Background—Plaque erosion leads to exposure of subendothelial collagen, which may be targeted by glycoprotein VI (GPVI). We aimed to detect plaque erosion using 64Cu-labeled GPVI-Fc (fragment crystallized).

Methods and Results—Four-week-old male apolipoprotein E-deficient (ApoE−/−) mice (n=6) were fed a high-fat diet for 12 weeks. C57BL/6J wild-type (WT) mice served as controls (n=6). Another group of WT mice received a ligation injury of the left carotid artery (n=6) or sham procedure (n=4). All mice received a total activity of ≈12 MBq 64Cu-GPVI-Fc by tail vein injection followed by delayed (24 hours) positron emission tomography using a NanoPET/computed tomographic scanner (Mediso, Hungary; Bioscan, USA) with an acquisition time of 1800 seconds. Seventy-two hours after positron emission tomography/computed tomography, all mice were scanned 2 hours after intravenous administration of 0.2 mmol/kg body weight of a gadolinium-based elastin-specific MR contrast agent. MRI was performed on a 3-T clinical scanner (Philips Healthcare, Best, The Netherlands). In ApoE−/− mice, the 64Cu-GPVI-Fc uptake in the aortic arch was significantly higher compared with WT mice (ApoE−/−: 13.2±1.5 Bq/cm³ versus WT mice: 5.1±0.5 Bq/cm³; P=0.028). 64Cu-GPVI-Fc uptake was also higher in the injured left carotid artery wall compared with the intact right carotid artery of WT mice and as a trend compared with sham procedure (injured: 20.7±1.3 Bq/cm³ versus intact: 2.3±0.5 Bq/cm³; P=0.028 versus sham: 12.7±1.7 Bq/cm³; P=0.068). Results were confirmed by ex vivo histology and in vivo MRI with elastin-specific MR contrast agent that measures plaque burden and vessel wall remodeling. Higher R1 relaxation rates were found in the injured carotid wall with a T1 mapping sequence (injured: 1.44±0.08 s⁻¹ versus intact: 0.91±0.02 s⁻¹; P=0.028 versus sham: 0.97±0.05 s⁻¹; P=0.068) and in the aortic arch of ApoE−/− mice compared with WT mice (ApoE−/−: 1.49±0.05 s⁻¹ versus WT: 0.92±0.04 s⁻¹; P=0.028).


Key Words: atherosclerosis ■ magnetic resonance imaging ■ positron-emission tomography and computed tomography

Rupture of vulnerable atherosclerotic plaque is a major cause of coronary thrombosis and subsequent myocardial infarction. Fibrillar collagen is the most abundant extracellular matrix protein in artery walls. It acts as a strong platelet activator and initiates platelet-dependent thrombus formation.1,2 Platelet glycoprotein VI (GPVI) binds to exposed subendothelial collagen as a result of vascular injury or atherosclerosis.3 We recently performed optical imaging experiments in a mouse model of vascular injury to visualize the binding of fluorescein isothiocyanate (FITC)–labeled GPVI-Fc (fragment crystallized) to the injured endothelium both in the carotid arteries and in the aortic arch. Binding of GPVI-Fc–FITC to collagen, in both models, could be inhibited by unlabeled GPVI-Fc administered before injection of...
GPVI-FCT. To allow clinical translation of this approach, radiolabeling of GPVI-Fc is promising because of the high sensitivity of positron emission tomography (PET) and the relative ease of performing first-in-man studies. Compared with $^{124}$I and other PET isotopes, $^{64}$Cu may be preferred because of its improved spatial resolution (higher image quality) and adequate half-life time (12.7 hours) for delayed PET studies. Thus, GPVI-Fc radiolabeling using $^{64}$Cu may be a promising approach to image exposed subendothelial collagen and ultimately vulnerable plaques in patients with suspected coronary artery disease.

The aim of this study was to investigate whether $^{64}$Cu-labeled GPVI-Fc allows noninvasive detection and quantification of subendothelial collagen because of plaque erosion or rupture in a mouse model of accelerated atherosclerosis and mechanical vessel wall injury, which may have important therapeutic implications.

