Int J Clin Exp Med 2017;10(9):13625-13631
www.ijcem.com /ISSN:1940-5901/IJCEM0053555

Original Article

Virtual histology-intravascular ultrasound imaging for plaque properties in stable coronary heart disease patients with coronary intermediate lesion

Zhi-Hong Zhao, Sai-Hua Wang, Jun Luo, Xin-Ming Li

Department of Cardiology, Shanghai Pudong New Area Zhoupu Hospital, Shanghai University of Medicine & Health Sciences, Shanghai 201318, P. R. China

Received March 23, 2017; Accepted July 15, 2017; Epub September 15, 2017; Published September 30, 2017

Abstract: Objective: This study aims to examine the plaque properties of stable coronary heart disease patients with coronary intermediate lesion by virtual histology-intravascular ultrasound imaging (VH-IVUS). Methods: From Feb. 2015 to Dec. 2016, patients in our hospital with stable coronary heart disease were identified as coronary intermediate lesion by receiving coronary angiography examination. The screening patients were further received VH-IVUS to evaluate the plaque character. Results: A total of 265 coronary intermediate lesion patients were included in the study. The average age is 66.93±9.75. Among the cases, thin-cap fibroatheroma (TCFA) is 127; thick-cap fibroatheroma (ThCFA) is 93; pathological intimal thickening (PIT) is 41; fibrotic plaque (FT) is 4; fibrocalcific plaque (FC) is 0. Compared with ThCFA, TCFA had more cases of diabetes and hyperlipidemia. Compared with ThCFA and PIT, TCFA patients had coronary artery atheromatous plaque more than 10% of necrotic core of plaque area, increased high density calcified components, more cases with the minimal lumen area <4.0 mm^2. Conclusion: The dominated plague type of coronary intermediate lesion is TCFA/ThCFA. TCFA combined with plague load and clinical symptom might be regarded as the basis for the evaluating the unstable condition of stable coronary heart disease patients.

Keywords: Sable coronary heart disease, virtual histology-intravascular ultrasound imaging, coronary intermediate lesion, diagnostic imaging

Introduction

The occurrence and development of atherosclerosis is throughout the individual from young to old age of the growth process [1]. On the individual, the development of coronary atherosclerotic plaque is a long process and spanning for several years to several decades. As the patient's age, gender, health status, pain sensitivity, disease progression, collateral circulation degree, clinical manifestations of atherosclerosis were diversified. The mortality rate for coronary heart disease in developed countries accounts for 50% of the total mortality rate and 25% in developing countries [2]. Virtual histology-intravascular ultrasound imaging (VH-IVUS) can accurately detect the diameter of the vessel and provides more accurate and reproducible coronary artery disease information than coronary angiography. Coronary critical lesions usually refer to coronary angiography under the visual stenosis of 40% to 70% of the lesions [3]. The evaluation results for different surgeons or the same surgeon at different times are different. Intervention strategies for critical lesions have been a hot topic in the discussion of coronary intervention. The aim of this study was to investigate the character of the critical lesion of coronary artery, with a view to providing a basis for its intervention strategy.

Materials and methods

Patients

This study included 3396 patients with stable coronary heart disease and they were received coronary angiography examination from Feb. 2015 to Dec. 2016 in our hospital. 1530 cases of them accepted percutaneous coronary intervention (PCI) treatment. The coronary angiogra-

