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ORIGINAL PAPER

Reproducibility of Shin's method for necrotic core and calcium content in atherosclerotic coronary lesions treated with bioresorbable everolimus-eluting vascular scaffolds using volumetric intravascular ultrasound radiofrequency-based analysis

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Abstract Although Virtual Histology intravascular ultrasound (VH-IVUS) is increasingly used in clinical research, the reproducibility of plaque composition remains unexplored in significant coronary artery and stented lesions. The purpose of this study was to assess the reproducibility of necrotic core and calcium content in atherosclerotic coronary lesions that were treated with a bioresorbable everolimus-eluting vascular scaffold (BVS) using a new measurement method (Shin's method) by VH-IVUS. Eight patients treated with a BVS (Abbott Vascular, Santa Clara, CA, USA) were analyzed with serial VH-IVUS assessments, i.e., pre- and post-stenting, and at 6 months and 2 years follow-up. A total of 32 coronary segments were imaged to evaluate the reproducibility of volumetric VH-IVUS measurements. In Shin's method, contours are drawn around the IVUS catheter (instead of the lumen) and vessel. Overall, in the imaged coronary segment, for necrotic core and dense calcium volumes, the relative intra-observer differences were 0.30 ± 0.22, 0.19 ± 0.16% for observer 1 and 0.45 ± 0.41, 0.36 ± 0.47% for observer 2, respectively. The inter-observer relative differences of necrotic core and dense calcium volumes were 0.51 ± 0.79 and 0.56 ± 1.01%, respectively. The present study demonstrates a good reproducibility for both, intra-observer and inter-observer measurements using Shin's method. This method is suitable for the measurement of necrotic core and dense calcium using VH-IVUS in longitudinal studies, especially studies on bioresorbable scaffolds, because the degradation process will be fully captured independently of the location of the struts and their greyscale appearance.

Keywords Intravascular ultrasound virtual histology · Reproducibility · Bioabsorbable stent

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Introduction

Necrotic core volume is a key determinant of plaque vulnerability [1]. Virtual Histology intravascular ultrasound (VH-IVUS), which permits the analysis of coronary plaque composition in vivo with a high predictive accuracy, is increasingly used in clinical research [2–10]. While previous VH-IVUS showed acceptable reproducibility in mild to moderate atherosclerotic coronary artery disease, reproducibility of compositional measurements was lower than that of geometrical IVUS measurements [11, 12]. We introduced Shin's method in a previous study; the method entails drawing the catheter contour instead of the lumen contour and it is therefore suitable to measure necrotic core and dense calcium content with good reproducibility in non-stented lesions [13]. However, there is no data about reproducibility of necrotic core and calcium in stented lesion especially treated with bioresorbable everolimus-eluting vascular scaffold (BVS) using VH-IVUS.

The purpose of this study was therefore to assess the reproducibility of necrotic core and calcium content in atherosclerotic coronary lesions that were treated with a BVS using a new measurement method (Shin's method) by VH-IVUS.

Methods

Study patients

Images were obtained from 8 out of the 30 patients participating in the ABSORB Cohort A trial who were treated with a BVS (Abbott Vascular, Santa Clara, CA, USA) [14]. These patients were chosen because they had truly serial IVUS imaging, that is IVUS pre- and post- stenting, at 6 months and 2 years follow-up (Fig. 1). The study protocol was approved by the institutional ethics committee, and a written informed consent was obtained from all patients.

