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Virtual Histology-Intravascular Ultrasound

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Abstract Although gray-scale intravascular ultrasound (IVUS) has been an established method for assessing coronary lesion morphology and quantifying the atheroma, its role in plaque characterization is limited. Based on the spectral analysis of the primary raw backscattered radiofrequency signal, virtual histology (VH)-IVUS provides detailed tissue maps. Despite some methodological pitfalls, VH-IVUS has been used in recent clinical trials that suggested thin-cap fibroatheroma and large plaque burden as the predictors of future cardiovascular events related to non-culprit lesions. In addition, VH-IVUS helps us to understand coronary artery disease and the effects of local or systemic treatment on natural history of coronary atherosclerosis. Also, VH-IVUS can be used to identify the high-risk coronary lesions for distal embolization during percutaneous coronary intervention.

Keywords VH-IVUS · IVUS · Clinical trials

Introduction

Virtual histology intravascular ultrasound (VH-IVUS) is an IVUS-based post-processing modality for signal-based analysis of coronary plaque characteristics and has been used as an imaging tool for clinical practice and research purposes. Even though grayscale IVUS has been the most useful invasive imaging technique, its role in plaque characterization is limited by its poor spatial resolution (approximately 200 μm of axial and lateral resolution using 40-45 MHz IVUS transducers). While grayscale IVUS imaging uses only the envelope (amplitude) of the reflected Doppler signals, VH-IVUS (Volcano Corp, Rancho Cordoba, CA) is based on the spectral analysis of the primary raw backscattered radiofrequency signal to provide detailed tissue maps. Even with similar amplitudes, frequency and power of the signal may differ among various tissues. When the spectral signatures of tissue types are programmed and processed by using autoregressive models, the tissues can be color-coded as four major components such as dense calcium (white), necrotic core (red), fibro-fatty (light green), and fibrous tissue (dark green) [1, 2]. Currently, VH-IVUS can be performed with either a 20 MHz, 2.9 F phased-array transducer catheter (Eagle Eye™ Gold, Volcano Therapeutics) or a 45 MHz 3.2 F rotational catheter (Revolution®, Volcano Therapeutics) that acquires electrocardiogram-gated IVUS data [3] Figs. 1 and 2.

Validation of VH-IVUS

As an ex vivo validation, Nair et al. compared the VH-IVUS tissue maps with histology in 184 plaques of 51 coronary arteries. The overall diagnostic accuracies were 93.5 % for fibrous tissue, 94.1 % for fibro-fatty tissue, 95.8 % for the necrotic core, and 96.7 % for dense calcium. The sensitivity and the specificity were 95.7 % and 90.9 % for fibrous tissue, 72.3 % and 97.9 % for fibro-fatty tissue, 91.7 % and 96.6 % for the necrotic core, and 86.5 % and 98.9 % for dense calcium, respectively [1]. Nasu et al. validated in vivo VH-IVUS images compared with in vitro histopathology obtained by directional coronary atherectomy [4]. The predictive accuracies were 87.1 % for fibrous tissue, 87.1 % for fibro-fatty

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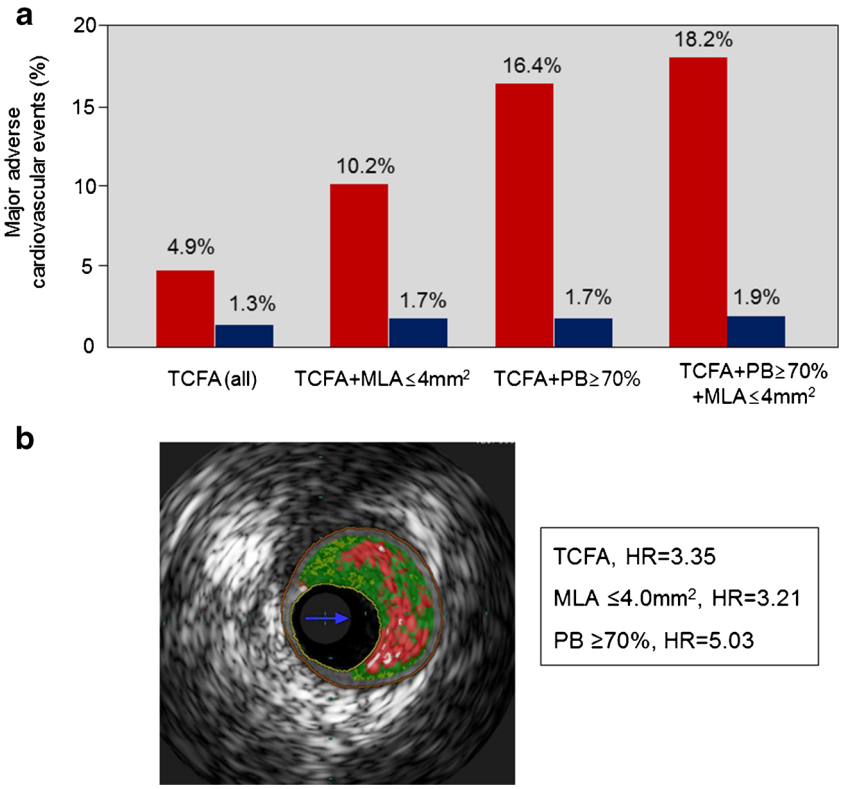

