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Potential contribution of virtual histology plaque composition to hemodynamic–morphologic dissociation in patients with non-ST elevation acute coronary syndrome

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ABSTRACT

Objective: Histologic plaque characteristics may influence the hemodynamic effect generated by physiologically significant unstable coronary lesions where plaque content and surface related factors are expected to contribute to the maximum translesional pressure drop. In this study, we aimed to identify local lesion specific virtual histological characteristics that may potentially affect hemodynamic outcome measures.

Methods: Forty-eight consecutive patients with non-ST-elevation acute coronary syndrome (NSTEACS) having paired hemodynamic and morphological data were enrolled. A dual sensor guide-wire was used for the assessment of fractional flow reserve (FFR) and stenosis resistance (HSR) in the culprit vessel. Virtual histology intravascular ultrasound imaging was performed after obtaining hemodynamic data.

Results: In a hemodynamically significant lesion subset (FFR < 0.75 [$n = 34$]), after controlling for lesion length, MLA and coronary artery compliance, FFR correlated with necrotic core (NC) area ($r = -0.423$, $p = 0.028$) at MLA and NC volume ($r = -0.497$, $p = 0.008$) and dense calcium (DC) volume ($r = -0.332$, $p = 0.03$) across the entire lesion segment. Likewise, NC ($r = -0.544$, $p = 0.005$) and DC ($r = 0.376$, $p = 0.03$) areas at MLA and NC ($r = 0.545$, $p = 0.005$) and DC ($r = 0.576$, $p = 0.003$) volumes across the entire lesion segment were associated with HSR in the hemodynamically significant lesion group (HSR > 0.80 [$n = 33$]). However, no correlation has been observed between intracoronary hemodynamic end-points and plaque components in hemodynamically insignificant lesions.

Conclusions: This study demonstrated that for a given coronary stenosis geometry and arterial compliance, plaque composition may influence hemodynamic outcome measures in functionally significant stenoses in patients with NSTEACS.

1. Introduction

Lesion specific invasive indices, such as fractional flow reserve (FFR) and hyperemic stenosis resistance (HSR), are widely accepted as indispensible tools in the evaluation of hemodynamic significance of coronary stenoses. Lesion and vessel related factors such as lesion eccentricity, length [1] and vessel compliance [2,3] may influence the hemodynamic effect produced by a given coronary stenosis. To this end, unraveling potential influences of stenosis related morphological and geometric factors on epicardial conductance, and in turn FFR and HSR, may contribute significantly to our understanding concerning the interplay between an anatomical substrate and its physiological consequence. In the literature, however, there are only a few studies examining the possible impact of the geometry and composition of the coronary plaques on their hemodynamic effects [4–6].

Identification of the anatomical/morphological characteristics of coronary plaques such as plaque composition and rupture [7], lesion length and eccentricity [8], arterial wall compliance [2,3] and plaque composition, all of which may influence the hemodynamic effect of a given stenosis, can be possible with the aid of intravascular ultrasound imaging combining spectral analysis of radiofrequency ultrasound backscatter signals by virtual histology (VH-IVUS) [9]. In this study, we hypothesized that coronary plaque characteristics may contribute to the hemodynamic effect generated by stenoses, particularly the ones classified as physiologically significant, in which plaque surface

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related frictional loses are expected to contribute to the maximum translesional pressure drop. We, therefore, aimed to identify local lesion specific virtual histological characteristics that may potentially affect hemodynamic outcome measures such as FFR and HSR.

2. Methods

2.1. Patient population

Fifty-four consecutive patients with non-ST-elevation acute coronary syndrome (NSTEACS) undergoing clinically indicated coronary angiography between January 2014 and June 2014 were prospectively enrolled for intracoronary hemodynamic evaluation by pressure and flow measurement and VH-IVUS imaging. Patients with previous coronary artery by-pass surgery and severe valvular disease were not included in the study. The study was conducted in accordance with the Declaration of Helsinki, and the local ethical review board approved the study protocol. Written informed consent was obtained from all patients.

2.2. Study protocol

2.2.1. Intracoronary hemodynamic measurements

For the assessment of the hemodynamic significance of a given coronary stenosis, a dual-sensor guide-wire having a Doppler crystal at the tip and a pressure sensor 1.5 cm before the tip (Combo Wire, Volcano Corporation), was advanced across the lesion. Aortic pressure (Pa) was obtained from the guiding catheter and distal coronary pressure (Pd) and average peak flow velocity (APV) were assessed with the dual-sensor guide wire. All hemodynamic signals were recorded at baseline and during maximum hyperemia induced by a bolus of intracoronary papaverine (15 mg for the right coronary artery and 20 mg for the left coronary artery).

Pressure and flow velocity signals were recorded on a device console (Combo Map, Volcano Corporation) during the procedure and extracted from the digital archive and analyzed offline. FFR was calculated as the ratio of mean distal coronary pressure to mean aortic pressure during maximum hyperemia. A velocity-pressure based index of HSR was calculated as the mean hyperemic stenosis pressure gradient across stenosis (Pa–Pd) divided by hyperemic APV distal to the stenosis.

