

ORIGINAL RESEARCH

Regional Differences in the Level of Inflammation Between the Right and Left Coronary Arteries – a Coronary Computed Tomography Angiography Study of Epicardial Fat Attenuation Index in Four Scenarios of Cardiovascular Emergencies

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ABSTRACT

Introduction: The pericoronary fat attenuation index (FAI) is an emerging computed tomography-derived marker for measuring vascular inflammation at coronary vessels. It holds prognostic significance for major cardiovascular events and enhances cardiac risk assessment, complementing traditional risk factors and coronary artery calcium scores. However, the impact of local coronary circulation factors on pericoronary inflammation development in right versus left coronary arteries has not been clearly understood. **Objective:** This study aimed to investigate the regional differences in inflammation levels between the right and left coronary arteries in four clinical scenarios: acute coronary event in the follow-up period, post-COVID patients, recent percutaneous intervention, and unstable angina with significant lesions on native coronary arteries. **Methods:** The study included 153 patients (mean age 62 years, 70.5% male) who underwent clinically indicated coronary computed tomography angiography (CCTA). Vulnerable plaque features were analyzed to identify high-risk plaques. FAI and the FAI score, a score integrating risk factors and age, were calculated for each case at the left

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anterior descending artery (LAD), circumflex artery (LCX), and right coronary artery (RCA).

Results: A total of 459 coronary arteries were analyzed. Both FAI and FAI scores were higher in the RCA (15.23 ± 11.97) compared to the LAD (10.55 ± 6.78) and (11.48 ± 6.5) LCX ($p = 0.02$). FAI values showed a significantly higher level at the RCA (-71.25 ± 7.47 HU) compared to the LCX (-76 ± 7.68 HU) and the LAD (-73.04 ± 8.9 HU, $p < 0.0001$). This trend persisted across all subgroups, including post-COVID CT scans (-75.49 ± 7.62 HU for RCA vs. -72.89 ± 9.40 HU for the LCX vs. -71.28 ± 7.82 HU for the LAD, $p = 0.01$) and patients with high-risk plaques (20.98 ± 16.29 for the RCA vs. 11.77 ± 7.68 for the LCX vs. 12.83 ± 6.47 for the LAD, $p = 0.03$).

Conclusion: Plaques in different coronary areas show varied vulnerability and inflammation levels. The RCA, in particular, demonstrates greater inflammation susceptibility, with higher inflammation scores in areas surrounding the coronary plaques.

Keywords: fat attenuation index, CariHeart score, cardiac computed tomography angiography, pericoronary inflammation

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INTRODUCTION

Coronary artery disease (CAD), a leading cause of acute myocardial infarction (MI), significantly affects both lifespan and quality of life,¹ while also placing a considerable financial strain on healthcare systems. Historically, stable chest pain was primarily diagnosed using ischemia tests, but these days, coronary computed tomography angiography (CCTA) is gaining prominence. CCTA offers detailed anatomical insights by identifying coronary atherosclerotic plaques, even when significant myocardial ischemia is not present.

The widespread adoption of CCTA as the first-line diagnostic approach for CAD is supported by large studies and trials, such as the Scottish CT of the Heart trial.² This shift is evident in various national and international guidelines, including those from the National Institute for Health and Care Excellence and the European Society of Cardiology.³ In the United Kingdom, following the recommendations of the National Institute for Health and Care Excellence could potentially save up to £16 million by prioritizing CCTA for diagnosing stable chest pain.¹

The latest guidelines of the European Society of Cardiology also prioritize CCTA as a Class I recommendation for chronic coronary syndromes. However, it is crucial to recognize that CCTA and functional imaging have distinct roles; CCTA can detect early CAD stages in asymptomatic individuals without significant ischemia, which is not always achievable with functional imaging.³

In individuals at 'low risk' and in early stages of CAD without ischemia, determining the best diagnostic and management strategies remains a challenge. The Agatston coronary artery calcium (CAC) score is a common tool for detecting atherosclerosis in asymptomatic people and is known for its value in predicting primary prevention out-

comes. However, while it helps to modify risk assessments, the CAC score cannot rule out the presence of noncalcified plaques, which might still be of high risk.⁴ Additionally, treatments like statins, which lower cardiovascular risk, often increase the CAC score.⁵ Notably, studies show that about half of MI events occur in patients without obstructive coronary atherosclerosis, often due to the rupture or erosion of vulnerable plaques.⁶

CCTA, by focusing on the anatomy of plaques rather than their hemodynamic impact, has enhanced our understanding of 'unstable plaques' and their high-risk characteristics. Despite these advancements, there remains an urgent need to identify more precise and dynamic biomarkers for recognizing vulnerable patients and plaques.

