

Impact of analyzing less image frames per segment for radiofrequency-based volumetric intravascular ultrasound measurements in mild-to-moderate coronary atherosclerosis

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Abstract Volumetric radiofrequency-based intravascular ultrasound (RF-IVUS) data of coronary segments are increasingly used as endpoints in serial trials of novel anti-atherosclerotic therapies. In a relatively time-consuming process, vessel and lumen contours are defined; these contours are first automatically detected, then visually checked, and finally (in most cases) manually edited to generate reliable volumetric data of vessel geometry and plaque composition. Reduction in number of cross-sectional images for volumetric analysis could save analysis time but may also increase measurement variability of volumetric data. To assess whether a 50% reduction in number of frames per segment (every second frame) alters the reproducibility of volumetric

measurements, we performed repeated RF-IVUS analyses of 15 coronary segments with mild-to-moderate atherosclerosis (20.2 ± 0.2 mm-long segments with $46 \pm 13\%$ plaque burden). Volumes were calculated based on a total of 731 image frames. Reducing the number of cross-sectional image frames for volumetric measurements saved analysis time (38 ± 9 vs. 68 ± 17 min/segment; $P < 0.0001$) and resulted for only a few parameters in (borderline) significant but mild differences versus measurements based on all frames (fibrous volume, $P < 0.05$; necrotic-core volume, $P = 0.07$). Compared to the intra-observer variability, there was a mild increase in measurement variability for most geometrical and compositional volumetric RF-IVUS parameters. In RF-IVUS studies of mild-to-moderate coronary disease, analyzing less image frames saved analysis time, left most volumetric parameters greatly unaffected, and resulted in a no more than mild increase in measurement variability of volumetric data.

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Keywords Intravascular ultrasound · Radiofrequency · Virtual histology · Plaque composition · Necrotic core · Vulnerable plaque · IVUS · VH-IVUS · Reproducibility · Variability · Atherosclerosis · Coronary artery disease · Coronary vessels

Abbreviations

IVUS Intravascular ultrasound
RF Radiofrequency

Introduction

Volumetric intravascular ultrasound (IVUS) data used in serial studies of coronary atherosclerosis can be obtained from motorized transducer or catheter pullbacks by applying the trapezium method (modification of the Simpson's rule) to cross-sectional area data [1–6]. While most previous IVUS studies assessed vessel geometry using only grey-scale IVUS, [3, 7–9] radiofrequency-based IVUS (RF-IVUS) permits measurements of both vessel geometry and plaque composition [10–15]. RF-IVUS systems automatically detect the coronary vessel and lumen boundaries; however, in order to generate *reliable* volumetric IVUS data, these automatically-detected contours have to be visually checked and in a majority of cases manually corrected [16–20]. As this is a relatively time-consuming process, theoretically it makes sense to reduce the number of cross-sectional IVUS frames (number of frames per cm) used for volumetric measurements and thus to be corrected [6]. As recent serial IVUS studies measured only small changes in plaque volume or tissue composition, such reduction in cross-sectional IVUS frames should not have a significant impact on the variability of volumetric RF-IVUS data [18, 21–23].

Therefore, in the present study we evaluated the impact of reducing the number of cross-sectional IVUS image frames used to generate RF-IVUS volumetric data. Our study was performed in coronary segments with mild-to-moderate atherosclerosis in order to reflect the degree of atherosclerosis typically assessed in current progression-regression trials.

Methods

Study population

We repeatedly analyzed IVUS image sets of 20 mm-long, mild-to-moderately diseased coronary segments from non-target and non-treated coronary arteries with an angiographic lumen diameter stenosis <50% and absence of severe calcification or vessel tortuosity. IVUS image sets were obtained from motorized IVUS pullbacks at 0.5 mm/s from 15 patients in regular sinus rhythm in whom IVUS was performed during clinically-driven, elective diagnostic cardiac

catheterizations ($n = 8$) or percutaneous coronary interventions (of another vessel) ($n = 7$). Informed consent was obtained prior to cardiac catheterization from all patients in accordance with the directives of the Local Medical Ethics Committee.