Fig. 1 **a**: Non-culprit related major adverse cardiac events at a median follow-up of 3.4 years. TCFA=thin-cap fibroatheroma, MLA=minimal lumen area, PB=plaque burden. **b**: A non-culprit lesion showed 3.7 mm^2 of MLA, 75 % of PB, and the presence of TCFA. Independent correlates of major adverse cardiovascular events were shown in the box

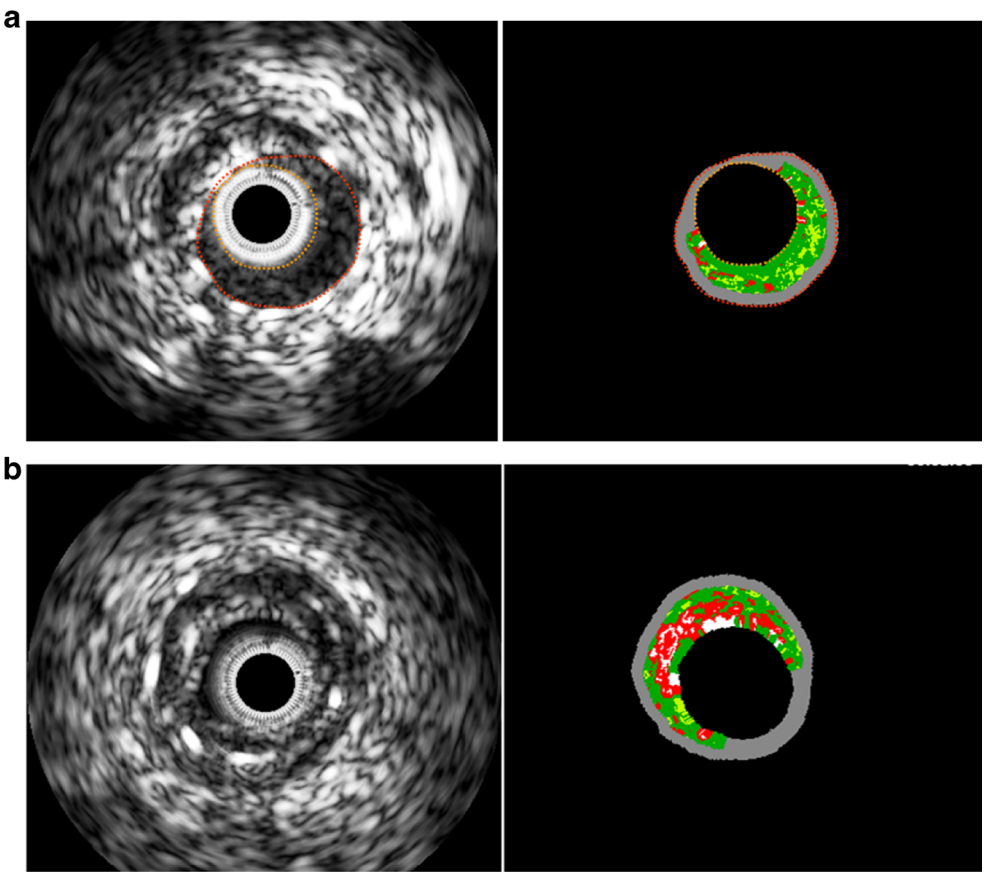

Fig. 2 Neointimal characteristics assessed by VH-IVUS. The region of interest was placed between the luminal border and the inner border of the struts, and tissue composition was represented as percentages of the intimal area. **a**: Neointima showed no confluent necrotic core 6 months after paclitaxel-eluting stent implantation. **b**: At follow-up duration of 5 years, neointima within sirolimus-eluting stent had a large necrotic core with calcification suggesting in-stent neoatherosclerosis

tissue, 88.3 % for the necrotic core, and 96.5 % for dense calcium. The sensitivity and the specificity for predicting the necrotic core were 67.3 % and 92.9 %, respectively.

