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Quantitative measurement of lipid rich plaque by coronary computed tomography angiography: A correlation of histology in sudden cardiac death

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ABSTRACT

Background and aims: Recent advancements in coronary computed tomography angiography (CCTA) have allowed for the quantitative measurement of high-risk lipid rich plaque. Determination of the optimal threshold for Hounsfield units (HU) by CCTA for identifying lipid rich plaque remains unknown. We aimed to validate reliable cut-points of HU for quantitative assessment of lipid rich plaque.
Methods: 8 post-mortem sudden coronary death hearts were evaluated with CCTA and histologic analysis. Quantitative plaque analysis was performed in histopathology images and lipid rich plaque area was defined as intra-plaque necrotic core area. CCTA images were analyzed for quantitative plaque measurement. Low attenuation plaque (LAP) was defined as any pixel < 30, 45, 60, 75, and 90 HU cut-offs within a coronary plaque. The area of LAP was calculated in each cross-section.
Results: Among 105 cross-sections, 37 (35.2%) cross-sectional histology images contained lipid rich plaque. Although the highest specificity for identifying lipid rich plaque was shown with <30 HU cut-off (88.2%), sensitivity (e.g. 55.6% for <75 HU, 16.2% for <30 HU) and negative predictive value (e.g. 75.9% for <75 HU, 65.9% for <30 HU) tended to increase with higher HU cut-offs. For quantitative measurement, <75 HU showed the highest correlation coefficient (0.292, $p = 0.003$) and no significant differences were observed between lipid rich plaque area and LAP area between histology and CT analysis (Histology: 0.34 ± 0.73 mm^2, QCT: 0.37 ± 0.71 mm^2, $p = 0.701$).
Conclusions: LAP area by CCTA using a <75 HU cut-off value demonstrated high sensitivity and quantitative agreement with lipid rich plaque area by histology analysis.

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1. Introduction

The most common mechanism of acute coronary syndrome (ACS) is plaque rupture overlying advanced atheroma [1,2]. Histopathology studies have identified vulnerable plaque characteristics (VPC) indicative of plaque instability and high risk of rupture [3,4]. Increased lipid content in coronary atherosclerotic plaque, such as in intra plaque necrotic core, is a typical pathologic feature of VPC.

Abbreviations: ACS, acute coronary syndrome; VPC, vulnerable plaque characteristics; CCTA, coronary computed tomography angiography; QCT, quantitative coronary atherosclerotic plaque analysis CT; HU, Hounsfield units; LAP, low-attenuation plaque; NPV, negative predictive value; PPV, positive predictive value; IVUS, intravascular ultrasound; DECT, dual energy CT.

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Previous coronary imaging studies showed that lipid content in plaque is closely associated with a future ACS event [5,6].

Recently, improving spatial and temporal resolution of coronary computed tomography angiography (CCTA) has allowed for detailed plaque assessment, including VPCs [5,7,8]. Quantitative coronary atherosclerotic plaque analysis CT (QCT) software can perform accurate, semi-automated quantification of atherosclerotic plaque volume that is well correlated with intravascular ultrasound [9–11]. By reducing the need for invasive testing and time to analyze, CCTA with QCT may be a promising tool to bring VPC identification into routine clinical practice.

Plaque characterization by CCTA relies upon differences in Hounsfield units (HU) between fibrous and lipid rich plaque, identifying low-attenuation plaque (LAP) as a marker of plaque vulnerability [5]. However, the HU threshold for LAP has been inconsistent in previous studies between 30 and 90 [5,12–15]. In addition, for accurate differentiation of plaque characteristics, a reliable HU cut-off value for LAP needed to be confirmed. We, therefore, aimed to validate the cut-off value of HU by CCTA for quantitative assessment of LAP using semi-automated QCT software against necrotic core area, as lipid rich plaque, by histopathologic plaque analysis.

2. Materials and methods

2.1. Study overview

In this prospective, cross-sectional study, CCTA was compared to histopathology in de-identified *ex-vivo* human hearts. Necropsy hearts were explanted from decedents at the Office of the Chief Medical Examiner in Baltimore, Maryland, USA, who required consultation for suspected coronary cause of death. Hearts were excluded from analysis if they could not undergo *ex-vivo* CCTA or histology due to tissue disruption or decomposition, or if the patient had a history of coronary artery bypass graft surgery. Hearts underwent *ex-vivo* CCTA, then histopathologic examination (CVPath Institute, Gaithersburg, MD). CCTA images were compared and co-registered to serial histology cross-sections, and underwent blinded QCT. All procedures were approved by the institutional review board.

