Noninvasive Detection and Localization of Vulnerable Plaque and Arterial Thrombosis With Computed Tomography Angiography/Positron Emission Tomography

Kusai Aziz, MD; Kevin Berger, MD; Kate Claycombe, PhD; Ruiping Huang, PhD; Roshan Patel, MD; George S. Abela, MD

Background—It has been shown that plaque uptake of fluorodeoxyglucose is proportional to macrophage density. We tested the hypothesis that arterial thrombosis occurs in areas with high fluorodeoxyglucose uptake and that computed tomography angiography (CTA) can detect thrombi in vessels.

Methods and Results—Twenty New Zealand White rabbits were studied before and after atherosclerosis induction through de-endothelialization and a high-cholesterol diet; 14 were then thrombus triggered. CTA/positron emission tomography scans were performed before cholesterol diet, at the middle diet feeding, at the end of diet feeding, and after triggering. Serum inflammatory markers were measured. Maximal standardized uptake value was measured over the thoracic and upper and lower abdominal aortas and correlated with thrombosis and macrophage density on sections from the same sites. Aortic diameters averaged 2.84±1.16 mm. The sensitivity, specificity, and accuracy of CTA for detecting thrombi were 92%, 89%, and 90%, respectively. Plasminogen activator inhibitor-1 and C-reactive protein levels increased with atherosclerosis and thrombosis triggering. Maximal standardized uptake value at baseline was 0.62±0.13, 0.96±0.33 at the middle of feeding, and 1.06±0.38 at the end of feeding. Segments that developed thrombosis had the highest maximal standardized uptake value of 1.32±0.69 (113% increase; \(P=0.002\)) and had a 129% increase in macrophage density compared with segments without thrombi (\(P=0.01\)).

Conclusions—Fluorodeoxyglucose uptake was proportional to the duration of cholesterol feeding and peaked with plaque disruption and thrombosis. CTA was highly accurate in detecting thrombi. Our findings in this animal model of atherosclerotic plaques with high macrophage density showed that CTA/positron emission tomography can be used to identify and localize inflamed plaques and thrombosis. With the currently available technology and nuclear tracers, however, many challenges remain before clinical applications are possible. (Circulation. 2008;117:2061-2070.)

Key Words: angiography ■ plaque ■ positron-emission tomography ■ inflammation ■ thrombosis

Recent advances using noninvasive imaging in positron emission tomography (PET) and computerized tomography angiography (CTA)\(^7\)–\(^10\) can be applied to detecting vulnerable plaque. Recently, it has been shown that fluorine-18 fluorodeoxyglucose (FDG-18) uptake in plaques is proportional to the degree of inflammation and macrophage density.\(^11\),\(^12\) However, so far, no correlation has been established between these findings and plaque rupture and thrombosis.

Systemic inflammatory markers have been widely investigated. C-reactive protein (CRP) has been shown to be an important marker for predicting risk of acute cardiovascular events\(^13\) and may play a role in promoting atherothrombosis by increasing the recruitment of monocytes and their synthesis of tissue factor.\(^14\),\(^15\) It also has been shown that CRP exerts its proatherothrombotic effect directly on endothelial cells by increasing plasminogen activator inhibitor-1 (PAI-1). Importantly, increased PAI-1 levels have been shown to enhance thrombosis, and administration of antibodies directed against PAI-1 has been shown to be effective in preventing thrombosis.
Atherosclerosis

Under general anesthesia (ketamine 50 mg/kg and xylazine 20 mg/kg IM), balloon-induced de-endothelialization of the aorta was performed with a 4F Fogarty arterial embolectomy catheter (Baxter Healthcare Corp, Irvine, Calif) introduced via a right femoral artery cutdown. The catheter was advanced in a retrograde fashion to the ascending aorta, inflated with 1 mL air, and pulled back. This was repeated 3 times; the femoral artery was then ligated, and the skin incision was sutured. These rabbits were then fed a high-cholesterol diet (Harlan-Sprague Dawley, Inc, Indianapolis, Ind) for 1 to 9 months (average, 6.3 months). Details of this model have been reported previously.21

Pharmacological Triggering

Thrombus triggering was induced in 14 rabbits by Russell’s viper venom (0.15 mg/kg IP, Sigma Chemical Co, St Louis, Mo) and histamine (0.02 mg/kg IV, Sigma Chemical Co) given at 48 and 24 hours before euthanasia as previously reported.21 Procedures were performed according to the Michigan State University Animal Care and Use Committee–approved protocol.

