Development of Integrated Backscatter Intravascular Ultrasound for Tissue Characterization of Peripheral Artery and Comparison with Angioscopy

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Background: The purpose of the present study was to determine the differences in integrated backscatter (IB) values between a new IB intravascular ultrasound (IB-IVUS) mode for peripheral artery and the previous mode for coronary arteries for the tissue characterization of plaques.

Methods: A cross-validation study was performed with the 40 patients divided into a training study to determine the difference in IB value and the most appropriate correction for ultrasound signal attenuation between the mode for coronary and peripheral arteries (n = 20) and a testing study to validate the similarity of the images (n = 20). Comparison between the findings of IB-IVUS and angioscopy was performed in 10 patients.

Results: In the training study, 57 cross sections were subjected to the comparison. The IB value of +4.5 dB was the most appropriate setting compared with the mode for coronary arteries. The slope of regression lines were 1.00 in the measurement of lipid area and 1.00 in the measurement of fibrous area. The most appropriate correlation for ultrasound signal attenuation was +3.0 dB/mm. In the testing study, the slopes of regression lines in the measurement of lipid and fibrous areas were excellent in 20 cross sections (1.00 and 1.02, respectively) based on the settings that were determined in the training study. In the comparison with angioscopy, thickness of fibrous cap was associated with the color of plaques in peripheral arteries.

Conclusions: The IB-IVUS system with the new mode for peripheral arteries provides high diagnostic accuracy for the analysis of tissue characteristics of plaques.

Key words: integrated backscatter, intravascular ultrasound, angioscopy, peripheral artery

Introduction

Endovascular therapy for peripheral artery disease has been widely performed as a minimally invasive therapy compared with surgical treatment. In addition, outcomes of endovascular therapy for peripheral artery disease have been improved due to the recognition for the treatment such as techniques and devices.1) One of the remaining issues for the improvement of outcomes after endovascular therapy for peripheral artery disease is tissue characterization of plaques. Reports that elucidate the relationships between the tissue characteristics and outcomes after endovascular therapy is scarce, whereas several reports suggested that tissue characterization of coronary plaques provide a superior means of predicting outcomes after percutaneous coronary intervention (PCI) as compared with the degree of coronary artery stenosis.2–4)

We developed integrated backscatter intravascular ultrasound...
(IB–IVUS) that allowed characterization of the tissue components of coronary arterial plaques in the clinical setting.\textsuperscript{5-10} We recently improved the lateral resolution of IB–IVUS images by increasing vector lines of the radio frequency signal and the digital sampling rate.\textsuperscript{11} However, the frequency of ultrasound (38 MHz and 43 MHz) has a limited penetration depth (5 mm) for the peripheral arteries that have relatively large diameter (5–10 mm) comparing with coronary arteries (2–5 mm). Thus, we developed a novel IVUS mode that receives 25 MHz ultrasound signals with relatively deep penetration depth (8 mm) using a previous IB–IVUS system. However, validation of this new mode to characterize arterial plaques has not been evaluated.

The purposes of the present study were to determine the differences in IB values between a new IB–IVUS mode for peripheral artery and the previous mode for coronary arteries for the tissue characterization of plaques, and to compare the IB–IVUS findings with angioscopic findings.

Methods

Study protocol

This was a multi-center study consisting of 40 patients with stable angina pectoris who were undergoing PCI and 10 patients with arteriosclerosis obliterans (ASO) who were undergoing percutaneous transluminal angioplasty (PTA). IB–IVUS was performed in each patient in non-targeted plaques (plaque burden at the minimal lumen area \(>40\%\) but \(\leq 80\%\)). Then, IB–IVUS images were compared between a mode for coronary artery (E–mode and F–mode) and a mode for peripheral artery (C–mode), and lipid area, fibrous area and calcified area were compared in the two modes. A cross-validation study was performed with the patients divided into a training study to determine the difference in IB value and the most appropriate correlation for ultrasound signal attenuation between the modes for the coronary and peripheral arteries, and a testing study to validate the similarity of the images.