2.2. CCTA image acquisition

CCTA examinations were performed using a 64-detector row CT scanner (Discover CT750 HD; GE Healthcare, Milwaukee, WI). After cleansing the explanted heart with normal saline, a cardiovascular pathology expert (R.K.) dissected epicardial fat away from the surface of the left main and proximal RCA, to expose approximately 1 cm or less of each vessel. A small tunnel was made under each proximal vessel to allow passage of a short length of twine under the vessel. A metal probe with an introducer sheath was inserted into each proximal vessel. The tip of the introducer sheath was lightly heat flared so that it could be secured in place with a twine ligature after vessel insertion. The scan parameters were as follows: prospective ECG-triggering, 64×0.625 mm collimation, 120 kVp tube voltage, 440 mA tube current, 350 ms gantry rotation time. The dual-phase contrast protocol was: Iohexol (Omnipaque 350, GE healthcare) 5 cc in 95 ml saline at 3 cc/sec for 8 s with 6 s delay. The contrast protocol was developed by trial and error to achieve complete end-vessel and branch opacification with a typical in vivo lumen contrast density of 250–400 HU without undue myocardial enhancement. Axial images were reconstructed with a slice thickness of 0.6 mm and adaptive statistical iterative reconstruction technique (ASIR; GE Healthcare, Milwaukee, WI) with a blending factor of 40%. CCTA images were interpreted using an offline 3D workstation (Advantage Workstation version 4.3/4.4, General Electric, Milwaukee, WI).

2.3. Histology preparation and plaque analysis

Histology plaque analysis was conducted by personnel (R.K., K.Y., S.T., R.V.) in a specialized cardiovascular pathology laboratory (CVPath laboratory, Gaithersburg, MD). Following perfusion-fixation with 10% neutral buffered formalin, coronary arteries were sectioned serially at 3 mm intervals and submitted to paraffin embedding. Histologic sections were cut at 6 μm and stained with hematoxylin-eosin and Movat pentachrome. Quantitative plaque measurements were performed in each histology cross-section for vessel area, lumen area, and plaque area. Plaque area was further classified by plaque type: plaque area, calcification area, and necrotic core area. For the purpose of this study, lipid rich plaque area was defined as necrotic core area. Morphometric measurement of coronary sections was performed using image-processing software (IPLabs, Scanalytics, Rockville, MD) on slides stained with Movat pentachrome. Quantitative planimetry included area analysis of the vessel area, lumen area, and plaque area.

2.4. Co-registration and quantitative CT image analysis

CT image data were transferred to an offline workstation for plaque analysis by semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands). Independent level III–experienced readers performed analyses on the CCTA data blinded to clinical and histology results. After an automatic extraction of centerline, straightened multiplanar reformatted reconstruction was performed with automatic detection of inner lumen and outer vessel wall contours and manual editing if needed. Standard displays (e.g., width 740 Hounsfield Unit (HU), level 220 HU) were adjusted by contrast level of the most proximal site of the coronary lumen (155% and 65% mean luminal intensity). CCTA images were co-registered with corresponding histology slides based on coronary branch points, distance from the cannula tip, and calcium landmarks by an investigator who did not participate in the QCT measurement (D.H.). We included histology slides that were located at proximal or middle coronary segments according to the 18-segment model in the current guidelines [16] with a vessel diameter more than 2 mm. Then, blinded QCT plaque analyses were performed in each co-registered cross-section: vessel area, lumen area, plaque area [10]. LAP was defined as any pixel <30, <45, <60, <75, and <90 HU threshold within a coronary plaque. Lipid-rich plaque on CCTA was defined as the cross-section with presence of LAP. LAP area was measured in each cross-section according to the HU threshold (Fig. 1). Calcified plaque was measured using the threshold HU $\geq$ 130. Plaque composition was defined as none, non-calcified (>70% non-calcified), partially calcified (30–70% non-calcified or calcified), and calcified (>70% calcified) [16]. The mean HU of lumen was measured in 105 cross-sections by manually placing the region of interest in the center of the vessel lumen.

2.5. Statistical analysis

Continuous variables were reported as means with standard deviation and categorical variables were reported as counts with proportions. Vessel and plaque parameters were compared between QCT and histology analysis using the Pearson correlation or Spearman correlation coefficient (r) with two sided p-values. The paired *t*-test was performed for comparison of covariates between histology and QCT analysis. Bland-Altman plots with 95% confidence intervals (CI) were calculated for correlation. The diagnostic

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