CTA/PET Imaging

CTA/PET imaging was performed 2 hours after intravenous injection of 2 mCi FGF-18. Under general anesthesia (ketamine 50 mg/kg and xylazine 20 mg/kg IM), the rabbits were held in a supine position on plastic boards with medical tape to minimize motion artifact and were placed inside the CT/PET tube for scanning. Imaging was performed with a GE Discovery ST (a fusion PET/CT scanner). After a noncontrast CT examination for attenuation correction, a PET 2-dimensional acquisition-per-bed-position scan was acquired over 30 minutes. On completion of PET imaging, a CTA was performed using the integrated 16-slice CT. During hand injection of 10 cm³ Visipaque 320, the CTA was performed (200 mA, 120 kV peak) at 0.625-mm collimation.

Cholesterol and Serum Marker Analysis Methods

Blood samples were collected to measure serum cholesterol, CRP, and PAI-1 before each CTA/PET scan. In the triggered group, additional samples were collected just before triggering and 12, 24, 36, and 48 hours after triggering before the CTA/PET. CRP was measured with an ELISA kit from Immunology Consultant Laboratory (Newberg, Ore). PAI-1 was measured with an ELISA kit from Molecular Innovations (Southfield, Mich). The Cholesterol Kit (Thermo Electron Corp, Louisville, Colo) was used to measure serum cholesterol concentrations measured according to the manufacturer’s instructions.

Methods

Rabbits Groups

A total of 34 CTA/PET scans on 20 male New Zealand White rabbits (weight, 3.2±0.32 kg) as follows: at baseline (normal control; n=3), at 1 to 4 months after induction of atherosclerosis (middle of feeding; n=3), at 6 to 9 months after induction of atherosclerosis (end of feeding; n=14), and after triggering for thrombosis (triggered group; n=14) (Table). To maximize plaque FDG uptake and to standardize results, the rabbits were not fed overnight (8 to 12 hours) before the CTA/PET studies were performed. In the triggered group, CTA/PET was performed 48 hours after triggering; the rabbits were then euthanized.

Despite the fact that some rabbits were studied in >1 group and therefore had >1 CT/PET examination, analyses were performed with each examination treated as an independent entity. In addition, per-segment analysis did not account for the multiple measurements made in the same rabbit.

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Image Analysis

CTA Images

CTA images were analyzed in the cross-sectional, sagittal, and coronal views. Each aorta was divided into 3 regions: thoracic (from the aortic root to the diaphragm), upper abdominal (from the diaphragm level to the renal arteries), and lower abdominal (from the renal arteries to the aortic bifurcation). Thrombi were visually identified, and a thrombus was defined as a filling defect seen in any 2 views. The thrombi were categorized as small if ≤1 cm in length and as large if >1 cm in length. The CTA image analysis was performed by a reader blinded to the pathology results. Findings of the CTA images were then compared with pathology.

PET Images

Standardized uptake values (SUVs) were calculated with adjustment for subject weight, injected dose, and FDG-18 decay. Maximal SUV
(SUVmax) was measured over the thoracic and upper and lower abdominal aortas of each rabbit by a reader blinded to the pathology and CTA results. SUVmax was determined by placing a region of interest over the thoracic and upper and lower abdominal aortas. Each CTA/PET scan was analyzed 2 different ways as follows. In the per-region analysis, each aorta was divided into 3 regions (thoracic and upper and lower abdominal) to detect the diagnostic accuracy of the scans per region or segment because inflammation and thrombosis usually occur in discrete areas and do not involve the whole vessel. In the per-animal analysis, to link inflammatory marker changes to SUV changes, we had to average the SUVmax of all segments of the same rabbit to relate the general inflammatory status of the animal by SUVmax and by markers.

Pathology

Gross Examination
At postmortem, the aortas were dissected and removed. The aortas and iliofemoral arteries were opened by a longitudinal incision exposing the intimal surface for inspection. Gross examination of the aortas was performed, and thrombi in all aortic segments were identified visually and confirmed by histology. On the pathological specimens, the thoracic aorta included the aortic root to the origin of the last pair of intercostal arteries, the upper abdominal aorta ended at the origin of the renal arteries, and the lower abdominal aorta was defined to extend from the renal arteries to the aortic bifurcation. Findings of the pathology segments were then compared with the corresponding CTA segments.