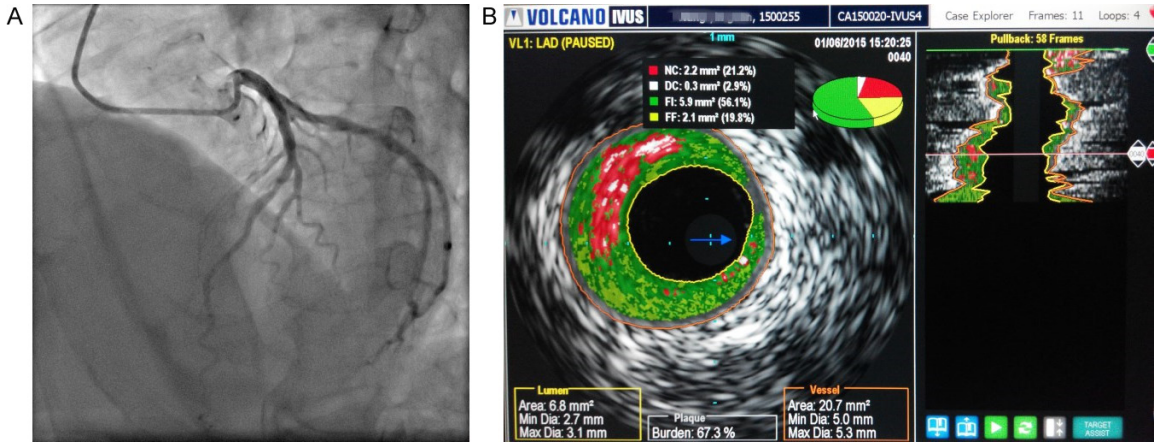

Figure 1. Plague analysis of a male patient. A: Coronary arteriography showed the critical lesions in the middle of left anterior descending coronary artery. B: VH-IVUC and data presentation for the critical lesions; the dark green area, fibrous tissue; the light green area; red area, the necrotic core (necrotic core).

phy indications include chest pain (boring), coronary artery stenosis indicated by the electrocardiogram, positive sport tablet examination and coronary CT. For coronary intermediate lesion, the inclusion criterion is visually stenosis degree accounting for 40%~70% of the lesions under coronary angiography [3]. The exclusion criteria: poor quality and retracement of IVUS, VH-IVUS cannot confirm the lesions. All patients have signed the informed consent forms about coronary angiography and VH-IVUS. Hypertension diagnostic criteria refer to the Chinese Hypertension Prevention Guide (Revised version 2013); diabetes diagnostic criteria refer to the Chinese type 2 diabetes prevention (version 2013); hyperlipidemia diagnosis refers to Chinese hyperlipidemia treatment guidelines.

After admission, the fasting venous blood was taken into EDTA anticoagulant tube and used for the detection of total cholesterol, low density lipoprotein, high density lipoprotein, urea nitrogen, creatinine, uric acid, brain natriuretic, etc. with biochemical tests in the Abbott C1600 automatic biochemical analyzer (American Abbott).

Coronary angiography and VH-IVUS

Before coronary angiography, all patients had conventional oral 100 mg aspirin enteric-coated tablets, 300 mg clopidogrel hydrogen sulfate. Coronary angiography examined the number of right coronary artery (RCA), left circumflex (LCX) and left anterior descending (LAD). Basing on the examination, patients with severe coronary artery bifurcation, left coronary artery lesion, coronary artery critical lesion and partial stent implantation or coronary occlusion stent implantation were received VH-IVUS using a Volcano S5™ ultrasound apparatus with 3.2F, 20 MHz phased array Eagle Eye® Gold VUS ultrasonic probe. During the VH-IVUS procedure, 200 μg of nitroglycerin was pre-injected into coronary artery and 6000 U heparin was intravenous injection; guidelines catheter delivery 0.014 inch guide wire arrived at the distal end of the coronary artery. IVUS catheter retraction was withdrawn at 1.0 mm/s speed to access the VH-IVUS images. All images are retained and stored in the video workstation for analysis. For analysis of chronic stable angina pectoris coronary critical disease, the patients with poor quality and poor withdrawing of IVUS, VH-IVUS cannot clearly confirm the critical coronary artery disease were excluded. Eventually, 265 cases were selected, including 121 males and 144 females and the average age of 66.93±9.75 years old.

Statistical analysis

Data analysis used the SPSS 19.0 software. Measurement data are presented as x±s and the comparison between groups used *t* test; count data are presented as percentage and the comparison among groups are analyzed by chi-square test. *P* value less than 0.05 was recognized as statistical significance.