2.2.2. IVUS and VH-IVUS imaging

After obtaining hemodynamic measurements, the IVUS catheter (Eagle Eye Gold, Volcano Corporation) was advanced over the dual sensor tipped guide wire and automated pull back was performed at a speed of 0.5 mm/s. Quantitative gray scale and VH-IVUS analyses were performed and reported at the site of a minimum lumen area (MLA) and across the entire lesion segment according to consensus document recommendations in interpretation and reporting VH-IVUS parameters [10]. External elastic membrane (EEM) and lumen cross-sectional area (CSA) were measured. Plaque plus media (P&M) CSA was calculated as EEM minus lumen CSA and plaque burden at the MLA site was calculated as P&M divided by EEM CSA; volumes were calculated using Simpson's rule. Remodeling was assessed by means of the remodeling index (RI), expressed as the external elastic membrane CSA (MLA site) divided by the reference external elastic membrane CSA. The 4 VH-IVUS plaque components (fibrous, fibro-fatty, dense calcium, and necrotic core) were measured in every recorded frame in the entire diseased segment and expressed as absolute amounts and as a percentage of plaque area or plaque volume. We have also calculated a necrotic core to dense calcium ratio. VH-IVUS derived thin cap fibro-atheroma (TCFA) was defined as a lesion meeting the following two criteria in at least three consecutive frames: (1) focal necrotic core-rich lesions (>10%) without evident overlying fibrous tissue and (2) % plaque-volume > 40%.

We calculated coronary artery wall compliance at proximal reference site based on the external elastic lamina (EEM) dimensions measured on three different time for each and averaged. Measurements were made at two points in the cardiac cycle at each position; immediately before the onset of the Q wave (end-diastole) and at the peak of the T wave (systole). Differences in EEM area were calculated over the cardiac cycle (Δarea). Cross-sectional compliance ($mm^2\ mm\ Hg^{-1}$) was calculated as systolic–diastolic EEM area divided by pulse pressure (PP). Distal intracoronary pressures obtained from Combowire were used in the calculation of compliance for the coronary segments distal to the stenosis. Cross-sectional compliance coefficient ($mm^2\ mm\ Hg^{-1}$) was calculated as systolic–diastolic EEM areas at proximal and distal reference segments divided by PP. Normalized compliances were calculated for proximal and distal reference segments as follows: [11]

$$\frac{[(\text{Systolic EEM area–diastolic EEM area})/\text{diastolic EEM area}]}{\text{Pressure difference}} \times 10^3\left(\text{mm Hg}^{-1}\right).$$

2.2.3. Statistical analysis

Statistical tests were performed with the Statistical Package for the Social Sciences version 17.0 program (SPSS Inc., Chicago, Illinois). Continuous variables were expressed as mean ± standard deviation. Relationships between continuous variables were examined by using Pearson correlation or linear regression analysis. Relations between hemodynamic parameters (FFR, HSR) and plaque components were examined by controlling for anatomical factors that may affect hemodynamic outcomes including IVUS MLA, lesion length and EEM compliance by using partial correlation analysis. Significance was accepted as $p < 0.05$.

3. Results

3.1. Patient characteristics

Obtaining reliable Doppler envelopes, meaning the adequate waveform, could be possible in 48 patients for which paired pressure waveforms and VH-IVUS images were also available. Therefore, a total of 48 lesions, which had paired hemodynamic and morphological data, were evaluated. Patient demographics and angiographic findings were summarized in Table 1. A total of 35 lesions (73%) were treated with percutaneous coronary intervention after hemodynamic and morphologic

Table 1
Patient characteristics ($n = 48$).

Clinical and demographical characteristics		
Male, *n* (%)		35 (73)
Age		58.1 ± 11.5
Diabetes mellitus, *n* (%)		16 (33)
Chronic kidney disease, *n* (%)		7 (14)
Hypertension, *n* (%)		21 (44)
Smoking, *n* (%)		33 (69)
Total cholesterol level (mg/dL)		205.2 ± 42.3
LDL cholesterol level (mg/dL)		128.6 ± 36.2
HDL cholesterol level (mg/dL)		38.9 ± 10.2
Triglyceride level (mg/dL)		182.3 ± 74.5
Ejection fraction, %		50.8 ± 7.3
Angiographic characteristics		
Coronary vessels, *n* (%)	LAD	25 (52)
	Diagonal	2 (4)
	Intermediate	2 (4)
	Circumflex	6 (13)
	RCA	13 (27)
Stenosis location, *n* (%)	Proximal	30
	Mid	16
	Distal	2
Angiographic (visually estimated) stenosis, (%)		65.8 ± 15.8
Stent length, mean (mm)		18.6 ± 5.7

LAD, left anterior descending artery; RCA: right coronary artery.