



Research article

Reliability of coronary computed tomography angiography in acute coronary syndrome in an emergency setting



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ABSTRACT

Background: Cardiovascular computed tomography (cardiovascular CT) is currently used as a fast non-invasive method for the visualization of coronary plaques and walls and the assessment of lumen stenosis severity. Previous studies demonstrated the high negative predictive value of CT for the exclusion of coronary lumen stenoses. In this study we hypothesize that coronary CT angiography (CTA) represents a reliable method as diagnostic procedure in acute coronary syndrome (ACS) even in emergency settings.

Methods: 36 patients (51 lesions) with ACS who underwent cardiovascular CT, intravascular ultrasound (IVUS) and invasive coronary angiography (ICA) within 48 h were included. The percentage of coronary stenoses were measured and compared by three methods. Influence of available predictors that can potentially affect the measurement results was assessed.

Results: Cardiac CTA provided comparable results to IVUS (mean difference -0.45%, PPV: 98%, NPV: 75%). ICA tends to estimate lower stenoses degrees than cardiac CTA and IVUS (mean difference 13.19% and 13.64%, respectively). The final diagnosis and positive remodeling did not lead to any significant influence on measurements.

Conclusions: The cardiovascular CT results show that even in emergency settings it is possible to identify morphological changes as sequels of coronary artery sclerosis with comparable results to the reference method IVUS. Deviations of IVUS and cardiovascular CT from ICA are comparable and can to a large extent be explained by differences in the measurement technique.

1. Introduction

Cardiovascular diseases are the number one cause of deaths worldwide [1]. In 2016, 9.4 million people died from ischemic heart disease (IHD) [2], which has as its morphological basis atherosclerosis of the coronary arteries. Conventional invasive coronary angiography (ICA) is considered the gold standard for the visualization of the coronary artery lumen [3, 4]. However, ICA, as an invasive method, is associated with a small risk of intraoperative complications [5, 6].

Cardiovascular computed tomography (cardiovascular CT) is currently used as a fast non-invasive method for the visualization of coronary plaques and walls [7, 8, 9, 10, 11, 12, 13, 14] and the assessment of lumen stenosis severity [15, 16, 17, 18, 19, 20]. In comparison to intravascular ultrasound (IVUS) [21, 22, 23], the accuracy of cardiovascular CT for the identification of coronary plaques could be confirmed showing high sensitivity and specificity values in the detection of stenosis >50% [14]. Furthermore, the extent of coronary lumen stenosis measured by coronary CT angiography (CTA) revealed a high diagnostic accuracy compared to either IVUS [24] or ICA [15, 25, 26]. These studies

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- only sporadically performed in emergency settings - mainly emphasize the high negative predictive value of coronary CTA in exclusion of severe coronary stenotic lesions [27, 28, 29, 30, 31, 32].

Because of the known advantages of coronary CTA (non-invasive, easy to perform, fast, widely available and suitable for work-up and differential diagnosis of acute chest pain) it is of interest to perform coronary CTA in emergency settings with high prevalence of coronary stenotic lesions to test if the positive predictive value shows comparable results as for the exclusion of stenotic lesions. The aim of this study is to test the hypothesis that coronary CTA can replace ICA and the rarely used IVUS in acute coronary syndrome as diagnostic procedure even in emergency settings.

2. Materials and methods

The present study was performed to evaluate the applicability of CTA for coronary stenosis measurement in patients with IHD and its potential for fast decision making in emergency admission.

We compared the percentage of coronary stenosis measured by cardiovascular CT, IVUS and ICA. The degree of stenosis was determined as “1–2 (narrowest vessel diameter)/(reference prestenotic + poststenotic diameters)”. Influence of available predictors that can potentially affect the measurement results was assessed. The Study protocol was approved by the Ethics Committee of National Medical Research Center of Cardiology, Moscow, Russian Federation (EKN 193/27012014). All included patients signed informed consent before the study and gave approval for the use of their data for clinical investigation.

2.1. Patients

Between January 2014 and January 2016, 150 patients were admitted to the emergency department for symptoms of ACS. Patients with new onset angina, progressive angina and early post infarction angina were included.

