Lumen and calcium characteristics within calcified coronary lesions. Comparison of computed tomography coronary angiography versus intravascular ultrasound

Charakterystyka światła naczynia i zwapnienia w uwapnionych zmianach miażdżycowych w tętnicach wieńcowych. Porównanie tomografii komputerowej i ultrasonografii wewnątrznaczyniowej

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Abstract

Introduction: Computed tomography coronary angiography (CTCA) is a diagnostic method used for exclusion of coronary artery disease. However, lower accuracy of CTCA in assessment of calcified lesions is a significant factor impeding applicability of CTCA for assessment of coronary atherosclerosis.

Aim: To provide insight into lumen and calcium characteristics assessed with CTCA, we compared these parameters to the reference of intravascular ultrasound (IVUS).

Material and methods: Two hundred and fifty-two calcified lesions within 97 arteries of 60 patients (19 women, age 63 ±10 years) underwent assessment with both 2 × 64 slice CT (Somatom Definition, Siemens) and IVUS (s5, Volcano Corp.). Coronary lumen and calcium dimensions within calcified lesions were assessed with CTCA and compared to the reference measurements made with IVUS.

Results: On average CTCA underestimated mean lumen diameter (2.8 ±0.7 mm vs. 2.9 ±0.8 mm for IVUS), lumen area (6.4 ±3.4 mm² vs. 7.0 ±3.7 mm² for IVUS, p < 0.001) and total calcium arc (52 ±35° vs. 83 ±54°). However, analysis of tertiles of the examined parameters revealed that the mean lumen diameter, lumen area and calcium arc did not significantly differ between CTCA and IVUS within the smallest lumens (1st tertile of mean lumen diameter at 2.1 mm, and 1st tertile of lumen area at 3.7 mm²) and lowest calcium arc (mean of 40°).

Conclusions: Although, on average, CTCA underestimates lumen diameter and area as well as calcium arc within calcified lesions, the differences are not significant within the smallest vessels and calcium arcs. The low diagnostic accuracy of CTCA within calcified lesions may be attributed to high variance and not to systematic error of measurements.

Key words: computed tomography, intravascular ultrasound, coronary angiography, coronary artery disease.

Streszczenie

Wstęp: Badanie tomografii komputerowej (TK) tętnic wieńcowych stosuje się w celu wykluczenia istotnych zwiężeń w tętnicach wieńcowych. Niższa wartość diagnostyczna metody w ocenie zmian uwapnionych stanowi istotny czynnik ograniczający zastosowanie TK w ocenie osób z chorobą wieńcową.

Cel: Ocena charakterystyki światła naczynia i zwapnienia w TK w porównaniu z badaniem referencyjnym – ultrasonografii wewnątrznaczyniowej (intravascular ultrasound – IVUS).

Materiał i metody: Przy użyciu 2 × 64-rzędowego TK (Somatom Definition, Siemens) i IVUS (s5, Volcano Corp.) oceniono 252 uwapnione zmiany miażdżycowe w 97 tętnicach u 60 chorych (19 kobiet, wiek: 63 ±10 lat). Wymiary światła naczynia i zwapnienia oceniono w miejscu minimalnego światła naczynia.

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**Introduction**

Computed tomography coronary angiography (CTCA) is currently used for exclusion of significant coronary stenoses. However, the high potential of the non-invasive assessment of coronary wall and lumen is currently underutilized due to current computed tomography (CT) technology limitations. One of the most significant constraints of CTCA remains its inaccuracy in assessing calcified lesions [1-6]. Since presence of coronary calcifications is synonymous with the presence of atherosclerosis, this limitation translates into lower accuracy of CTCA in assessment of atherosclerotic lesions or in more general terms patients with coronary artery disease.

Despite the fact that coronary calcium is one the main sources of diagnostic errors of CTCA, there is a paucity of data regarding this phenomenon.

**Aim**

Therefore, we compared calcium and lumen characteristics as assessed with CTCA to the reference images obtained with IVUS.