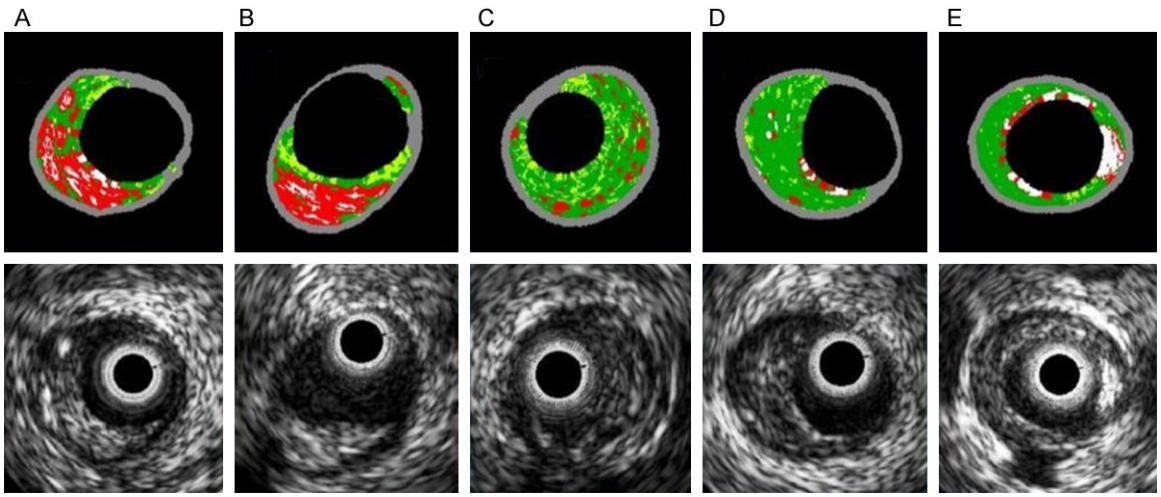

Figure 2. Plaque classification diagram. A: Thin-cap fibroatheroma (TCFA) plaques. B: Thick-cap fibroatheroma (ThCFA) plaque. C: Pathological intimal thickening (PIT) plaques. D: Fibrotic (FT) plaque. E: Fibrocalcific Plaque (FC) plaques.

Results

Classification of coronary artery atheromatous plaque

Plaque character of coronary artery disease lesions from VH-IVUS examination results was analyzed with echoPlaque4 software (US, INDEC). **Figure 1** showed one the typical case of critical lesions of coronary atherosclerosis coronary artery disease lesions. The dark green area is fibrous tissue; the light green area is fiber Fibro-fatty tissue; red area is the necrotic core (necrotic core), which constituted by a large number of dead cells and lipid composition; the white area is dense calcium, which is deposited by a large number of calcium salt crystals.

Coronary atherosclerotic plaques IVUS classification [4]: 1) thin-cap fibroatheroma (TCFA) plaque, plaque necrosis/calcification components close to the plaque surface appear at least three consecutive cross sections, and coronary atherosclerotic plaque necrosis core area accounted for more than 10% of plaque area (**Figure 2A**); 2) thick-cap fibroatheroma (ThCFA) plaque, plaque necrosis/calcification components away from the plaque surface at least 3 consecutive cross-sectional out and coronary atherosclerotic plaque necrosis of the core area <10% (**Figure 2B**); 3) pathological intimal thickening (PIT), plaque are dominant with fibrous plaque and fiber fatty plaques with fibrous fatty plaque area ≥15% and calcified area <10% (**Figure 2C**); 4) fibrotic plaque (FT), plaque are dominant with fibrous plaque with fibrous fatty plaque area <15% and calcified area <10% (**Figure 2D**); 5) fibrocalcific Plaque (FC) plaques, calcified area >10% (**Figure 2E**).