Inclusion criteria for further examination were defined as follows:

- 1) Acute angina attack with chest pain lasting for at least 20 min, with and without ST-segment elevation;
- 2) Stable clinical cardiovascular situation,
- 3) No previous coronary bypass surgery or coronary dilatation;
- 4) Creatinine Clearance >45 ml/min (glomeruli filtration rate >60 ml/min).

Exclusion criteria were:

- 1) Intolerance or allergy against iodinated contrast agent;
- 2) Pregnancy;
- 3) No informed consent;
- 4) Agatston score >600 HU on noncontrast coronary CTA scans [33].

All methods and specialized staff had to be available within the following 48 h for definitive patient inclusion. All patients underwent the examinations in the same order, starting with coronary CTA followed by IVUS and ICA within 48 h. 36 patients with 51 coronary wall lesions for all imaging modalities (ICA, IVUS and coronary CTA) who met the inclusion criteria were included in analysis. The image quality in 51 studied coronary segments was acceptable for all three imaging methods. No patients were excluded due to insufficient image quality.

2.1.1. Cardiovascular CT

Cardiovascular CT was performed using a 64-slice CT scanner (Aquilion 64, Toshiba Medical System, Tokyo, Japan). A non-ionic contrast agent with an Iodine concentration of 370 mg/ml was injected intravenously (4.5 ml/s) using an automatic syringe (Mallinckrodt plc., UK). The amount of contrast agent was adjusted according to body weight (1.5 ml/kg). Standard coronary CTA protocols were used for

noncontrast and contrast-enhanced cardiac CT. There was no use of nitroglycerin for coronary vessel dilation. Oral beta blockers (Metoprolol 50–100 mg) were administered to reduce the heart rate below 65 bpm. The tube voltage was 120–140 kV (depending on the patient's body mass index), the temporal resolution 100–200 ms, and the detector row width 0.5 mm. The device registered the total radiation dose automatically. Data post-processing was carried out on the workstation Vitrea 2 (versions 2.0 and 4.0; Vital images Inc., USA, which offers to measure the extent of given stenoses, the maximum and minimum lumen diameter and the semi-automatic determination of lumen boundaries). Three-dimensional and multi-planar reconstructions for the visualization of the total length of all coronary arteries were obtained. Evaluation of the degree of coronary artery stenosis was performed both on longitudinal and cross-sectional coronary artery reconstructions (see Figure 1a,d,e, the degree of a coronary lumen stenosis was defined following [34]).

2.1.2. ICA

All patients underwent ICA (Philips Allura Xper FD angiography system, Netherlands) in standard projections using radial access [5]. Using “Xcelera software” (Philips, Netherlands) the degree of artery stenosis (%) was determined automatically on standard longitudinal projection images (Figure 1b,c). If necessary, it was corrected manually based on visual inspection [5].

2.1.3. IVUS

IVUS was performed using the iLAB IVUS Console unit (Boston Scientific) equipped with an Atlantis 40 MHz intravascular ultrasound catheter. The catheter was introduced into the coronary artery with an outer diameter of at least 2.5 mm having a minimal residual lumen of 1.5 mm. Afterwards, the catheter was pulled back (length: >40 mm, speed: 0.5 mm/s or 1 mm/s; covering a length of the coronary artery <110 mm). All types of coronary plaques were determined automatically by the iLAB software (color code map of plaque components) and, if necessary, visually corrected in the gray scale [22]. The degree of coronary stenosis and the Index of Remodeling were calculated on coronary cross-sectional images (Figure 1f,g) with manually corrected automatic boundaries on a dedicated workstation (Atlantis SR Pro and iLab, Boston Scientific, Boston, MA, USA). The available IVUS system allowed a stenosis degree evaluation between 30 % and 90 %.

2.2. Data analysis

Cardiovascular CT images analysis was performed by 2 blinded and independent observers with 7- and 15-year experience in cardiac CT. Consensus agreement was reached for each patient. ICA and IVUS were processed by 1 invasive cardiologist with 13-year experience, who was blinded to the coronary CTA results.

The following parameters were evaluated:

- 1) Presence or absence of visible plaques in the wall of coronary arteries (coronary CTA and IVUS);
- 2) Coronary plaque composition (coronary CTA and IVUS);
- 3) Degree of coronary stenosis (all three methods [%]);
- 4) Possible effect of coronary artery remodeling on the estimation of the severity of a given stenosis (following the protocols in [35, 36]).

