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Association between carotid and coronary atherosclerotic plaque morphology: a virtual histology intravascular ultrasound study

Dace Sondore[1], Kārlis Trušinskis[1,2], Matīss Linde[2]*, Ieva Briede[1,3], Inga Narbute[1,3], Sanda Jēgere[1,3], Kārlis Griķis[1,3], Kārlis Štrenge[1,3], Andrejs Ērglis[1,3]

[1]Latvian Centre of Cardiology, Pauls Stradins Clinical University Hospital, Riga, Latvia, [2]Department of Internal Diseases, Faculty of Medicine, Riga Stradins University, Riga, Latvia, [3]Department of Cardiology and Cardiosurgery, Faculty of Medicine, University of Latvia, Riga, Latvia.

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**Corresponding authors:*
Matīss Linde
Faculty of Medicine, Riga Stradins University, Riga, Latvia.
Tel: +371 28141749
Email: matiss.linde@rsu.lv

ABSTRACT

Background and Aim: Atherosclerosis is considered to be a systemic disease; however, evidence exists on the heterogeneous nature of atherosclerotic disease. To date, continuous research seeks to determine the morphological differences between carotid and coronary artery disease. This study aimed to evaluate the relationship of morphological characteristics assessed by virtual histology intravascular ultrasound (VH-IVUS) between carotid and coronary plaque composition among patients with and without a history of cerebrovascular events.

Methods: This study was a single-center prospective study (n = 100; age 69.6 ± 8.4). All patients were scheduled for carotid or coronary artery stenting and underwent VH-IVUS examination of the carotid and coronary arteries before intervention.

Results: There was a modest, but statistically significant correlation between the carotid and coronary necrotic core ([NC] r = 0.46, P < 0.01), fibrofatty ([FF] r = 0.38, P < 0.01), dense calcium (r = 0.56, P < 0.01), and fibrous (r = 0.42, P < 0.01) plaque composition. The high amount of NC was detected in both arteries of the carotid artery stenting (CAS) group with higher proportion in the coronary artery (20.2% ± 9.4% vs. 22.7% ± 6.8%, P = 0.02). More fibrolipid content was observed in carotid plaque compared to coronary (19.6% ± 9.9% vs. 12.2% ± 8.1%, P < 0.01). Patients with a history of cerebrovascular events had a numerically greater proportion of necrotic tissue in the carotid artery compared to asymptomatic and symptomatic CAS group patients (23.5% ± 10.7% vs. 18.9% ± 8.2% and 18.7% ± 9.5%, P = 0.11).

Conclusion: The percentage of all analyzed plaque components was moderately correlated between coronary and carotid artery plaques. Nevertheless, the proportion of NC plaque tissue was greater in the coronary arteries, while the carotid arteries showed more %FF atherosclerotic lesions. CAS group patients with a history of cerebrovascular events had a tendency of greater proportion of necrotic tissue in analyzed carotid plaques compared to others in the CAS group.

Relevance for Patients: In this study, we found that patients with a history of cerebrovascular event had a tendency of increased NC content in culprit lesion of carotid artery. Complementary use of non-invasive and invasive imaging modalities allows to detect high-risk atherosclerotic plaques and adjust treatment strategy.

1. Introduction

Atherosclerosis is a chronic systemic inflammatory disease affecting the arterial wall throughout the human body. Common clinical manifestations are ischemic cardiovascular events, such as cerebrovascular accidents and myocardial infarctions, which are the results of atherosclerotic changes in the extracranial carotid and coronary arteries. Associations

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between carotid atherosclerotic changes and the extent and severity of coronary artery disease (CAD) are well-known [1-4]. Virtual histology (VH) is an established technique that allows for the in vivo assessment of plaque composition [5]. As such, VH intravascular ultrasound (VH-IVUS) provides information about plaque features, such as necrotic core (NC) tissue, which among others characterize the so-called vulnerable plaque [6]. VH-IVUS allows to assess coronary plaque composition and to detect thin cap fibroatheroma which, along with the degree of plaque burden, is predictors of adverse outcome [7,8].

The aim of the present study was to evaluate the relationship of morphological characteristics assessed by VH-IVUS between carotid and coronary plaque composition among patients with a history of cerebrovascular accidents and subjects without a prior adverse event.