RF-IVUS and image acquisition

Details regarding the RF-IVUS technique and validation have previously been described [11–15, 24]. In brief, spectral analysis of IVUS RF-data is used to create tissue maps in order to classify atherosclerotic plaques into four major components (fibrous, fibro-lipidic, calcium, and necrotic-core). These four plaque components are represented according to a dedicated colour code (green, light-green, white, and red, respectively).

RF-IVUS data was acquired with commercially available phased-array IVUS catheters (Eagle-EyeTM 20 MHz, Volcano Corporation, Rancho Cordova, CA, USA) by a dedicated RF-IVUS console (InVision GoldTM, Volcano Corporation). Image acquisition was ECG-gated; the catheter probe was advanced ≥ 10 mm distal to the most distal side-branch. Angiographic cine runs were performed to define the position of the IVUS catheter. After intracoronary injection of 200 μ g nitroglycerine, a continuous pullback of the IVUS catheter was performed at a speed 0.5 mm/s. Data were stored on hard disk for off-line analyses.

IVUS image analysis

The IVUS analysis was performed off-line by an experienced IVUS analyst who recorded the time spent to perform the analysis. The region of interest was a mild-to-moderately diseased atherosclerotic coronary segment (20 mm length) located between two adjacent side-branches that contained no major calcification that could have limited quantitative assessment of vessel cross-sectional area.

Vessel and lumen borders were traced using a semi-automated contour detection program (Volcano pcVH software program version 2.2 by Volcano Therapeutics Inc., CA, USA). The automatically detected borders of each cross-sectional image were visually checked and, if required, contours were corrected by computer-assisted manual editing. The vessel border involved tracing the leading edge of the

adventitia, and the lumen border involved tracing the leading edge of the intima. Plaque + media (vessel minus lumen) was used as a measure of atherosclerotic plaque [4].

For each coronary segment, volumetric data of vessel, lumen, and plaque + media, as well as fibrous, fibro-lipidic, necrotic core, and calcified tissue (absolute and relative amount of the plaque) were generated by application of the trapezium method (modification of the Simpson's rule) to the cross-sectional area measurements [17]. The pcVH software program uses this method that considers the exact spacing between individual image frames to calculate volumes from the cross-sectional area data. Volumetric plaque burden (%) was calculated as [(plaque + media volume/total vessel volume) × 100].

IVUS data analysis and rationale

We obtained volumetric IVUS data (geometrical and compositional) from different analyses, each performed on all 15 coronary segments. These different volumetric analyses were performed to obtain insight into the effect of reducing the number of cross-sectional image frames per segment on which the volumetric measurements were based. Analyses were spread over a period of 3 months; the analyst was blinded to the results of previous analyses.

Contour detection with manual correction of every cross-sectional image frame was performed to generate volumetric data (Analysis I, Fig. 1). This analysis was then performed a second time (Analysis II, Fig. 1) to assess intra-observer variability.

In addition, following the automated contour detection (always performed by the pcVH software on all frames), the contours of every other frame were skipped (i.e., they were not checked, not corrected, and not used for calculation of volumetric data). Manual contour editing was performed on this reduced number of image frames in order to generate new volumetric data (Analysis III, Fig. 1). In other words: Analysis III was based on contours obtained from less cross-sectional image frames (less data and potentially more difficult contour editing).

In an attempt to assess the mechanism (less data vs. more difficult image analysis) of a potential difference between analysis I and III, we finally recalculated volumes based on the contours of Analysis I, using only the cross-sectional area data of every

other frame (i.e., measurements based on less data *but without* potentially more difficult image analysis). Thus, volumetric data obtained by the latter analysis as well as Analyses III were both based on 50% of the image frames of the total set of images.

Statistical analysis

Analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Dichotomous data are presented as frequencies. Quantitative data are presented as mean ± 1SD and compared using student *t*-test. To test the correlation between the different analyses at individual level, the intraclass correlations were calculated. According to Bland and Altman, the agreement between two measurements were assessed by determining the mean ± 2SD of the between measurement differences [25]. A two-sided *P*-value <0.05 was considered significant.