To investigate the effect of available predictors (gender, age, obesity, body mass index [BMI], smoking, family history of IHD, hypertension, diabetes, increase of total cholesterol, total cholesterol, increase of triglycerides, triglycerides, history of myocardial infarction, acute myocardial infarction, unstable progressive angina, new onset of angina, positive remodeling) on the differences of the measurement techniques, univariate linear mixed models were fitted. Since no relevant significant effects on the difference between examinations (cardiovascular CT-IVUS, cardiovascular CT-ICA, ICA-IVUS) were found, no multiple regression models were fitted.

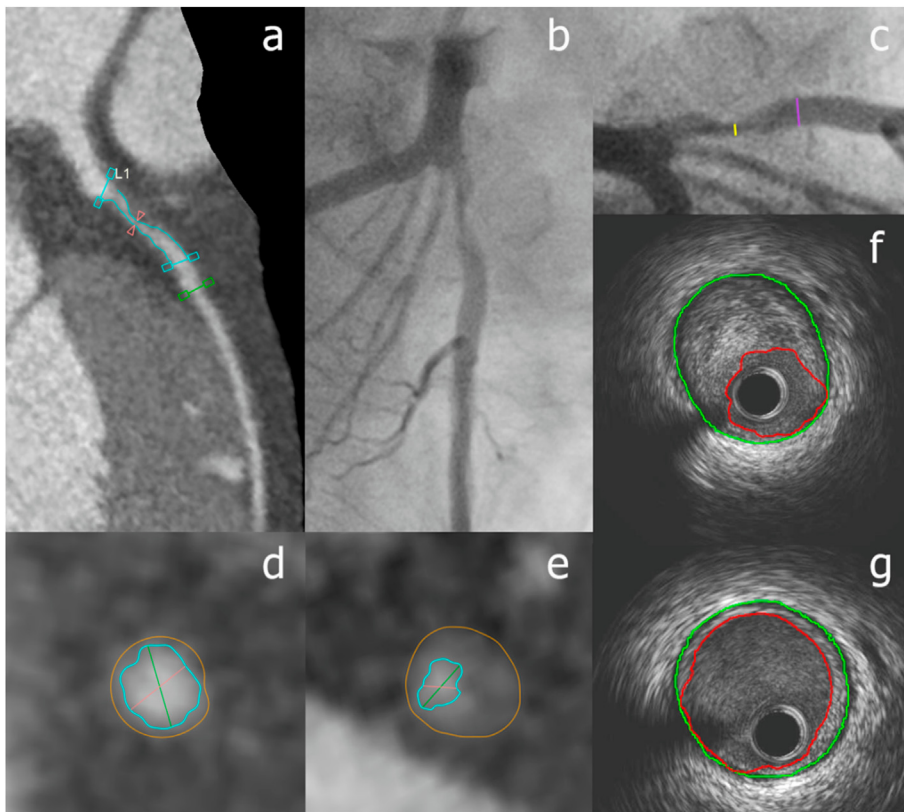


Figure 1. Long-axis view of the LAD on a CT reformatted image (a), plaque extent (blue), maximum stenosis location (red), reference post-stenotic site (green). Corresponding ICA image (b) and enlarged angiogram (c) were used for minimal diameter at the lesion site (yellow) and reference post-stenotic diameter (purple) measurements. Minimal cross-sectional luminal area of the vessel determined by CT (e, blue) including minimal (red) and maximal (green) lumen diameter and IVUS (f, red line). Luminal area at the reference sites calculated using CT (d, blue) and IVUS (g, red).

2.3. Statistical analysis

Statistical analysis was performed using R 3.4.3 (Vienna, Austria). For the quantitative description, mean values and standard deviations were calculated for metric baseline demographics and clinical characteristics of the patients. Absolute and relative frequencies were calculated for categorical baseline demographics and clinical characteristics of the patients. In order to compare the three measurement techniques, Bland-Altman plots were drawn for each pairwise comparison of the methods. Sensitivity and specificity of detected stenosis >50 % for each pair were computed. Linear mixed models were fitted to explain differences in the measurements in dependence of the average values. To

investigate the effect of given predictors and the final diagnosis on the differences of the measurement techniques, univariate linear mixed models were fitted. A *p*-value of <0.05 was considered statistically significant. Calculated *p*-values serve only descriptive purposes; hence no multiple testing corrections were applied.