2. Study Design

This was a single-center and cross-sectional study performed at the Latvian Center of Cardiology, Pauls Stradins Clinical University Hospital. Study participants were consecutive patients referred to the center with symptoms of ischemia (cerebral or cardiac) for invasive diagnosis of artery disease. After coronary/carotid artery angiography, patients were scheduled for percutaneous coronary intervention (PCI) or carotid artery stenting (CAS). Based on this qualification, all patients were divided into two groups: The CAS and PCI group. Indications for this procedure in the CAS group were stenosis ≥60% in the ipsilateral carotid artery in patients with current symptoms, a history of cerebrovascular event, or hemodynamically significant stenosis (≥75%) in asymptomatic patients. In the PCI group, patients with hemodynamically significant coronary artery narrowing were scheduled for PCI. All patients had atherosclerotic lesion with <50% narrowing in other vascular bed (non-culprit) and no other lesions requiring revascularization. Both, the culprit and non-culprit lesion, were selected for VH-IVUS analysis. The study included 78 patients who underwent CAS and 22 patients who underwent PCI. Patients in the CAS group were categorized in asymptomatic, symptomatic, and history of cerebrovascular event subgroups. PCI group was divided into stable angina and asymptomatic patients. The study was approved by the Local Ethics Committee, and all subjects provided informed written consent.

2.1. VH

All patients underwent VH-IVUS examination of coronary and carotid plaques. Under fluoroscopy, an IVUS catheter (Eagle Eye™; *Volcano Therapeutics Inc.*; *CA*, *USA*) was positioned in the carotid artery and then in the coronary artery. The IVUS catheter was pulled back at a continuous speed of 0.5 mm/s from the distal part of the carotid or coronary artery. The length of the pullback segment varied according to plaque length. The pullback was initiated 10–20 mm distal to the plaque and terminated 10–20 mm proximal to the plaque. In the carotid artery, if a cerebral protection device was used, the IVUS pullback catheter was positioned on the cerebral protection device wire. For CAS procedures, but not for carotid artery imaging with IVUS in the absence of intervention [9], distal protection devices (Spider, EV3; Filter wire EZ, Boston Scientific; Emboshield, Abbott) were used.

2.2. Statistical analysis

Continuous data are represented as mean ± standard deviation, whereas categorical data were expressed as numbers or frequencies of occurrence. For the categorical data analysis, we used a Chi-square test. For the continuous data, we first assessed normality using visual inspection of a normal probability plot and a formal test, the Shapiro–Wilk test. Differences between carotid and coronary VH-IVUS findings were analyzed using a non-parametric related samples test, the Wilcoxon signed-rank test, and a parametric paired samples *t*-test. Pearson's correlations were used to assess the relation between carotid and coronary atherosclerotic plaque components. Two-way analysis of variance test was used to test for the main effects of each independent variable, as well as the interaction effect between them. All statistical analyses were performed using the IBM SPSS software package (IBM SPSS Statistics 22.0, Chicago, IL, USA). $P < 0.01$ was considered to indicate statistical significance.

3. Results

A total of 100 patients were enrolled in this study, and VH-IVUS examination was performed on the carotid and coronary arteries. In the CAS group, the mean age between asymptomatic, symptomatic, and with a history of cerebrovascular events patients varied from 67 to 69 years, and predominantly more men were present in each group. Furthermore, the SYNTAX score for each CAS subgroup is shown in Table 1. Overall, baseline clinical characteristics of the study population are shown in Tables 1 and 2.

Table 3 summarizes the VH-IVUS characteristics of the analyzed carotid and coronary artery plaques in the CAS group. Carotid arteries were larger according to the analyzed VH-IVUS parameters and had a higher plaque burden and necrotic tissue percentage in analyzed arteries compared to coronary arteries. The analyzed segment length did not differ between the coronary and carotid arteries (17.1 ± 9.9 mm and 15.8 ± 8.3 mm, $P = 0.26$).

Procedural and VH-IVUS characteristics of the PCI group are shown in Table 4.

VH comparison between carotid and coronary arteries is shown in Table 5. The analyzed segment of the carotid artery had a lower percentage of necrotic tissue and calcium, but a significantly higher percentage of fibrolipids. The percentage of fibrotic tissue did not differ among the analyzed vascular beds.