**Methods**

**Mouse Models**

Experimental atherosclerosis was investigated in a previously described mouse model of progressive atherosclerosis. Four-week-old homozygous male apolipoprotein E-deficient (ApoE−/−) B6.129P2−apoE−/−J (C57BL/6J background) mice (n=6) were switched to a high-fat diet containing 21% fat from lard and 0.15% (wt/wt) cholesterol (Special Diets Services, Witham, United Kingdom) for 12 weeks. Specific pathogen-free 16-week-old male C57BL/6J wild-type (WT) mice were fed a normal diet and served as controls (n=6). Another group of WT mice received a ligation injury of the left carotid artery (n=6) or sham procedure (n=4) and were imaged after 24 hours. In 12 additional WT mice, a ligation-induced injury of the left carotid artery was performed. The carotid arteries were removed 13 to 14 hours after injury, and tracer injection was analyzed by optical imaging.

Both ApoE−/− and WT mice were obtained from Charles Rivers Laboratories (Edinburgh, United Kingdom). Institutional review board approval was obtained. Animal studies were performed in accordance with UK Research Councils' and Medical Research Charities’ guidelines on Responsibility in the Use of Animals in Bioscience Research under a UK Home Office License.

**Labeling of the Molecular Imaging Biomarker**

We conjugated GPVI-Fc to the bifunctional chelator S-2-(4-Isothiocyanatobenzyl)-1,4,7,10-tetrazacyclododecane-1,4,7,10-tetraacetic acid (p-SCN-Bn-NOTA) using standard methods. Briefly, using this method, the protein is stripped of metal ions using EDTA and then the buffer exchanged into 0.1 mol/L HEPES buffer pH 8.9 by ultra-centrifugation. p-SCN-Bn-NOTA (as a 40-fold molar excess to protein) in dimethyl sulfoxide is added, and the conjugation is allowed to proceed at ambient temperature for 3 hours. The conjugated protein is then purified, and the buffer is exchanged into the radiolabeling buffer, 0.1 mol/L ammonium acetate, by ultra-centrifugation and stored at −20°C until required for radiolabeling.

$^{64}$Cu was prepared by $^{64}$Ni(p,n)$^{64}$Cu nuclear reaction on a CTI RDS 112 1 MeV cyclotron. The irradiated $^{64}$Ni was dissolved in minimal concentrated HCl (100–150 µL) and $^{64}$Cu purified to yield $^{64}$CuCl, by loading onto an anion exchange column (Biorad AG1-X8 resin). Excess $^{64}$Ni was removed by elution in 9 mol/L HCl. HCl (6 mol/L) was then used to raise the pH before elution of $^{64}$CuCl, in 0.1 mol/L HCl. $^{64}$CuCl was converted to $^{64}$Cu acetate by dilution in 1 mol/L ammonium acetate buffer solution (pH 6) before radiolabeling.

NOTA-GPVI-Fc, in 0.1 mol/L ammonium acetate buffer (pH 6), was radiolabeled with $^{64}$Cu by the addition of $^{64}$Cu acetate. The resulting solution was incubated at ambient temperature for 20 minutes to yield the novel biomarker, $^{64}$Cu-GPVI-Fc. Analysis to confirm successful radiolabeling was performed by size exclusion high-performance liquid chromatography. Radiolabeling experiments for $^{64}$Cu-GPVI-Fc revealed a radiochemical purity of >99% (Figure 1A).

The novel imaging biomarker was cloned, partly expressed in Chinese hamster ovary cells as soluble immunoadhesin (GPVI-Fc), and successfully tested for purity in vitro (Western blot, SDS-PAGE).

**PET/Computed Tomographic Imaging**

To demonstrate the specific avidity of $^{64}$Cu-labeled GPVI-Fc to subendothelial collagen in vivo, we used the model of ligation-induced vascular injury of the carotid artery and performed PET/computed tomography (CT) 24 hours after ligation and $^{64}$Cu-labeled GPVI-Fc injection in vivo. The surgical procedure has been described in detail previously. In addition, PET/CT imaging was performed in high-fat diet–fed atherosclerotic ApoE−/− mice. All mice received a total activity of ≈12 MBq $^{64}$Cu-GPVI-Fc by injection into the tail vein followed by delayed (24 hours) PET using a NanoPET/CT scanner (Mediso, Budapest, Hungary; Bioscan, Washington DC), with an acquisition time of 1800 seconds.

To verify anatomic structures, CT imaging was performed using microCAT2 (Siemens Preclinical Solutions, Knoxville, TN) with a recording time of 10 minutes 40 seconds (Figure I in the online-only Data Supplement). For visualizing the blood vessels, a contrast agent (0.375 mL Fenestra VC; Aleron Biomedical, San Diego, CA) was injected intravenously.