**Material and methods**

In a prospective, cross-sectional study, from June 2009 to January 2011, we enrolled 60 consecutive patients with suspected coronary artery disease. All patients underwent both CTCA and invasive angiography examinations for clinical indications. The inclusion criteria were: the presence of at least one coronary stenosis, which was either non-diagnostic or of ambiguous clinical significance caused by embedded coronary calcium deposit. Exclusion criteria were uncorrectable motion artifacts on CTCA study, body mass index (BMI) above 40 kg/m², atrial fibrillation, previous bypass surgery, and unstable clinical condition. The invasive angiography and intravascular ultrasound (IVUS) was performed on average 43 ±37 days after the CTCA study.

The study protocol was approved by the institutional ethics committee, and all patients gave informed consent to participate.

**Computed tomography coronary angiography and intravascular ultrasound**

Computed tomography coronary angiography (CTCA) was performed using a 2 × 64-slice CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) after sublingual administration of nitrates (0.8 mg). In cases with a heart rate ≥ 70 beats/min, an additional intravenous bolus of metoprolol (sequential doses of 5 mg, maximal dose 20 mg) was given. A bolus of 60-80 ml of the contrast agent iomeprol (Iomeron 400, Bracco, Italy) was injected intravenously at 6 ml/s. An electrocardiogram-gated retrospective acquisition protocol was used in all patients, with 330-ms rotation time, 0.6-mm collimation, and 100 kV to 120 kV tube voltage. Scan data were reconstructed routinely in mid- to end-diastole (60% to 70% of RR interval) and mid systole (40% to 50% of RR interval). Datasets containing motion artifacts were individually optimized by changing the reconstruction window.

Intravascular ultrasound was performed after administration of intracoronary nitroglycerin (0.2 mg). The 20 MHz IVUS catheter (Volcano Corporation, San Diego, California) was advanced to the distal segment of the examined vessel and retrograde imaging was performed with an automatic pullback (0.5 mm/s).

**Calcium analysis**

A single calcification was defined based on visual assessment of CTCA obtained images, and contained at least one calcium deposit. The calcium deposit was a structure brighter than the surrounding vessel wall tissue that could be visualized separately from the contrast-enhanced coronary lumen either because it was “embedded” within noncalcified plaque or because it was discernible from the contrast-enhanced lumen, visible on contrast CTCA study in at least two independent planes including cross-sectional images and with a density of above 130 HU [7-9]. Separate calcifications were identified if there was at least one boundary transverse cross-section without overlapping calcium deposits. Therefore the single calcification could contain either a single calcium deposit or a series of calcium deposits, as long as they overlapped each other in the longitudinal vessel axis. Within each calcification the minimal lumen area (MLA) cross-section was identified. The lumen areas within the calcified and the reference sites were automatically measured and manually corrected if necessary using Sure-plaque™ (ver. 3.9 Toshiba Medical Systems). Since the traditional calcium threshold of 130 HU was inappropriate for quantitative analysis of calcium within the contrast-enhanced vessel, we chose a previously validated thresh-
old of 350 HU for calcium measurements within the contrast-enhanced coronary artery [10, 11]. For IVUS analysis precisely the same MLA and reference sites as selected for the CTCA study were identified based on anatomic landmarks. Off-line IVUS analysis of MLA was performed by a single experienced observer blinded to patients’ CTCA measurements.

**Statistical analysis**

Continuous data are presented as mean (± standard deviation) and categorical data are reported as frequencies. Student t test and ANOVA were used for comparison of continuous variables as appropriate. Categorical variables were compared using the χ² test. Pearson’s correlation was used for assessment of the relationship between CTCA and IVUS parameters within tertiles. Intraclass correlation coefficient (a method of agreement for continuous variables) was used to assess intraobserver variability in IVUS and CTCA measurements. Bland-Altman plots were produced to visualize the difference between measurements by the imaging techniques. All tests were two-sided. Value of p < 0.05 was considered statistically significant. All analyses were performed with SPSS 9.0 (SPSS Inc, Chicago, Ill) or MedCalc Software, Mariakerke, Belgium.