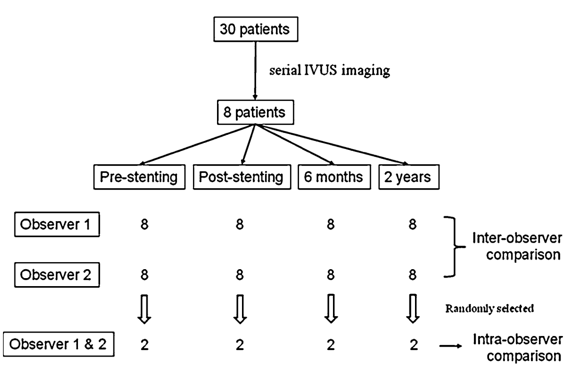

Fig. 1 Study profile

VH-IVUS

IVUS data were acquired with commercially available phased-array IVUS catheters (Eagle Eye Gold 2.9-F 20 MHz, Volcano Corporation, Rancho Cordova, USA) by a dedicated VH-IVUS console (Volcano Therapeutics, Rancho Cordova, USA). Spectral analysis of VH-IVUS data were used to create tissue maps to classify atherosclerotic plaques into four major components (fibrous: green; fibro-fatty: light-green; dense calcium: white; and necrotic core: red). Image acquisition was ECG-gated. After intracoronary injection of 200 µg nitroglycerine, continuous pullback of the IVUS catheter was performed using a motorized pullback device at 0.5 mm/s. Data of both pullbacks were stored on a hard disk for off-line analysis. VH-IVUS analysis was performed by two experienced IVUS analysts (E.S.S., G.S.) in an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) using pcVH 2.2 offline software analysis.

Shin's method of analysis

In Shin's method, instead of measuring the lumen as described previously for the conventional method for VH-IVUS analysis, the lumen contour is drawn around the IVUS catheter, that is, without following the leading edge of the interface lumen intima. According to Shin's method, when there is a "flare" (ring-down artefact) around the IVUS catheter, this catheter contour must be drawn away from this flare. The catheter contour was manually detected. To avoid coverage of scaffold struts by the superimposed medial stripe in VH-IVUS frames, the vessel contour was purposefully drawn slightly outwards from the struts but without including the adventitia. To compare only the reproducibility of Shin's method, in terms of necrotic core and dense calcium content, the same contour of the vessel and same segments were used. In addition, to compare intra-observer reproducibility of both; Shin's method and the vessel contour, one observer analyzed the same segments twice (time interval was 1 month).

Using Shin's method the following information was obtained:

1. necrotic core and dense calcium areas and volumes.
2. vessel area and volume.

Data analysis

We report the intra-observer and inter-observer variability, pooling all phases. For the intra-observer variability of the Shin's method, 2 patients from each phase were randomly selected. Also, we report the intra-observer reproducibility for the vessel contour measurement.

Statistical analysis

Analyses were performed with SPSS 16.0 (SPSS Inc., Chicago, Illinois). Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± 1SD. Inter- and intra- observer agreements were assessed using Bland–Altman plots, the agreement between two measurements were assessed by determining the mean ±2SD of the between measurement differences. [15] For the Bland–Altman analysis, both the absolute and relative difference (absolute difference divided by the mean value of both measurements) of the measurements were analyzed. A two-sided *P* value of less than 0.05 indicated statistical significance.

Results

Study patients

Table 1 shows the patients' characteristics. The mean age was 60 years, and 6 out of the 8 participants were men. The study vessels were the left anterior descending artery in 2, the left circumflex artery in 4 and the right coronary artery in 2 of the cases. The segment lesion length was 22.2 ± 4.7 mm with a volumetric plaque burden of 53.3 ± 7.3%. There were no complications related to IVUS imaging.

Intra-observer agreement of Shin's method (using same vessel contour)

Within observers, the correlations of necrotic core and dense calcium volumes (first time vs. second time) were r = 1, and r = 1; all $P < 0.001$. The intra-observer relative differences in necrotic core and dense calcium volumes were 0.30 ± 0.22, 0.19 ± 0.16% for observer 1 and 0.45 ± 0.41, 0.36 ± 0.47% for observer 2, respectively (Table 2). Bland–Altman plots showed that the limits of agreement for necrotic core and dense calcium volumes were −0.007 to 0.009 and −0.005 to 0.007 mm^3, respectively (Fig. 2).

Table 1 Study population

	N = 8
Age, years	60 ± 8
Male	6 (75.0)
Diabetes	1 (12.5)
Hypertension	4 (50.0)
Current smoker	2 (25.0)
Hypercholesterolemia	5 (71.4)
Study vessel	
LAD	2 (25.0)
LCX	4 (50.0)
RCA	2 (25.0)
Segment length (mm)	22.2 ± 4.7
Plaque burden (%)	53.3 ± 7.3

Values are presented as number (%) or mean ± SD. *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

Inter-observer agreement of Shin's method (using same vessel contour)

Between observers, the correlations of necrotic core and dense calcium volumes were r = 1, and r = 1; all $P < 0.001$. The inter-observer relative differences in necrotic core and dense calcium volumes were 0.51 ± 0.79 and 0.56 ± 1.01%, respectively (Table 3). Bland–Altman plots showed that the limits of agreement for necrotic core and dense calcium volumes were −0.44 to 0.38 and −0.15 to 0.19 mm^3, respectively (Fig. 3).