Risk factors for coronary artery disease were evaluated in enrolled patients, including type 2 diabetes mellitus (medication-dependent or hemoglobin (Hb) A1c \(\geq 6.5\%\)), hypertension (medication-dependent or systolic BP \(\geq 140\) mmHg and/or diastolic BP \(\geq 90\) mmHg), dyslipidemia (medication-dependent, LDL cholesterol \(\geq 140\) mg/dl and/or HDL cholesterol < 40 mg/dl) and current smoking. The protocol was approved by the institutional ethics committees, and informed consent was obtained from each patient.

Integrated backscatter intravascular ultrasound system and data acquisition

An IVUS imaging system (VISIWave, Terumo, Tokyo, Japan) was used to obtain cross-sectional IB–IVUS images. Ultrasound backscattered signals were acquired using a mechanically-rotating IVUS catheter (ViewIT, Terumo, Tokyo, Japan) that receives 25 MHz ultrasound signals with low band pass filter (\(\geq 22\) MHz) (C–mode), 38 MHz ultrasound signals (E–mode) and 43 MHz ultrasound signals (F–mode). The details of the system and its clinical usefulness have been reported previously.\textsuperscript{7, 10-12} Before the measurements, we administered an optimal dose of intracoronary isosorbide dinitrate for the prevention of coronary spasm. We analyzed one cross-section in each lesion. Conventional IVUS images and IB–IVUS color-coded maps were displayed side-by-side on a monitor immediately. Color-coded maps of the entire coronary arteries were finally constructed after excluding the vessel lumen and area outside the external elastic membrane by manually tracing the vessel lumen and external elastic membrane on the conventional IVUS images. Color-coded maps consist of four major components (fibrous [green], dense fibrosis [yellow], lipid pool [blue or purple], calcification [red]). Fibrous area was defined as the area with fibrous (green) and dense fibrous (yellow) in the present study. Plaques with an arc of calcification \(>60\degree\) were excluded because acoustic shadow due to calcification affected rigorous measurement of plaque.

Comparison of ultrasound mode for peripheral arteries with ultrasound mode for the coronary arteries

In the training study, each IB–IVUS image of coronary arteries acquired with the new ultrasound mode for peripheral arteries was compared with current ultrasound mode for coronary arteries at the same cross-sections, and IB values were adjusted to make the two images show the same lipid and fibrous areas (Fig. 1). The two IB–IVUS images were obtained by changing the mode without moving a catheter position.

In the testing study, the lipid, fibrous and calcification area were compared between the new mode (C–mode) and the current mode (E–mode and F–mode) for coronary arteries using the settings of IB values and appropriate correlation for ultrasound signal attenuation.

Comparison with angioscopic findings

In the comparison study, IB–IVUS (C–mode) and angioscopy were performed in the 30 lesions in 10 patients with ASO who were undergoing PTA. We defined ASO using the definition (ankle-brachial index < 0.90) in Trans–Atlantic Inter–Society Consensus (TASC) II.\textsuperscript{13} We also classified types of lesions using TASC II classification, and classified symptoms using Fontaine classification. Catheterization was performed via the femo-
IB value: +4.5 dB, Attenuation correction: +3.0 dB/mm (Training study)

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IB value: +4.0 dB, Attenuation correction: +3.0 dB/mm (Training study)

IB value: +4.5 dB, Attenuation correction: +2.5 dB/mm (Training study)

IB value: +4.5 dB, Attenuation correction: +3.5 dB/mm (Training study)

