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FULL PAPER

Photon counting spectral CT component analysis of coronary artery atherosclerotic plaque samples

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Objective: To evaluate the capabilities of photon counting spectral CT to differentiate components of coronary atherosclerotic plaque based on differences in spectral attenuation and iodine-based contrast agent concentration.

Methods: 10 calcified and 13 lipid-rich non-calcified histologically demonstrated atheromatous plaques from post-mortem human coronary arteries were scanned with a photon counting spectral CT scanner. Individual photons were counted and classified in one of six energy bins from 25 to 70 keV. Based on a maximum likelihood approach, maps of photoelectric absorption (PA), Compton scattering (CS) and iodine concentration (IC) were reconstructed. Intensity measurements were performed on each map in the vessel wall, the surrounding perivascular fat and the lipid-rich and the calcified plaques. PA and CS values are expressed relative to pure water values. A comparison between these different elements was performed using Kruskal-Wallis tests with pairwise

post hoc Mann-Whitney *U*-tests and Sidak *p*-value adjustments.

Results: Results for vessel wall, surrounding perivascular fat and lipid-rich and calcified plaques were, respectively, 1.19 ± 0.09 , 0.73 ± 0.05 , 1.08 ± 0.14 and 17.79 ± 6.70 for PA; 0.96 ± 0.02 , 0.83 ± 0.02 , 0.91 ± 0.03 and 2.53 ± 0.63 for CS; and 83.3 ± 10.1 , 37.6 ± 8.1 , 55.2 ± 14.0 and $4.9 \pm 20.0 \text{ mmol l}^{-1}$ for IC, with a significant difference between all tissues for PA, CS and IC ($p < 0.012$).

Conclusion: This study demonstrates the capability of energy-sensitive photon counting spectral CT to differentiate between calcifications and iodine-infused regions of human coronary artery atherosclerotic plaque samples by analysing differences in spectral attenuation and iodine-based contrast agent concentration.

Advances in knowledge: Photon counting spectral CT is a promising technique to identify plaque components by analysing differences in iodine-based contrast agent concentration, photoelectric attenuation and Compton scattering.

The role of atherosclerotic plaque rupture in acute coronary events is well established.¹ Plaques prone to rupture display a large lipid-rich core, a thin fibrous cap and an inflammatory infiltration.² CT is now considered as a reliable tool to assess coronary artery stenosis,³ but still has two main shortcomings. Firstly, differentiating between intraluminal iodine-based contrast agent and plaque calcification remains challenging in small vessels such as the coronary arteries, leading to an erroneous estimation of the degree of stenosis. Secondly, CT is limited in correctly identifying plaque components, especially for the detection of the lipid core out of the normal wall or the fibrous plaque components.⁴⁻⁸ These problems are related to the insufficient spatial resolution available with the current clinical system and to the overlaps

of the Hounsfield values between iodine and calcifications on one hand and the lipid core and other soft components of the arterial wall on the other hand. Improved differentiation between calcification and iodine was obtained with energy CT.^{8,9}

Furthermore, photon counting spectral CT has recently been proposed to improve tissue characterization by improving the measurement of the energy dependence of the attenuation of various tissues in comparison with conventional CT scanners. This spectral resolution allows obtaining a map of the iodine concentration (IC) by utilizing its K-edge at 33.2 keV in the X-ray absorption spectrum, as well as an accurate decomposition of the X-ray attenuation into photoelectric absorption (PA) and

Compton scattering (CS) instead of a single global attenuation number as provided by conventional CT.^{10–12}

We evaluated the capabilities of a photon counting spectral CT scanner to differentiate between the different components of coronary artery atherosclerotic plaque based on differences in spectral attenuation and iodine-based contrast agent maps.

METHODS AND MATERIALS

This study was supported by the Philips Research Laboratories (Hamburg, Germany) by providing access to the experimental scanner. The authors who are not employees of either Philips Research Laboratories or Philips Healthcare (Cleveland, OH) (LB, MS and PD) had full control of inclusion of any data and information that might present a conflict of interest to those authors (PC, AT, ER and GM) who are employees of Philips Research Laboratories or Philips Healthcare.