**Results**

We evaluated 252 coronary cross-sections within 97 arteries of 60 patients. Clinical characteristics of study patients and the CT scan parameters are presented in Table 1. Intraobserver variability expressed with intraclass correlation coefficient (ICC) was used to assess intraobserver variability in IVUS and CTCA measurements. Bland-Altman plots were produced to visualize the difference between measurements by the imaging techniques. All tests were two-sided. Value of p < 0.05 was considered statistically significant. All analyses were performed with SPSS 9.0 (SPSS Inc, Chicago, Ill) or MedCalc Software, Mariakerke, Belgium.

| Table 1. Baseline characteristics |
|-----------------------------------|
| **Clinical characteristics**      | **Prevalence/60 Mean ± SD** |
| **Hyperlipidemia**                | 55/60                        |
| **Hypertension**                  | 52/60                        |
| **Family history of coronary disease** | 16/60                     |
| **Diabetes**                      | 16/60                        |
| **Smoking**                       | 15/60                        |
| **Serum creatinine [µmol/l]**     | 87 ±19                       |
| **Height [cm]**                   | 172 ±9                       |
| **Weight [kg]**                   | 80 ±14                       |
| **Body mass index [kg/m²]**       | 27 ±4                        |
| **Calcium score**                 | 433 ±353                     |
| **Scan parameters:**              |                             |
| **kV**                            | 115 ±9                       |
| **mA**                            | 271 ±44                      |

SD – standard deviation

| Table 2. Comparison of the calcium characteristics as assessed with CTCA vs. IVUS |
|------------------------------------------|
| **Characteristics**                      | **Number, mean ± SD, total = 252** |
|                                          | **CTCA** | **IVUS** | **Value of p** |
| Separate calcium deposits                |          |          |                |
| 1                                        | 1/2/3     | 181/16/2 | < 0.001        |
| 2                                        | 20/24/4   | 21/1/1   |                |
| 3                                        |           |          |                |
| Location                                 |          |          |                |
| Superficial                              | 167/21/3  | 33/7/1   | < 0.001        |
| Mid                                      | 3/9/1     |          |                |
| Deep                                     | 9/8/3     |          |                |
| Calcium contacting/overlapping lumen     | Contacting/overlapping |        |                |
| Contacting                               | 182/28    | 27/15    | < 0.001        |
| Overlapping                              |           |          |                |
| Maximum calcium arc [°]                  | 52 ±35    | 83 ±54   | < 0.001        |
| Total calcium arc [°]                    | 61 ±44    | 90 ±56   | < 0.001        |
| Distance between opposite lumen wall and calcium edge [mm] | 2.4 ±0.8 | 2.8 ±0.8 | < 0.001        |
| Lumen area [mm²]                         | 6.4 ±3.4  | 7.0 ±3.7 | < 0.001        |
| Maximum lumen diameter [mm]              | 3.2 ±0.8  | 3.2 ±0.8 | 0.366          |
| Minimum lumen diameter [mm]              | 2.3 ±0.7  | 2.6 ±0.7 | < 0.001        |
| Mean lumen diameter [mm]                 | 2.8 ±0.7  | 2.9 ±0.8 | < 0.001        |
| Lumen eccentricity index                 | 1.4 ±0.3  | 1.2 ±0.1 | < 0.001        |

Data presented as means (± standard deviation) and numbers for proportions. Values of p derived from χ² and Student t-test for comparison of categorical and continuous data respectively.
Fig. 1. Bland-Altman plots and comparison of tertiles (± 2 SD) of relative (percent) differences between respective lumen and calcium parameters as assessed by intravascular ultrasound (IVUS) vs. computed tomography coronary angiography (CTCA): A – maximum calcium arch, B – total calcium arch, C – minimum lumen diameter

Wykresy Bland-Altmana oraz porównanie tercyli (± 2 SD) względnej (%) różnicy pomiędzy odpowiednimi parametrami światła naczynia i zwapnienia ocenionych w ultrasonografii wewnątrznaczyniowej (IVUS) i tomografii komputerowej (CTCA): A – maksymalny kąt zwapnienia, B – całkowity kąt zwapnienia, C – minimalna średnica światła
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**Fig. 1.** Continued: D – maximum lumen diameter, E – mean diameter, F – minimum lumen area

**Ryc. 1.** Ciąg dalszy: D – maksymalna średnica światła, E – uśredniona średnica światła, F – minimalne pole światła naczynia
Discussion

Our data indicate a significant discrepancy between CTCA and IVUS in assessment of calcified coronary lesions. The discrepancies regard both the lumen and the calcium dimensions, and are dependent on the size of these structures.