3. Results

3.1. Patients and coronary artery lesions

Clinical characteristics and baseline data as well as the final diagnosis of the included patients are presented in Table 1. In coronary CTA, 51

Table 1. Baseline demographic and clinical characteristics of patients (n = 36).

Clinical characteristics	Categorical (N/%)	Metric (mean ± STD)
Male gender	29 (86.5 %)	
Average age, years		55.4 ± 13.9
Alimentary obesity	8 (26.7%)	
Average BMI (kg/m ²)		26.8 ± 4.0
Smoking	18 (34.6%)	
Family history	8 (23.3%)	
Hypertension	21 (70.0%)	
Diabetes mellitus	1 (3.3%)	
Increase of total cholesterol levels	10 (33.3%)	
Average cholesterol (mmol/l)		4.9 ± 1.0
Increased triglycerides level	4 (13.3%)	
Average triglyceride level (mmol/l)		1.9 ± 1.1
History of myocardial infarction	7 (23.3%)	
Final diagnosis	Acute myocardial infarction	12 (33.3%)
	Unstable progressive angina	18 (50%)
	New onset of angina	6 (16.7%)

coronary lesions in 36 patients were found. Each of the patients suffered from at least one stenosis. Twenty-five patients had one stenosis, 7 patients had 2, and 4 patients had 3 stenoses. In coronary CTA, stenoses less than 50% were found in 3 segments, stenoses of 50–69% in 20 segments and stenoses of 70–99% in 28 segments. In ICA, stenoses of less than 50% were found in 15 segments, stenosis of 50–69% in 14 segments and stenoses of 70–99% in 22 segments. In IVUS, stenoses less than 50% were found in 6 segments, stenoses of 50–69% in 12 segments and stenoses of 70–99% in 33 segments (Table 2 and Figure 2). In coronary CTA, coronary plaques were described as noncalcified plaques in 26, as partially calcified plaque in 21 and as calcified plaques in 4 lesions. For detailed description of plaque characteristics see Table 3.

3.2. Coronary CTA versus IVUS

The largest differences in the estimation of the degree of a stenosis between coronary CTA and IVUS are -25% and +26%. The mean difference is -0.45%, while the 95% confidence interval for the mean difference is [-3.5%, 2.6%]. The standard deviation is 10.8%. While not significant ($p = 0.068$), we observe a trend in the plot (see Figure 3, grey line, Intercept: -14.621, SE: 7.305, $p = 0.053$ and Mean: 0.201, SE: 0.101, $p = 0.068$), that is, the lower the mean grade of a stenosis, the lower the coronary CTA measurements in comparison to the IVUS measurements and vice-versa. Sensitivity of stenosis >50% detection of coronary CTA compared to IVUS was 95%, specificity was 86%, PPV was 98% and NPV 75%.

3.3. Coronary CTA versus ICA

The largest differences between coronary CTA and ICA are -15% and 55%. The mean difference is 13.19%, while the 95% confidence interval for the mean difference is [9.1%, 17.3%]. The standard deviation is 14.5%. This means that on average, ICA estimates lower grades of stenosis. We observe a significant ($p < 0.001$) trend in the plot (Figure 4,

grey line, Intercept: 38.397, SE: 5.739, $p = 0.00$, Mean: -0.397, SE: 0.085, $p = 0.0004$), that is, the lower the mean grade of stenosis, the higher the coronary CTA measurements in comparison to the ICA measurements and vice-versa. Sensitivity of stenosis >50% detection of coronary CTA compared to ICA was 100%, specificity was 36%, PPV was 67%, and NPV was 100%.

