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Original article

Pathologic Intimal Thickening Plaque Phenotype: Not as Innocent as Previously Thought. A Serial 3D Intravascular Ultrasound Virtual Histology Study

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ABSTRACT

Introduction and objectives: Pathologic intimal thickening (PIT) has been considered a benign plaque phenotype. We report plaque phenotypic changes in a baseline/follow-up intravascular ultrasound-based virtual histology study.

Methods: A total of 61 patients with stable coronary artery disease were analyzed from the HEAVEN trial (89 patients randomized between routine statin therapy vs atorvastatin 80 mg and ezetimibe 10 mg) with serial intravascular ultrasound imaging of nonculprit vessels. We compared changes in 693 baseline and follow-up 5-mm long segments in a novel risk score, Liverpool Active Plaque Score (LAPS), plaque parameters, and plaque composition.

Results: The PIT showed the highest increase of risk score and, with fibrous plaque, also the LAPS. Necrotic core (NC) abutting to the lumen increased in PIT (22 ± 51.7; $P = .0001$) and in fibrous plaque (17.9 ± 42.6; $P = .004$) but decreased in thin cap fibroatheroma (TCFA) (−15.14 ± 52.2; $P = .001$). The PIT was the most likely of all nonthin cap fibroatheroma plaque types to transform into TCFA at follow-up (11% of all TCFA found during follow-up and 35.9% of newly-developed TCFA), but showed (together with fibrous plaque) the lowest stability during lipid-lowering therapy (24.7% of PIT remained PIT and 24.5% of fibrous plaque remained fibrous plaque).

Conclusions: Over the 1-year follow-up, PIT was the most dynamic of the plaque phenotypes and was associated with an increase of risk score and LAPS (together with fibrous plaque), NC percentage (together with fibrous plaque) and NC abutting to the lumen, despite a small reduction of plaque volume during lipid-lowering therapy. The PIT was the main source for new TCFA segments.

Fenotipo del engrosamiento intimal patológico: no tan inocente como se pensaba. Estudio de la histología virtual de una serie de casos con ecografía intravascular 3D

Palabras clave:
Placa ateroesclerótica
Ecografía intravascular
Angina estable
Estudio de seguimiento
Lípidos

RESUMEN

Introducción y objetivos: Se ha considerado que el engrosamiento intimal patológico (EIP) es un fenotipo de placa benigno. Se presentan los cambios fenotípicos de la placa en un estudio comparativo entre situación basal y seguimiento mediante un estudio de reconstrucción histológica virtual por ecografía intravascular.

Métodos: Se estudió a 61 pacientes con enfermedad coronaria estable del ensayo HEAVEN (89 pacientes aleatorizados al tratamiento estándar con estatinas o atorvastatina 80 mg y ezetimiba 10 mg) por ecografía intravascular seriada de las arterias no culpables. Se compararon los cambios examinando al inicio del estudio y durante el seguimiento 693 segmentos de 5 mm de longitud mediante una nueva puntuación de riesgo, la *Liverpool Active Plaque Score* (LAPS), los parámetros de la placa y la composición de esta.

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Resultados: El EIP es el tipo que mostró mayor aumento de la puntuación de riesgo y, junto con las placas fibrosas, también de la LAPS. El *core* necrótico (CN) próximo a la luz aumentó tanto en las placas con EIP (22 ± 51,7; p = 0,0001) como en las placas fibrosas (17,9 ± 42,6; p = 0,004), pero disminuyó en el fibroateroma de capa fina (FCF) (−15,14 ± 52,2; p = 0,001). El EIP es el tipo de placa de fibroateroma de capa no fina con mayor probabilidad de transformación a FCF durante el seguimiento (el 11% del total de FCF hallados durante el seguimiento y el 35,9% de los FCF de nueva aparición), pero también el que mostró (junto con las placas fibrosas) menor estabilidad durante el tratamiento hipolipemiante (el 24,7% de los EIP y el 24,5% de las placas fibrosas se mantuvieron estables).
Conclusiones: En 1 año de seguimiento, el EIP fue el fenotipo de placa más dinámico y se asoció a un aumento de la puntuación de riesgo y de la LAPS (junto con la placa fibrosa), el porcentaje de CN (junto con la placa fibrosa) y el CN próximo a la luz, a pesar de una pequeña reducción del volumen de la placa durante el tratamiento hipolipemiante. El EIP fue el principal origen de los nuevos segmentos con FCF.