**Magnetic Resonance Imaging**

To assess plaque burden and vascular remodeling noninvasively, a novel elastin-specific MR contrast agent was used as previously described by our group. Thus, 72 hours after PET/CT imaging, all mice were scanned 2 hours after intravenous administration of 0.2 mmol/kg body weight of elastin-specific MR contrast agent. Delayed enhancement MRI and T1 mapping were performed on a 3-T clinical scanner (Philips Healthcare, Best, The Netherlands) using a dedicated single-loop surface coil (23 mm). After a 3D GRE scout scan, contrast-enhanced angiographic images were acquired for visualization of the aortic arch and the brachiocephalic and carotid arteries with a field of view (FOV)=30×30×8 mm, matrix=200×200, in-plane resolution=0.15×0.15 mm (reconstructed=0.10×0.10 mm), slice thickness=0.5 mm, repetition time/echo time (TR/TE)=15/6.1 ms, and flip angle=40°. The maximum intensity projection images were used to plan the subsequent delayed enhancement (DE) and T1 mapping scans. The T1 mapping sequence comprised 2 inversion recovery-modified Look-Locker trains using initial inversion times of 12 and 73 ms followed by 8 segmented readouts. For T1 mapping, the acquisition parameters were FOV=360×22×8 mm, matrix=192×102, in-plane resolution=0.18×0.22 mm, measured slice thickness=0.5 mm, slices=16, TR/TE=9.6/4.9 ms, and flip angle=10°.

**Histology, Immunohistochemistry, Transmission Electron Microscopy, and Autoradiography**

For tissue harvesting, mice were anesthetized with isoflurane, cuffed with a ketamine/xylazine overdose, and perfused through the left ventricle with 10% formaldehyde for 10 minutes. Brachiocephalic arteries, aortic arch, and carotid arteries were processed for paraffin sectioning. Sections were stained with hematoxylin–eosin for cellular infiltration, Miller’s elastica van Gieson for elastin, and Masson trichrome for collagen deposition. Immunostaining with a specific antibody was performed for human Fc to locate binding of the adhesin, GPVI-Fc. According to a previous study, serial sections were blocked with H2O2 and 3% BSA (Sigma, Steinheim, Germany) and incubated with a peroxidase-conjugated goat anti-human IgG antibody Fc fragment specific (Jackson Immunoresearch Laboratories Inc, West Grove, PA) for 1 hour at room temperature. Transmission electron microscopy was performed as described previously. In brief, samples of the brachiocephalic arteries of atherosclerotic ApoE−/− mice were dehydrated through ethanol and embedded in epoxy resin. Sections of 0.09 µm were collected on 150-nm copper grids for immunogold staining with a mouse anti-human IgG-F(ab’2) antibody (1:50 dilution) followed by a goat anti-mouse IgG (1:20 dilution) and the subsequent treatment with 5-nm gold-labeled donkey anti-goat IgG antibodies (1:50 dilution). Stained grids were observed at 100-kV acceleration voltage on a Philips CM 120 transmission electron microscope (Philips, Eindhoven, The Netherlands).
grids and double stained with uranyl acetate and lead citrate for electron microscopy (H7650; Hitachi, Tokyo, Japan). Immunostaining for GPVI-Fc was quantified in 10 sections per mouse using digital image analysis system and defined by area fraction as the ratio of thresholded chromogen and vascular area according to a previous report.15

For morphological lipid staining, formaldehyde-fixed vessels were stained with Sudan III (Sigma, Steinheim, Germany), and high-resolution autoradiograms were performed with the identical vessels in a storage phosphor imager as previously described (STORM; Amersham Biosciences, USA).16