3.4. ICA versus IVUS

The largest differences between ICA and IVUS are -49% and 27%. The mean difference is -13.64%, while the 95% confidence interval for the mean difference is [-18.1%, -9.2%]. The standard deviation is 15.8%, thereby ICA tends to measure lower grades of stenosis than IVUS on average. We observe a significant ($p < 0.001$) trend in the plot (Figure 5, grey line, Intercept: -51.128, SE: 6.064, $p = 0$), that is, the lower the mean grade of stenosis, the lower the ICA measurements in comparison to the IVUS measurements and vice versa. Sensitivity of stenosis >50% detection of ICA compared to IVUS was 66%, specificity was 100%, PPV was 100% and NPV was 32%.

3.5. Effect of predictors on the different measurement techniques

Possible effects of given predictors on the differences of the measurement techniques were evaluated using univariate linear mixed models (Table 4).

There was no significant effect of the influence of positive remodeling on the measured severity of the coronary stenosis. Thus, the methods were not influenced in a different way by positive remodeling.

4. Discussion

The presented results showed a good agreement of the measured degree of coronary stenosis between cardiovascular CT and IVUS (as reference method) based on morphological changes of the coronary wall

Table 2. Detailed description of stenosis degree determined by invasive coronary angiography (ICA), intravascular ultrasound (IVUS), and coronary CT angiography (CTA).

number	stenosis ICA %	stenosis IVUS %	stenosis CTA %	number	stenosis ICA %	stenosis IVUS %	stenosis CTA %
N ^o 1	99	90	98	N ^o 27	40	79	67.5
N ^o 2	20	67	60	N ^o 28	60	76	72.5
N ^o 3	95	82	97.5	N ^o 29	60	66	70
N ^o 4	50	70	50	N ^o 30	98	80	96
N ^o 5	99	72	98	N ^o 31	35	62	62.5
N ^o 6	30	45	50	N ^o 32	70	87	80
N ^o 7	10	53	65	N ^o 33	80	80	82.5
N ^o 8	60	78	85	N ^o 34	50	65	70
N ^o 9	30	59	72.5	N ^o 35	70	78	75
N ^o 10	80	76	75	N ^o 36	70	86	85
N ^o 11	70	68	67.5	N ^o 37	70	78	82.5
N ^o 12	80	80	70	N ^o 38	10	59	52.5
N ^o 13	40	50	45	N ^o 39	75	78	85
N ^o 14	70	84	62.5	N ^o 40	85	86	70
N ^o 15	60	81	65	N ^o 41	70	76	70
N ^o 16	50	75	67.5	N ^o 42	50	75	65
N ^o 17	20	55	30	N ^o 43	70	83	77.5
N ^o 18	80	88	90	N ^o 44	20	41	50
N ^o 19	60	82	67.5	N ^o 45	80	86	95
N ^o 20	30	45	50	N ^o 46	50	42	62.5
N ^o 21	60	79.5	77.5	N ^o 47	30	56.6	55
N ^o 22	75	84	80	N ^o 48	20	39	22.5
N ^o 23	50	73	75	N ^o 49	20	46	50
N ^o 24	40	74.5	73.5	N ^o 50	95	87	98
N ^o 25	50	58	57.5	N ^o 51	70	81	95

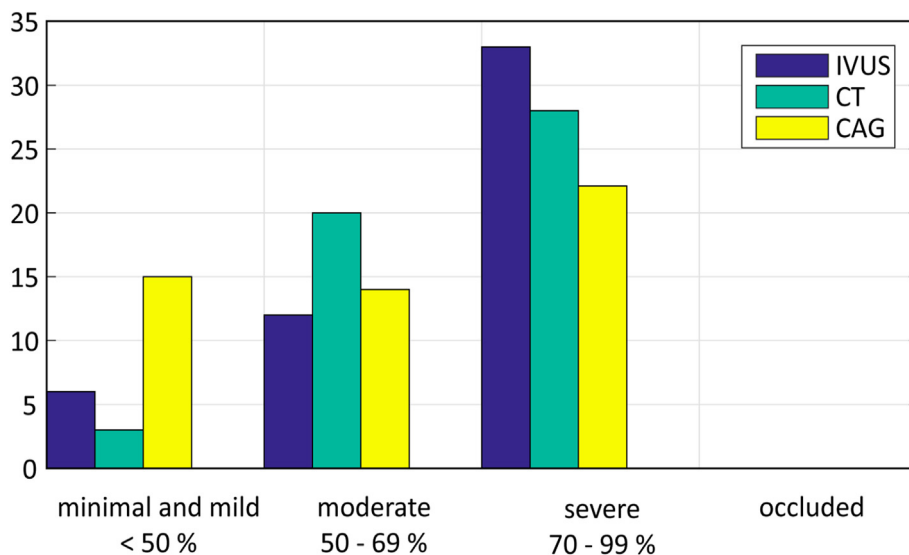


Figure 2. Classification of stenoses according to recommended quantitative stenosis grading by method.

