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Quantification of Vasa Vasorum Density in MSCT Coronary Angiograms – Role of CT-Image Voxel Size

Regina Moritz, M.D.¹, Diane R. Eaker, M.S.E.E.¹, Alexander C. Langheinrich, M.D.², Steven M. Jorgensen, B.S.E.E.¹, Rainer M. Bohle, M.D.³, and Erik L. Ritman, M.D., Ph.D.¹

¹ Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN, USA

² Department of Radiology, Justus-Liebig-University, Giessen, Germany

³ Department of Pathology, Saarland University, Homburg/Saar, Germany

Abstract

Objective—This study is motivated by the possibility of using CT to detect early coronary atherosclerosis by the increased CT-values within the arterial wall resulting from vasa vasorum proliferation.

Methods—Coronary arteries (n=5) with early atherosclerotic changes were injected with Microfil® and scanned (micro-CT). Noise was added to the scan projection data sets (to represent the radiation exposure of current clinical CT-scanners), and then reconstructed to generate 3D-images at different voxel sizes.

Results—Higher CT-values were detected due to contrast agent in vasa vasorum if voxel size was less than (150μm)³. Contrast in the main lumen increased CT-values dramatically at voxels greater than (100μm)³, whereas CT-values of the same specimen without contrast in the main lumen remained constant.

Conclusion—Voxel sizes < (200μm)³ are needed to quantitate arterial wall opacification due to vasa vasorum proliferation.

Keywords

CT-Angiography; Coronary Atherosclerosis; Vasa Vasorum

INTRODUCTION

Acute coronary syndrome including myocardial infarction and sudden death, often occurs as the first manifestation of coronary artery disease.¹ Patients with “classic” coronary atherosclerosis tend to have the classic risk-factor profile (hypertension, hyperlipidemia, diabetes mellitus)² and develop coronary artery stenosis. Patients suffering sudden death often do not have any “classic” symptoms of coronary artery disease (e.g., angina) before the terminal event takes place. The lesion which is most likely to cause the sudden occurrence of cardiac death is called vulnerable plaque (thin-cap fibroatheroma)³. These plaques tend to rupture and often lead to thrombotic occlusions of the coronary arteries. These lesions lack the typical characteristics of advanced atherosclerotic plaques such as stenosis of the main lumen or

Corresponding author: Erik L. Ritman, M.D., PhD. Professor, Physiology and Medicine; Mayo Clinic College of Medicine, Department of Physiology and Biomedical Engineering, Alfred 2-409, 200 First St SW, Rochester, MN 55905, Phone: (507) 255-1939, Fax: (507) 255-1935, elran@mayo.edu.

calcification of the vessel wall. Instead they often present a large plaque volume (mostly fat deposits +/- necrotic core) without narrowing of the vessel lumen (positive remodeling)^{4,5} and with high density of “new” vasa vasorum in the surrounding media/adventitia area.^{6,7,8} Current clinical imaging techniques like angiography, or cardiac CT-scanning are limited in detecting atherosclerotic lesions without stenosis of the lumen, calcifications or reduced opacity (CT-fatty deposits) within the arterial wall.^{9,10} Imaging techniques like intravascular ultrasonography,^{11,12} contrast-enhanced ultrasound techniques and optical coherence tomography imaging allow detection and characterization of vulnerable plaques, but these are invasive.¹³ Therefore new, less invasive techniques are needed to detect vulnerable plaques and their precursor lesions.

In this study we explore the CT imaging spatial resolution requirements needed to detect non calcified, non stenosing atherosclerotic plaques by virtue of increased vasa vasorum density within the arterial wall.

MATERIAL AND METHODS

Specimens

Epicardial human coronary arteries (n=5) were obtained at the Giessen Institute of Pathology from approved autopsy cases from anonymous patients without manifestations of coronary artery syndrome, and without (histologically detectable) calcification of the vessel wall and significant stenosis of the lumen (i.e., we only included coronary arteries with atherosclerotic lesions type I, II, and III).^{14,15} The study fulfilled the requirements of the State Ministry of Science and Arts and of the Mayo Foundation IRB.