Figure 1. Feasibility of radiolabeling, positron emission tomography (PET)/computed tomography (CT) injury model, and MRI. A, Top, The ultraviolet chromatogram of ⁶⁴Cu (NOTA-glycoprotein VI [GPVI]-Fc); bottom, chromatogram of ⁶⁴Cu (NOTA-GPVI-Fc) with a radiochemical purity of 99.2%; NOTA/protein: 1.15. B, In wild-type (WT) mice, PET/CT shows higher tracer uptake (arrow) of ⁶⁴Cu-GPVI-Fc 24 hours after ligation injury in the left injured carotid artery (right) compared with sham procedure (left). The residual uptake in the sham procedure without vessel damage is related to tissue injury and scarring because of the incision (arrow). C, Quantification by standardized uptake value (SUV) showed significantly higher uptake in the injured vessel compared with the intact right carotid artery (left) and as a trend compared with sham procedure (right). D, Distinct Sudan III staining and enhanced uptake of ⁶⁴Cu-GPVI-Fc in the carotid arteries after sham procedure (left) compared with ligation injury (right) using autoradiography. E, Optical imaging revealed higher binding of fluorescence-labeled active GPVI-Fc (group 1) compared with controls (P=0.033) such as Fc control (group 2), prior blocking with unlabeled GPVI-Fc (group 3), and heat-inactivated GPVI-Fc (group 4; after post hoc testing, group 1 vs 2: P=0.043; 1 vs 3: P=0.082; 1 vs 4: P=0.064). F, There was also higher uptake (arrow) of a gadolinium-based elastin-binding contrast agent, elastin-specific MR contrast agent, in WT mice after ligation injury of the left carotid artery (right) compared with sham procedure (left). G, Using a T1 mapping sequence, higher R1 relaxation rates were found in the injured compared with intact vessel (right) and as a trend compared with sham procedure (left), suggesting vessel wall remodeling after injury. Fc indicates fragment crystallized.
Image Analysis

To quantify the PET/CT signal, partial volume correction was performed as described previously.15 As shown in a previous publication, the partial volume effect of a structure of 1 mm leads to a 5-fold underestimation of activity.16 To address the limited spatial resolution of PET, we also performed sham procedures, which can result in tracer uptake in the incision wound. The uptake pattern in animals with mechanical vessel wall injury was, however, distinct from those with sham procedure. Quantification of tracer uptake was expressed as standardized uptake value by biodistribution from the corrected images. To calculate the standardized uptake values, Bq/cm³ were divided by the Becquerels injected (decay corrected to the scan start time) and multiplied by the mouse weight. Images were fused using proprietary Bioscan InVivoScope software.

To quantify extracellular matrix remodeling by MRI, we generated T1 maps and calculated the T1 for the injured and noninjured vessel wall. T1 maps from 20 slices were calculated using custom-made software implemented in MATLAB (MathWorks, Natick, MA).19

Optical Imaging

Fluorescence labeling of GPVI-Fc with FITC (Sigma, Hamburg, Germany) was performed as described previously.1 Fluorescence-labeled GPVI-Fc (2 mg/kg body weight), either active or heat inactivated (95°C; 10 minutes), or fluorescence-labeled Fc control (equimolar) was injected intravenously via tail vein in WT mice (each, n=3). Another group received unlabeled GPVI-Fc (20 mg/kg body weight) to block GPVI-Fc binding 45 minutes before ligation and injection of labeled GPVI-Fc. After 13 to 14 hours of ligation, the animals were killed and perfused with PBS. The left and right carotid arteries were removed and stored in 4% paraformaldehyde.

To measure GPVI-Fc binding to injured endothelium, optical imaging was performed (macroscopic imaging system AequoritaTM, dual-mode cooled charge-coupled device camera ORCAII-BT-1024, software Wasabi version 2.0; Hamamatsu Photonics, Herrsching, Germany). For excitation, a band-pass filter with a bandwidth of 490±20 nm was used in front of the camera’s objective lens. For fluorescence imaging, an exposure time of 180 seconds at 100% excitation light intensity was applied. The exposure times were kept constant to allow semiquantitative comparison of the light emission intensity between the individual tissue samples. The mean detected optical signal of the region of interest was calculated and corrected for background fluorescence by subtracting the mean data of the background fluorescence.

Statistical Analysis

Values are presented as mean±SD. P<0.05 was considered statistically significant, and data were evaluated with the Wilcoxon ranksum test. To compare >2 groups simultaneously, the Kruskal–Wallis test was applied, which was followed by the Dunnett test as a multiple comparison procedure.

The Spearman correlation measured associations between 2 variables. All statistical analyses were performed using SPSS Statistics software for Windows version 19 (IBM SPSS Inc, Chicago, IL).