In an ex vivo study using a porcine model, the accuracies for identifying the presence of fibrous tissue, fibro-fatty tissue, and the necrotic core were 58.3 %, 38.3 %, and 38.3 %, respectively [5]. In a porcine coronary artery model, there was no correlation of necrotic core size between VH-IVUS and histology, which was different from the previous data evaluating human coronary arteries [6]. In an in vivo validation with a rabbit model of atherosclerosis, VH-IVUS data showed high sensitivity, specificity, and positive predictive value for the detection of non-calcified thin-cap fibroatheroma (88 %, 96 %, and 87 %, respectively) and calcified thin-cap fibroatheroma (95 %, 99 %, and 93 %, respectively). The lowest values were shown in pathological intimal thickening (74 %, 92 %, and 70 %, respectively). For all plaque types, VH-IVUS had a kappa-value of 0.79 [7].

With regard to detecting the necrotic core, Brugaletta et al. compared the accuracy of VH-IVUS vs. real histology in an ex vivo human model of coronary arteries [8]. Necrotic core areas assessed by VH-IVUS and histology were 0.24± 0.43 mm^2 and 0.16±0.43 mm^2, respectively ($p<0.001$). At the cross-section level, the correlation between the necrotic core area measured by VH-IVUS and histology was modest in absolute ($r=0.50$, $p<0.001$) and poor in relative values ($r=0.43$, $p=0.120$). At the segment level, this correlation improved in terms of absolute values ($r=0.80$, $p=0.01$). Although VH-IVUS has 94 % of sensitivity to detect histologic necrotic core, its specificity and positive predictive value were low (53 % and 48 %, respectively).

More recently, VH-IVUS using a high-frequency IVUS catheter was validated. The 45-MHz VH-IVUS (Revolution®, Volcano Therapeutics) showed an acceptable reproducibility (intra-class coefficients ranging from 0.82 to 1.00) in geometrical and compositional assessments in ex vivo human coronary arteries [9]. Particularly, fibrous-fatty area showed a higher relative difference (17.5 % in the inter-catheter assessment) compared to fibrous tissue (6.5 %), the necrotic core (8.4 %), and dense calcium (6.4 %) areas.

Pitfalls and Artifacts

As a major limitation of RF-based methods, they do not take into account acoustic shadowed areas. Because the presence of dense calcium induces an artifactual coding of necrotic core in adjacent structures, the amount of necrotic core can be overestimated. The radiofrequency-based technique provides no signal profile of metallic stent struts in the tissue signal profile databases. Metallic struts are colored by white like calcium. Moreover, the characterization of peri-stent plaque is limited by a red halo surrounding the white stent metal, which should not be interpreted as peri-strut inflammation or necrotic core. However, applying the tissue composition methods is useful to detect and to quantify as a surrogate the absorption of bioresorbable vascular scaffolds. VH-IVUS can provide more details for the performance of this new interventional technology.

Because the VH-IVUS axial resolution of 200-250 μm is insufficient to directly measure the thickness of the fibrous cap, there is a gap between histologic thin-cap fibroatheroma (TCFA) vs. VH-defined TCFA. VH-IVUS-derived TCFA has been defined as a necrotic core-rich >10 % plaque without evident overlying fibrous tissue and with a percent plaque volume of 40 % seen on at least three consecutive frames.

For the detection of tissue behind calcified areas, the radiofrequency signals are more likely to contain noise. The radiofrequency signals cannot penetrate thick layers of calcium and will reflect all acoustic energy back to the transducer. The signal processing software will incorrectly assign the pixels in the shadowed regions to any of four tissue components within their database based on the noise.

When VH-IVUS is used in a serial follow-up study, the electrocardiogram-gated method limits an accurate comparison between baseline and follow-up of plaque composition at the corresponding site. The poor longitudinal resolution with approximately 0.5 mm-inverval between the frames has also been a concern.

Clinical Trials Using VH-IVUS

VH-IVUS has provided qualitative and quantitative parameters that are used as endpoints in clinical trials. The PROSPECT trial evaluated the natural history of coronary atherosclerosis in 697 patients with acute coronary syndrome who underwent three-vessel coronary imaging including gray scale and radiofrequency VH-IVUS after successful percutaneous coronary intervention of culprit lesion. Both culprit and non-culprit lesions showed similar rates (12.9 % and 11.6 %, respectively) of major adverse cardiovascular events such as cardiac death, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina over 3 years. Independent predictors of a future cardiovascular event were the presence of VH-TCFA (hazard ratio, 3.35; 95 % CI, 1.77 to 6.36; $p<0.001$), a plaque burden ≥70 % (hazard ratio, 5.03; 95 % confidence interval [CI], 2.51 to 10.11; $p<0.001$) and a minimum lumen area ≤4.0 mm^2 (hazard ratio, 3.21; 95 % CI, 1.61 to 6.42; $p=0.001$) [10].

