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Feasibility of Macrophage Plaque Imaging Using Novel Ultrasmall Superparamagnetic Iron Oxide in Dual Energy CT

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ABSTRACT

Purpose: While ultrasmall superparamagnetic iron oxide (USPIO) is useful for identifying atherosclerotic lesions as an MRI contrast medium, there are limitations in its power to quantitatively evaluate and resolve USPIO in atherosclerotic lesions of the heart. Computed tomography (CT) has a higher resolution than MRI, and Dual Energy CT is capable of visualizing iron atoms, the main component of USPIO. More recently, a new USPIO capable of achieving longer retention times in blood circulation compared to the previous USPIO has been developed. The objective of this study was to investigate the feasibility of visualizing and quantifying the new USPIO by dual energy CT.

Materials and Methods: USPIO with iron concentrations adjusted in 5 steps from 2.5 to 50 mg/mL was visualized by dual energy CT to measure the contrast on virtual monochromatic imaging (40 and 70 keV). In parallel experiments, iodine contrast medium was diluted to the same concentrations and visualized by dual energy CT to measure the contrast at 70 keV. The linearity of the contrast against the iron and iodine concentrations was measured for the quantitative evaluation. Further, a vascular phantom simulating clinical cases (divided into 4 layers: meat alone, meat + USPIO, vascular lumen, and with or without calcification) was prepared. The iron density image was overlaid on the image at 70 keV to evaluate the visualization of the USPIO medium.

Results: In the imaging of the medium with an iron concentration of 25 mg/mL, the CT numberat 70 keV was 117.0 HU, or about 17% of that of iodine (664.4 HU). The CT number rose to 319.9 HU at 40 keV, or to about 48% of that of iodine. The linearity of the contrast against the iron concentration in USPIO was $R^2 = 0.9996$, indicating a strong correlation. In the simulated vascular phantom, the iron concentration significantly increased in the region containing USPIO, and the quantity could be visualized by overlaying the iron density image displayed with a color scale on the 70-keV image.

Conclusion: Our results suggested that macrophages could be both quantified and visualized by USPIO on dual energy CT.

1. Introduction

No method has been established to predict and prevent the onset of acute coronary syndrome, a set of symptoms that develop suddenly without forewarning [1]. Given that the chief pathology of acute coronary syndrome is thrombotic occlusion, the problem may be largely solvable through the accurate identification of vulnerable plaque, that is, plaque that induces thrombotic occlusion at a high rate. Vulnerable plaque causing rupture, the cause of acute coronary syndrome in about 60% of cases, is one of the most important targets [2]. Vulnerable plaque is characterized by thin fibrous caps (thinner than 65 μm) and positive remodeling, as well as the presence of abundant oxidatively modified low density lipoprotein and macrophages [3–5]. While vulnerable plaque can be identified noninvasively by imaging the coronary artery using coronary CT angiography and coronary MR angiography [6–8], but problems remain with the objectivity, quantitative, and diagnostic performance of those techniques. Inflammation also provides valuable diagnostic information by dint of its important actions in destabilizing plaque [9], but no molecular imaging method capable of evaluating inflammation has been established in a clinical setting.

Ultrasmall superparamagnetic iron oxide (USPIO) is retained in the blood circulation for a long time because of the very small size of the

Abbreviations: CCTA, coronary computed tomographic angiography; DECT, dual energy computed tomography; USPIO, ultrasmall superparamagnetic iron oxide; CMEADM, carboxymethyl-diethylaminoethyl dextran magnetite ultrasmall superparamagnetic iron oxide; VMI, virtual monochromatic image; MDI, material density image

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particles that compose it (about 50 nm), and the medium is also unlikely to be incorporated by Kupffer cells in the liver. The accumulation of USPIO in macrophages in atherosclerotic lesions has been confirmed in studies using MRI [10,11]. Researchers have also developed carboxymethyl-diethylaminoethyl dextran magnetite USPIO (CMEADM-U, The Nagoya Research Laboratory Meito Sangyo, Aichi, Japan), a new USPIO that remains within the blood circulation for longer than the original USPIO [12]. While CMEADM-U holds strong potential, two factors limit its effective use for the evaluation of the coronary artery: the inferior resolution of MRI versus CT and the challenges in quantitative evaluation. Dual energy CT (DECT) is now capable of both preparing a virtual monochromatic image (VMI) and acquiring a material density image (MDI) in a clinical setting [13,14]. Images can be acquired at a specifically changed effective energy using VMIs, and the contrast can be freely changed after the VMIs are obtained. Specific substances can now be emphasized or suppressed in the MDIs acquired. Virtual non-contrast images can be obtained from water/(iodine) images prepared by suppressing the iodine component of contrast imaging using iodine contrast medium and acquiring water/(fat) images with the fat component suppressed and iron/(water) images with the iron component emphasized. Meanwhile, the iron content can also be measured by setting a region of interest (ROI) in the target region.