Intra-observer agreement for both Shin's method and vessel contour

The intra-observer relative differences in necrotic core and dense calcium volumes were 1.14 ± 1.13, 0.79 ± 1.08%, respectively (Table 4). In the Bland–Altman plots, the limits of agreement for vessel

Table 2 Shin's method using same vessel contour: intra-observer measurements for mean area and volume of necrotic core and dense calcium

	First time	Second time	Absolute △	Relative △ (%)
Observer 1				
NC area, mm^2	1.12 ± 0.61	1.12 ± 0.62	0.003 ± 0.002	0.28 ± 0.20
DC area, mm^2	0.57 ± 0.35	0.57 ± 0.35	0.001 ± 0.001	0.19 ± 0.18
NC volume, mm^3	24.28 ± 15.43	24.31 ± 15.49	0.07 ± 0.06	0.30 ± 0.22
DC volume, mm^3	11.79 ± 7.22	11.80 ± 7.21	0.02 ± 0.02	0.19 ± 0.16
Observer 2				
NC area, mm^2	1.30 ± 0.73	1.29 ± 0.74	0.004 ± 0.003	0.45 ± 0.41
DC area, mm^2	0.71 ± 0.39	0.71 ± 0.39	0.003 ± 0.003	0.36 ± 0.46
NC volume, mm^3	27.43 ± 16.36	27.36 ± 16.40	0.09 ± 0.07	0.45 ± 0.41
DC volume, mm^3	14.80 ± 7.05	14.77 ± 7.06	0.05 ± 0.05	0.36 ± 0.47

Values are presented as mean ± SD. *NC* necrotic core, *DC* dense calcium, △ difference

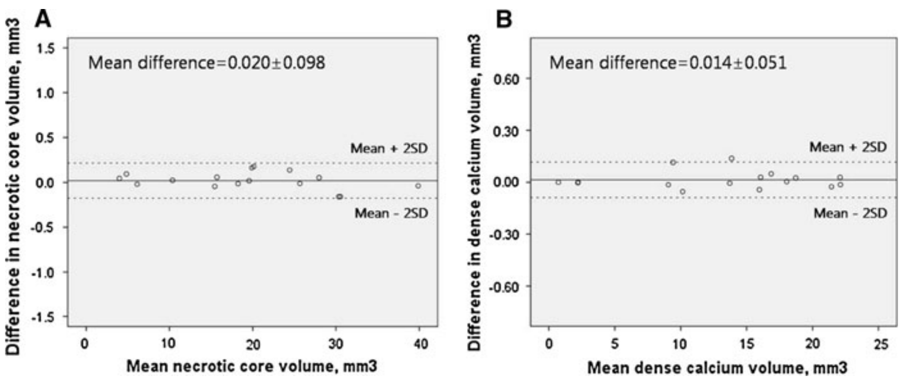

Fig. 2 Shin's method using same vessel contour: intra-observer measurements for necrotic core (**a**) and dense calcium volumes (**b**)

Table 3 Shin's method using same vessel contour: inter-observer measurement differences for mean area and volume of necrotic core and dense calcium