Results of coronary atherosclerotic plaques classification of all cases

Basing on the plaques classification, TCFA accounted for the largest proportion (127/265, 47.92%) and ThCF, PIT, Fibrous plaques and fibrous-calcified atherosclerotic plaque were respectively (93/265, 35.09%), (41/265, 15.47%), (4/265, 1.51%), zero. Compared with ThCFA group, TCFA group had more cases of diabetes mellitus and dyslipidemia. The difference of gender, age, characteristics, cardiac function grade, laboratory index, coronary artery lesion and coronary stent implantation ratio between these two groups was not statistically significant. PIT group had less men cases and more hyperlipidemia cases (**Table 1**).

Compared with ThCFA group, TCFA group accounted for more than >10% coronary atherosclerotic plaque necrosis core area of plaque area and had increased high-density calcification and more cases of the smallest lumen area ≤4.0 mm^2 cases. The ThCFA group had increased fibrous tissue and fibrous adipose tissue. Compared with ThCFA group and TCFA group, PIT group accounted for 15.47% and had smaller plaque load and plaque area; its plaque was dominant with fiber fatty patch

Table 1. Clinical data of coronary intermediate lesion patients

	TCFA (n=127)	ThCFA (n=93)	PIT (n=41)
Age	68.15±9.89	66.46±9.34	64.37±10.27
Male [cases (%)]	61 (48.03)^{*,b}	43 (46.24)^{*,c}	15 (36.59)
Smoke [cases (%)]	28 (22.05)	26 (27.96)	8 (19.51)
Diabetes [cases (%)]	35 (27.56)^{**,a,b}	19 (20.43)^{**,c}	7 (17.07)
Hypertension [cases (%)]	90 (70.87)	69 (74.19)	31 (75.61)
Hyperlipemia [cases (%)]	21 (16.54)^{**,a}	9 (9.68)^{*,c}	14 (34.15)^{**,b,c}
NYHA class I~II [cases (%)]	121 (95.28)	88 (94.62)	39 (95.12)
NYHA class III~IV [cases (%)]	6 (4.72)	5 (5.38)	2 (4.87)
Cerebrovascular events [cases (%)]	12 (9.45)	7 (7.53)	5 (12.2)
Total cholesterol (mmol/l)	4.35±1.09	4.48±1.16	4.41±1.27
High-density lipoprotein-C (mmol/l)	1.10±0.29	1.1±0.30	1.12±0.29
Low-density lipoprotein-C (mmol/l)	2.66±0.86	2.71±0.9	2.52±0.87
Triglyceride (mmol/l)	1.59±0.96	1.64±1.22	1.4±1.0
Urea nitrogen (mmol/l)	5.52±1.94	4.73±3.2	5.87±2.7
Creatinine (mmol/l)	66.14±23.9	54.4±35.65	70.43±25.84
Uric Acid (mmol/l)	334.59±122.66	330.55±116.81	313.7±174.17
Brain natriuretic peptide (ng/L)	249 (143,487)	241 (53,630)	341 (155,720)

*P<0.05, **P<0.01; ^{a}TCFA VS. ThCFA, ^{b}TCFA VS. PIT; ^{c}ThCFA VS. PIT. TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma; PIT, pathological intimal thickening.

Table 2. Coronary arteriography and VH-IVUS

	TCFA (n=127)	ThCFA (n=93)	PIT (n=41)
Coronary artery disease			
Anterior descending left coronary artery [cases (%)]	76 (59.8)	56 (60.21)	22 (53.66)
Circumflex left coronary artery [cases (%)]	23 (18.11)	9 (9.68)	8 (19.51)
Right coronary artery	28 (22.05)	28 (30.11)	11 (26.83)
Coronary artery stent implantation [cases (%)]	34 (26.77)	20 (21.51)	9 (21.95)
VH-IVUS			
Plaque burden (%)	63.14±9.13	64.06±7.43	59.1±12.38^{*,b,c}
Plaque area (mm^2)	10.14±3.7	10.81±3.38	8.81±3.49^{*,b,c}
Vascular cross-sectional area (mm^2)	15.89±4.96	16.73±4.3	14.64±4.57^{*,c}
Minimum lumen area (mm^2)	5.75±1.98	5.92±1.6	5.83±2.12
Minimum lumen area less than 4.0 mm^2 [cases (%)]	22 (17.32)^{*,a}	8 (8.6)	6 (14.63)^{*,c}
Fibrous tissue area (%)	50.89±13.08	59.04±10.49^{*,a}	59.11±12.1^{*,b}
Fiber adipose tissue area (%)	11.43±10.79	14.83±8.61^{*,a}	27.46±15.57^{**,b,c}
Necrotic core area (%)	26.98±11.85^{**,b}	21.79±9.04^{**,c}	10.81±9.41
High density calcified area (%)	10.7±8.77	4.33±5.63	4.03±5.58