THE FAT ATTENUATION INDEX: A NEW MARKER FOR ENHANCING CARDIAC RISK ASSESSMENT

The fat attenuation index (FAI) is an innovative imaging-derived feature designed to meet the need for more specific cardiovascular disease markers. It is a computed tomography (CT)-based marker that assesses three-dimensional changes in CT attenuation within the pericoronary adipose tissue (PCAT) around affected coronary artery segments, aiding in the detection of vascular inflammation.⁷ Pericoronary FAI, as a new CT-derived marker, quantifies vascular inflammation directly at the coronary vessels. Its ability to predict major adverse cardiovascular events enhances cardiac risk assessment, offering a significant improvement over traditional risk factors and the CAC score.

Atherosclerosis is fundamentally an inflammatory process, and inflammation plays a crucial role in both the development and progression of atherosclerotic plaques.⁸ Various hypotheses tried to explain the progression of atheromatous plaques towards an unstable phenotype

or, on contrary, towards stabilization.^{9,10} Artificial intelligence tools are currently used in an attempt to explain these different patterns of evolution.¹¹ Consequently, the pursuit of noninvasive techniques to detect vascular inflammation has often been seen as a pinnacle objective in cardiovascular diagnostics. This emphasis stems from the understanding that early detection of inflammation could lead to the timely identification of seemingly healthy individuals who are, in reality, at considerable risk for cardiovascular disease.

When vascular inflammation is present, the human perivascular adipose tissue experiences a change in its characteristics due to the influence of proinflammatory signals (such as TNF- α , IL-6, and IFN- γ) released by the nearby blood vessel in a paracrine manner. These signals appear to stimulate the breakdown of fats and inhibit the development of adipocytes, leading to a transition from a lower to a higher water-to-lipids ratio. This alteration in the perivascular fat composition leads to a shift in its attenuation on CCTA, whereby the Hounsfield unit (HU) values become less negative (e.g., closer to -30 HU) in the aqueous phase, as opposed to the more negative values (e.g., closer to -190 HU) associated with lipid-rich regions.⁷

While the role of epicardial fat inflammation in atherosclerosis progression is now widely accepted, to the author's knowledge there are very few studies investigating regional differences in levels of inflammation.¹² The influence of local factors related to coronary circulation in the right versus left coronary bed on the development of pericoronary inflammation has not been elucidated so far.

The aim of this study was to investigate whether there are any regional differences in the level of inflammation between the right and left coronary arteries in patients with unstable coronary plaques.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

The study enrolled 153 patients who exhibited typical angina, had a low to intermediate clinical probability of ischemic coronary artery disease, underwent clinically indicated CCTA and presented atheromatous plaques with characteristics indicating vulnerability at CCTA. The participants had a mean age of 62 ± 10 years, and 68% ($n = 104$) of them were men. These patients were categorized into four distinct clinical scenarios (CS):

- CS 1 consisted in 26 patients who underwent a CCTA examination and presented an acute coronary syn-

drome (ACS) in the post-CCTA follow-up period;

- CS 2 consisted in 72 patients who underwent CT imaging after COVID-19;
- CS 3 consisted in 18 patients with a history of percutaneous coronary angioplasty and a residual lesion in a different coronary artery;
- CS 4 consisted in 37 patients with unstable angina and significant lesions on native coronary arteries.

CCTA SCAN AND PLAQUE ASSESSMENT

In this study, each participant underwent a CCTA scan at the CardioMed Center for Multimodality Imaging in Târgu Mureș, Romania. The scans were performed using a Siemens Somatom Definition AS 128-slice CT scanner (Siemens Healthcare, Erlangen, Germany). The scanning parameters included a tube voltage of 120 kV, a gantry rotation time of 0.33 seconds, and a collimation of 128×0.6 . The scans were done using retrospective gating. To ensure an optimal heart rate for the examination, ideally below 65 bpm, patients were administered beta-blockers prior to the scan.