Abbreviations

IVUS-VH: intravascular ultrasound based virtual histology
LAPS: Liverpool Active Plaque Score
NC: necrotic core (necrotic tissue)
PIT: pathologic intimal thickening
TCFA: thin cap fibroatheroma
ThCFA: thick cap fibroatheroma

INTRODUCTION

Recent work suggests coronary artery plaque composition may predict future clinical events.[1] Intravascular ultrasound-based virtual histology (IVUS-VH) can assess plaque composition by processing a raw radiofrequency signal from intravascular ultrasound (IVUS). IVUS-VH has exhibited > 90% correlation with conventional histology.[2] Using IVUS-VH image data, 6 types of plaque phenotypes can be determined. They correspond to the descriptions of the American Heart Association's Committee on Vascular Lesions.[3] Much of the work in this area has focused on fibroatheromas (thin cap fibroatheromas [TCFA] and thick cap fibroatheromas [ThCFA]), as risk factors for future cardiac events, with TCFA established as the highest-risk lesion for the development of acute coronary syndromes.[4] Other plaque phenotypes have been considered stable lesions.[1,5] Further studies suggest that 1 type of stable plaque phenotype, pathologic intimal thickening (PIT), may serve as a precursor to fibroatheromas.[6,7]

We sought to investigate the dynamic properties of various plaque phenotypes—in patients with stable coronary artery disease treated by lipid-lowering therapy—by using an established 3-dimensional (3D) angiography-fusion IVUS-VH imaging protocol in baseline and follow-up studies.

METHODS

Study Population, Angiographic Protocol and Intravascular Ultrasound Imaging

From a database of 89 serial IVUS-VH studies of patients who underwent elective coronary angiography for stable coronary artery disease and were analyzed in the HEAVEN trial[8] (a multicenter, randomized trial comparing routine statin therapy vs aggressive treatment: atorvastatin 80 mg plus ezetimibe 10 mg per day), we analyzed 61 baseline and follow-up data sets that met the following criteria: *a)* IVUS-VH of a native coronary artery with stenosis ≤ 50% of lumen diameter determined by angiography, with no indication for either percutaneous coronary intervention or coronary artery bypass grafting at the time of initial imaging; *b)* good-quality baseline and follow-up IVUS-VH pullbacks (ie, without noticeable pullback speed discontinuity); *c)* imaged vessels free of severe calcification to avoid inconsistency of IVUS-VH plaque type determination in areas of acoustic shadowing, and *d)* both baseline and follow-up pullbacks at least 30-mm long, with at least 25-mm long overlap after registration in 1 coronary artery.

One segment from each patient was chosen for the study. In case of multiple lesions, a lesion located in a more proximal location, or (in case of similar locations) a lesion with a higher plaque burden was chosen for the analysis.

From 89 patients included in the HEAVEN trial, we used 61 patients. Examinations from 15 patients had an overlap between baseline and follow-up of < 25 mm, angiography of 8 participants were not suitable for 3D reconstruction and in 5 patients either the baseline or follow-up IVUS examinations were noncontinual.

All participants provided informed consent. The study was approved by the institutional review boards of Charles University in Prague.

Creation of 3D Models, Coregistration and Intravascular Ultrasound Analysis

The IVUS-VH was performed using an IVUS phased-array probe (Eagle Eye 20 MHz 2,9 Fr, Volcano Corporation; Rancho Cordova, California, United States), IVUS console, Gold standard software, with automatic pullback at 0.5 mm/s (research pullback, model R-l00, Volcano Corporation). After administration of 200 μg of intracoronary nitroglycerin, the IVUS catheter was inserted into the target vessel beyond a distal fiduciary point and was then pulled back to the aorto-ostial junction. The proximal fiduciary point was the left main bifurcation in the left coronary artery, and the first branch or a well-defined calcification in the right coronary artery. After 8-14 (mean, 12 ± 2.1) months, patients underwent repeat angiography with IVUS-VH of the same coronary artery.

We used geometrically correct fully 3D vessel reconstruction to ensure precise alignment of baseline and follow-up measurements in this study.

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