Results

Study population and RF-IVUS data

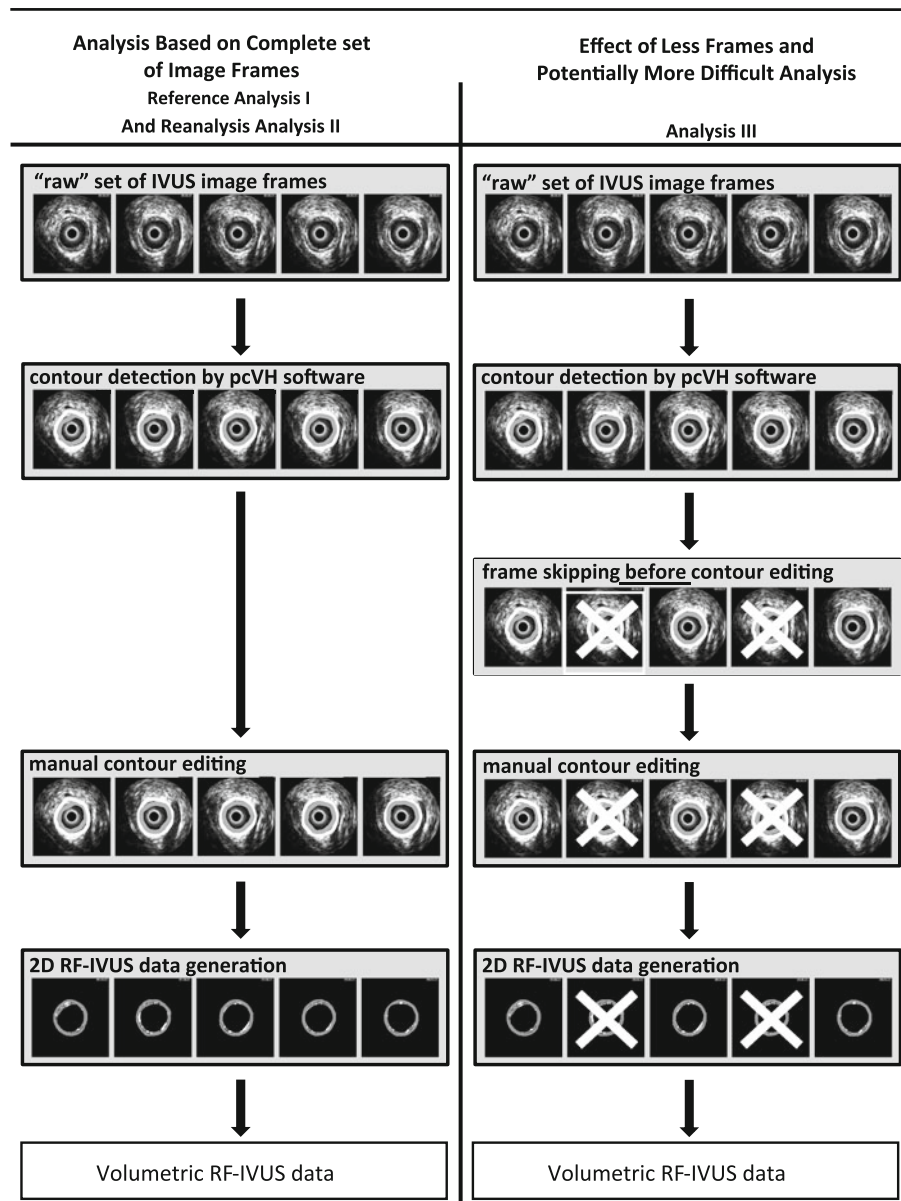
A total of 15 diffusely diseased, mild-to-moderately atherosclerotic coronary segments (4 RCA, 7 LAD, and 4 LCX) from 15 patients with stable angina (12 men; 60 ± 8 years of age) were studied. The heart rate during IVUS examination was 75 ± 19/min. There were no complications related to IVUS imaging.