	Observer 1	Observer 2	Absolute △	Relative △ (%)
Total				
NC, mm^2	1.13 ± 0.70	1.13 ± 0.70	0.005 ± 0.009	0.50 ± 0.80
DC, mm^2	0.58 ± 0.34	0.58 ± 0.34	0.003 ± 0.004	0.57 ± 1.01
NC, mm^3	25.2 ± 17.5	25.2 ± 17.5	0.11 ± 0.17	0.51 ± 0.79
DC, mm^3	12.8 ± 7.9	12.7 ± 7.9	0.05 ± 0.07	0.56 ± 1.01
Pre-stenting				
NC, mm^3	12.2 ± 8.3	12.1 ± 8.3	0.02 ± 0.04	0.35 ± 0.65
DC, mm^3	6.2 ± 5.3	6.2 ± 5.2	0.02 ± 0.03	0.94 ± 1.75
Pooled data from post-stenting, 6 months and 2 years				
NC, mm^3	29.5 ± 17.7	29.6 ± 17.7	0.14 ± 0.19	0.56 ± 0.84
DC, mm^3	14.9 ± 7.5	14.9 ± 7.4	0.06 ± 0.08	0.43 ± 0.61

Values are presented as mean ± SD. *NC* necrotic core, *DC* dense calcium, △ difference

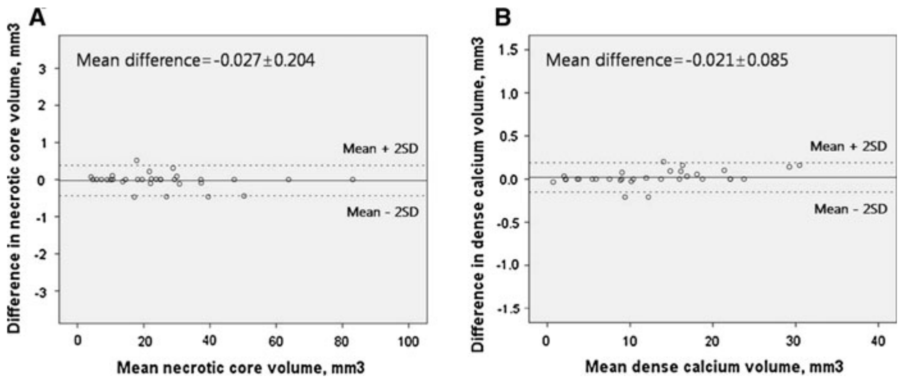

Fig. 3 Shin's method using same vessel contour: inter-observer measurement differences for necrotic core (**a**) and dense calcium volumes (**b**)

volume, necrotic core and dense calcium volumes were −0.23 to 1.42, −0.0 to 0.29 and −0.04 to 0.13 mm^3, respectively (Fig. 4).

Discussion

This report is the first to show the reproducibility of a new measurement method (Shin's method) for necrotic core and dense calcium using volumetric VH-IVUS analysis in stent studies. The main findings of this study are: (1) Overall, necrotic core and dense calcium volume determined by Shin's method showed good reproducibility in intra- and inter-observer comparisons; (2) In particular, the analysis for treated with BVS segment showed also good reproducibility between the 2 observers.

VH-IVUS is very much influenced by the precision of contour detection, which in turn is highly time-consuming thus rendering its clinical use today for online clinical decisions not practical and not widely accepted. In a recent study, we introduced a new measurement method for necrotic core and calcium (Shin's method) that is a catheter contour based method in contrast to the conventional lumen contour based one. We showed that Shin's method has a good correlation with the conventional method, with shorter measuring time and good reproducibility in non-stented legions. For area of the necrotic core and dense calcium, the means of the differences between the two measurements were nearly zero, and the reproducibility coefficients were within 1% of the means of the two measurements. Mean analysis time for both measurements was 26.8 ± 6.7 min/segment in the conventional method and 3.3 ± 0.6 min/segment in Shin's method [13].

A previous study showed much larger relative differences for lumen contour-based reproducibility between two observers, namely 2.5% for lumen area, and the inter-catheter variability was from 6–8% for necrotic core and dense calcium when analyzed by the same observer [11]. However, Shin's method showed that relative differences for necrotic core and dense calcium were only 1% in intra-observer comparisons. In longitudinal studies, Shin's method may be, therefore, useful, especially when one of the endpoints is the serial change of necrotic core.