The analyzed segments showed moderately positive, statistically significant correlations among the analyzed vascular beds – NC (r = 0.46, $P < 0.01$), fibrotic tissue (r = 0.42, $P < 0.01$), fibro-fatty tissue ([FF] r = 0.37, $P < 0.01$), and dense calcium tissue ([DC] r = 0.56, $P < 0.01$). The correlation between carotid and coronary plaque composition of all analyzed lesions is displayed in Figure 1.

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Table 1. Baseline characteristics of CAS group

Characteristic	Asymptomatic, *n*=31	Symptomatic, *n*=32	H/O cerebrovascular event, *n*=15	*P*-value
Age, years	69.26±8.36	69.63±8.64	67.27±9.15	0.17
Body mass index, kg/m^2	27.05±3.61	27.55±5.64	28.37±3.81	0.44
Gender				
Male, *n* (%)	23 (74.2)	18 (56.3)	10 (66.7)	0.32
Female, *n* (%)	8 (25.8)	14 (43.8)	5 (33.3)	0.32
Analyzed artery				
Left internal carotid artery, *n* (%)	15 (48.4)	17 (53.1)	9 (60.0)	0.76
Right internal carotid artery, *n* (%)	16 (51.6)	15 (46.1)	6 (40.0)	0.76
Left anterior descending coronary artery, *n* (%)	16 (51.6)	13 (40.6)	8 (53.3)	0.60
Left circumflex coronary artery, *n* (%)	8 (25.8)	6 (18.8)	2 (13.3)	0.59
Right coronary artery, *n* (%)	7 (22.6)	13 (40.6)	5 (33.3)	0.31
SYNTAX score	17.66±4.42	16.32±5.42	19.51±3.68	0.78
Smoking				
Active smoker, *n* (%)	2 (6.5)	3 (9.4)	4 (26.7)	0.12
Former smoker, *n* (%)	9 (29.0)	8 (25.0)	4 (26.7)	0.94
Non-smokers, *n* (%)	11 (35.5)	17 (53.1)	5 (33.3)	0.27
Diabetes mellitus, *n* (%)	7 (22.6)	9 (28.1)	5 (33.3)	0.73
Dyslipidemia, *n* (%)	30 (96.8)	31 (96.9)	15 (100)	0.78
Arterial hypertension, *n* (%)	26 (83.9)	27 (84.4)	15 (100)	0.25
Myocardial infarction, *n* (%)	12 (38.7)	11 (34.4)	6 (40.0)	0.91
PCI in history, *n* (%)	12 (38.7)	12 (37.5)	4 (26.7)	0.71
Peripheral arterial disease, *n* (%)	15 (48.4)	8 (25.0)	7 (46.7)	0.12
Familial history of cardiovascular disease, *n* (%)	7 (22.6)	3 (9.4)	5 (33.3)	0.15
Atrial fibrillation				
Permanent, (%)	6 (19.4)	6 (18.8)	3 (20.0)	0.99
Paroxysmal, (%)	1 (3.2)	4 (12.5)	4 (26.7)	0.06
None, (%)	23 (74.2)	22 (68.8)	8 (53.3)	0.36