Similarly, the VIVA (VH-IVUS in Vulnerable Atherosclerosis) trial was a prospective analysis of 170 patients with stable angina or acute coronary syndrome who underwent three-vessel VH-IVUS before and after percutaneous coronary intervention of culprit lesion. At a median of 1.7 years, 19 lesions (13 non-culprit and six culprit lesions)

resulted in major adverse cardiac events (death, myocardial infarction, and unplanned revascularization). Non-culprit lesion factors associated with non-restenotic event were VH-TCFA and plaque burden >70 % TCFA. A plaque burden >70 % and minimum lumen area <4.0 mm^2 were linked with total clinical events, suggesting that VH-IVUS can identify plaques with a high risk of subsequent events [11].

The ATHEROREMO-IVUS study evaluating 581 patients with non-culprit coronary lesions also demonstrated that the presence of VH-derived TCFA lesions (present 10.8 % vs. absent 5.6 %; adjusted hazard ratio: 1.98; 95 % confidence interval: 1.09–3.60; p=0.026) and lesions with a plaque burden of ≥70 % (present 16.2 % vs. absent 5.5 %; adjusted hazard ratio: 2.90; 95 % confidence interval: 1.60–5.25; p=0.001) were found to be independently associated with a higher event rate. The TCFA lesions were also independently associated with the composite of death or acute coronary syndrome only (present 7.5 % vs. absent 3.0 %; adjusted hazard ratio: 2.51; 95 % confidence interval: 1.15–5.49; p=0.021) [12•].

In atherosclerotic plaques with thrombi, a VH-IVUS study showed a similarity of plaque composition (%necrotic core and VH-TCFA) irrespective of the presence or the absence of angioscopic plaque rupture, which suggested a spectrum of underlying morphologies causing thrombosis in the absence of a ruptured plaque, including classic erosions, small (and undetectable) plaque ruptures, and potentially unruptured TCFA with superimposed thrombosis [13].

VH-IVUS is also useful to assess serial changes in vulnerable plaque morphology. Kubo et al. evaluated 216 non-culprit lesions (plaque burden ≥40 %) in 99 patients to see the dynamic nature of coronary artery lesion morphology with serial (baseline and 12-month follow-up) VH-IVUS data. The VH-TCFA detected at baseline was healed in 75 % of cases (changed into thick-cap fibroatheroma in 65 % and fibrotic plaque in 10 %), and 25 % of VH-TCFAs remained unchanged. Twelve new VH-TCFAs developed. Furthermore, VH-TCFAs and thick-cap fibroatheromas showed significant plaque progression compared with fibrous and fibrocalcific plaques [14].

Distal Embolization

It has been hypothesized that plaque composition is a contributing factor in the occurrence of distal embolization after percutaneous coronary intervention. Previous studies have shown the usefulness of VH-IVUS for predicting the risk of embolization during stenting. Kawaguchi et al. evaluated 71 patients with ST elevation myocardial infarction who underwent primary PCI [15]. After a thrombectomy with an aspiration catheter, a VH-IVUS of the infarct-related vessel was performed. Eleven patients presented with ST segment re-elevation after stenting without embolic protection. The total plaque volume was similar, while necrotic core volume was significantly higher in the group of patients with vs. without ST segment re-elevation (32.9±14.1 mm^3 vs. 20.4±19.1 mm^3, p<0.05). The necrotic core volume best predicted post-stenting ST re-elevation with a cut-off of 33.4 mm^3 (with a sensitivity of 81.7 % and a specificity of 63.6 %). Ohshima et al. also reported that VH-TCFA, which contain a large amount of necrotic core, were more common in patients with distal embolization [16].

In a meta-analysis including 11 studies, a larger necrotic core or the presence of VH-TCFA was associated with distal embolization in all but two studies [17]. More recently a meta-analysis including 16 studies of 1697 patients using IVUS and VH-IVUS data showed that the plaque volume and the necrotic core are closely related to the occurrence of distal embolization [18]. Thus, identification of lesions with a large amount of necrotic core on VH-IVUS could identify lesions that might potentially benefit from the selective use of embolic protection devices.