Specimen preparation

Three right coronary arteries, visually presenting with important macroscopic atherosclerosis in order to get enough plaque for the analysis, were excised from human hearts at autopsy, regardless of the cause of death and the age of the patient. The mean size of the specimens was 8.1 ± 1.2 cm. Specimens were stored at -30°C and thawed at ambient temperature at the beginning of the experiment. All side branches of the artery were ligated, and the proximal and distal ends mounted on modified 6-French guide catheters (inserted to about 1 cm) within a closed-loop perfusion system in 120 mmol l^{-1} iodine solution (Hexabrix®; Guerbet, Paris, France) and immersed in the same iodine solution, as leakage from the coronaries could not be prevented. The study was performed in compliance with the requirements of our institution's review board.

Photon counting spectral CT scanner

An experimental research photon counting spectral CT scanner (Philips Research Laboratories), previously described in detail,¹² was used for imaging. For all acquisitions presented in this article, the beam voltage was set to 70 kVp to achieve about the same X-ray flux above and below the K-edge energy of the iodine-based contrast agent. The beam current was set to $100 \mu\text{A}$ resulting in an X-ray flux of about 2.3×10^5 counts per pixel per second. The primary X-ray flux was made intentionally

low compared with the typical range used in clinical imaging of 10^8 – 10^9 counts per pixel per second owing to count rate limitations of the present detector system. The gantry rotation time was set to a very low value of 200 seconds per rotation resulting in 20 mAs to enable good photon statistics while maintaining a rather low photon flux on the detector.

The X-ray tube has a beryllium exit window. An additional filtration of 2.0 mm of aluminium was used. The source spectrum was measured by using a high-purity germanium detector and is depicted in Figure 1.

A single-row photon counting cadmium telluride array (MEXC; Gamma Medica Ideas, Northridge, CA) was used as a detector. The X-rays enter the detector through a 0.5-mm aluminium protection window. The detector is equipped with 1024 pixels with a 0.4-mm average pixel pitch. The active area of each pixel is 0.4×1.6 mm, with a crystal thickness of 3 mm. A lead slit placed in front of the detector crystals collimates the illuminated detector height to 1.2 mm. For each pixel, six independent comparator threshold levels can be set by using an in-house built software defining six energy bins in order to classify each individual photon according to its energy. The choice in the number of energy bins was made based on previous studies: it is higher than the absolute minimum number of three bins that would allow successful differentiation between the three attenuation components, and it takes into account the fact that increasing N to higher and higher values results in an increase in the detector's complexity and cost with no considerable improvement in signal-to-noise ratio (SNR) in the K-edge image.^{13,14} To fit with iodine K-edge (33.2 keV; Figure 2), the thresholds were set to 25, 33, 39, 44, 49 and 55 keV, respectively. The measurement of the emission spectrum of the X-ray tube

Figure 1. Primary X-ray spectrum for 70 kVp.

Figure 2. Illustration of the different X-ray mass attenuation effects for typical CT energy range (20–140 keV). Examples of photoelectric absorption (PA, dashed line) and Compton scattering (CS, dotted dashed line) effects of water. Mass attenuation coefficients for PA decrease when X-ray energy increases, whereas CS remains nearly constant. Attenuation of iodine (solid line) presents with a peak at 33.2 keV corresponding to the K-edge effect. The mass attenuation values were generated using the program XCOM® (NIST, Gaithersburg, MD).¹⁵

allows precise calculation of the attenuation in the scanned samples for each energy bin.

For this study, we have used a magnification factor of 6 (100 mm distance from source to isocentre and a 500 mm distance from isocentre to detector centre) resulting in a 60-mm field of view (FOV). A high spatial resolution approximately corresponding to the voxel size of 0.1×0.1 mm (in plane) $\times$ 0.2 mm slice thickness was achieved.