CAS: carotid artery stenting, PCI: Percutaneous coronary intervention

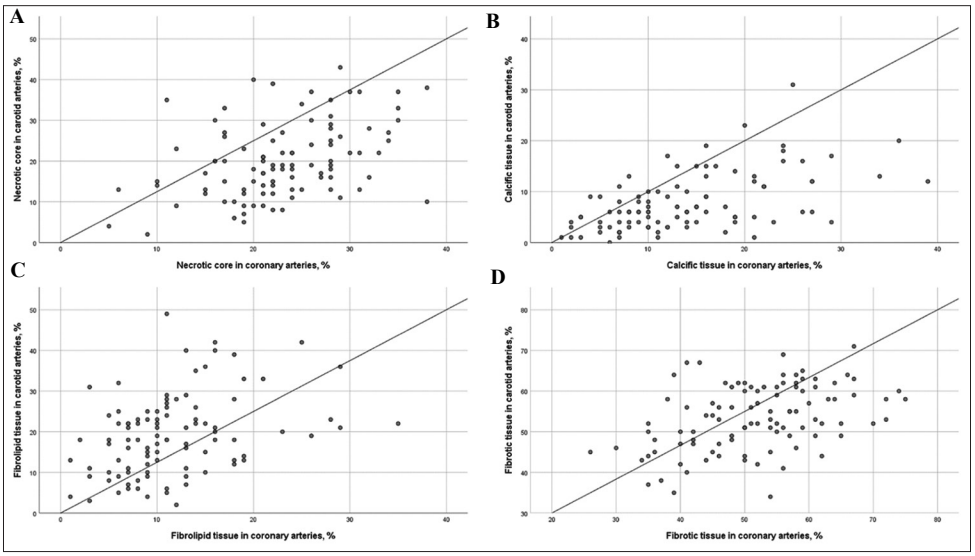

Figure 1. Correlation between carotid and coronary plaque composition in study patients. Correlation of: A) necrotic cores, B) calcified tissue, C) fibrolipidic tissue, and D) fibrotic tissue among carotid and coronary arteries.

Patients with history of cerebrovascular event had a tendency toward a higher percentage of necrotic tissue and a lower percentage of fibrolipids in carotid artery plaques. Fibrotic tissue and calcium in the carotid artery did not differ between patients

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Table 2. Baseline characteristics of PCI group

Characteristic	Stable angina (*n*=16)	Asymptomatic (*n*=6)	*P*-value
Age, years	69.47±8.31	67.27±8.60	0.42
Body mass index, kg/m^2	27.59±3.83	28.13±3.95	0.50
Gender			
Male, *n* (%)	8 (50.0)	1 (16.7)	0.21
Female, *n* (%)	8 (50.0)	5 (83.3)	0.21
Analyzed artery			
Left internal carotid artery, *n* (%)	12 (75.0)	3 (50.0)	0.31
Right internal carotid artery, *n* (%)	3 (18.8)	3 (50.0)	0.35
Left anterior descending coronary artery, *n* (%)	5 (31.3)	2 (33.3)	0.40
Left circumflex coronary artery, *n* (%)	3 (18.8)	1 (16.7)	0.88
Right coronary artery, *n* (%)	7 (43.8)	3 (50.0)	0.64
Smoking			
Active smoker, *n* (%)	3 (18.8)	0 (0.0)	0.25
Former smoker, *n* (%)	1 (6.3)	1 (16.7)	0.45
Non-smokers, *n* (%)	12 (75.0)	4 (66.7)	16
Diabetes mellitus, *n* (%)	2 (12.5)	2 (33.3)	0.26
Dyslipidemia, *n* (%)	16 (100)	6 (100)	n/a
Arterial hypertension, *n* (%)	15 (93.8)	6 (100)	0.53
Acute cerebral event in history, *n* (%)	7 (43.8)	1 (16.7)	0.24
Myocardial infarction, *n* (%)	4 (25.0)	3 (50.0)	0.26
PCI in history, *n* (%)	3 (18.8)	3 (50.0)	0.14
Peripheral arterial disease, *n* (%)	7 (43.8)	2 (33.3)	0.66
Familial history of cardiovascular disease, *n* (%)	5 (31.3)	1 (16.7)	0.48
Atrial fibrillation			
Permanent, (%)	2 (12.5)	0 (0.0)	0.36
None, (%)	14 (100)	6 (100)	0.36

PCI: Percutaneous coronary intervention

Table 3. Procedural and VH-IVUS characteristics of CAS group

Characteristic	Carotid artery (*n*=78)	Coronary artery (*n*=78)	*P*-value
CAS artery			
Left internal carotid artery, *n* (%)	41 (52.6)	-	-
Right internal carotid artery, *n* (%)	37 (47.4)	-	-
Analyzed artery			
Left anterior descending coronary artery, *n* (%)	-	37 (47.4)	-
Left circumflex coronary artery, *n* (%)	-	16 (20.5)	-
Right coronary artery, *n* (%)	-	25 (32.1)	-
Minimal lumen diameter, mm, mean±SD	2.5±0.6	2.1±0.4	<0.01
Mean lumen diameter, mm, mean±SD	4.3±0.8	3.0±0.5	<0.01
Minimal lumen area, mm, mean±SD	7.9±4.0	4.8±1.7	<0.01
Minimal vessel diameter, mm, mean±SD	5.8±0.7	3.8±0.7	<0.01
Mean vessel diameter, mm, mean±SD	7.2±0.7	4.6±0.7	0.36
Vessel volume, mm^3, mean±SD	715.2±476.6	258.8±159.4	<0.01
Plaque volume, mm^3, mean±SD	439.8±306.4	153.2±105.7	0.22
Plaque burden, %, mean±SD	61.8±10.4	56.4±8.5	<0.01
Segment length, mm, mean±SD	17.1±9.9	15.8±8.3	0.26
Necrotic tissue, %, mean±SD	20.2±9.4	22.7±6.8	0.02
Fibrotic tissue, %, mean±SD	52.5±7.7	51.7±10.3	0.37
Fibrolipids, %, mean±SD	19.6±9.9	12.2±8.1	<0.01
Calcium, %, mean±SD	8.24±5.9	13.7±6.8	<0.01