*P<0.05, **P<0.01; ^{a}TCFA VS. ThCFA, ^{b}TCFA VS. PIT; ^{c}ThCFA VS. PIT. TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma; PIT, pathological intimal thickening.

and had less high density calcification (**Table 2**).

Discussion

On the individual, the occurrence and development of the coronary artery plaque is a long process and spanning for several years to several decades, during which intermittent development may accelerate. Clinically, the current coronary CT and coronary angiography is usually not a routine physical examination of the project and patients were examined only when chest tightness (pain). Thus the coronary atherosclerotic plaque evolution is gradually explored in recent years.

VH-IVUS technology is an interventional diagnosis method that basing on traditional gray-type intravascular ultrasound catheter and is used to distinguish different types of atherosclerotic plaque to detect the progression of atherosclerotic plaques. VH-IVUS can now identify four major plaque tissue components of coronary atherosclerosis including fibrous plaques, fibrous fat patches, necrotic cores and calcification. Considering the composition and distribution, the plaque are clinical divided into six types, including thin-cap fibrous atherosclerotic plaques, thick-cap fibrous atherosclerotic plaques, pathological endometrial thickening, fibrous plaques, fibrous-calcium atherosclerotic plaques, and fibrous atherosclerotic plaques.

VH-IVUS can further objectively evaluate the character of coronary plaques and is important for the development of intervention strategies [5]. VH-IVUS has some limitations, such as coronary artery disease coronary artery stenosis produced by the hemodynamic significance cannot be judged use a single IVUS boundary value. It should be combined with other factors to assess, including lesion length, eccentricity, reference to the diameter of the vessel and the lesion dominated by the blood vessels [6].

Studies have shown that the plague load of coronary arteriosclerosis and the severity of coronary stenosis by IVUS detection are independent risk factors for acute coronary syndrome (ACS) patients [7]. VH-IVUS of ACS patients showed that TCFA mainly locates at the proximal anterior descending branch, near the middle of circumflex branch and near the middle of right coronary. Plague rupture is more likely to occur in the anterior descending proximal. TCFA in ACS criminal blood vessels and non-criminals accounted for the proportion of blood vessels were 55.0% and 36.6%, stable coronary heart disease in the proportion of blood vessels accounted for 14.4%, suggesting that TCFA is a decisive factor in coronary atherosclerotic plaque instability [8]. It has also been found that VH-IVUS of ACS patients with non-ST-elevation, necrotic core of coronary artery lesions significantly increased [9]. PROSPECT study suggests that ACS patients with non-criminal blood vessels, TCFA plaques, IVUS examinations showing that the coronary plaque load exceeds 70% and the vascular window <4 mm^2 are three risk factors for coronary artery events occurrence in 3 years [10]. Cardiovascular events recurrence of ACS patients with non-criminal blood vessels is positively correlated with plaque rupture and lumen area, plaque load, as well as with coronary artery proximal site. The plaque nature of the heavy plaque load is not consistent with the nature of the high-risk vulnerable plaque [11].