Edge Vascular Responses

A remaining plaque burden and necrotic core tissue at the edges when the "normal to normal" landing of the device has not been achieved are considered to be predisposing factors of an abnormal edge vascular responses. However, little is known about the correlation between modifications in plaque composition at stent edges and changes in vessel geometry. A previous in vivo study was performed to investigate the temporal changes occurring at the edges of paclitaxel-eluting stents using VH-IVUS [19]. Serial expansive vascular remodeling was observed at the proximal and distal stent edges in response to tissue growth mainly due to increased fibro-fatty tissue assessed by VH-IVUS. When necrotic core-rich areas were left unstented (necrotic core 17.0±13.5 % at the 5-mm proximal edge and 18.5±16.5 % at the 5-mm distal edge), there was a marked reduction in the percentage of fibrotic tissue and necrotic core at the edges of both bare metal and drug-eluting stents, and a positive correlation was seen between the increasing percentage of the fibro-fatty component and increases in plaque area (r=0.78, p=0.01) [20]. More recently, the introduction of bioresorbable scaffolds for the treatment of coronary artery disease has prompted the re-evaluation of the edge vascular response, which has been assessed up to 2 years after implantation of the scaffolds [21].

Neointimal Characterization

Although VH-IVUS in the neointima has not yet been validated with histology, VH-IVUS findings suggesting in-stent

neoatherosclerosis have been reported. A previous study evaluated 70 drug-eluting stents and 47 bare metal stents with in-stent restenosis (intimal hyperplasia >50 % of the stent area by VH-IVUS) [22]. The region of interest was placed between the luminal border and the inner border of the struts, and tissue composition was represented as percentages of the intimal area. With the mean follow-up time of 43.5 months for bare metal stents lesions and 11.1 months for drug-eluting stents, in both groups, the necrotic core and dense calcium suggesting in-stent neoatherosclerosis were greater, especially in the lesions with longer implant duration. In lesions with in-stent restenosis, the agreement between VH-IVUS and optical coherence tomography for identifying TCFA-containing neointima was 78 % [23]. Another study showed that neointimal tissue characteristics appeared similar for both bare metal stents and drug-eluting stents [24]. At long-term follow-up beyond 3 years after implantation, the percent volumes of the necrotic core (16.1 % [9.7, 20.3] vs. 9.7 % [7.0, 16.5], p=0.062) and dense calcium (9.5 % [3.8, 13.6] vs. 2.7 % [0.4, 4.9], p=0.080) in the neointima tended to be greater in bare metal stents. However, in-stent VH-TCFA did not significantly differ between bare metal stents versus drug-eluting stents.

Effect of Statin on Plaque Stabilization

Although the precise mechanisms of coronary plaque regression and progression have not been well understood, human coronary atherosclerosis is a dynamic process with potential for the replacement of fibrous tissue by necrotic core. VH-IVUS has proven to be beneficial in assessing plaque compositional changes and the effect of medical treatment. Using VH-IVUS, Taquchi et al. reported the effects of statins on the progression and regression of coronary plaques in patients with acute coronary syndrome. In the plaque regression group, the necrotic core component showed a tendency to increase at 2-3 weeks (+12.5 %), but decreased at 8-10 months (-6.3 %). In the progression group, the fibrofatty and fibrous components increased at short-term (+37.5 %, +11.3 %) and at medium-term (+50.5 %, +13.2 %) time-points; however, the necrotic core decreased both at the short-term (-19.0 %) and medium-term (-23.8 %) evaluations [25]. The previous multicenter IBIS-2 trial showed that treatment with darapladib was associated with a decrease in the necrotic core, but was not associated with a decrease in the percentage atheroma volume. Prolonged pharmacological inhibition stabilized plaque vulnerability by reducing the necrotic core compared to the placebo group, indicating a direct effect on human atheroma [26].

Regarding the course of coronary plaque regression by statin therapy, Nozue et al. showed that plaques began to reduce the volume of fibro-fatty and fibrous components in the early phase, associated with a transiently increased necrotic core component assessed by VH-IVUS. Furthermore, even in the case of plaque progression, statins caused a reduction in the necrotic core. However, statin therapy did not halt the incidence in plaque vulnerability [27].

VH-IVUS may also be useful in the assessment of complex lesions. A comparison of the distribution of necrotic core in coronary bifurcations showed that bifurcation lesions appear to have a larger plaque burden with a more vulnerable plaque composition compared to non-bifurcation lesions [28].

Conclusions

In both clinical and research aspects, VH-IVUS is a validated imaging modality to improve our understanding of coronary atherosclerotic disease and its natural history. Despite its pitfalls and methodological limitations, VH-IVUS is useful to identify the high-risk coronary lesions for future cardiovascular events and to assess the effect of local or systemic treatment.

Compliance with Ethics Guidelines

Conflict of Interest Soo-Jin Kang declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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