Fontanez, Sharath Subramanian, Maros Ferencik, Thomas J. Brady, Udo Hoffmann and Ahmed Tawakol

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SUPPLEMENTAL MATERIAL

Supplemental Figure:

Figure demonstrating analysis of FDG uptake in different aortic segments.

Regions of interests were drawn at 5 mm increment on axial sections, around the circumference of aorta, beginning at ascending aorta at the level of inferior border of pulmonary artery, and ending at the corresponding level at the descending aorta.

Red arrow points to an aortic segment with significant spill over activity from adjacent structures and hence was excluded from analysis.