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Radial artery intima-media ratio predicts presence of coronary thin-cap fibroatheroma: A frequency domain-optical coherence tomography study

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ABSTRACT

Background: Peripheral arterial disease is a risk factor for cardiac mortality but pathophysiologic mechanisms linking atherosclerosis of peripheral arteries with coronary events in the single patient have not been established.
Method and results: We evaluated by frequency-domain optical coherence tomography (FD-OCT) the possible association between culprit coronary plaque characteristics and proximal radial artery features in a cohort of 51 patients symptomatic coronary artery disease undergoing coronary procedures by transradial route. FD-OCT coronary artery analysis included assessment of TCFA and thrombus. FD-OCT radial artery analysis included intimal thickness index (*ITI*: intimal area/medial area), intima-media ratio (*IMR*: the maximum intimal thickness/medial thickness), and percentage of luminal narrowing [*%LN*: (intimal area + medial area)/external elastic membrane area × 100]. Coronary TCFA and thrombus were detected in 19 (37%) and 7 (14%) patients, respectively. TCFA was significantly associated with higher values of radial artery ITI (0.35 vs. 0.26, p = 0.02) and IMR (0.45 vs. 0.32, p = 0.03), but not with %LN. In contrast, coronary thrombus was only associated with higher %LN (26.7 vs. 22.8, p = 0.02). Multivariate logistic regression analysis identified proximal radial artery IMR (OR 16.3, 95% CI 1.1 to 245.1) as an independent predictor of TCFA.
Conclusions: In patients with symptomatic coronary atherosclerosis, vessel wall modifications at the level of the proximal radial artery are associated with adverse coronary features like TCFA and thrombus.

1. Introduction

Atherosclerosis is a chronic inflammatory process, characterized by a transition from intimal hyperplasia to atherosclerotic plaque formation [1]. The coronary artery tree is frequently involved along with other vascular districts, supporting the notion of atherosclerosis as a systemic disease [2]. Several studies have reported a strong association between coronary artery disease and ultrasound-detected carotid intima-media thickness [3] as well as with the number of atherosclerotic plaques observed in the peripheral vascular system [4]. The radial artery (RA) is a medium-sized muscular artery that has been used as graft for coronary bypass procedures [5] and more recently as a safe and low risk vascular access for coronary procedures [6] (transradial intervention, TRI). The distal segment of RA is smaller and has a greater muscle cell component compared with both proximal RA segment and coronary arteries [7]. While the distal RA more frequently presents intimal hyperplasia [8] and (albeit with an overall low frequency) atheroma [9] than the proximal tract, this can be heavily influenced by iatrogenic manipulations in patients undergoing TRI [10,11]. Intimal hyperplasia in the proximal tract of RA might more closely reflect cardiovascular risk factors and inflammatory stimuli [12].

FD-OCT can be considered the current state-of-the-art technique for high-resolution imaging (in the order of 10–20 μm) of coronary plaques, allowing identification of high-risk structures such as thin-cap fibroatheroma (TCFA), a lesion characterized by a large necrotic core and a thin fibrous coverage, thought to account for a sizeable portion of sudden acute coronary events [13,14]. OCT imaging of radial arteries has been previously used to select conduit suitability for bypass grafting [9] and to evaluate the mechanical damage posed by transradial interventions [10].

Our study aimed to investigate the association between indexes of intimal hyperplasia in the proximal RA and coronary plaque morphology, taking advantage of FD-OCT excellent ability to resolve the intimal from the medial layer, a feat impossible with intravascular ultrasound-based imaging [11].

2. Methods

2.1. Study population

Fifty-one consecutive patients with a normal Allen test result undergoing FD-OCT investigation of both culprit/target coronary artery segment and RA between March 2011 and February 2012 were included in the study.

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All patients were admitted at department of cardiovascular medicine, "Policlinico A. Gemelli", Catholic University of Sacred Heart-Rome, Italy for either acute coronary syndrome (ACS) (16 patients) or stable angina (SA) (35 patients). All enrolled patients underwent coronary angiography by trans-radial approach followed by FD-OCT for a single, native, de novo culprit/target coronary lesion. The culprit lesion in ACS patients was identified on the basis of findings on coronary angiogram, electrocardiogram, and transthoracic echocardiogram. Target coronary lesion in SA patients was identified by objective evidence of ^{201}thallium scintigraphy and/or dobutamine echocardiography, and coronary angiography. Percutaneous coronary intervention (PCI) was subsequently performed in all ACS patients and in 33 out of 35 SA patients.