A total of 15 coronary segments (731 IVUS frames; 49 ± 10 frames/segment) was repeatedly analyzed. Segment length measured 20.2 ± 0.2 mm with a volumetric plaque burden of 46 ± 13%. The atherosclerotic segments contained pre-dominantly fibrous tissue. The number of frames/cm analyzed was 24 ± 11.5 for Analyses I and II (all frames) and 12 ± 2.4 for Analyses III (reduced number of frames). The mean distance between consecutive frames used for generation of volumetric data was 0.4 ± 0.1 mm (range 0.3–0.6) for Analyses I and II and 0.9 ± 0.2 mm (range 0.6–1.1) for Analyses III. IVUS data are presented in Table 1.

Time of analysis and measurement variability

Comparing Analysis I to Analysis II showed that there was little intra-observer variability (Table 2)

Fig. 1 Different ways of RF-data analysis and generation of volumetric data



with high intraclass correlations (all ≥ 0.997) and Bland–Altman plots that showed good agreement between measurements (Figs. 2, 3). This was true for both geometric volumes as well as volumes of the four plaque components.

The use of less cross-sectional image frames for the generation of volumetric data (contour editing on less images required; Analysis III) significantly reduced the time of analysis from 68 ± 17 to 38 ± 9 min ($P < 0.0001$). In addition, it resulted in mild

differences versus measurements based on all cross-sectional image frames (Analysis I versus Analysis III, Table 2; Figs. 2, 3); differences were only significant for fibrous volume and borderline significant for necrotic-core volume ($P < 0.05$ and $P = 0.07$, respectively). Intraclass correlations were high (all ≥ 0.992) and Bland–Altman plots showed good agreement. Plaque components, expressed as percentage of plaque, showed no differences ($P \geq 0.1$; data not shown).

Table 1 IVUS data of four different ways of RF-IVUS analysis

	Analysis I Reference	Analysis II Reanalysis based on complete set of frames	Analysis III Less frames and potentially more difficult analysis
<i>Vessel geometry</i>			
Total vessel volume (mm ³)	344.6 ± 100.3	344.3 ± 100.7	345.8 ± 101.1
Lumen volume (mm ³)	186.0 ± 72.4	186.9 ± 72.1	185.0 ± 73.0
Plaque + media volume (mm ³)	158.6 ± 61.6	157.4 ± 62.4	160.8 ± 65.3
Plaque burden (%)	45.9 ± 12.9	45.5 ± 13.0	46.3 ± 13.6
<i>Plaque composition</i>			
Fibrous volume (mm ³)	52.2 ± 32.5	51.9 ± 32.4	53.8 ± 34.5
Fibro-Lipidic volume (mm ³)	12.7 ± 11.6	12.7 ± 11.7	13.3 ± 12.5
Necrotic core volume (mm ³)	16.0 ± 13.5	15.9 ± 13.5	16.3 ± 13.7
Calcium volume (mm ³)	8.3 ± 7.1	8.3 ± 7.1	8.3 ± 7.1

Table 2 Measurement differences of RF-IVUS data derived from different ways of analysis