The coronary artery lesions in patients with stable coronary artery disease mostly locate at left coronary artery anterior descending artery. TCFA accounts for 47.92% of all cases and this group of patients characterized by diabetes mellitus, hyperlipidemia cases, and increased high-density calcification and the smallest lumen area ≤4.0 mm^2. This reflects the changes in the composition of atherosclerotic plaques. Patient with symptoms and coronary angiography and the diagnosis of stable angina commonly has TCFA as main feature. Classification of the most narrow plaque properties of critical coronary artery lesions, TCFA accounted for nearly half of the proportion, followed by ThCF, the total proportion of the two more than 80%, plus PIT type, more than 98%. This means, one of the salient features of atherosclerotic plaque at the critical lesion of stable angina is the process of several atherosclerotic plaque remodeling. The reasons for coronary plaque rupture before the formation of coronary artery stenosis are the formation of coronary artery thrombosis owning to the predomination of blood clots factors and plaque "healing" owning to anti-thrombotic factors, both of which lead to coronary atherosclerotic plaque into the remodeling process and the atherosclerotic plaque nature changes with the dynamic process. In a word, atherosclerotic plaque rupture stimulates the inflammatory response, local thrombosis/thrombosis dissipation, fibrosis scars, calcification, and necrosis of the core and a series of repair healing and is followed by acceleration of reconstruction of coronary plaques and increase in coronary stenosis.

Studies have shown that among classification of plaque type by VH-IVUS, TCFA, ThCFA and PIT are faster progress and have relatively stable fibrous plaques and fibrosis calcified plaque. TCFA can also change to ThCFA and fibrous plaques [12]. It is more worthy of attention that coronary plaque loads is persistent and serves as a predisposed indicator for cardiovascular events [13, 14]. However, there is still no evi-

dence that the assessment of individual plaque properties can better predict cardiovascular events.

We found that in patients with stable coronary heart disease, TFCA is more than ThCF type, coronary plaque more active, nearly half of unstable plaques are in an unstable period. Stable coronary heart disease patients being with a stable state of coronary plaques just like PIT type account for only in a few. The proportion of TFCA in patients with stable coronary heart disease is half but less than that of the TFCA type of acute coronary syndrome. Therefore, the plaque instability process of coronary artery stability disease patients with chest tightness (pain) symptoms requires more attention. This provides the possible foundation for drug treatment for such patients to alter atherosclerotic plaque composition, stabilization and reversal of plaques.

On the stability of coronary heart disease, coronary intervention has been in controversial state. Coronary intervention guidelines pointed out that intensive drug treatment causes a large range of myocardial ischemia and preselection of coronary stent or coronary artery bypass treatment of its potential benefits greater than the risk of those who can choose the appropriate treatment strategy according to the characteristics of the lesion. It is suggested that the degree of stenosis of coronary artery lesion should be used as the basis for decision-making. Lesion diameter narrow ≥90% can be directly intervened; when the lesion diameter narrow <90%, it is recommended only for the corresponding ischemic evidence, or blood flow reserve score ≤0.8 lesions should be directly intervened basing on the China percutaneous coronary intervention treatment guidelines. The further analysis of stability of coronary heart disease through VH-IVUS makes us understand the criticality of coronary lesions, and also adds reference value for the decision-making of coronary intervention. Our observation of TCFA patients, mean lesion vascular luminal surface is less than ThCFA and the smallest lumen area ≤4.0 mm^2 accounted for 17.3% supporting that for TCFA patients, small lumen area, repeated angina pectoris, drug poor treatment can be positively considered line coronary stent implantation; TCFA with poor anti-angina drug's efficacy, unstable plaque and repeated angina pectoris still positively consider coronary stent implantation.

This study is a study of the smaller sample of single center, and the results still need to be confirmed by large sample studies. This study was only VH-IVUS examination for target blood vessels lesion of stable coronary heart disease. We will further follow-up dynamic observation of the development of coronary artery disease in these patients and understand VH-IVUS criminal plaque characteristics in this type patient with acute coronary syndromes. Our observation provides more guidance significance for the choice of intensive drug therapy or early intervention therapy.