Macrophage Staining
To determine macrophage density, arterial tissue sections (7 μm thick) were obtained from the aortic segments (thoracic, upper abdominal, lower abdominal) of 13 rabbits (12 atherosclerotic, 1 normal), yielding a total of 39 segments. The aortic segments were fixed in 10% buffered formaldehyde overnight and then cut and embedded in paraffin on edge. Tissue sections were then mounted on glass slides and stained with hematoxylin and eosin, Masson’s trichrome, and RAM 11 (Laboratory Vision, Milford, Mass), the immunohistochemical stain for monoclonal antibodies to rabbit macrophages. Tissue sections were examined with a light microscope (Nikon Microphot FX, Tokyo, Japan) and photographed with a ×20.1 NA PlanApo Nikon objective. All sections were photographed at ×2 under identical conditions of illumination voltage and condenser settings. Photographs were corrected for uneven illumination and camera sensor response by dividing the tissue image by a blank image taken under identical settings with Image Arithmetic version 2.5. Images were analyzed with ImageJ version 1.37v (http://rsb.info.nih.gov/ij/). The total surface area measured of the arterial wall, including the intima, media, and adventitia, was based on the trichrome-stained sections. Macrophage activity was characterized for each RAM 11–stained section as the total area darker than a predetermined threshold representing relatively strong staining. Thrombus, when present, was excluded from measurements of the RAM 11 images. A ratio of RAM 11–stained tissue to the whole arterial segment was used to determine the percent density of the macrophages in the section. Macrophage density as an index of inflammation was then correlated with SUVmax and presence of thrombus in the aortic segment.

Statistical Analysis
GraphPad Prism (San Diego, Calif) was used for statistical analysis. Measured data were reported as mean±SD. A 1-way ANOVA was used to compare SUVmax data before the cholesterol diet was initiated, at the middle of feeding, and at the end of feeding, as well as in rabbits triggered without thrombosis and triggered with thrombosis. In addition, Tukey’s test was performed for multiple comparisons. For the triggered group that had repeated measurement
of inflammatory markers, repeated-measures ANOVA was used to compare CRP and PAI-1 levels over time separately for the groups that did and did not develop thrombosis; differences between these groups were then evaluated with 2-way ANOVA with repeated measures on 1 factor. Multiple comparisons with Bonferroni’s test were used to determine the statistical significance of the difference at any 1 specific time point.

An unpaired t test with unequal variance was used to calculate the statistically significant difference of the relation of macrophage density and SUVmax values between the thrombotic and nonthrombotic segments. Sensitivity and specificity of CTA for detecting platelet thrombi were calculated according to standard formulas, and the CIs for sensitivity and specificity were calculated using standard methods for proportions. Because of potentially highly skewed variables, correlation between cholesterol and CRP/PAI-1 was measured with Spearman’s correlation. A value of \( P < 0.05 \) was used to determine statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

CTA Results
The average diameter of the rabbit aortas was 2.84±1.16 mm: 3.88±0.48 mm for the proximal thoracic segments and 1.79±0.49 mm for the distal abdominal segments. Eight of the 14 triggered rabbits developed thrombi. CTA detected the presence of platelet thrombi in 13 of 14 aortic segments identified by gross examination and histology (sensitivity, 92%; 95% CI, 0.66 to 0.99) and correctly diagnosed the absence of thrombi in 25 of 28 segments (specificity, 89%; 95% CI, 0.72 to 0.98). The accuracy of CTA for detecting the presence or absence of thrombi was 90% (Figures 1 and 2). Six segments contained thrombi <10 mm in length, and 8 segments contained thrombi ≥10 mm in length. The smallest thrombus detected was 3 mm in length.

SUVmax Results
The per-segment analysis revealed that the average SUVmax for control aortas was 0.62±0.13; during the middle of the feeding period, 0.96±0.33 (55% increase from baseline); and at the end of feeding period, 1.06±0.38. The triggered segments that did not develop thrombus had a mean SUVmax of 1.22±0.41 (70% increase from baseline), and the segments that developed thrombosis had a mean SUVmax of 1.32±0.69 (113% increase from baseline). The difference among these groups was statistically significant (\( P = 0.002 \); Figure 3). There was statistical difference (\( P < 0.05 \)) between the control group and each of the other groups. There was no statistical difference (\( P = 0.22 \)) between the middle-of-feeding and end-of-feeding groups. The difference between the end-of-feeding group and the triggered group (combining both subgroups with and without thrombosis) was statistically significant (\( P = 0.03 \)); however, there was no significant difference between the triggered subgroups that developed thrombosis and the group that did not (\( P = 0.6 \)).