Imaging

Coronary atherosclerotic plaques were first detected as areas of lumen narrowing and/or calcifications by scanning with a standard clinical 40 slice multidetector CT (Brilliance 40; Philips Healthcare). The specimens were then transferred to the photon counting spectral CT scanner. Axial sections in the regions of the plaques were imaged with a thickness of 200 μ m. The measurements of the six energy bins of the photon-counting detector (Figure 3) were used to estimate the contributions to the attenuation of the PA and CS effect, and the IC. These calculations are based on a generalization of an empirical dual energy CT calibration method.^{16,17} In short, in dual energy X-ray imaging, a soft-tissue image and a bone image can be easily calculated from a linear combination of a high-energy and a low-energy image. This approach was extended in two ways in order to get material images: first, nonlinear effects were also taken into account by including quadratic terms in the linear combinations and second, the number of energy channels was six instead of two. Thus, a calibration measurement was performed with a phantom consisting of water, calcium chloride solution representing bone, and iodine solution. The measurement yielded 6 images, 1 for each energy bin of the detector, representing the linear terms in the linear combination, and 21 images for the second order coefficients, each of which were reconstructed from sinograms consisting of the products of sinograms of two energy bins. Then for each material (iodine, PA and Compton scatter), coefficients were determined that optimally reproduced the known concentrations in the phantom by a linear

combination of all 27 images. These optimized coefficients were then used to calculate the material images for this study. Images corresponding to the maps of PA, CS and IC were reconstructed. Furthermore, an integrated image (termed as CT-like image) was constructed by using data from all energy bins weighted by the mean bin energy and simulating a conventional energy-integrating detector CT image. The reconstructed maps are expected to be insensitive to partial volume averaging, because the decomposition was carried out per voxel.

Histological analysis

After the photon counting spectral CT scan, the coronary arteries were frozen for the histopathological analysis. Each coronary cross-section was processed for histological analysis (colouration with haematoxylin–eosin and elastic Van Gieson stains) and was analysed under light microscopy by a pathologist (JYS) blinded to CT image interpretation. A lipid-rich plaque was defined by lipid pools (with necrotic core or not) taking $>50\%$ of the plaque area, as calculated by planimetry. As for the calcification content, plaques were classified as mainly calcified and non-calcified. Complex plaques, including spotty calcifications or lipids within large fibrous areas were excluded from this study.

Measurements and statistics

Registration between CT-like images and the histological slices was performed for each coronary artery by measuring the distance from three radio-opaque markers (surgical clips) clipped on the arteries and localized on the photon counting spectral CT images. A region of interest (ROI) was then manually drawn consensually by two experienced radiologists (LB and PD) for the lipid-rich and the calcified plaques on the CT-like images and propagated to each map (PA, CS and IC). The surrounding perivascular fat has also been studied for each coronary artery on five different slices, as its fatty composition is different from that of the lipid plaque. Similarly, the normal vessel wall was measured on each slice in a healthy area when present. PA and CS values were expressed relative to theoretical pure water

Figure 3. Photon counting spectral CT scanner principles. Each individual X-ray interacts in the semi-conductor detector and directly generates a large number of electron-hole pairs proportional to its energy. The resulting charge pulse does not only allow counting individual X-ray photons but also determining their primary energy by measuring the pulse height of the corresponding peak with multiple thresholds.

values. Comparisons between these different elements were performed using Kruskal–Wallis tests (for PA, CS and IC) with pairwise *post hoc* Mann–Whitney *U*-tests. *p*-values were adjusted by using the Sidak method. Finally, a measurement was performed in the surrounding iodine solution on the IC map and compared with the theoretical IC of this solution using a *t*-test. All statistical analyses were performed using Intercooled Stata® v. 10.0 (StataCorp LP, College Station, TX).

RESULTS

23 plaques were detected in the 3 studied coronary arteries and scanned with the photon counting spectral CT. Histology demonstrated 10 calcified and 13 lipid-rich non-calcified plaques.

Typical examples of a CT-like image are presented in [Figures 4](#) and [5](#) with the corresponding histology and colour-coded IC maps. Results for PA, CS and IC for the different evaluated components are summarized in [Figure 6](#).

For PA, mean values, relative to water attenuation, in vessel wall, surrounding perivascular fat, lipid-rich and calcified plaques were, respectively, 1.19 ± 0.09 , 0.73 ± 0.05 , 1.08 ± 0.14 and 17.79 ± 6.70 . This led to a significant difference between all these components ($p < 0.0001$ on the Kruskal–Wallis test; maximal *p*-value = 0.012 on *post hoc* tests).