Table 3. Coronary plaques classified by coronary CTA and IVUS.

Coronary CTA	N (%)	IVUS	N (%)
Noncalcified plaque	26 (50)	Fibroatheroma	42 (82.35)
		Hematoma	1 (1.96)
		Spontaneous dissection with superficial thrombosis	1 (1.96)
		Fibrous plaques	2 (3.9)
		Calcified fibroatheroma	5 (9.8)
Partly calcified plaque	21 (40.4)		
Calcified plaque	4 (9.6)		

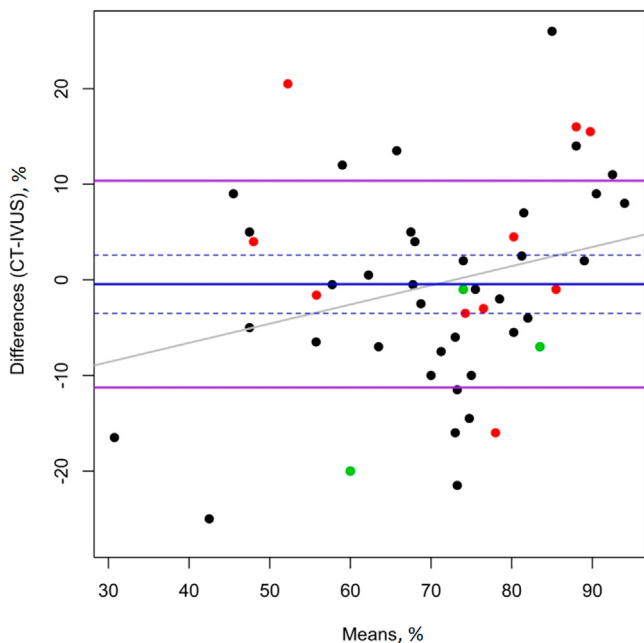


Figure 3. Bland-Altman plot of CT vs. IVUS. Figure 3–5: Black data points represent the first measurements of patients, red data points represent the second measurements of patients and green data points represent the third measurements of patients. The blue line represents the mean difference between the two measuring techniques, while the dashed blue lines represent the 95 percent confidence interval for the mean difference. The purple lines represent the mean difference ± the standard deviation of the difference. The grey line marks the fitted linear mixed model regression line.

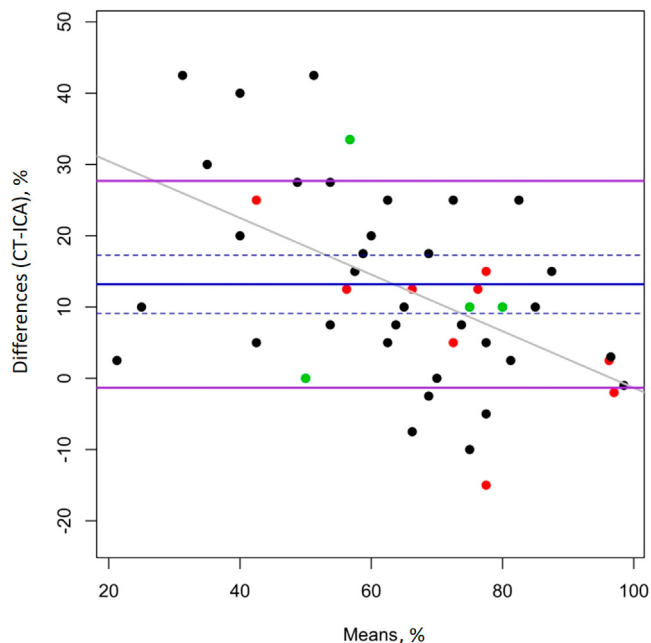


Figure 4. Bland-Altman plot of CT vs. ICA (explanation see Figure 3).

