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Association between cholesterol crystals and culprit lesion vulnerability in patients with acute coronary syndrome: An optical coherence tomography study

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ABSTRACT

Background: Cholesterol Crystals (ChCs) are recognized as a hallmark of advanced atherosclerotic lesions. Previous animal and histopathology studies have revealed that Cholesterol crystallization trigger a local inflammatory response and plaque rupture. We sought to investigate the in vivo relationship between ChCs and culprit lesion vulnerability in patients with acute coronary syndrome (ACS).

Methods: 206 culprit lesions from 206 patients with ACS who underwent optical coherence tomography (OCT) imaging were divided into 2 groups based on the presence or absence of ChCs. Culprit lesions characteristics were compared between ChCs and Non-ChCs groups.

Results: For overall ACS patients, culprit lesions with ChCs had higher incidence of macrophages accumulation (77.8% vs. 40.0%, $p < 0.001$), microchannel (67.9% vs. 24.8%, $p < 0.001$), plaque rupture (58.0% vs. 36.0%, $p = 0.001$), thrombosis (66.7% vs. 49.6%, $p = 0.016$) and spotty calcification (35.8% vs. 10.4%, $p < 0.001$). In addition, the mean lipid arc ($274.2 \pm 57.6^\circ$ vs. $228.1 \pm 66.3^\circ$, $p < 0.001$) was larger and the lipid index (3826.1 ± 2111.4 vs. 2855.0 ± 1753.0, $p = 0.001$) was greater. The frequency of ChCs was significantly higher in patients with STEMI, as compared with NSTEACS (50.8% vs. 34.7%, $p = 0.032$). Larger lipid arc, higher incidence of macrophages accumulation and that of microchannel were observed in culprit lesions with ChCs in both STEMI ($p = 0.028$, $p < 0.001$, and $p = 0.002$ respectively) and NSTEACS ($p < 0.001$, $p < 0.001$, and $p < 0.001$ respectively) subgroups.

Conclusion: ChCs were frequently associated with characteristics of vulnerable plaques in ACS culprit lesions as well as in STEMI and NSTEACS subgroups. ChCs and vulnerable plaque features were more often observed in culprit lesions of STEMI patients compared to NSTEACS patients.

1. Introduction

Cholesterol Crystals (ChCs) are recognized as a hallmark of advanced atherosclerotic lesions [1,2]. Previous study has demonstrated that ChCs emerged at the earliest time points of diet-induced atherogenesis together with the accumulation of macrophages in Apo-E-deficient mice [3]. In human atherosclerotic lesions, a sharp increase in the crystals content is observed as they progress from fatty streaks to advanced lesions [4]. Furthermore, ChCs in human macrophages can induce NLRP3 inflammasome activation and secretion of proinflammatory cytokines including interleukin (IL)-1β and IL-18 [3,5], which may represent an important link between ChCs and inflammation in atherogenesis.

Plaque rupture with subsequent thrombus formation is the leading cause of acute coronary syndrome (ACS) [1]. Crystallization of supersaturated cholesterol in atherosclerotic lesions may induce the plaque rupture [6–8]. A potential mechanism of the triggering of this process is the expansion in volume as cholesterol crystallizes

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from a liquid to a solid, which may change the plaque spatial configuration [7]. In addition, an autopsy study has revealed that needle-shaped ChCs pierce into fibrous caps overlying the necrotic core at sites of plaque rupture and ChCs content is an independent predictor of thrombus and symptoms [9]. The results of in vitro and autopsy studies lead to a hypothesis that the presence of ChCs may increase plaque vulnerability and trigger plaque rupture in patients with ACS. However, due to lack of available techniques, detection of cholesterol crystals in vivo has been limited.

Optical coherence tomography (OCT) is an intravascular imaging modality with high-resolution (10–20 μm) which is available in evaluating plaque microstructures, including fibrous cap thickness, lipid core arc, macrophages accumulation, thrombus and microchannel [10]. OCT has been shown to be able to visualize ChCs within atherosclerotic lesions in vivo [10–12]. In this study, we investigated the association between ChCs and culprit lesion vulnerability in patients with ACS by using OCT.

2. Methods

2.1. Study population

221 consecutive patients with ACS who underwent successful OCT imaging for the culprit lesion before percutaneous coronary intervention at the 2nd Affiliated Hospital of Harbin Medical University were included in this study. The main excluding criteria were: (1) Left main disease, chronic total occlusion, extremely tortuous or heavily calcified vessels; (2) Previous coronary artery bypass graft (CABG), previous stents implantation in the culprit vessel; (3) Serum creatinine >2.0 mg/dL or serious renal disease; (4) Cardiogenic shock or congestive heart failure with left ventricular ejection fraction (LVEF) <40%; (5) Serious liver dysfunction. The culprit lesion was identified by a combination of electrocardiogram (ECG), coronary angiogram, echocardiogram or left ventriculogram.