At the end of the coronary procedure, RA was imaged by FD-OCT (using the same probe used for coronary investigation) before complete sheath removal. A study flow chart is reported in Additional Fig. 1. Patient-related exclusion criteria were: FD-OCT for intra-stent restenosis or stent thrombosis. Other exclusion criteria were fever, malignancy, left ventricular ejection fraction less than 45%, atrial fibrillation (to avoid the possible impact of anticoagulation on the frequency of coronary thrombus) and reduced renal function (creatinine clearance<60 ml/min). Lesion-related exclusion criteria were left main or aorto-ostial involvement, heavily calcified lesion, tortuous vessel or angiographic evidence of coronary dissection.

ST-elevation myocardial infarction (STEMI) was defined as continuous chest pain lasting>30 min associated with new ST elevation at the J-point in two contiguous leads≥0.2 mV in men or ≥0.15 mV in women in leads V_2–$V_3$and/or ≥0.1 mV in other leads or a new left bundle branch block demonstrated at the ECG [15].

Non ST-elevation myocardial infarction (NSTEMI) was defined as progressive crescendo pattern or angina at rest associated with new horizontal or down-sloping ST depression≥0.05 in two contiguous leads, and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio>1 on ECG and increased admission TnT (at least greater than 0.03 mg/dl) [15]. Stable angina (SA) was defined as no change in frequency, duration or intensity of angina symptoms within 6 weeks before PCI.

The study was approved by the local ethical committee and conformed to the Declaration of Helsinki on human research, and informed consent was obtained after complete explanation of the protocol and potential risks.

2.2. PCI and FD-OCT procedures

Transradial coronary intervention (TRI) was performed with a 6Fr guiding-catheter in all patients using the right RA as vascular access. The RA sheath used was 25 cm long (6Fr-artery-sheath, Terumo Company, Japan). Unfractionated heparin was administered during the procedure, with a target activated clotting time of >250 s. After completion of diagnostic coronary angiography, intracoronary isosorbide dinitrate (2 mg) was administrated and FD-OCT was used to image the culprit/target coronary lesion.

FD-OCT images were acquired with a commercially available system (C7 System; LightLab Imaging Inc/ St Jude Medical, Westford, MA, USA) after the OCT catheter (C7 Dragonfly; LightLab Imaging Inc/St Jude Medical) was advanced to the distal end of the target lesion. The FD-OCT run was conducted before lesion manipulation in all patients. The entire length of the region of interest was scanned using the integrated automated pullback device at 20 mm/s. During image acquisition, coronary blood flow was replaced by continuous flushing of contrast media directly from the guiding catheter at a rate of 4 ml/s with a power injector (MedradAvanta, Siemens, Germany) in order to create a virtually blood-free environment. At the end of the coronary procedure the FD-OCT catheter was first advanced in the distality of the RA sheath (as we used a 25-cm long sheath, the position was close to the junction between RA and brachial artery), then the sheath was pulled back in the distal RA leaving the FD-OCT catheter in the proximal part of the RA. Thereafter, the RA was flushed with saline using a 30-ml syringe connected to the sheath side port and the first FD-OCT pullback was performed (Additional Figs. 2 and 3). The second and third FD-OCT pullbacks were performed using the same technique to obtain the entire imaged length of the RA. Thus, the image including the entire RA (proximal + distal RA) was obtained matching the three FD-OCT pullbacks using landmarks such as side-branches and/or calcifications. The middle cross-section of the entire image length was selected for identifying the border between distal and proximal RA (Additional Fig. 2). During image acquisition, blood flow was replaced by continuous flushing of saline solution directly from the sheath. No FD-OCT related complication was noted.

2.3. FD-OCT image analysis of coronary and radial artery

All images were recorded digitally, stored, and analyzed by 2 independent investigators (L.D.V. and G.P), who were blinded to patient data. Offline analysis was performed with proprietary software (LightLab Imaging) after confirming proper calibration settings of the Z-offset. The imaged coronary artery was defined culprit in ACS patients and target in SA patients. FD-OCT coronary analysis was targeted to plaque characterization and fibrous cap analysis. Ruptured plaque, TCFA, thrombus and micro-vessels were noted (Fig. 1A and b). When a plaque contained 2 or more lipid-containing quadrants, it was considered a lipid-rich plaque and lipid arc and cap thickness were measured. TCFA was defined as a lipid-rich plaque with a fibrous cap thickness of ≤65 μm [14,16]. A micro-channel was defined as a no-signal tubulo-luminal structure without a connection to the vessel lumen recognized on ≥3 consecutive cross-sectional OCT images [17]. Thrombus was identified as a mass of at least 200 μm in thickness with dorsal shadowing, protruding into the vessel lumen or discontinuous from the surface of the vessel wall [18].