We also analyzed the SUVmax value per animal to compare it with the corresponding inflammatory marker level. That comparison showed that the average SUVmax was 0.62±0.05 for control rabbits, 1.01±0.25 for the atherosclerotic rabbits, 1.15±0.06 for the rabbits that were triggered but
did not develop thrombosis, and 1.31±0.44 for the rabbits that developed thrombosis (Figure 4).

**CRP Results**

CRP levels were lowest in the control group, increased with atherosclerosis and after triggering, and reached a peak at 24 hours after triggering. The difference among samples measured repeatedly over time (at 12, 24, 36, and 48 hours) was statistically significant in the group that developed thrombosis ($P=0.038$) and not significant in the group that did not develop thrombosis ($P=0.10$). Trends over time in the no-thrombus group did not achieve statistical significance despite exhibiting larger differences than the thrombus group because of the small sample size in the no-thrombus group. In general, all values were higher in the rabbits that were triggered but did not develop thrombosis compared with those that developed thrombosis (Figure 5). The overall difference of the CRP values between the groups with and without thrombosis was statistically significant ($P=0.04$). However, multiple comparisons with Bonferroni’s test revealed no significant differences at any 1 specific time point.

**Figure 3.** Mean SUVmax as measured by PET at different stages of cholesterol feeding and thrombosis (per-segment analysis). Vertical lines represent SD.

**Figure 4.** The relationship among the means of CRP, PAI-1, and SUVmax (per-animal analysis) at different stages of atherosclerosis and thrombosis. Vertical lines represent SD.
PAI-1 Results

We found that PAI-1 values increased with cholesterol feeding and that there was a surge in the serum level after triggering for thrombosis (Figure 6). The peak PAI-1 level occurred 24 hours after thrombosis triggering and subsequently decreased in the samples obtained at 36 and 48 hours after triggering; however, it remained higher than baseline level. The PAI-1 level was higher in the rabbits that developed thrombosis at all sampling points (Figure 7). The difference among samples measured repeatedly (at 12, 24, 36, and 48 hours) was statistically significant in the group that developed thrombosis ($P < 0.031$) and not significant in the group that did not develop thrombosis ($P = 0.14$). Trends over time in the no-thrombus group did not achieve statistical significance because of the small sample size. The overall difference of PAI-1 level between the groups with and without thrombosis was statistically nonsignificant ($P = 0.051$); however, this probability value represents a trend that perhaps did not quite achieve statistical significance given the small sample size.

Serum cholesterol increased significantly ($P < 0.0001$) from 117.05 mg/dL in the control group to 926.05 mg/dL during the last phase of atherosclerosis, with a drop in rabbits that developed thrombosis to 760.9 mg/dL. There was no significant correlation between serum cholesterol and CRP (Spearman’s correlation, $r = -0.20$; 95% CI, −0.26 to 0.03; $P = 0.06$) or between cholesterol and PAI-1 ($r = 0.11$; 95% CI, −0.34 to 0.52; $P = 0.63$). Spearman’s correlation between CRP and PAI-1 also was nonsignificant ($r = -0.41$; 95% CI, −0.72 to 0.58; $P = 0.38$). The CI for the correlation between CRP and PAI is very wide, and the point estimate is moderate in magnitude. The analysis was underpowered because of a small sample size and the large variability of the data.

Macrophage Staining Results

The RAM 11–stained aortic specimens demonstrated an increased density of macrophages (manifested as brownish staining) in the segments that developed thrombosis, whereas they were not detected in the normal segments. The macrophages were distributed in all the arterial wall layers but were concentrated mainly in the subintima (Figure 8). The average macrophage percentage in the segments that developed thrombosis was 12.4 ± 9.3% and in the segments that did not develop thrombosis was 5.4 ± 7%; the difference between these 2 groups was statistically significant ($P = 0.01$). The macrophage density in the above groups corresponded to SUVmax values of 1.47 ± 0.66 and 1.01 ± 0.46, respectively. The difference between the SUVmax values for the segments that developed thrombosis and the segments that did not develop thrombosis also was statistically significant ($P = 0.02$).