Fig. 1. Continued: **G** – calcium-opposite wall distance, **H** – eccentricity index

**Ryc. 1.** Ciąg dalszy: **G** – odległość między zwapnieniem i przeciwną ścianą, **H** – średnica maks./min.
Coronary calcifications are a major source of stenosis overestimation by CTCA as compared to ICA (94% of false-positive findings) [4]. According to Brodoefel et al., calcifications are the single factor impacting diagnostic accuracy of CTCA [5]. It has also been shown that obstructive coronary artery disease is least accurately diagnosed within large calcifications as opposed to moderate or small ones [2]. Of quantitative calcium parameters, calcium arc above 90° has been shown to correlate with stenosis overestimation by CTCA as compared to ICA (94% of false-positive findings) [4].

Methods applied for our analysis differ significantly from those of previous studies exploring the relationship between calcifications and diagnostic accuracy of CTCA, which relied on the suboptimal reference of invasive angiography [12-15]. Invasive angiography does not provide optimal stenosis assessment within ostia or bifurcations (a frequent site of coronary calcifications), mainly due to the limited number of projections [12-15]. Also, calcified lesions may present with a filling defect, preempting accurate stenosis assessment on angiography [16, 17]. Application of IVUS as the reference study corrected for these limitations and allowed us to obtain unprecedented data.

The results of our study have several implications. First of all, the bi-directional, significant scatter of measurements, in particular within small (mean MLA: 3.7 mm²) calcified lumens, suggests caution with definite stenosis categorization in these patients based on CTCA. This is particularly important due to frequently observed lumen overestimation, posing a risk of missing significant stenoses. Our data also suggest that technology development required to improve assessment of calcified lesions should be aimed not only

### Table 3. Comparison of the calcium characteristics within their tertiles as assessed with CTCA versus IVUS

| IVUS characteristics | Tertiles, mean (range) for 1st/2nd/3rd | Value of p for difference between CTCA vs. IVUS within 1st/2nd/3rd tertiles |
|----------------------|---------------------------------------|--------------------------------------------------------------------------|
| Maximum calcium arc [°] | 40 (15-55)/70 (56-85)/139 (86-360) | 0.537/ < 0.001/ < 0.001                                                  |
| Total calcium arc [°] | 40 (15-56)/79 (58-105)/155 (110-360) | 0.265/ < 0.001/ < 0.001                                                  |
| Distance between opposite lumen wall and the calcium edge [mm] | 2.0 (1.4-2.3)/2.7 (2.4-3.0)/3.7 (3.30-5.40) | 0.001/ < 0.001/ < 0.001                                                  |
| Lumen area [mm²] | 3.7 (1.8-5.0)/6.0 (5.10-7.60)/11.2 (7.70-22.50) | 0.264/0.042/ < 0.001                                                     |
| Maximum lumen diameter [mm] | 2.4 (1.7-2.7)/3.0 (2.8-3.3)/4.1 (3.4-6.10) | 0.004/0.495/ < 0.001                                                     |
| Minimum lumen diameter [mm] | 1.9 (1.4-2.2)/2.5 (2.3-2.8)/3.4 (2.9-4.8) | 0.024/ < 0.001/ < 0.001                                                  |
| Mean lumen diameter [mm] | 2.1 (1.6-2.5)/2.8 (2.6-3.1)/3.8 (3.2-5.4) | 0.528/0.001/ < 0.001                                                     |
| Lumen eccentricity index | 1.11 (1.00-1.16)/1.21 (1.17-1.27)/1.39 (1.28-1.72) | < 0.001/ < 0.001/0.277                                                  |
at the correction of blooming but primarily at improvement of spatial resolution.

Contemporary CTCA technology applied for assessment of coronary artery disease has several limitations referring to assessment of coronary calcifications. These include suboptimal spatial resolution, and susceptibility to blooming artifacts. Although it is impossible to fully make up for these constraints, in this analysis we used the least subjective data derivation methods possible based on semi-automated SurePlaque™ software. Subsequently, the reference method of IVUS may be useful for provision of lumen and selected calcium parameters; however, due to acoustic signal shadowing it was impossible to compare calcium thickness or other volumetric calcium parameters, which could possibly provide further important information.

Conclusions

Assessment of calcified coronary arteries by CTCA is least accurate within small coronary lumens, already on the verge of physiological significance. In these circumstances even relatively minute lumen measurement disturbances caused by calcifications may lead to significant qualitative diagnostic errors.

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