	Analysis I versus ^a	
	Analysis II Reanalysis based on complete set of frames	Analysis III Less frames and potentially more difficult analysis
<i>Vessel geometry</i>		
ΔTotal vessel volume (mm ³)	0.35 ± 3.61 <i>P</i> = 0.7	-1.20 ± 5.16 <i>P</i> = 0.4
ΔLumen volume (mm ³)	-0.84 ± 3.87 <i>P</i> = 0.4	1.01 ± 4.32 <i>P</i> = 0.4
ΔPlaque + media volume (mm ³)	1.19 ± 3.55 <i>P</i> = 0.2	-2.20 ± 6.32 <i>P</i> = 0.2
ΔPlaque burden (%)	0.37 ± 1.00 <i>P</i> = 0.2	-0.37 ± 1.38 <i>P</i> = 0.3
<i>Plaque composition</i>		
ΔFibrous volume (mm ³)	0.23 ± 2.09 <i>P</i> = 0.7	-1.60 ± 2.85 <i>P</i> = 0.048
ΔFibro-lipidic volume (mm ³)	-0.02 ± 0.73 <i>P</i> = 0.9	-0.60 ± 1.48 <i>P</i> = 0.1
ΔNecrotic core volume (mm ³)	0.05 ± 0.54 <i>P</i> = 0.7	-0.36 ± 0.71 <i>P</i> = 0.07
ΔCalcium volume (mm ³)	-0.01 ± 0.28 <i>P</i> = 0.9	0.06 ± 0.48 <i>P</i> = 0.6

^a Two-sided *t*-test

Between data obtained in Analysis I versus Analysis III, there was a mild increase in measurement variability for most geometrical and compositional volumetric RF-IVUS parameters when being compared to the intra-observer variability (Analysis I versus Analysis II).

Potential mechanism of increased measurement variability

Re-calculation of volumes based on the contours of Analysis I but using only every other frame resulted in volumetric data that did not significantly differ versus