CAS: carotid artery stenting, VH-IVUS: Virtual histology intravascular ultrasound, SD: Standard deviation

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Table 4. Procedural and VH-IVUS characteristics of PCI group

Characteristic	Carotid artery (*n*=22)	Coronary artery (*n*=22)	*P*-value
PCI artery			
Left anterior descending coronary artery, *n* (%)	-	8 (36.4)	-
Left circumflex coronary artery, *n* (%)	-	4 (18.2)	-
Right coronary artery, *n* (%)	-	10 (45.5)	-
Analyzed artery			
Left internal carotid artery, *n* (%)	6 (27.3)	-	-
Right internal carotid artery, *n* (%)	16 (72.7)	-	-
Minimal lumen diameter, mm, mean±SD	3.6±0.6	2.0±0.7	<0.01
Mean lumen diameter, mm, mean±SD	5.0±0.5	2.9±0.1	<0.01
Minimal lumen area, mm, mean±SD	13.8±3.9	4.2±0.3	<0.01
Minimal vessel diameter, mm, mean±SD	6.3±1.0	3.8±0.1	<0.01
Mean vessel diameter, mm, mean±SD	7.4±0.8	4.5±0.2	<0.01
Vessel volume, mm^3, mean±SD	716.7±447.9	309.6±37.7	<0.01
Plaque volume, mm^3, mean±SD	390.3±268.5	182.3±24.0	<0.01
Plaque burden, %, mean±SD	53.4±7.7	57.8±5.8	0.03
Segment length, mm, mean±SD	15.4±8.3	18.1±1.5	0.17
Necrotic tissue, %, mean±SD	18.6±9.4	22.5±1.9	0.05
Fibrotic tissue, %, mean±SD	56.5±8.0	50.6±2.1	0.07
Fibrolipids, %, mean±SD	19.3±10.2	13.9±2.7	0.36
Calcium, %, mean±SD	5.6±4.4	13.6±1.8	<0.01

VH-IVUS: Virtual histology intravascular ultrasound, PCI: Percutaneous coronary intervention, SD: Standard deviation

Table 5. Virtual histology comparison between carotid and coronary arteries

Characteristic	Carotid artery (*n*=100)	Coronary artery (*n*=100)	*P*-value
Necrotic tissue, %, mean±SD	19.8±9.4	22.6±7.3	<0.01
Fibrotic tissue, %, mean±SD	53.4±8.0	51.7±10.3	0.09
Fibrolipids, %, mean±SD	19.6±9.6	12.5±9.1	<0.01
Calcium, %, mean±SD	7.7±5.6	13.6±8.2	<0.01

SD: Standard deviation

with and without a history of cerebrovascular event. In contrast, the percentage of all analyzed tissue types in the coronary arteries did not differ among patients with and without cerebrovascular event histories (Table 6).

Two patients had post-procedural acute ipsilateral cerebrovascular events. Their carotid plaque composition was similar to others in the CAS group. Non-ipsilateral post-procedural intrahospital cerebrovascular events were not observed in our study population.

Representative VH-IVUS case analysis is shown in Figure 2, in which increased necrotic tissue amount in carotid and coronary artery of 74.0% and 48.8%, respectively, was identified by VH-IVUS analysis of culprit lesion in the left internal carotid artery and non-culprit lesion in the mid-third of the right coronary artery. VH-IVUS data revealed higher amount of DC tissue in the analyzed coronary segment compared to carotid plaque (13.7% vs. 9.0%).