During autopsy the left and right coronary arteries were cannulated and perfused with a solution of 0.9% normal saline and heparin until the venous effluent was free of blood. Four arteries were infused with a lead-containing silicon polymer (Microfil® MV-122, Flow Tech, Carver, MA, USA) at a nominal pressure of 100mmHg. After polymerization of the contrast agent the arteries were cut in 2.5 – 3.5cm long segments along the entire length of the LAD and stored in 10% neutral buffered formalin. We also prepared a “baseline specimen” perfusing a left coronary artery with normal saline (0.9%) and heparin, as well as with 10% neutral buffered formalin. The vessel was not injected with the lead-containing contrast agent, but otherwise prepared like all the other specimens in the study.

Dual-Source CT scans

All arteries were scanned with a 64 slice CT-scanner (Definition, Siemens, Germany) at 80kVp at 250mAs with aluminum filter. CT image noise in the DSCT projection images was measured. The x-ray exposure in Gy units was calculated from the kVp, mAs values of the DSCT-scan and converted to the number of photons per mm² (in the scans’ multi angular projection images) by a conversion table.¹⁶

Synchrotron-Based Micro-CT

Scanning—The micro-CT scanner at the X2B-line at the National Synchrotron Light Source (NSLS) at the Brookhaven National Laboratories was used to scan the epicardial coronary artery segments as previously described.¹⁷ The photon energy was 26keV with a spectral width of 50eV. The scans involved generating 1440 x-ray projection images at 0.25 degree increments around the specimen and with (4µm)² detector pixels and 16 bit gray-scale.

Three-dimensional image reconstruction and display—Micro-CT images were reconstructed from the projection data using a filtered backprojection algorithm,¹⁸ and displayed using the ANALYZE image analysis software program (ANALYZE 8.1, Mayo

Clinic College of Medicine, Rochester, MN). We used the micro-CT scan data to generate CT images with a range of voxel sizes and also used it to simulate two temporal phases of a clinical CT-scan scenario. Shortly after injecting a bolus of contrast agent into the main lumen of coronary arteries the contrast agent also fills the local vasa vasorum and a fraction diffuses through the vasa vasorum endothelium into the surrounding vessel wall. After the contrast agent has washed out from the main lumen the vasa vasorum briefly contain some of the contrast dye and the extravascular contrast washes out up to 30 seconds later.¹⁹ To simulate this situation, in which there is prolonged opacification of the arterial wall after the contrast bolus has left the main lumen,²⁰ the contrast agent was “removed” from the main lumen in the $(4\mu\text{m})^3$ CT image and replaced by a CT-number representative of blood without contrast at 26keV (<http://physics.nist.gov>) using the ANALYZE image analysis software program (ANALYZE 8.1, Mayo Clinic College of Medicine, Rochester, MN) (Figure 1). These CT images were then reprojected to generate the projection images with $(4\mu\text{m})^2$ pixel size. These pixel values were then converted to their exponential values, i.e., the transmission x-ray images were recreated. Noise was then added to the $(4\mu\text{m})^2$ detector pixels by the method described below.

Changes in Voxel Size

Large detector pixel sizes were “generated” by incorporation of the appropriate number of contiguous $(4\mu\text{m})^2$ detector pixels lying within a square the size of the desired, larger, pixel. The x-ray transmission intensities (after the noise was added) of each of the contiguous pixels in each projection were summed so that, in effect, x-ray exposure per mm^2 remained constant at all detector pixel resolutions. The projections were then re-reconstructed using the MATLAB™ function “iradon”²¹ and the analysis were performed (Figure 2).