Fig. 1. Relationship of each tissue component between the previous mode and C-mode for peripheral arteries in the training study
An overall correlation of +4.5 dB for ultrasound signal and for the ultrasound attenuation of +3.0 dB/mm was determined to be the most appropriate, and this value was used to compare the each tissue area in the testing study. IB value: integrated backscatter value
ral artery using a 6-F sheath with an administration of heparin (5,000 IU). After an IVUS examination, a fiber catheter (VISILE, InterTec Co. Ltd., Osaka, Japan) and non-obstructive fiber imaging system (FT-203F, InterTec Co. Ltd., Osaka, Japan) were used for angioscopy. Prior to observation, the white balance was adjusted for color correction. A 4-F over-the-wire catheter (Medikit Co., Ltd. Tokyo, Japan) was inserted into the peripheral artery over the guide wire to the imaging position. After removing the guide wire, a fiber catheter was advanced through the over-the-wire catheter to the tip. Angioscopic observations were performed while blood was cleared from the view by the manual injection of 3% dextran-40 (1-2 mL/s). The lesions of peripheral artery that were objects of PTA were continuously studied, and angioscopic images and fluoroscopy were recorded simultaneously on hard-disk drive for the off-line analysis in order to identify the exact position of angioscopic catheter. Angioscopic findings were defined according to previous reports of coronary angioscopy.\(^{14}\) The color of plaques was investigated by visual inspection and the yellow grade of the plaque was classified semi-quantitatively based on the surface color as 0: white; 1: light yellow; 2: medium yellow; or 3: dark yellow. To clarify the rotational and cross-sectional position of the included segment, we checked and recorded the position of the IVUS transducer and the tip of a fiber catheter through a fluoroscope to use as reference points to compare the two imaging modalities. The Cohen’s \(\kappa\) values for the intraobserver and interobserver agreement of yellow grade were 0.90 and 0.85. When there was discordance between the observers, a consensus grade was obtained by two observers.

In order to measure the thickness of fibrous cap, IB-IVUS images were processed by a smoothing method averaging nine IB values in nine pixels located in a square field of the color-coded maps to reduce uneven surfaces of fibrous cap produced by the signal noise as reported previously.\(^{11}\)

**Statistical analyses**

Data are reported as the mean ± standard deviation. Relative areas of each tissue component between the new mode and the previous mode were compared with linear regression analysis. Thickness of fibrous caps among four groups was compared with one way analysis of variance followed by Scheffe's method for post hoc comparisons. A \(p\) value < 0.05 was considered statistically significant. Statistical analyses were performed using Stat View version 5.0 (SAS Institute Inc, Cray, NC, USA).

**Results**

**Patients’ characteristics and echocardiographic variables**

The patients’ clinical characteristics and IVUS variables in the training, testing and comparison studies are shown in Table 1. The plaque burden of the analyzed plaques was around 60% both in the three studies.

**Comparison of ultrasound mode for the peripheral arteries with ultrasound mode for the coronary arteries**

There was no cross section that was excluded from the analysis due to inadequate imaging quality because we carefully selected the subjected cross sections during the IVUS imaging. As shown in Fig. 1, in the training study, 57 cross sections in 20 patients were subjected to the comparison. The IB value of +4.5 dB was the most appropriate setting comparing with the mode for coronary arteries. The slope of regression lines were 1.00 in the measurement of lipid area and 1.00 in the measurement of fibrous area. We compared images between the new mode for peripheral arteries and the mode for coronary arteries using the setting of IB values of +4.0 dB and +5.0 dB. However, the slopes of regression lines were not closer to 1.00 compared with the setting of IB value of +4.5 dB.

Likewise, the most appropriate correlation for ultrasound signal attenuation was +3.0 dB/mm. We compared images between the new mode for peripheral arteries and the mode for coronary arteries using the correlation for ultrasound signal attenuation of +2.5 dB/mm and +3.5 dB/mm. However, the slopes of regression lines were not closer to 1.00 compared with the correlation for ultrasound signal attenuation of +3.0 dB/mm. Representative images of the two modes were shown in Fig. 2.

In the testing study, 20 cross sections in 20 patients were subjected to the validation for the differences between the two modes based on the settings that were determined in the training study. As shown in Fig. 3, the slopes of regression lines in the measurement of lipid and fibrous areas were excellent (1.00 and 1.02, respectively). However, calcification area was underestimated by the mode for peripheral arteries compared with the mode for coronary arteries (\(y = 0.63 x, r = 0.941, p < 0.001\)).