Shin's method aims at avoiding the variability in the drawing of the lumen contour. In this study, two observers drew manually the catheter contour, but in

Table 4 Shin's method and vessel contour reproducibility: intra-observer measurement differences for mean area and volume of necrotic core and dense calcium

	First time	Second time	Absolute △	Relative △ (%)
Vessel area, mm^2	14.5 ± 2.4	14.5 ± 2.4	0.06 ± 0.04	0.40 ± 0.32
NC area, mm^2	1.12 ± 0.61	1.12 ± 0.62	0.01 ± 0.01	1.12 ± 1.12
DC area, mm^2	0.57 ± 0.35	0.57 ± 0.35	0.004 ± 0.006	0.83 ± 1.06
Vessel volume, mm^3	313.3 ± 68.6	313.5 ± 68.9	1.13 ± 0.79	0.41 ± 0.32
NC volume, mm^3	24.28 ± 15.43	24.35 ± 15.54	0.23 ± 0.17	1.14 ± 1.13
DC volume, mm^3	11.79 ± 7.22	11.83 ± 7.25	0.08 ± 0.11	0.79 ± 1.08

Values are presented as mean ± SD. *NC* necrotic core, *DC* dense calcium, △ difference

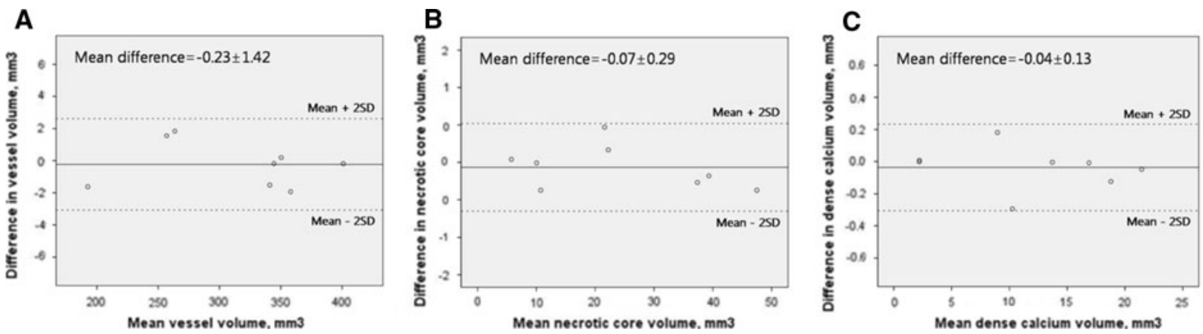

Fig. 4 Shin's method and vessel contour reproducibility: intra-observer measurement differences for vessel (**a**), necrotic core (**b**) and dense calcium volumes (**c**)

the future Shin's method could be automatically applied using automated catheter contour detection with a computer program, and analysis time will be therefore further decreased. This would also mean that the technique can be used in the catheterization laboratory to help operators in decision making based on the content of necrotic core or calcium.

It is worth mentioning that although Shin's method is applicable only for necrotic core and calcium quantification, a single catheter that permits simultaneous imaging with both IVUS (including radiofrequency analysis) and optical coherence tomography (OCT) during a single pullback is under development [1]. As it is expected that in the future lumen contour detection will be more reliable with OCT, Shin's method also could be used for compositional measurements. Therefore, all plaque component content could be assessed by combining OCT and Shin's method.

Although in human coronary arteries, the bioresorption process has been previously explored using VH-IVUS [16], some scaffold strut information might have been missed because of the presence of the medial grey stripe and also because of temporal changes in scaffold strut appearance which might have precluded proper contouring (i.e., struts in the vicinity of a calcified area are hard to discriminate from calcium). Shin's method draws a catheter contour (instead of a lumen contour), thereby including all the contents of the lumen and vessel wall which allows a complete analysis of serial changes in composition (i.e., necrotic core and dense calcium) and which can be used as a surrogate of bioresorption.

Limitations

This study has several limitations. (1) Although all patients having truly serial IVUS in the ABSORB trial were included, the sample size is small, (2) Shin's method by VH-IVUS has not been specifically validated for the assessment of the BVS in vitro and ex vivo.

Conclusions

The present study demonstrates a good reproducibility for both, intra-observer and inter-observer measurements using Shin's method. This method is suitable for serial measurements of necrotic core and dense calcium in longitudinal studies using VH-IVUS especially in BVS studies, because the degradation process will be fully captured independently of the location of the struts and their greyscale appearance.

Conflict of interest We declare that there is no conflict of interest for any author.

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