and subsequent narrowing of the coronary lumen. Comparing cardiovascular CT and IVUS, the Bland-Altman-plot (Figure 3) showed a mean difference in the degree of stenosis of -0.45% (95% CI [-3.5%, 2.6%]). The severity of coronary stenosis determined by cardiovascular CT is comparable to IVUS. Still, a non-significant trend that for small mean

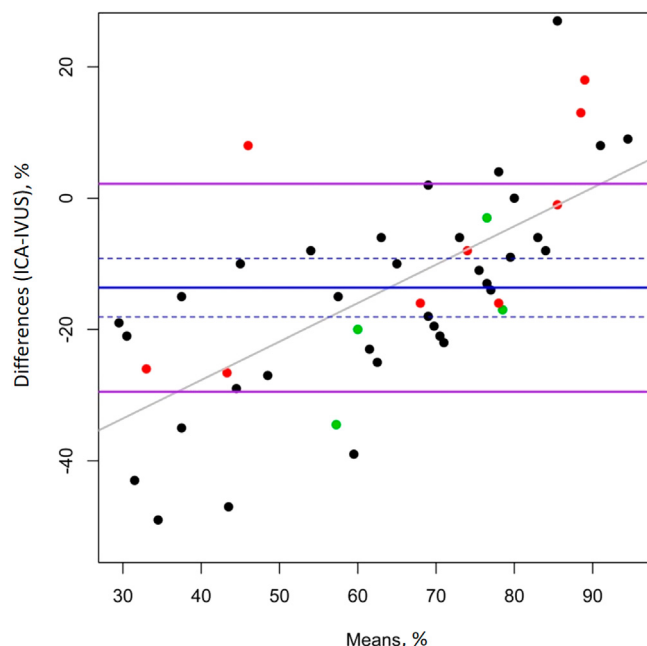


Figure 5. Bland-Altman plot of ICA vs. IVUS (Explanation see Figure 3).

stenoses IVUS tended to measure larger values than cardiovascular CT and some larger intra-individual differences could be observed. As the differences in the results could not be explained by the given predictors and the final diagnosis in Table 4, we conclude that both methods performed in a comparable way in patients with different clinical characteristics. However, the differences in the degree of stenosis will need further attention in future applications. Our results correspond well to comparable studies measuring the severity of coronary stenosis based on Dual Source Computed Tomography and IVUS [16].

Comparing cardiovascular CT and ICA (CT vs. ICA) as well as IVUS and ICA (IVUS vs. ICA), the mean differences are similar. ICA tended to measure smaller stenosis grades than IVUS and cardiovascular CT. For small mean grades of stenosis, cardiovascular CT and IVUS tended to measure larger values than ICA.

It could be shown that ICA tends to underestimate stenosis degrees in case of asymmetrically placed eccentric plaques that account for about 20–30% of all identified coronary plaques [27] since ICA measures the diameter of the lesion in the longitudinal and not in the cross-sectional view. Opposite to contrast-enhanced cardiovascular CT, in ICA the contrast agent is injected directly into a coronary artery, which may dilate the vessel [5, 6]. To prevent spasm of coronary vessels initiated by touching the coronary walls with a catheter or wire in ICA and similarly IVUS, intracoronary nitroglycerin is injected which again may have cause coronary dilatation [3, 5, 36]. In cardiovascular CT, the contrast agent is intravenously administered reducing the direct effect on the coronary arteries. No nitroglycerin was used in this cardiovascular CT study.

The direct comparison of ICA to IVUS/cardiovascular CT is restricted because of different imaging principles resulting in the application of different methods of stenosis measurements. ICA assesses stenosis degree by measuring the internal diameter at the site of arterial stenosis in comparison to the proximal and/or distal part of unaltered luminary reference diameter. IVUS and CT as cross-sectional imaging methods visualize vessel structures enabling similar intra-luminary diameter and stenosis measurements and deviate therefore in a similar way from ICA. Using this approach, positive remodeling did not have any significant effect on the estimation of the stenosis degree in IVUS or cardiovascular CT, as previously described [36].