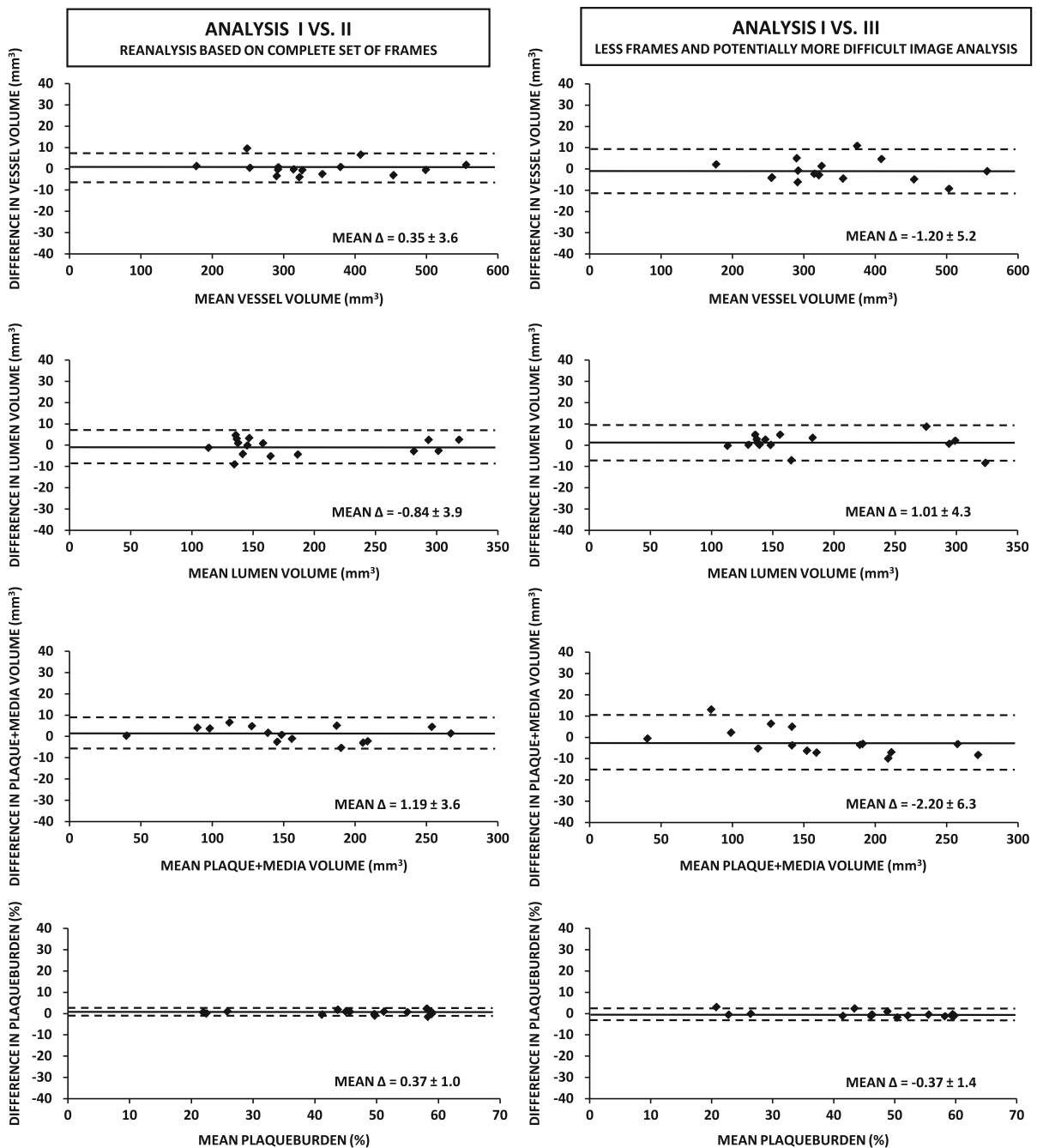


Fig. 2 Bland–Altman comparison of different ways of RF-IVUS analysis for geometrical data

Analyses I ($P = ns$). Intraclass correlations were high (all ≥ 0.997) and Bland–Altman plots showed good agreement (data not shown). For all volumetric parameters, measurement variability between these two analyses was lower than measurement variability between Analysis I versus Analysis III.

Discussion

In the present study we evaluated the impact of reducing the number of cross-sectional IVUS image frames on the calculation of RF-IVUS based volumetric data in coronary segments with mild-to-