Noise Generation

To simulate retaining the same radiation exposure as used in current clinical CT-scanners used for CTA, randomly generated noise was added to each $(4\mu\text{m})^2$ pixel in the micro-CT projection images as follows:

$$\begin{aligned} \text{Signal } I'(n^2) &= \sum_{i=1}^{n^2} I(i) * [\text{\#photons} / \sum_{i=1}^{150^2} I_{\text{WL}}(i)] \\ \text{Noise on } I'(n^2) &= \text{RANDNL} * \text{SQRT}[I'(n^2)] \end{aligned} \quad \text{eq. 1}$$

$\sum_{i=1}^{n^2} I(i)$ is the sum of the CT-values for all n^2 $(4\mu\text{m})^2$ pixels encompassed by the simulated larger detector pixel;

$I_{\text{WL}}(i)$ = intensity of white level (i.e., detector value without a specimen) in each $(4\mu\text{m})^2$ detector pixel;

n^2 = number of $(4\mu\text{m})^2$ pixels needed to make a larger detector pixel;

RANDL = random numbers generated with a mean of zero and a normal distribution with a SD = 1;

#PHOTONS = number of photons per $(600\mu\text{m})^2$ detector pixel calculated from a clinical CT scanner (typical scan is 1160 views) as follows:

$$\begin{aligned}
 &9.63\text{mGy} * 3 \times 10^8 \text{ photons/mm}^2/\text{mGy} = 2.9 \times 10^8 \text{ photons/mm}^2 \text{ per scan} \\
 &2.9 \times 10^8 \text{ photons/mm}^2 * (0.6\text{mm})^2 / 1160 \text{ views} \\
 &\approx 90,000 \text{ photons per } (600\mu\text{m})^2 \text{ detector pixel per view}
 \end{aligned}
 \tag{eq. 2}$$

That this method of adding quantum noise to the CT images is appropriate is indicated by the fact that the standard deviation of the gray-scale values in Regions of Interest over the lumen of the coronary artery (with and without contrast agent) decreased in a linear log/log relationship with increasing voxel size. The average CT-value in the same region did not change significantly for voxel sizes larger than $(20\mu\text{m})^3$. Figure 3 shows the effect of the added noise and voxel size on the CT image quality and how this simulation compares to the dual-source, multislice, CT scan performed on the same specimen.

Gray-Scale Measurements—We wanted to detect differences in gray-scale values in the media/adventitia area of vessels with/without contrast dye in the main lumen and/or in the vasa vasorum. Therefore, gray-scale values of voxels within Regions-of-Interest (ROIs) in the original and processed synchrotron-based micro-CT images were measured at different voxel sizes, with or without contrast in the main lumen and with or without noise. The obtained gray-scale values originally expressed as x-ray attenuation values (1000/cm) were converted in Hounsfield Units (HU) using the following formula:

$$\text{HU} = (\mu_{\text{tissue}} - \mu_{\text{water}}) / (\mu_{\text{water}} - \mu_{\text{air}}) * 1000
 \tag{eq. 3}$$

Where μ_{tissue} is the originally measured value in (1000/cm) and μ_{water} and μ_{air} are the linear attenuation coefficients of water and air at the micro-CT scan energy at 26keV.

As most of the vasa vasorum are located between media and adventitia and in the adventitia itself, the ROIs should include media as well as adventitia. However, if there is no fatty tissue surrounding the arterial wall, it is often difficult to identify the outer limits of the adventitia in micro-CT images and therefore the intima/media-to-adventitia thickness relationship in non atherosclerotic coronary arteries was examined in a histological study ($n=5$ vessels)²² so as to establish the adventitial thickness as a function of media thickness. In order to detect the impact of the tissue environment outside the adventitia the epicardial and myocardial aspects of the arterial wall were analyzed separately, because the CT-values of the pericardium and contiguous lung differ from those of the myocardium.

Statistical Analysis

In order to test the intra- and interobserver variability in the analysis three different test sets consisting of de-identified, randomly ordered, sequences of the same 48 different CT images at voxel sizes of $(100\mu\text{m})^3$ to $(600\mu\text{m})^3$ with and without contrast in the main lumen as well as with and without noise were prepared. Two colleagues (A.J.V. and R.M.), not familiar with the histological analysis of the different specimens at that time, analyzed the test sets.