4. Discussion

This study investigated the association between carotid and coronary plaque types as assessed by VH-IVUS in patients with multiple risk factors who were scheduled for carotid or coronary artery stenting. The findings of the present study were as follows: (1) the carotid plaque composition was significantly correlated with coronary plaque phenotype; (2) the percentage of NC and calcium tissue was significantly higher in the coronary arteries, whereas the amount of FF plaque component was greater in the carotid arteries; and (3) patients with a history of cerebrovascular events had a tendency of greater proportion of NCs in their carotid arteries compared to others in CAS group.

Inflammation in atherosclerotic plaque produces systemic effects, thus, active, ongoing inflammation at one vascular bed could enhance inflammation in another. A NC in VH corresponds to tissue areas in which the extracellular matrix is lacking (total loss of supporting collagen) and has been replaced by dead cells and lipid-rich cellular debris [10,11], thus, tissue characterized as the NC is the most vulnerable part of atherosclerotic lesions with ongoing inflammation. We observed that all analyzed tissue types by VH-IVUS, including NCs, were correlated between carotid and coronary vascular beds. Together with knowledge from previous studies, VH-IVUS analysis confirms that patients with more vulnerable plaque patterns at one site are at higher risk of having more vulnerable plaques at another site. However, different coronary and carotid impacts of shear stress, artery size, and static force are of great importance for the pattern of atherosclerosis in different vascular beds. Despite the correlation of the percentage of all analyzed tissue types in coronary and carotid artery plaques, we observed that the percentage of NCs was higher in the coronary artery (Table 3). Moreover, we observed that coronary arteries were more calcified, but carotid arteries

Table 6. Virtual histology analysis of CAS group

Characteristic	Asymptomatic (*n*=31)	Symptomatic (*n*=32)	H/O cerebrovascular event (*n*=15)	*P*-value
Carotid artery				
Necrotic tissue, %, mean±SD	18.9±8.2	18.7±9.5	23.5±10.7	0.11
Fibrotic tissue, %, mean±SD	54.4±7.3	52.1±8.4	53.3±8.6	0.47
Fibrolipids, %, mean±SD	20.3±9.4	20.9±10.5	15.9±9.7	0.15
Calcium, %, mean±SD	7.3±4.9	8.4±7.4	7.4±3.9	0.69
Coronary artery				
Necrotic tissue, %, mean±SD	22.8±7.9	21.8±6.8	23.1±6.9	0.74
Fibrotic tissue, %, mean±SD	50.4±10.3	52.6±11.2	53.0±9.2	0.53
Fibrolipids, %, mean±SD	12.8±9.8	12.8±9.4	11.6±7.3	0.87
Calcium, %, mean±SD	14.5±8.4	12.9±8.5	12.8±7.2	0.62