**Comparison with angioscopic findings**

The thickness of fibrous cap in white plaques (n = 15), light yellow plaques (n = 4), medium yellow plaques (n = 4) and dark yellow plaques excluding calcification (n = 4) were 396 ± 158, 117 ± 17, 80 ± 8 and 77 ± 10 \(\mu\)m, respectively. Although there were significant differences between the thickness of white and
Fig. 2. Representative images of conventional intravascular images and color-coded maps of integrated backscatter intravascular ultrasound.

(Upper) Images that were constructed by previous mode for coronary plaques (Lower) Images that were constructed by C-mode (new mode) for peripheral plaques. Images that were constructed by previous mode for coronary arteries and C-mode for peripheral arteries were almost same, whereas C-mode underestimated calcification area comparing with the previous mode.

Table 1. Patient characteristics

|                         | Training study (n = 20) | Testing study (n = 20) | Comparison study (n = 10) |
|-------------------------|-------------------------|------------------------|---------------------------|
| Men, n (%)              | 15 (75)                 | 18 (90)                | 8 (80)                    |
| Age, y                  | 66 ± 11                 | 73 ± 8                 | 74 ± 9                    |
| Systolic blood pressure, mmHg | 136 ± 18                | 141 ± 15               | 139 ± 23                  |
| Diastolic blood pressure, mmHg | 73 ± 15                 | 66 ± 9                 | 81 ± 14                   |
| Ankle brachial index    | NA                      | NA                     | 0.67 ± 0.13               |
| Fontaine classification | NA                      | NA                     | I 1 (10)                  |
| TASC II classification  | NA                      | NA                     | II 8 (80)                 |
|                         | NA                      | NA                     | III 1 (10)                |
|                         | NA                      | NA                     | B 4 (40)                  |
|                         | NA                      | NA                     | C 5 (50)                  |
|                         | NA                      | NA                     | D 1 (10)                  |
| Clinical history, n (%) |                         |                        |                           |
| Prior myocardial infarction | 6 (30)                  | 9 (45)                 | 2 (20)                    |
| Hypertension           | 16 (80)                 | 13 (65)                | 8 (80)                    |
| Dyslipidemia           | 13 (65)                 | 10 (50)                | 6 (60)                    |
| Current smoker     | 5 (25)                  | 3 (15)                 | 8 (80)                    |
| Diabetes mellitus type 2 | 8 (40)                  | 8 (40)                 | 1 (10)                    |
| Medications, n (%)      |                         |                        |                           |
| Antiplatelet medication | 20 (100)                | 20 (100)               | 10 (100)                  |
| Statin                 | 15 (75)                 | 11 (55)                | 4 (40)                    |
| Calcium channel blockers | 11 (55)                 | 9 (45)                 | 5 (50)                    |
| Beta-blockers          | 8 (40)                  | 5 (25)                 | 1 (10)                    |
| Insulin                | 0 (0)                   | 2 (10)                 | 0 (0)                     |
| ACE inhibitors or ARB  | 8 (40)                  | 9 (45)                 | 4 (40)                    |
| Laboratory parameters  |                         |                        |                           |
| Total cholesterol, mg/dl | 176 ± 28                | 161 ± 30               | 180 ± 43                  |
| Triglycerides, mg/dl   | 139 ± 67                | 137 ± 66               | 123 ± 57                  |
| HDL cholesterol, mg/dl | 50 ± 10                 | 45 ± 11                | 50 ± 10                   |
| LDL cholesterol, mg/dl | 98 ± 26                 | 88 ± 29                | 106 ± 38                  |
| C-reacting protein, mg/dl | 0.44 ± 0.64             | 0.39 ± 0.58            | 0.41 ± 0.69               |
| Hemoglobin A1c, %       | 5.7 ± 0.8               | 6.4 ± 0.9              | 5.9 ± 0.6                 |