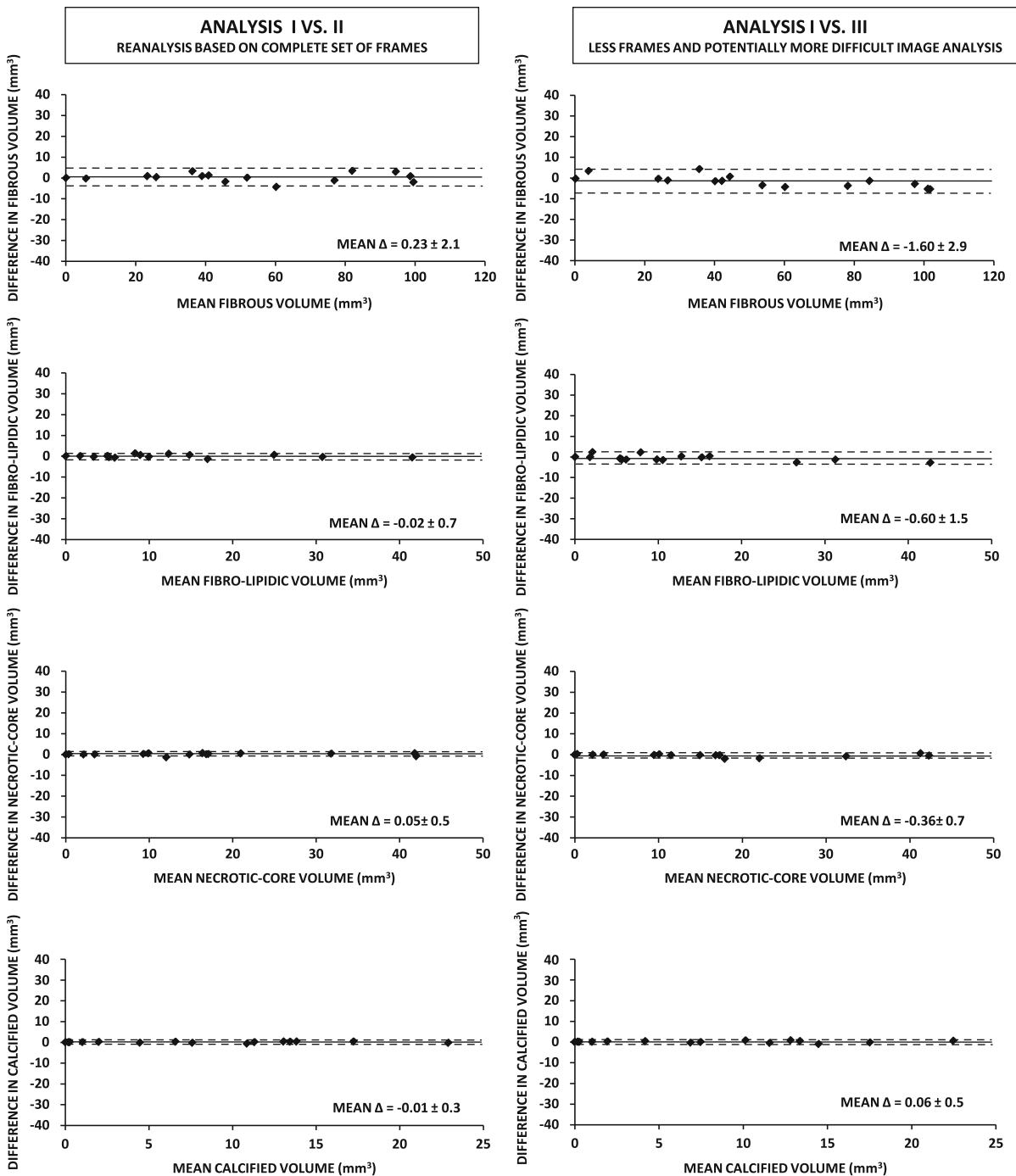


Fig. 3 Bland–Altman comparison of different ways of RF-IVUS analysis for compositional data

moderate atherosclerosis. Reducing the number of cross-sectional image frames for volumetric measurements (=Analysis III) significantly saved analysis time and resulted for only a few parameters in

(borderline) significant but mild differences versus measurements based on all frames. In general, observed differences were higher than the intra-observer variability. This *increase in measurement*

variability appears to be the result of a somewhat more difficult image analysis (Analysis III, contour editing on a reduced number of image frames and less data), as the generation of volumes from 50% of the already contour-edited images of Analysis I (only less data) showed a lower measurement variability.

Reproducibility of RF–IVUS

An important pre-requisite for the meaningful interpretation of data obtained by RF–IVUS is the assessment of measurement reproducibility [12, 16, 26, 27]. Rodriguez-Granillo et al. [27] tested the measurement variability of two-dimensional RF–IVUS data obtained from 16 coronary atherosclerotic lesions. The relative intra-observer difference was $\leq 3\%$ for geometric cross-sectional area measurements; conversely, compositional measurements were more variable than geometric measurements and, on average, varied by up to 13% on repeated pullbacks [27]. Prasad et al. [26] reported that RF–IVUS measurements of plaque composition volumes in 12 coronary segments (11 ± 4 mm) had a high measurement reproducibility (on average $\leq 6\%$). Our own group found in 33 coronary segments (27 ± 7 mm) a relatively high measurement reproducibility of volumetric RF–IVUS composition analyses (on average $\leq 3\%$) [16]. However, volumetric RF–IVUS analyses are very time consuming due to the contour detection and manual correction of most image frames per segment [16]. As demonstrated in the current study, reduction of the number of image frames used for the generation of volumetric measurements is time sparing, but resulted in a mild increase in measurement variability for most geometrical and compositional volumetric RF–IVUS parameters; there were only for a few parameters (borderline) significant but mild differences versus measurements based on all frames. Of the four plaque components, calcified tissue showed the lowest measurement variability. In general, differences in plaque composition may be the result of small variations in vessel and lumen border detection and/or differences in the interpolation of the vessel and lumen contour at the site of side branches. As calcified tissue was more often located centrally in the plaque, this tissue component may be less dependent on editing of the vessel and lumen contours.