Discussion

The diameter of the rabbit aortas was comparable to that of human coronary arteries, which means that the resolution of CTA and PET will be sufficient to detect the changes described above in humans. So far, CTA has been used as a noninvasive diagnostic tool for the severity of stenosis. However, in our study, we have shown that it is feasible to detect small thrombi with CTA. The PET resolution is relatively low ($≈ 6.5 \text{ mm}$), which is one of the weaknesses of nuclear imaging modalities, including PET.
However, the coregistration with CTA (CTA is used concurrently for plaque localization and PET is used for the characterization of such a plaque) can help to overcome this limitation. Lower peak kilovolt values (60 to 90 kV peak), which have an important impact on reducing radiation exposure, could have been used in our study. However, newer generations of CT scanners have collimation <0.625 mm, which could enhance the accuracy of CTA in detecting smaller thrombi. In our study, it was not possible to quantify the thrombi because of multiple factors, including limited resolution, irregular geometry of thrombi, and motion artifact. However, we were able to detect thrombi as small as 3 mm in length and to accurately semiquantify thrombi as small (<10 mm in length) and large (≥10 mm in length).

FDG uptake has been evaluated in human carotid arteries and shown to be related to inflammation in postoperative plaque specimens. So far, there have been few observations of FDG uptake in coronary arteries, and its origin has not been elucidated.

Although the magnitude of difference of SUV values is relatively small, the percent increase from control was sufficient to provide a noninvasive measure to differentiate normal from highly inflamed plaques. It is noteworthy that the SUVs in our model are similar to those of human carotids reported recently.

In this work, we were able to demonstrate for the first time a relationship between SUV and the development of arterial thrombosis. FDG uptake and hence plaque inflammation increased proportionally with the duration of cholesterol feeding. In addition, segments with thrombosis had the highest plaque FDG uptake, indicating a high degree of inflammation.

We also were able to show that the segments with thrombosis had significantly higher macrophage density and SUVmax values compared with the segments without thrombosis. The increase was of high magnitude (~129% increase in macrophage density and 47% increase in SUVmax). Our findings confirmed previous reports of high macrophage density in areas of plaque rupture; however, the signifi-

Figure 8. A, Transverse section of atherosclerotic rabbit aorta stained with RAM 11 at the site of thrombus. The stain is localized to the plaque with macrophage accumulation. B, The same arterial site stained with trichrome, demonstrating the thrombus and underlying plaque. C, Light micrograph of normal rabbit aorta with RAM 11 demonstrating no staining for macrophages. D, Light micrograph of normal rabbit aorta (same as in C) with trichrome stain showing normal arterial wall morphology.
cantly high SUV_{max} in the thrombotic segments is a novel concept that could have future clinical applications.

**Use of SUV as an Indicator of Plaque Inflammation**

Radiologists frequently use FDG to differentiate between benign and malignant tumors, but its use in measuring plaque inflammation noninvasively is a novel application. Increased FDG-PET uptake has been demonstrated in a variety of inflammatory processes. Particularly, active granulomatous disease shows marked FDG-18 uptake in disease processes such as tuberculosis, histoplasmosis, and sarcoidosis. Some have proposed using FDG-PET to assess for the presence of active disease as a method of following up patients with sarcoidosis, for example. FDG uptake also has been demonstrated in vasculitis. In each of these inflammatory conditions, FDG uptake in macrophages is a typical proposed mechanism.

**Serum Inflammatory Markers**

Serum inflammatory markers increased significantly during atherosclerosis and after triggering and thrombosis. The relative drop in CRP in rabbits that developed thrombosis could be explained by local uptake by the phagocytizing cells, or it could be due to random variation. The individual PAI-1 levels were variable and overlapped among different stages of atherosclerosis and thrombosis as shown in Figure 6. However, our study was not designed to address this issue. One possibility is genetic variation in the rabbits that leads to variable response to atherosclerosis and thrombosis triggering. PAI-1 gene polymorphism has been described and attributed as a cause of poor association of PAI-1 levels and clinical events in humans. Another possibility is that thrombosis could have developed at any time within the 48 hours after triggering, leading to the variability in the peak serum levels of both markers (CRP and PAI-1) in relation to the diagnosis of thrombosis by imaging and postmortem analysis performed at a fixed point (48 hours) after triggering.

It also should be noted that the level of serum inflammatory markers is much higher than the values noted in humans. This likely is attributed to the high thrombus load in the rabbits relative to their total weight and surface area.