Results

Injury Model

Delayed PET/CT imaging showed enhanced tracer uptake of 64Cu-GPVI-Fc 24 hours after tracer injection in the left injured carotid artery compared with the noninjured right carotid artery of WT mice and less uptake in WT mice with sham procedure (Figure 1B). The residual uptake in WT mice with sham procedure is most likely related to tissue injury and scarring because of the incision. Quantification by standardized uptake value revealed significantly higher 64Cu-GPVI-Fc tracer uptake in the injured vessel compared with the intact right carotid artery and as a trend compared with sham procedure (injured: 20.7±1.3 Bq/cm³ versus intact: 2.3±0.5 Bq/cm³; P=0.028; injured versus sham: 12.7±1.7 Bq/cm³; P=0.068; Figure 1C). Enhanced uptake of 64Cu-GPVI-Fc in the carotid arteries was found after ligation injury compared with sham procedure using autoradiography (Figure 1D). To show specificity of GPVI-Fc binding, mice received either active or heat-inactivated fluorescence-labeled GPVI-Fc, Fc control protein, or unlabeled GPVI-Fc to block the binding. After 13 to 14 hours of injury, the mice treated with active FITC-labeled GPVI-Fc (group 1) showed a higher fluorescence signal compared with controls (P=0.033) such as Fc control (group 2), prior blocking with unlabeled GPVI-Fc (group 3), and heat-inactivated GPVI-Fc (group 4; after post hoc testing, group 1 versus 2: P=0.043; 1 versus 3: P=0.082; 1 versus 4: P=0.064; Figure 1E). PET imaging results of ligation injury were in agreement with a gadolinium-based elastin-binding contrast agent that measures vessel wall remodeling (rS=0.939; P=0.018; Figure 1F). Higher R1 relaxation rates were found in the injured carotid wall with a T1 mapping sequence (injured: 1.44±0.08 s⁻¹ versus intact: 0.91±0.02 s⁻¹; P=0.028; injured versus sham: 0.97±0.05 s⁻¹; P=0.068; Figure 1G). Correspondingly, vascular injury was found in histology and immunohistology detecting GPVI-Fc as shown in Figure 2A–2C.

Immunohistological quantification revealed a higher area fraction in vascular lesion compared with the intact vessel (area fraction: 0.004±0.003 versus 0.0003±0.00002; P=0.005) and correlated with the higher R1 relaxation rates (rS=0.829; P=0.042).

Model of Accelerated Atherosclerosis

In ApoE−/− mice on a 12-week high-fat diet, there was localized uptake of the radiolabeled tracer in the aortic arch, which was not observed in WT mice (Figure 3A). Quantification by standardized uptake value revealed significantly enhanced 64Cu-GPVI-Fc uptake in the aortic arch of ApoE−/− mice compared with WT mice (ApoE−/−: 13.2±1.5 Bq/cm³ versus WT mice: 5.1±0.5 Bq/cm³; P=0.028; Figure 3B). Distinct Sudan III staining at bifurcation sites and enhanced uptake of 64Cu-GPVI-Fc were found in the aortic arch of ApoE−/− compared with WT mice (ApoE−/−: 13.2±1.5 Bq/cm³ versus WT mice: 5.1±0.5 Bq/cm³; P=0.028; Figure 3B). Thus, we found higher R1 relaxation rates in the aortic arch of ApoE−/− mice compared with WT mice (ApoE−/−: 1.49±0.05 s⁻¹ versus WT: 0.92±0.04 s⁻¹; P=0.028; Figure 3E). Increased plaque burden in the aortic arch of ApoE−/− compared with WT mice was confirmed by histology and was in good agreement with the PET and MRI findings (Figure 2D–2G). GPVI-Fc was detected using immunohistology, which was significantly higher in ApoE−/− compared with WT mice (area fraction: 0.007±0.003 versus 0.000±0.00003; P=0.005) and correlated with the higher R1 relaxation rates (rS=0.956; P=0.003). Furthermore, damage of endothelial cells could be detected using transmission electron microscopy in the injury model (Figure 2H and 2I), and denuded regions with thrombosis were also observed in atherosclerotic ApoE−/− mice (Figure 2J).
Discussion

The merits of $^{64}\text{Cu}$-GPVI-Fc for the minimally invasive and noninvasive visualization and quantification of plaque erosion and mechanical vascular injury at predisposed sites in the vasculature, including the aortic arch and carotid arteries, were shown in high-fat diet–fed ApoE$^{-/-}$ mice and in a WT mouse model of ligation-induced vascular injury of the carotid arteries using PET/CT in vivo. Imaging results were confirmed with histology and immunostaining for the corresponding plaques ex vivo. In addition, MRI with a gadolinium-based elastin-binding contrast agent that measures vessel wall remodeling was in good agreement with PET/CT and histological findings.

The majority of vulnerable plaques have little calcification, are nonstenotic, and resemble a type IV lesion as classified by the American Heart Association. Minor criteria include endothelial dysfunction, remodeling, surface calcifications, yellowish appearance, or plaque hemorrhage, whereas major criteria include active inflammation, thrombogenicity, and plaque injury.