Similarly, measurements of CS attenuation relative to water attenuation on the same ROIs were, respectively, 0.96 ± 0.02 , 0.83 ± 0.02 , 0.91 ± 0.03 and 2.53 ± 0.63 ($p < 0.008$). This led to a significant difference between all these components ($p < 0.0001$ on the Kruskal–Wallis test; maximal *p*-value = 0.006 on *post hoc* tests).

Finally, a significant difference in ICs was also found between all tissues. Mean values were $83.3 \pm 10.1 \text{ mmol l}^{-1}$ in the vessel wall, $37.6 \pm 8.1 \text{ mmol l}^{-1}$ in surrounding perivascular fat, $55.2 \pm 14.0 \text{ mmol l}^{-1}$ in lipid-rich plaque and $4.9 \pm 20.0 \text{ mmol l}^{-1}$ in calcified plaques for 120 mmol l^{-1} iodine solution in the lumen and the surrounding of the arteries. This led to a significant difference between all these components ($p < 0.0001$ on the Kruskal–Wallis test; maximal *p*-value = 0.012 on *post hoc* tests). No difference was found between this theoretical iodine solution concentration and the mean measured value ($118.2 \pm 1.0 \text{ mmol l}^{-1}$; $p = 0.06$).

DISCUSSION

This study demonstrates the capability of energy-sensitive photon counting spectral CT to differentiate between calcifications and iodine-infused regions of human coronary artery atherosclerotic plaque samples by analysing differences in spectral attenuation and iodine-based contrast agent concentration.

The analysis of the coronary artery wall is challenging because of the small size of the considered vessel and the limited difference in average attenuation for the different soft tissues involved. The potential of multiple-energy CT for the assessment of coronary plaque components has been predicted by the very recent work with dual-energy CT.¹⁸ In this study, differentiation between the normal wall, the lipid-rich plaque, the calcification and the surrounding adventitial and perivascular fat was possible by two different techniques.

Firstly, the analysis of IC shows significant differences between the different tissues. Spectral analysis with contrast agent K-edge detection allows precise detection and quantification of the contrast agent that can be isolated from other attenuating components.¹² This K-edge method is based on the discontinuity in spectral attenuation at the binding electron of the K-shell electron in the contrast element. This phenomenon occurs at a specific energy (33.2 keV for iodine, for example). Using its spectral resolution, the photon counting technique allows measurement of the attenuation in several energy windows and thus characterizes and quantifies the concentration of a given element if its K-edge is in the range of energy sensitivity of the system (25–70 keV in the reported experiment). Choosing one of the energy thresholds coincident with the K-edge energy of the iodine contrast material yields optimal results. It was possible to differentiate between iodine-free calcifications and the iodine-filled lumen and thus to better quantify calcified plaque, as has previously been reported in a phantom study by Feuerlein *et al.*¹⁰ This could help in better quantifying plaque-related stenosis by separating the calcifications from the narrowed lumen. Differences in IC can also be used to differentiate between arterial wall soft components as reported in our study, where a significant difference in IC was found between vessel wall, lipid-rich and the surrounding perivascular fat. Nevertheless, as our experiment was performed *ex vivo*, with a few hours of exposition of the tissue to iodine solution, it is not possible to conclude on a potential difference of *in vivo*.

Figure 4. Slice of a coronary artery presenting with a calcified plaque (black arrows). Histological slice (left part) and photon counting spectral CT images with CT-like image (centre) and iodine concentration (right part) map [linear scale from black (0 mmol l^{-1}) to white (130 mmol l^{-1})].

Figure 5. Slice of a coronary artery presenting with a lipid-rich plaque (white arrows): histological slice (left part) and photon counting spectral CT images with CT-like image (centre) and color-coded iodine concentration (right part) maps [linear scale from black (0 mmol l^{-1}) to white (70 mmol l^{-1})]. Surrounding perivascular fat is also present on the slices (arrow heads).

concentration between the studied tissues, as this would need further *in vivo* investigation. Furthermore, K-edge imaging with iodine as a contrast agent will certainly be problematic in humans. Indeed the iodine K-edge is low (33.2 keV) and, even if it can apply to animal studies, it will be difficult to use this contrast agent in humans owing to an almost complete

absorption of photons with energies below the K-edge energy in human-sized objects. Other contrast materials with higher K-edge energies, such as gadolinium (50.2 keV),¹⁰ gold (80.6 keV)¹⁹ or bismuth,²⁰ would be certainly preferable, provided potential toxicity problems in terms of required concentrations can be resolved.