The inter- and intraobserver agreement was assessed using two separate analyses. First inter- and intraobserver reliability coefficients were estimated using JMP® 7 (JMP R7, SAS, Cary, NC, USA).²³ Then the Bland-Altman Test was performed and mean differences, standard deviation (SD), and 95% limits of agreement for the two observers were calculated.²⁴

The analysis of the arteries is presented as mean $\pm$ SD. Regression analysis was performed using MATLAB™ (Mathworks, R2008a).

Histology

To characterize the atherosclerotic lesions, we performed histological examinations after the CT-scans were completed. The specimens were embedded in paraffin, and serial sections at 3mm intervals were stained with hematoxylin and eosin (3 per artery), elastica (3 per artery), and Prussian blue (3 per artery). The cross-sections were digitized and analyzed by two experienced pathologists (R.M.B. and R.M.) in consensus. The pathologists were blinded to the results of the micro-CT image analysis as well as to any patient information.

First, the degree of the atherosclerotic changes (using the WHO-classification) was determined.^{14,15}

It is often difficult to identify the abluminal surface of the adventitia in micro-CT images, so the intima/media to adventitia ratio was established from the histological images. For this purpose five additional coronary arteries with no signs of atherosclerotic lesions were studied. Contiguous sections were stained with elastica (n=3/artery). The area of lumen, intima/media and adventitia was measured using a Leica DM 2000 microscope (Frankfurt/Main, Germany), a QImaging Camera (Surrey, Canada) and the Image Pro[®] Plus Software (Version 6.2 for Windows[™], Bethesda, MD, USA).

RESULTS

Ratio of Intima/Media to Adventitia Area

Using coronary arteries without atherosclerotic changes, a linear relationship between the area of the intima/media and the area of the adventitia ($R^2=0.9582$) was observed. The measurements also showed that the intima/media is approximately 60% of the vessel wall thickness and the adventitia approximately 40%. Consequently, we included the “double-media-thickness” into our ROI gray-scale measurements to be sure not to miss any vasa vasorum located in the adventitia.

Inter- and Intraobserver Variability

The intra- and interobserver reliability coefficients of 0.922 and 0.865 respectively indicate high consistency in the measurements of the individual observer as well as between the two different observers. However, the Bland-Altman analysis shows that there is a significant difference between the observers' measurements and the true value (as measured from the $(4\mu\text{m})^3$ CT-images) especially for voxel sizes greater than $300\mu\text{m}$ (Figure 4).

Influence of Gray-Scale Noise

To obtain gray-scale values in CT images at the entire range of voxel sizes, we used the same ROIs imposed on images at the same voxel size without added gray-scale noise. CT-values in specimens without noise and those with appropriate gray-scale noise added didn't show significant differences at different voxel sizes or in specimens with or without contrast in the main lumen or in the vasa vasorum.

Influence of Voxel Size and Presence/Absence of Contrast Agent in the Main Lumen and in the Vasa Vasorum

Identification of the vessel wall thickness becomes problematic at voxel sizes greater than $(200\mu\text{m})^3$. In four specimens (with Microfil[®]) CT-values at different voxel sizes, without or with contrast in the lumen, were measured. Contrast agent in the main lumen lead to a dramatic increase in CT-values in the arterial wall at a voxel size greater than $(100\mu\text{m})^3$. Figure 5 shows CT-values at different voxel sizes in the four different specimens with contrast agent in the vasa vasorum and no contrast agent in the main lumen (artificially removed) compared with

the baseline specimen. With a voxel size less than or equal to $(150\mu\text{m})^3$, CT-values in specimens with contrast agent in the vasa vasorum were higher than in the control specimen (without contrast agent in the vasa vasorum). The quantum noise mimicking the exposure used in clinically available scanners did not influence these CT-values significantly.

DISCUSSION

The study showed that voxel sizes smaller than $(150\mu\text{m})^3$ are needed to detect differences in gray-scale values in the media/adventitia area in coronary arteries with and without contrast agent in vasa vasorum. Current MSCT-scanners²⁵ provide voxel sizes greater than $(350\mu\text{m})^3$, although under certain circumstances, the newest high-resolution scanners are able to provide a voxel resolution of approximately $(240\mu\text{m})^3$. The quantum noise affecting the CT-images at small voxel sizes (radiation exposure equals radiation used in clinical scanners) obscures, but does not destroy the “image information”. The problem is to delineate the correct extent of the arterial wall and to use only voxels in the ROI that include exclusively arterial wall.