We can conclude that the combination of CTA and FDG-PET could be a noninvasive alternative to angioscopy because of its very high sensitivity for detecting thrombosis and its ability to characterize high-risk plaques with increased SUV compared with yellow plaques seen on angioscopy. Our study implies that it is feasible to use elevated CRP and PAI-1 to identify vulnerability for thrombosis and FDG uptake to diagnose and localize vulnerable plaques and to predict thrombosis.

**Study Limitations**

The study is limited by being performed in a rabbit model with a high macrophage content in plaques, which could make it easier to detect with PET scanning. Some of the rabbits were studied in >1 group such as middle and end of feeding or end of feeding and triggering. Another limitation is that the per-segment analysis did not account for the multiple measurements made within the same rabbit, a result of the small sample size and the death of some rabbits during cholesterol feeding and after triggering for thrombosis. Ideally, the same large group of rabbits should have been followed up at all stages (control, at middle of feeding, at end of feeding, and after triggering); however, this was difficult because some of the rabbits died during the cholesterol feeding or after triggering but before scanning and needed to be replaced by another rabbit with a similar duration of atherosclerosis. The occurrence of death in rabbits on a high-cholesterol diet is a known limitation of this atherosclerotic model, and it takes at least 6 months to replace a rabbit. Treating multiple CT/PET exams in the same rabbit as independent entities does not overcome the limitation of the same rabbit appearing in multiple groups. The small sample size, especially in the control and early atherosclerosis groups, gave us a small number of data points to understand the early behavior of plaque and whether this could identify vulnerable area for plaque formation.

Another limitation is that we used CTA/PET software derived from human data rather than from rabbits. This could be a potential source of bias in the data analysis, but this effect was constant in all rabbits. An additional limitation is that we studied the aortas rather than coronaries. Performing the same technique on coronaries will be more challenging because of cardiac motion, but this challenge could be overcome by gating.

In the present rabbit model, the cardiac FDG uptake had a minor adverse effect on the interpretability of the data because it is relatively far from the aorta; other organs like the liver, kidneys, and urinary bladder represented a bigger limiting factor owing to their large size, higher FDG uptake, and close vicinity to the aorta. However, with the currently available technology and tracers, cardiac FDG uptake can be problematic, so FDG coronary imaging may not be feasible because the coronaries and the myocardium may overlap. Previous reports have shown that myocardial FDG uptake can be reduced by lowering the patient’s blood glucose level to ≤120 mg/dL. However, these results remain experimental without a definite solution to the limitation of myocardial FDG uptake.

In regard to the inflammatory marker data, we were unable to demonstrate statistical significance over time in CRP in the group that did not develop thrombosis despite larger change, likely because of the small sample size and the fact that 70% of the triggered rabbits develop thrombosis.

**Conclusions**

In the present study, we were able to detect plaque inflammation (using FDG PET) and thrombosis (using CTA) in small vascular beds. Vascular inflammation and thrombosis were associated with a surge of serum inflammatory markers. These findings could be the basis for a novel approach to detect vulnerable plaque. This is a feasibility study in the aorta of a rabbit model of ather-
sclerosis and thrombosis that may ultimately have clinical relevance.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

The identification of vulnerable plaque can add a new dimension to the evaluation of cardiovascular atherosclerosis. Using an atherosclerotic rabbit model of plaque disruption and thrombosis, we demonstrated that positron emission tomography can localize inflamed plaques with high macrophage density and quantify the degree of inflammation in arteries comparable in size to human coronary arteries. These inflamed arteries were significantly more thrombotic. Currently, treatment decisions are based on the degree of stenosis, but this approach frequently fails to predict cardiac events. This was demonstrated recently by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial, the results of which were explained in part by more interventions on severely stenotic but more stable plaques instead of less stenotic but vulnerable plaques. Therefore, localizing inflamed plaques and quantifying their degree of inflammation can potentially enhance the accuracy of decisions regarding therapy. The present study also has shown that computerized tomography angiography can be used accurately to diagnose small thrombi in atherosclerotic arteries similar in size to human coronaries. However, the application of these findings to humans still awaits solutions to multiple technical limitations. Nevertheless, some of our findings can serve as the basis for future research in noninvasive plaque characterization with computerized tomography angiography/positron emission tomography technology. It is expected that such research would be more easily performed in the carotid rather than coronary arteries because of their larger size and proximity to the skin. More investigations are needed to detect vulnerable plaques and arterial thrombosis in humans using the noninvasive computerized tomography angiography/positron emission tomography technology.
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