Values are mean ± SD. Numbers in parenthesis are percentage. TASC: Trans-Atlantic Inter-Society Consensus, ACE: Angiotensin converting enzyme, ARB: Angiotensin II receptor blockers, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, NA: not applicable.
Fig. 3. Relationship of each tissue component between the previous mode and C-mode for peripheral arteries in the testing study
(Upper) Linear regression analyses (Lower) Bland-Altman plots

Fig. 4. Representative images of the comparison between IVUS images and angioscopic images
Arrow in the IB-IVUS images: lesions by angioscopy *: shadow of guide wire
(A) Dark yellow plaque LCAL: lipid core abutting lumen (B) White plaque (C) Dark yellow plaque that indicated calcification. Note that lesion with calcification and lesion with thin fibrous cap also showed yellow color by angioscopy. IB-IVUS: integrated backscatter intravascular ultrasound
light yellow plaques ($p = 0.006$), white and medium yellow plaque ($p = 0.018$), and white and dark yellow plaques ($p = 0.016$), there were no significant differences among the thickness fibrous cap of light, medium or dark yellow plaques (Figs. 4, 5). Intriguingly, superficial calcification that was detected by IVUS also showed dark yellow (Figs. 4, 5).

Discussion

In the present study, we determined the differences in IB values between the new IB–IVUS mode for peripheral arteries and the previous mode for coronary arteries, and developed the new mode (C-mode) for the tissue characterization of peripheral arterial plaques. The new mode based on the settings that were determined in the present study showed excellent similarity with the previous system for the tissue characterization of plaques.

Tissue characterization for peripheral arteries

A previous study demonstrated that the tissue components of coronary plaques could be characterized using IVUS with an autoregressive classification scheme (Virtual Histology IVUS: VH–IVUS) rather than depending on the classic Fourier method.\textsuperscript{15} iMap is also one of the IVUS techniques for tissue characterization of coronary plaques. The iMap algorithm is based on a neural network theory especially for pattern recognition called the k-nearest neighbor method.\textsuperscript{16} However, these methods were not validated for the tissue characterization of peripheral plaques. We previously developed IB–IVUS that allowed characterization of the tissue components of coronary plaques. In the present study, we developed IB–IVUS for the tissue characterization of peripheral plaques by comparing the new mode with the images for coronary plaques (E-mode or F-mode) as a gold standard. The previous IB–IVUS system that received 38 MHz or 43 MHz ultrasound signals was developed for coronary plaques has a limitation of penetration depth (5 mm) for the peripheral arteries. The new mode that received 25 MHz ultrasound signals with low band pass filter ($\geq 22$ MHz) has a relatively deep penetration depth (8 mm), and can be used for peripheral arteries with large diameters.

Diagnostic accuracies for the measurements of each tissue area

In the testing study, the slopes of regression lines between the new mode and the previous mode in the measurement of lipid area and fibrous area were excellent ($y = 1.00x$ and $y = 1.02x$, respectively) using the overall correlation of $+4.5$ dB and the attenuation correlation of $+3.0$ dB/mm. Bland–Altman plots showed narrow limits of agreement ($-0.014 \pm 0.706$ mm$^2$ for lipid area and $-0.049 \pm 0.552$ mm$^2$ for fibrous area, respectively). However, the calcification area was underestimated by the new mode for peripheral arteries comparing with that measured by the mode for coronary arteries ($y = 0.63x$) because we focused on the establishment of accuracies of lipid area and fibrous area in the present study for the reason that it was essentially inappropriate to evaluate calcification area using ultrasound techniques.

In the coronary arteries, several previous studies have reported that plaque tissue components which were evaluated by IB–IVUS and thickness of fibrous cap that was measured by optical
coherence tomography were associated with outcomes after stent implantation.\(^6\) In the peripheral arteries, few studies described the association between plaque components and outcomes after PTA in ASO patients, whereas morphological parameters (such as post-procedure minimum stent area) were a predictor of intrastent restenosis in superficial femoral arteries.\(^18\) Recently, Maezawa et al. reported that the necrotic core that was evaluated by VH-IVUS developed more frequently in the debris group than in the small debris group in the iliac and femoral arteries.\(^19\) They concluded that distal protection during PTA would be considered when the lesion is an ulcerative and contained necrotic core that was determined by VH-IVUS. However, regarding the relationships between tissue components of the peripheral arteries and outcomes of PTA, further studies are needed.