CAS: carotid artery stenting, SD: Standard deviation

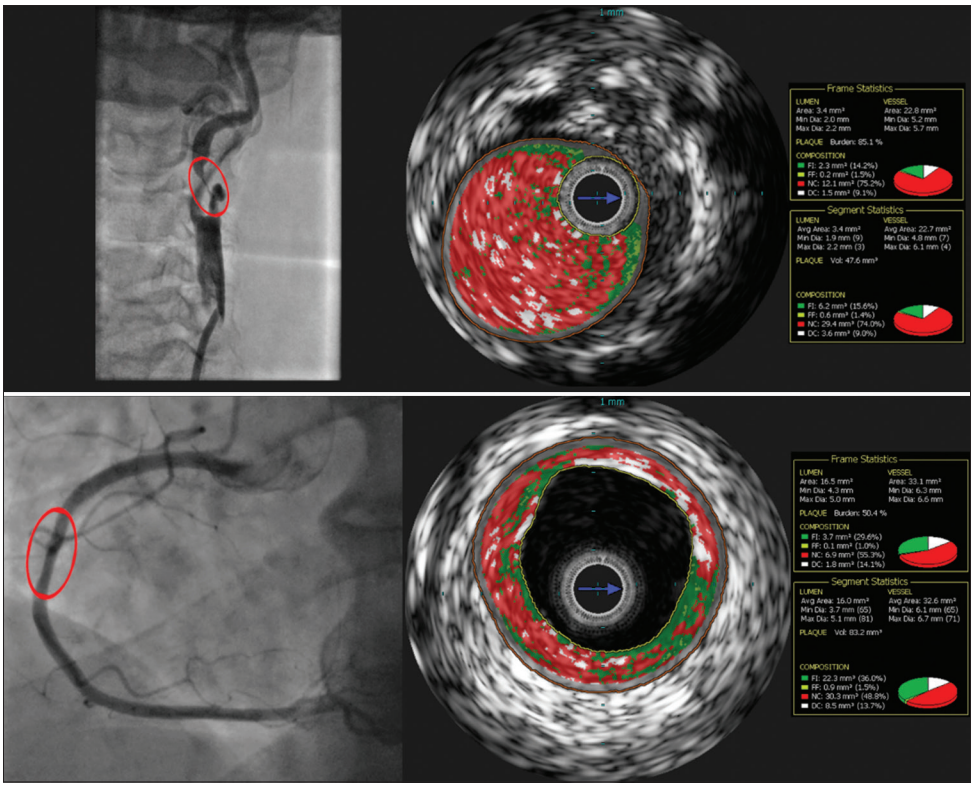

Figure 2. Representative case example of VH-IVUS analysis in the CAS patient.

contained more fibrolipids. A study by Samady *et al*. showed that wall shear stress alters the progression and composition of coronary atherosclerotic plaques [12]. Similarly, Eshtehardi *et al*. showed that low wall shear stress was associated with a NC and calcium coronary plaque tissue, emphasizing the impact of local hemodynamic conditions on plaque phenotype and atherosclerotic changes in the vessel wall [13]. As such, although atherosclerosis is considered a systemic inflammatory disease, its manifestations are heterogeneous within the same individual due to differences in arterial geometry, shear stress, and static forces.

Analyzing atherosclerotic plaques among patients with and without cerebrovascular events, we observed a tendency toward a higher NC in carotid plaques in patients with previous cerebrovascular events, but no difference between symptomatic and asymptomatic patients. Interestingly, two animal studies found no correlation between the VH-IVUS size of the NC and histological findings [14,15]. However, in the CAPITAL study, 15 patients underwent VH-IVUS examination of carotid plaque immediately followed by carotid endarterectomy. The results showed a strong correlation between VH-IVUS carotid plaque characterization and the true histological examination of the plaque, particularly in "vulnerable" plaque types [16]. These differences can be explained by different tissue types in animal and human atherosclerotic lesions. In the clinical setting, a series of 25 patients undergoing CAS reported a strong association between total plaque volume and FF volume on VH IVUS and

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the quantity of atherosclerotic debris obtained on retrieval of the distal embolic protection device [17]. Winston *et al*. showed an association between periprocedural cerebrovascular events and plaque composition by VH-IVUS [18]. We compared patients with and without cerebrovascular complications (cerebral infarction and transitory ischemic attack <24 h) after CAS and found no difference in carotid tissue composition by VH-IVUS. However, our study was not designed and does not have sufficient power to draw conclusions regarding post-procedural cerebrovascular complications. Similar carotid plaque composition in symptomatic and asymptomatic patients by VH-IVUS analysis highlights a need for further research to detect high-risk plaques combining invasive and non-invasive imaging modalities.

In our study, we found a higher percentage of calcium in the coronary compared to carotid arteries. A global registry of more than 3000 patients undergoing coronary VH IVUS showed that NC and DC content increases with age, were more common in men than in women, and were positively associated with serum low-density lipoprotein cholesterol, diabetes, and hypertension [19]. Pooled data from two clinical trials showed coronary calcium increase in patients receiving long-term high-dose statin therapy without impact on adverse cardiovascular events suggesting plaque stabilization [20]. All patients in our study received guideline-directed lipid-lowering therapy which could explain higher amount of DC in analyzed coronary arteries. In line with published evidence, our data confirm the systemic characteristics of atherosclerosis and the similar carotid and coronary plaque composition, but differences in calcium distribution between arterial territories.

The main limitation of our study was lack of blinded core laboratory VH-IVUS analysis. Furthermore, patients included in the CAS group were in greater proportion compared to the PCI group.

5. Conclusion

The percentage of all analyzed plaque components was correlated among coronary and carotid artery plaques. Nevertheless, coronary arteries contained more NCs and calcium, while carotid arteries had a higher percentage of fibrolipidic tissue. Patients with cerebrovascular events had a tendency toward a higher percentage of NCs in the carotid plaques.

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Conflicts of Interest

None.

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