To assess the CAC score in the arteries, an initial native scan was conducted. Then, patients were administered an iodine-containing contrast agent, varying between 80–100 mL based on their body weight. To clear the contrast agent, a 50 mL saline solution was injected at a rate of 5.5–6 mL/s while the patient held their breath.

The CCTA examinations were stored in a specialized electronic database, allowing for offline imaging post-processing and cloud-based distribution. During analysis, all classical plaque features linked to vulnerability were examined to identify high-risk plaques. The FAI and the corresponding FAI score, which considers risk factors and age, were calculated for each case at the level of the left anterior descending artery (LAD), circumflex artery (LCX), and right coronary artery (RCA). The post-processing, PCAT mapping, and FAI analysis were conducted using a validated algorithm from Caristo Diagnostics (Oxford, United Kingdom).

FAI was measured in HU and reflects how X-rays are attenuated or weakened as they pass through adipose tissue. It serves as an unadjusted, visual representation of inflammation levels in the three main epicardial coronary arteries. A higher FAI value, nearing -30 HU, indicates more inflammation in the perivascular adipose tissue, whereas a lower FAI value, of around -180 HU, suggests less inflammation. The FAI score, calculated for each primary coronary artery, incorporates the FAI and adjusts it based on technical scan parameters like tube voltage, anatomi-

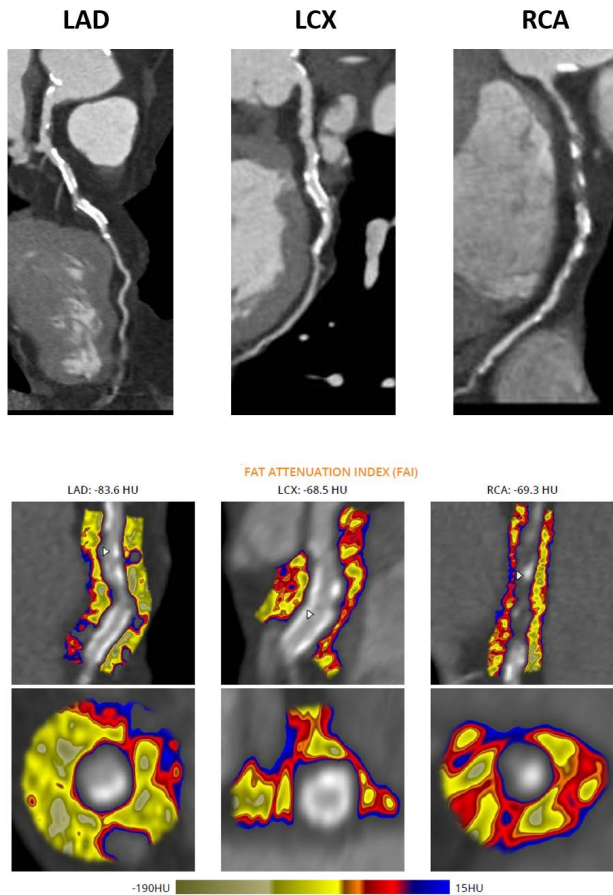


FIGURE 1. CCTA image of the three major coronary arteries and a color representation of FAI analysis for the same patient. Yellow areas represent zones with low inflammation, while red and blue areas represent zones with high inflammation.

cal factors influencing fat distribution around the arteries, and basic demographic data such as age and gender. Higher FAI scores are associated with an increased risk of fatal cardiac events. This score is further refined using specific nomograms for each coronary region, offering a tailored assessment of inflammation in those areas and providing FAI score percentiles. In essence, FAI quantifies the X-ray attenuation by adipose tissue, while the FAI score offers a personalized indication of coronary inflammation, adjusting for age and gender, and expressed as a relative risk.

Figure 1 shows an example of CCTA images of the three major coronary arteries and the inflammation analysis with the resulting FAI map. Blue colors represent a higher level of inflammation and yellow ones a lower level of inflammation. Figure 2 shows two examples of FAI score percentiles: a patient with a high level of inflammation and a high FAI score percentile (Figure 2A) and a patient with a moderate level of inflammation and moderate FAI score percentile (Figure 2B).