Novel noninvasive imaging modalities such as PET/CT or MRI may help to overcome limitations of conventional techniques to visualize unstable atherosclerotic plaques. However, the development of target-specific imaging biomarkers of plaque vulnerability remains challenging, although promising approaches have been demonstrated by targeting structures of the extracellular matrix, platelet–endothelium interactions, inflammation, and prothrombotic state.

Platelets play an important role in the initial phase of atherothrombosis after plaque rupture. Platelets, directly labeled with $^{99m}\text{Tc}$ or through radiolabeled antibody targeting of their surface receptors such as the platelet fibrinogen receptor...
and glycoprotein IIb/IIIa, have been used in attempts to identify vulnerable plaques.

Our group focused on imaging the platelet-based targets of platelet collagen receptor GPVI to identify ruptured or eroded plaques, which play a key role in ischemic heart disease and stroke. Based on a previous study, plaque erosion may be detected in PET and is adequately seen in the ApoE−/− mouse model, as we confirmed vascular lesions with dysfunctional and detached endothelial cells using electron microscopy. Due to our experience with partial volume correction for brain PET, we felt confident to assess structures of the size of the carotid and aortic arch in the murine model.34

The results of the present study revealed that a 64Cu-GPVI-Fc–based imaging system may help to detect not only potentially thrombogenic plaque, but also vascular injury (eg, because of stent implantation) and, thus, may be a useful tool to monitor different stages of reendothelialization after coronary stenting. Besides other novel interesting approaches to characterize and identify plaque vulnerability, 64Cu-GPVI-Fc seems to be promising for monitoring therapeutic effects of different antiplatelet drugs. In addition, we demonstrated that vessel wall remodeling can be assessed noninvasively with a gadolinium-based elastin-binding MR contrast agent. Although promising, our results should be judged as a proof-of-concept study but warrant further investigation in patients with suspected vascular disease. Thus, this multimodal imaging approach may have the potential to guide and monitor treatment using novel combined PET/MR.

We have also shown that local catheter-based pharmacological GPVI-Fc administration may attenuate postinterventional thromboembolic events caused by reduced neointima and thrombus formation at sites of arterial injury and that
pharmacological strategies can be adapted to reduce the time of dual antiplatelet treatment for the optimal trade-off between low risk of stent thrombosis and bleeding complications and other side effects.38

Thus, soluble GPVI could be used for both imaging and treatment and may be a promising therapeutic alternative for combined systemic antiplatelet therapy in the future, presently tested in a phase II study in patients with stroke.39

In conclusion, we demonstrate the merits of a novel imaging biomarker, 64Cu-labeled GPVI-Fc, in the identification of ruptured and eroded plaques and vascular injury in a mouse model of experimental atherosclerosis and vascular injury. 64Cu-labeled GPVI-Fc, thus, may have potential for noninvasive identification of unstable vascular lesions and to guide medical treatment.

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Disclosures

Drs Ungerer and Gawaz are shareholders of AdvanceCor GmbH, which provided glycoprotein VI-Fc. Dr Onthank is an employee of Lantheus Medical Imaging, which provided the elastin-binding contrast agent, elastin-specific MR contrast agent. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Rupture of the vulnerable atherosclerotic plaques is the major cause of arterial thrombosis and subsequent myocardial infarction. Plaque rupture and erosion lead to exposure of subendothelial collagen, a potential biomarker for plaque instability. Platelet glycoprotein VI binds to plaque-associated subendothelial collagen. In this study, we demonstrate that a platelet glycoprotein VI-binding positron emission tomographic imaging agent allows identification of exposed subendothelial collagen in injured wild-type mice and high-fat diet–fed apolipoprotein E–deficient mice. 64Cu-platelet glycoprotein VI-Fc, thus, may have potential for noninvasive identification of unstable vascular lesions and to guide medical treatment. Based on this novel noninvasive imaging system, future pharmacological strategies may help to attenuate postinterventional thromboischemic events and may lead to a reduced time of dual antiplatelet treatment.
Positron Emission Tomography/Computed Tomographic and Magnetic Resonance Imaging in a Murine Model of Progressive Atherosclerosis Using $^{64}$Cu-Labeled Glycoprotein VI-Fc

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Supplementary Figure 1. Computed Tomography (CT).

To verify anatomical structures, CT imaging (microCAT, Siemens) was performed. To visualize the blood vessel, a contrast agent (Fenestra VC) was used. As the aortic arch is not located in one single slice, the three images show the aortic arch and branches (arrows) in several slices. The images are flipped left right. The heart is on the right side.