Changes observed in serial IVUS studies and implications of this study

Serial volumetric IVUS data are increasingly used as endpoints in pharmacological intervention trials as changes in IVUS plaque dimensions may be linked to a significant increase or decrease in risk of clinical events [1, 8, 18, 23]. Besides coronary plaque progression/regression, changes in atherosclerotic plaque composition may also alter the risk of cardiovascular events [28–30]. RF–IVUS discriminates between plaque vulnerability versus plaque stability (necrotic core vs. fibrous tissue) [11, 12, 14, 20, 31]. Therefore, RF–IVUS is increasingly used in studies that evaluate plaque stabilization during pharmacological interventions with novel atherosclerosis-modifying drugs [18, 21–23]. Necrotic core and fibro-lipidic tissue are both markers of plaque vulnerability and may be more interesting imaging endpoints than fibrous tissue which is a marker of plaque stability. Fibrous tissue is often located adjacent to the lumen border and variation in editing the lumen contour may result in misinterpretation of blood as fibrous (and sometimes fibro-lipidic) tissue [32]. This may result in an increased variability of fibrous and fibro-lipidic tissue measurements (in the present study >5 and $>11\%$, respectively). Importantly, a relatively low measurement variability for necrotic core ($<5\%$ in the present study) is a prerequisite for use of this imaging parameter as an endpoint of pharmacological intervention trials.

The recently published data of IBIS-2 (Integrated Biomarker and Imaging Study II) reported changes in volumetric RF–IVUS data during 12 months of treatment with the lipoprotein-associated phospholipase-A2 inhibitor darapladib versus placebo [23]. In the placebo-group, necrotic core volume increased by 4.5 ± 17.9 mm³ ($P = 0.009$) whereas patients on darapladib showed no increase in necrotic core volume with no significant change in plaque volume or plaque burden. The relatively small changes in overall plaque volume and the volume of each plaque component that have been reported in these aforementioned serial studies suggest that measurement reproducibility is critical [12, 16, 17, 26, 27]. The present study showed that saving time of analysis by reducing the number of cross-sectional images used for volumetric data and thus analyzed (24 ± 11.5 vs. 12 ± 2.4 frames/cm) is offset by a significant but mild increase in

measurement variability that is higher than the level of the intra-observer measurement variability. Consequently, RF–IVUS studies of mild-to-moderate coronary atherosclerosis should ideally analyze all image frames of the coronary segments in order to minimize measurement variability; however, it could be considered (partly related to the parameters of interest) whether all frames or a reduced number of frames should be used.

Limitations

The number of coronary segments studied ($n = 15$) was limited. Other studies that addressed the reproducibility of VH-IVUS measurements examined series of $n = 16$ –33 coronary segments [16, 26, 27]. Recent pharmacological intervention trials with IVUS endpoints examined 10–40 mm-long coronary segments and 10 mm-long subsegments with the greatest disease burden [8, 21, 22]. The segment length of the present study (20.2 ± 0.2 mm) reflects this choice and is in accordance with recent recommendations of an expert panel [10]. All patients had stable angina. Similar to other studies with IVUS and RF–IVUS, we excluded tortuous and severely calcified vessels that could have hampered the uniform pullback speed and IVUS image interpretation [16, 18, 23, 26, 27]. In addition, extensive circumferential calcified tissue may limit the detection of vessel contours, which is a known limitation of IVUS. In this study, we analyzed IVUS image runs with limited circumferential calcification, which may have facilitated vessel contour detection to some extent; measurement reproducibility could be somewhat lower in cases with extensive calcification. The data of this study do not predict whether a reduction of image density may introduce an additional measurement variability (for instance when data are sampled at a pullback speed of 1.0 mm/s instead of 0.5 mm/s). In serial studies, [33] potential variability between different IVUS catheters or IVUS systems may add to the overall measurement variability of RF–IVUS studies [34].

Conclusions

Analyzing less cross-sectional image frames saved analysis time on the generation of volumetric RF–IVUS data in mild-to-moderate coronary disease,

left most volumetric parameters greatly unaffected, and resulted in a no more than mild increase in measurement variability of volumetric data.

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