Figure 6. Successive graphs of photoelectric absorption (PA), Compton scattering (CS) and iodine concentration values of vessel wall, perivascular fat, lipid-rich plaque and calcified plaque. The y-axis of the PA graph is interrupted in order to display the upper values of PA in calcified plaque. Error bars represent the standard deviations. For each measured parameter, all values are significantly different ($*p < 0.001$) between the four measured tissues.

Secondly, differences between all the studied components were also detected by analysing their different photoelectric attenuation and CS effects. The difference relative to water was larger for PA than for CS for calcified plaque, as PA is proportional to the atomic number (Z) to the fourth, whereas CS is proportional to Z .²¹ Nevertheless, both PA and CS, even with the smallest differences, remained significant between all the soft tissues. As for the iodine map, the utilization of PA will not be fully transposable to humans owing to the higher X-ray energies used in clinical imaging. As can be seen in Figure 2, the fraction of X-rays absorbed owing to PA decreases with increasing energy, and correspondingly, the SNR in the computed PA maps will decrease in human images, compared with the results presented in this article²¹ (Figure 2).

In this report, the high spatial resolution we used certainly plays an important role in the good plaque component depiction we obtained. Indeed, lack of spatial resolution of conventional human-sized CT scanners has been reported as a main limitation in coronary wall analysis with dual energy CT scanners.⁹ In this publication, the spatial resolution was around 0.4 mm leading to an insufficient depiction between the iodine-filled lumen on one hand and the wall components on the other hand. This lack of spatial resolution is even more critical in the presence of calcified plaques. Indeed, the limited spatial resolution associated with the high density of calcified plaques is responsible for blooming artefacts that usually result in an overestimation of the stenosis.^{22–25} There is a trend in conventional CT to reduce detector pixel size to improve the spatial resolution, but this is usually at a price of increasing noise, which has to be counter-balanced by increasing the radiation dose. In this context, photon counting spectral CT scanner has a small advantage compared with energy integrating CT as it allows, for the same detector size, a slightly lower dose for the same image quality.^{26,27}

Our study is a preliminary *in vitro* study and has several limitations. Regarding the experimental scanner itself, the current photon counting detector we used has a very limited counting rate performance, which is currently not compatible with the

X-ray flux required for clinical applications. To avoid pile-up effects, very low tube currents were used leading to a very long scan time to get sufficient signal statistics, which is not compatible with *in vivo* studies. This limitation could be overcome by using detectors with a higher count rate capability, as proposed by Steadman et al.²⁸ Another limitation is due to the limited quality of the first generation of photon counting detectors that were used. This led, in addition with a suboptimal calibration, to important ring artefacts in the images and thus added noise to our measurements. Then, the highest spatial resolution of the experimental scanner, with 0.2-mm slice thickness and a 0.1×0.1 mm in plane voxel size was reached for a small FOV of 60 mm. This could be valuable for small animal studies but not for clinical scanner. Regarding this topic, further improvements are mandatory, particularly in terms of acquisition time, motion correction and image reconstruction, including compressed sensing methods.²⁹ Finally, despite a consensual and careful ROI delineation of plaque components and registration using radio-opaque markers, it is difficult to account for a potential shrinkage of the specimen during histological preparation and to ensure that no iodine or fibrous tissue was embedded in the measurement of the calcifications and the lipid-rich plaque, respectively.

In conclusion, this first reported study about human coronary artery plaque analysis with photon counting spectral CT scanner shows promising results about the ability of this technique to identify plaque components by analysing differences in contrast agent concentration and/or spectral attenuation. Evolution first to a small animal scanner allowing *in vivo* scans and then to a human clinical scanner will need improvements in detector and scanner hardware, spectral calibration and reconstruction and will necessitate high K-edge contrast agent development.

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