Comparison with angioscopic findings

Ozaki et al. reported that the axial resolution of IB-IVUS system (VISIWISE, Terumo, Tokyo, Japan) was 69 ± 6 μm, and lipid core abutting lumen (LCAL) suggested a fibrous cap thickness of 75 μm.\(^20\) The thickness of fibrous cap that was measured by IB-IVUS had a strong correlation with what was measured by optical coherence tomography \((r = 0.91, p < 0.001)\) and the limit of agreement evaluated by a Bland–Altman plot was 4.4 ± 98.7 μm.\(^20\) There were several reports that demonstrated that plaque color of coronary arteries were associated with the thickness of fibrous cap in the comparison between angioscopy and IB-IVUS,\(^6\) and the comparison between angioscopy and OCT.\(^21\) We also demonstrated in the present study that plaque color of peripheral arteries were also associated with the thickness of fibrous cap. However, there was no significant difference among the thickness of fibrous cap of light, medium or dark yellow plaques. This may due to the limitations of small number of the lesions. In addition, instability of the lesions was associated with the grade of yellow color in the coronary arteries.\(^21\) However, clinical relevance between the instability of the lesions and the grade of yellow color in the coronary arteries has not been established yet in the peripheral arteries. Actually, the significance of “vulnerable plaque” may differ between coronary arteries and aorta.\(^22\) Studies that include a large number of lesions would be required to prove the clinical value of tissue characterization of peripheral arteries for the prediction of therapeutic outcomes of PTA.

Study limitations

There were a few limitations of the present method. First, the angle dependence of the ultrasound signal makes tissue characterization unstable when lesions are not perpendicular to the axis. A previous report demonstrated the degree of angle dependence of 30 MHz ultrasound.\(^23\) In that report, the angle dependence of 30 MHz ultrasound in the arterial intima and media was 1.11 dB/10°. This angle dependence of the ultrasound signal may decrease the diagnostic accuracy for differentiating tissue components.

Second, the pulsation of the coronary arteries hindered the rigorous comparison of new mode and previous mode. The shape and location of each tissue component was slightly different in the new mode and the previous mode, even in the same cross-sections, because it was difficult to obtain the two images during the same cardiac cycle.

Third, calcification is a perfect reflector for ultrasound, causing the acoustic shadowing so typical in the IVUS images. The ultrasound signals cannot penetrate, or pass through the calcified layer and are reflected back towards the transducer.\(^24\) Therefore, an accurate tissue characterization of the areas behind calcification was not possible as well as with conventional IVUS. This may also decrease the diagnostic accuracy for differentiating tissue components. In the treatment of ASO lesions, existence and severity of calcification are significant factors that influence the outcomes after PTA. This limitation typically affects the ability of prediction for outcomes after PTA. In the present study, we excluded plaques with an arc of calcification > 60° because of acoustic shadow due to calcification affected a rigorous measurement of plaque. However, calcification in the peripheral lesions is common in clinical settings. Prevalence of calcification in the peripheral arteries hinders the evaluation by IVUS for the prediction of outcomes after PTA.

Finally, comparison of tissue characterization was not directly performed with pathological specimen, whereas the new mode showed the excellent similarity with the previous system. Direct comparison with pathological specimen of peripheral plaques is required for detailed validation.

Conclusions

We developed an IB-IVUS imaging system for tissue characterization of peripheral plaques. The use of the correlation of IB values for discriminating lipid pool, fibrosis and calcification resulted in tissue characterization of large arteries. The IB-IVUS system with a new mode for peripheral arteries provides the same diagnostic accuracy for the analysis of tissue characteristics of plaques as the IB-IVUS for coronary arteries.

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Disclosure

We have no financial or other relations that could lead to conflict of interest.

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