Our group speculates that it may be possible to visualize the macrophages present in coronary arterial lesions using USPIO to quantitatively evaluate the lesions by preparing MDIs of iron, the main component of USPIO, from DECT images. In this study we investigated the feasibility of imaging and evaluating USPIO using DECT.

2. Materials and Methods

CMEADM-U was used as the USPIO contrast medium in our experiments. Some of the hydroxyl groups in CMEADM-U are substituted by carboxyl and diethyl amino groups (Fig. 1). As a consequence, the medium is retained in the blood for a shorter period than the original USPIO medium [12].

2.1. Quantitative evaluation using dilute contrast medium

Lots (φ30 mm) of CMEADM-U adjusted to 5 iron concentrations, 2.5, 5, 10, 25, and 50 mg/mL, were placed in an acrylic phantom (φ200 mm) and visualized by DECT against a background filled with water (Fig. 2). Similarly, iodine contrast medium was diluted at the same dilution rate and visualized by DECT under the same conditions. In the VMI, the effective energy was changed and the CT number was measured at 70 keV (corresponding to 120 kVp) and 40 keV. The coefficient of determination (R^2) was calculated to evaluate the correlation between the dilution concentration and CT number. In parallel, iron/(water) images scaled against the iron density values on the MDIs were prepared to measure the iron content (mgFe/cm^3).

2.2. Evaluation of visualization using simulated blood vessels

A simulated vascular phantom (Fuyo Corporation, Tokyo, Japan) divided into 4 layers (meat alone, meat + CMEADM-U, vascular lumen, and with or without calcification) (Fig. 3) was placed in an acrylic phantom (φ200 mm) and visualized by DECT. Table 1 shows the composition of each layer. The iron concentration of the CMEADM-U was set in 3 steps, namely, 5, 25, and 50 mg/mL, and the background was filled with water. An earlier study reported an accumulation of USPIO in plaque on imaging at 24 or more hours after administration of the medium [11]. The simulated vascular phantom in the present study was therefore prepared on the assumption that the CMEADM-U accumulated only in regions in which macrophages were present. Regarding the acquisition of images after 24 hours, the CMEADM-U was assumed to be fully washed from the phantom, leaving none remaining in the vascular lumen. Meanwhile, a phantom with the vascular lumen filled with iodine contrast medium was also prepared to allow us to simultaneously determine the stenosis rate of the coronary artery and evaluate the plaque based on CMEADM-U by intravenously administering iodine contrast medium and acquiring CCTA images at the same time.

Color scale maps of images were prepared by plotting the iron and water contents on the vertical and horizontal axes, respectively using a Gemstone Spectral Imaging (GSI) scatter plot and overlaid on a 70-keV VMI on the display (Fig. 4).

2.3. Acquisition conditions

The X-ray CT images were taken using a Discovery CT750 HD system (CT750, GE healthcare, Milwaukee, USA). The CT750 allows the use of a fast kV switching-mode DECT in which dual energy data can be acquired by rapidly switching between 140 and 80 kVp during a single rotation of the X-ray tube [14]. The acquisition conditions were as follows: tube voltage, 140 kVp/80 kVp; tube current, 600 mA; tube rotation time, 1.0 s; acquisition mode, axial scan; slice thickness, 0.625 mm; slice interval, 0.625 mm; matrix, 512 × 512; Recon kernel, Standard. The images were analyzed using a Gemstone Spectral

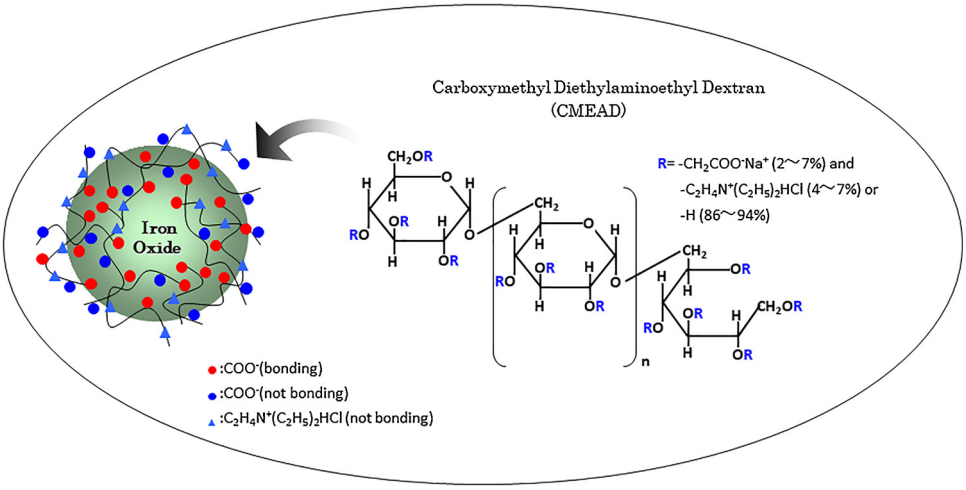

Fig. 1. Composition of Carboxymethyl-diethylaminoethyl Dextran Magnetite USPIO.
USPIO: Ultrasmall Superparamagnetic Iron Oxide.