All three examinations were carried out for all patients included, leading to a total of 153 measurements to compensate for the small number of patients available for the analysis. A bias in our study may arise from the fact that all examinations were performed in the same order (cardiovascular CT, IVUS, ICA) for all patients. The degree of stenosis may change within the period of max. 48 h in consequence of patho-/physiologic mechanisms and/or because of the application of cardiac and pain medication.

The use of cardiovascular CT-technology leads to faster diagnosis as well as faster discharge from hospital in case of negative findings compared to standard approach [27, 31]. Since all patients had to undergo all three examinations, we cannot add any information about the possibilities of faster diagnosis and faster discharge. Further studies will be necessary.

To the best of our knowledge this is one of the first clinical studies evaluating the use of cardiovascular CT as primary option for diagnosis and decision-making in patients with ACS in an emergency setting

Table 4. Differences between cardiovascular CT-IVUS, ICA-IVUS and cardiovascular CT-ICA with respect to patient demographics in univariate linear mixed models (LMMs) for used predictors.

Predictor	Cardiovascular CT- IVUS			ICA-IVUS			Cardiovascular CT-ICA		
	Est	SE	p-value	Est	SE	p-value	Est	SE	p-value
Gender	-4.807	4.089	0.248	2.269	6.294	0.721	-6.694	5.854	0.261
Age	-0.096	0.126	0.452	-0.026	0.189	0.892	-0.051	0.176	0.776
Obesity	2.577	4.006	0.524	2.065	5.979	0.732	0.162	5.675	0.977
BMI	-0.065	0.402	0.872	-0.033	0.599	0.957	-0.084	0.575	0.885
Smoking	-2.745	3.279	0.408	-5.378	4.829	0.273	2.949	4.673	0.597
Family history	-8.269	3.580	0.027	-0.526	5.884	0.929	-9.202	5.516	0.104
Hypertension	2.471	3.343	0.465	1.602	4.986	0.750	1.173	4.768	0.807
Diabetes	0.113	11.33	0.992	15.821	16.600	0.348	-15.743	15.274	0.311
Increase of total cholesterol	-3.495	3.636	0.344	-2.447	5.556	0.663	4.105	7.629	0.594
Total cholesterol	-0.551	1.691	0.746	-1.311	2.538	0.609	0.885	2.434	0.719
Increase of triglycerides	-0.149	5.209	0.977	-5.166	7.763	0.511	4.105	7.629	0.594
Triglycerides	-0.786	1.694	0.646	-1.069	2.535	0.676	-0.160	5.338	0.840
History of myocardial infarction	-4.606	4.219	0.283	6.781	6.263	0.287	-11.389	5.680	0.053
Acute myocardial infarction	0.966	3.524	0.786	2.442	5.251	0.645	-1.825	5.002	0.718
Unstable progressive angina	-0.432	3.304	0.897	-0.620	4.929	0.901	0.710	4.700	0.881
New onset of angina	-2.794	4.749	0.560	-10.228	6.864	0.145	7.651	6.916	0.276
Positive remodeling	-1.342	3.062	0.668	-1.420	4.442	0.754	0.148	3.699	0.969

sequentially comparing all measurement methods (IVUS, ICA, cardiovascular CT).

Although the studied group of patients was limited, the results appear convincing as all imaging methods were performed in every patient in a very narrow time-frame and in contrast to other studies not by exclusion of the disease (negative prediction value) but by high numbers of diseased patients (positive prediction value). These findings are supported by the fact that the final diagnosis did not lead to any significant differences in the measurement results.

5. Conclusion

The cardiovascular CT results show that even in emergency settings it is possible to identify morphological changes as sequels of coronary artery sclerosis with comparable results to the reference method IVUS. Deviations of IVUS and cardiovascular CT from ICA are comparable and can to a large extent be explained by differences in the measurement technique.

Declarations

Author contribution statement

S. Ternovoy and A. Rienmueller: Conceived and designed the experiments.

M. Shariya, M. Shabanova and S. Gaman: Performed the experiments.

D. Ustyuzhanin and T. Rienmueller: Analyzed and interpreted the data; Wrote the paper.

L. Meyer: Analyzed and interpreted the data.

N. Serova, V. Mironov and I. Merkulova: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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