The RA analysis was targeted to the proximal tract only (from the RA ostium to the middle cross-section of the entire image length), as the distal part of the RA was considered to be more influenced by iatrogenic manipulations such as intimal tears and medial dissections [10]. Moreover, the proximal RA is more anatomically comparable to a coronary artery [8]. FD-OCT pullback of the proximal RA was inspected in every millimeter to measure the overall length of the pullback containing clear cross sectional images, defined as clear image length (CIL). The CIL was expressed in millimeters and was the cumulative number of clear image segments (CIS) containing at least one Clear Image Frame (CIF) within the pullback. The CIF was defined as a FD-OCT cross-sectional image frame in which the boundary between the lumen and the vessel wall was discernible along a continuous arc of at least 270° relative to the center of the lumen, as previously described [19]. The radial artery was imaged by FD-OCT as a three-layered structure. The intima layer appeared as a bright area while media layer as a low intensity signal area. These two layers were separated by internal elastic lamina (IEL). The adventitia was imaged as a bright area surrounding the media layer. The external elastic lamina (EEL) was the line between the media and the adventitia layers [20]. Both area and maximum thickness were measured for intima and media. Intima + media area was the sum of both areas (Fig. 1C and D). Intimal hyperplasia indexes were defined as intimal thickness index (*ITI*: intimal area/medial area), intima-media ratio (*IMR*: the maximum intimal thickness/medial thickness) measured at the maximum intimal thickness [10], and percentage of luminal narrowing [*%LN*: (intimal area + medial area)/external elastic membrane area × 100] [10].

An eccentricity of intima distribution was identified when the ratio of minimal intimal thickness/maximal intimal thickness (named intimal eccentricity index) was less than 0.5 [17].

The imaged proximal RA segment was divided in tertiles and intimal hyperplasia indexes were measured on each tertile cross-section to obtain the average value of the proximal RA. A consensus between the two FD-OCT readers was obtained for selecting the analyzed cross-sections.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, Illinois). Categorical variables are presented as frequencies and analyzed with the Chi-square test or Fisher's exact test. Most continuous variables were not normally distributed as assessed by the Kolmogorov–Smirnov test for normality, thus were presented as median and interquartile range (IQR) and logarithmic transformation was applied to the data to allow Student's *t* test to be used. Univariate and multivariate logistic regression analyses were performed to assess the impact of a set of factors on TCFA presence (dependent variable). Univariate analysis was first performed and then the variables which were significantly associated with TCFA at univariate analysis were included en bloc into the multivariate model. Model fit was assessed using the Hosmer–Lemeshow goodness of fit model. Cox and Snell R squared and Nagelkerke R squared were used to identify the amount of variation in the dependent variable explained by the model. Intra-observer and inter-observer differences were investigated with kappa measure of agreement for coronary TCFA and with Pearson correlation coefficient and Bland–Altman analysis for IMR. A p value<0.05 was considered significant.

3. Results

A total of 51 patients were enrolled in the study. The characteristics of enrolled patients are presented in Table 1. Briefly, clinical presentation was ACS in 16 patients (32%; one STEMI and 15 NSTEMI) and SA in 35 patients (68%). The single STEMI patient had TIMI flow 3 and an angiographic thrombus score of 1–2. All patients were pretreated with double antiplatelet therapy (aspirin and clopidogrel) and statins (63% of patients were on chronic statin therapy before admission). Of note, 25 patients had no previous history of transradial catheterization of the investigated RA while the remaining 26 patients had a previous transradial catheterization.

3.1. FD-OCT coronary results

In total 51 native, de novo coronary lesions were imaged (Table 2). TCFA was imaged in 37% of cases, while lipid plaque, ruptured plaque and thrombus in 41%, 25% and 14%, respectively.

Patients presenting with ACS, compared with SA patients, had greater prevalence of TCFA (62% vs. 25%; p = 0.022) and wider lipid arc (235° (163–289) vs. 143° (99–211), p = 0.009). No other significant differences were observed.