The patients with ACS consisted of STEMI and NSTEACS. ST-elevation–myocardial infarction (STEMI) was defined as: continuous chest pain for >30 min; arrival at hospital <12 h from the onset of chest pain; ST-segment elevation >0.1 mV in ≥2 contiguous leads, or new left bundle-branch block on the 12-lead ECG; and elevated levels of cardiac markers (creatine kinase-MB or troponin T/I). The NSTEACS included Non-ST-elevation–myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). NSTEMI was defined as ischemic symptoms in the absence of ST-segment elevation on the ECG and with elevated cardiac markers. UAP was defined as new-onset angina, a progressive crescendo pattern of angina, or angina at rest within 2 weeks.

This study was approved by the Ethics Committee of the 2nd Affiliated Hospital of Harbin Medical University (Harbin, China), and all patients provided written informed consent.

2.2. Angiogram and analysis

Coronary angiography was performed via the radial or femoral approach after intracoronary administration of 100–200 μg nitroglycerin. Patients were pretreated with aspirin (300 mg) and clopidogrel (300 mg) at least 2 h prior to the angiography procedure. Angiographic analysis was performed at an independent core laboratory using a quantitative coronary angiogram analysis program (Cardiovascular Angiography Analysis System 5.10, Pie Medical Imaging B.V., Maastricht, the Netherlands). The reference vessel diameter (RVD) was calculated as the averaged diameter of the proximal and distal reference; minimal lumen diameter (MLD) was defined as the smallest lumen diameter in the segment of a lesion; diameter stenosis (DS) was calculated as (reference vessel diameter − minimal lumen diameter)/(reference vessel diameter) × 100%.

2.3. OCT image acquisition and analysis

Intracoronary OCT procedure was conducted as described previously [13,14]. Briefly, a 0.016-inch OCT catheter (Image Wire; LightLab Imaging/Saint Jude Medical, Westford, MA, USA) was advanced to the distal site of the target lesion through a 3-F occlusion balloon catheter. The occlusion balloon was inflated at 0.5–0.7 atm at the proximal site of the plaque. Lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5–2.0 mL/s by a high-pressure injector. The vessel was imaged with an automatic pullback device at 3 mm/s. In patients with Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤2, aspiration thrombectomy was performed before OCT imaging, but pre-dilation by balloon catheter was not allowed.

OCT image analysis was performed by using offline software (LightLab Imaging) at an independent core laboratory at the 2nd Affiliated Hospital of Harbin Medical University. Two experienced investigators (J.D. and S.L.) who were blinded to the clinical information performed the assessment of OCT images according to the criteria of the Clinical Expert Consensus Document on OCT [10]. When there was discordance between the observers, a consensus was obtained from a third investigator.

The culprit lesions were explored from proximal reference to distal reference by OCT. ChCs were defined as linear, highly backscattering structures within the plaque (Fig. 1A) [10,11]. Plaques were classified into 2 categories: (1) Fibrous plaque (homogeneous and high-backscattering region) or (2) Lipid plaque (low signal region with a diffuse border). If the culprit lesion was lipid plaque, lipid arc was measured at every 1 mm interval throughout the entire lesion, and fibrous cap thickness (FCT) was measured at its thinnest part 3 times and the average value was calculated. A thin-cap fibroatheroma (TCFA) was defined as a plaque with lipid content in ≥2 quadrants and the thinnest part of fibrous cap <65 μm (Fig. 1B). Lipid length was recorded on a longitudinal view, and plaque lipid content was semi-quantified according to the lipid index, which was defined as mean lipid arc multiply lipid length. Ruptured plaque was defined as a lipid plaque with fibrous cap discontinuity and a clear cavity formation within the plaque (Fig. 1C). For ruptured plaque, FCT was measured at the thinnest part of the remnant fibrous cap and the minimal FCT values for each OCT image were used for analysis. Plaque erosion was defined as the presence of attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of thrombus, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus (Fig. 1D) [10]. Macrophages accumulation was defined as signal-rich, distinct or confluent punctuate regions with heterogeneous backward shadows (Fig. 1E). A microchannel was defined as a black hole with a diameter of 50–300 μm within a plaque that was present on at least 3 consecutive frames (Fig. 1F) [13,14]. Thrombus was defined as a mass (diameter >250 μm) attached to the lumen surface or floating within the lumen (Fig. 1G). Spotty calcification was also recorded when a calcification within an arc <90° (Fig. 1G). Calcification was defined as well-delineated, low backscattering heterogeneous regions (Fig. 1H).

2.4. Statistical analysis

Data were analyzed using SPSS v17.0 (SPSS, IBM, Armonk, NY, USA). The Kolmogorov–Smirnov test and normal probability (Q–Q)