In addition to the need for decreased voxel size, the timing of scanning following contrast agent injection needs to also be precisely identified (this could be achieved by continuous scanning for retrospective selection of the appropriate time slot, but this would increase radiation exposure), so that the vasa vasorum are still opacified after the contrast bolus has washed out of the main arterial lumen.

LIMITATIONS

The study has several limitations:

Ex-vivo coronary arteries were used and therefore our data are not fully comparable to an in situ clinical situation.

The specimens were filled with contrast agent (Microfil[®]) thereby lacking the chance to scan the same specimens prior to contrast agent injection. So different specimens were compared to a control specimen with no Microfil[®] in the main lumen and in the vasa vasorum.

The uniform concentration of the lead-containing dye within the vascular lumen provides different x-ray attenuation characteristics than the nonuniform concentration of the iodine-based contrast agent as used in clinical practice.

The CT-image monochromatic 26keV x-ray photons have different contrast characteristics than clinical scanners using a bremsstrahlung broad spectrum x-ray at a nominal 80kVp.

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Figure 1.

These are 3-D volume rendered micro-CT images of a coronary artery segment (LAD). Upper panel: The main lumen as well as the vasa vasorum are white (filled with Microfil[®]). Lower panel: The CT-values in the lumen were replaced with CT-values for non opacified blood to reduce the impact of the partial volume effect of the lumen contrast into the arterial wall.

Figure 2.

Left panel is a synchrotron micro-CT imaged cross-section of a coronary artery at a voxel size of $(4\mu\text{m})^3$ with contrast agent in the main lumen and in the vasa vasorum. Right panel shows the same cross-section with contrast removed (mathematically) from the lumen. CT-numbers (mean, SD) were measured in different areas (1: main arterial lumen, 2: specimen mounting media (wax), 3: periarterial fat).

Figure 3. CT-images displayed at identical gray-scale threshold window

Left upper panel: CT-image ((4μm)³ voxel) shows cross-sections of a coronary artery with contrast agent in the main lumens (gray arrows) as well as in the vasa vasorum (white arrows). In the other upper panels the voxel sizes were increased progressively up to (600μm)³. At a voxel size of (200μm)³ no individual vasa can be identified. At a voxel size of (600μm)³ identification of the vessel wall is not possible. The middle panels are similar to those in the upper panels except that appropriate gray-scale noise was added. The noise affects image quality significantly at smaller voxel sizes. The lower panels show CT-images reconstructed at smaller voxel sizes using the reconfigured (600μm)² pixel micro-CT projection images. The right lower panel is the DSCT-image of the same specimen (* voxel size: 315×315×600μm³).

Figure 4.

Agreement-plot of the CT-values (mean of the two observers' values). The central solid line indicates the mean and the top and the bottom dashed lines indicate the 95% limits of agreement. **x** marks the range ($\pm$ SD) of "true" CT-values of the artery wall without contrast in the main lumen or vasa vasorum.

***** indicates the range of "true" CT-values of specimens without contrast in the main lumen but with contrast in the vasa vasorum, and this is statistically greater than the no contrast value (**x**). **≠** indicates the range of "true" CT- values of the walls with contrast agent in main lumen and vasa vasorum obtained from the original ($4\mu\text{m}$)³ voxel image data. CT-value differences between readers were higher in specimens with contrast in the main lumen and voxel sizes greater than ($200\mu\text{m}$)³.

Figure 5.

Difference in CT-values of vessels with contrast in vasa vasorum and no contrast in the main lumen compared to vessels without contrast in the vasa vasorum and the main lumen of approximately 100 HU is detectable up to a voxel size of $(200\mu\text{m})^3$. But for voxel sizes bigger than $(200\mu\text{m})^3$ no difference can be detected.