Acknowledgements

This study was supported by Science and Technology Development Special Fund of Shanghai Health and Family Planning Commission [Grant No. ZK2015A17] and Science and Technology Development Special Fund of Zhoupu Hospital [Grant No. ZP2014A-01].

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xin-Ming Li, Department of Cardiology, Shanghai Pudong New Area Zhoupu Hospital, Shanghai University of Medicine & Health Sciences, Shanghai 201318, P. R. China. Tel: +86-021-68135590; E-mail: xinmingli6@126.com

References

[1] Ayer J, Charakida M, Deanfield JE and Celermajer DS. Lifetime risk: childhood obesity and cardiovascular risk. Eur Heart J 2015; 36: 1371-1376.

[2] Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol 2014; 11: 276-289.

[3] Tobis J, Azarbal B and Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. J Am Coll Cardiol 2007; 49: 839-848.

[4] Garcia-Garcia HM, Mintz GS, Lerman A, Vince DG, Margolis MP, van Es GA, Morel MA, Nair A, Virmani R, Burke AP, Stone GW and Serruys PW. Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. EuroIntervention 2009; 5: 177-189.

[5] Lee JH, Shin DH, Kim BK, Ko YG, Choi D, Jang Y and Hong MK. Early effects of intensive lipid-lowering treatment on plaque characteristics assessed by virtual histology intravascular ultrasound. Yonsei Med J 2016; 57: 1087-1094.
[6] Lansky AJ, Ng VG, Maehara A, Weisz G, Lerman A, Mintz GS, De Bruyne B, Farhat N, Niess G, Jankovic I, Lazar D, Xu K, Fahy M, Serruys PW and Stone GW. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. JACC Cardiovasc Imaging 2012; 5: S62-72.
[7] Picano E and Paterni M. Ultrasound tissue characterization of vulnerable atherosclerotic plaque. Int J Mol Sci 2015; 16: 10121-10133.
[8] Cascon-Perez JD, de la Torre-Hernandez JM, Ruiz-Abellon MC, Martinez-Pascual M, Marmol-Lozano R, Lopez-Candel J, Cano P, Fernandez C, Ramos JL, Villegas M and Pico-Aracil F. Characteristics of culprit atheromatous plaques obtained in vivo by intravascular ultrasound radiofrequency analysis: results from the CULPLAC study. Am Heart J 2013; 165: 400-407.
[9] Ivanovic M, Rancic M, Rdzanek A, Filipjak KJ, Opolski G and Cvetanovic J. Virtual histology study of atherosclerotic plaque composition in patients with stable angina and acute phase of acute coronary syndromes without ST segment elevation. Srp Arh Celok Lek 2013; 141: 308-314.
[10] Yun KH, Mintz GS, Farhat N, Marso SP, Taglieri N, Verheye S, Foster MC, Margolis MP, Templin B, Xu K, Dressler O, Mehran R, Stone GW and Maehara A. Relation between angiographic lesion severity, vulnerable plaque morphology and future adverse cardiac events (from the providing regional observations to study predictors of events in the coronary tree study). Am J Cardiol 2012; 110: 471-477.
[11] Zheng B, Mintz GS, McPherson JA, De Bruyne B, Farhat NZ, Marso SP, Serruys PW, Stone GW and Maehara A. Predictors of plaque rupture within nonculprit fibroatheromas in patients with acute coronary syndromes: the PROSPECT Study. JACC Cardiovasc Imaging 2015; 8: 1180-1187.
[12] Kubo T, Maehara A, Mintz GS, Doi H, Tsujita K, Choi SY, Katoh O, Nasu K, Koenig A, Pieper M, Rogers JH, Wijns W, Bose D, Margolis MP, Moses JW, Stone GW and Leon MB. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol 2010; 55: 1590-1597.
[13] Arbab-Zadeh A and Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. J Am Coll Cardiol 2015; 65: 846-855.
[14] Albaghdadi MS and Muse ED. Vulnerable plaque: absence of evidence or evidence of absence. J Am Coll Cardiol 2015; 66: 757-758.