All study procedures were performed in accordance with the Declaration of Helsinki. All patients gave informed consent for participation in the study, and the study was approved by the ethics committee of the hospital.

STATISTICAL ANALYSIS

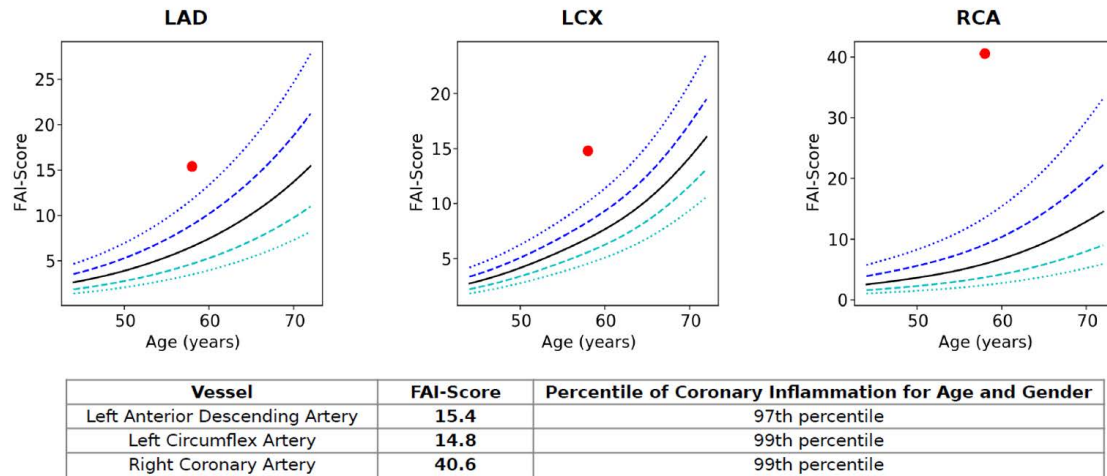
The PCAT-FAI data for each coronary artery was stored in a Microsoft Excel database (Microsoft Corporation, Redmond, USA) and analyzed using GraphPad Prism 9.5 software (GraphPad Software Inc., San Diego, USA). This analysis involved comparing the RCA with the left coronary arteries (LCA, averaging values from the LAD and the LCX) for all patient groups and subgroups. Additionally, comparisons were made between the RCA, LAD, and LCX. Categorical variables were analyzed using the chi-squared test, and numerical data with Mann-Whitney or Student's *t*-tests. When appropriate, one-way analysis of variance (ANOVA) was performed. Pearson correlation was used to assess relationships between PCAT-FAI and other variables, with a two-sided *p* value of ≤ 0.05 deemed significant.

RESULTS

In total, 459 coronary arteries of the 153 patients were included in the analysis, and both FAI and FAI score were higher at the level of the RCA compared with the LAD and the LCX. Patient characteristics, together with main biochemistry, echocardiographic data and calcium score at CT for each clinical scenario are presented in Table 1.

The results of FAI analysis in the entire group and in the different CSs are presented in Table 2. A statistically significant difference was found between right and left coronary circulation in the entire study lot (Figure 2). The FAI score was 15.23 ± 11.97 at the RCA vs. 10.55 ± 6.78 at the LAD and 11.48 ± 6.5 for the LCX ($p = 0.02$). Interestingly, there was also a significant difference between the RCA and the two LCAs taken separately, as indicated in Figure 3. A significantly higher value of FAI at the level of the RCA was noted in comparison with the other two coronary arteries: -76 ± 7.68 HU for the LCX compared to -73.04 ± 8.9 HU for the LAD and -71.25 ± 7.47 HU for the RCA ($p < 0.0001$).

This difference was more expressed in post-COVID patients (FAI score 16.86 ± 14.9 for the RCA vs. 10.48 ± 6.24 for the LCX and 10.48 ± 6.24 for the LAD, $p = 0.01$), and in patients with residual lesions after PCI (20.98 ± 16.29 for the RCA vs. 11.77 ± 7.68 for the LCX and 12.83 ± 6.47 for the LAD, $p = 0.08$ (Table 3).



FAI-SCORE - RELATIVE RISK, ADJUSTED FOR AGE AND GENDER

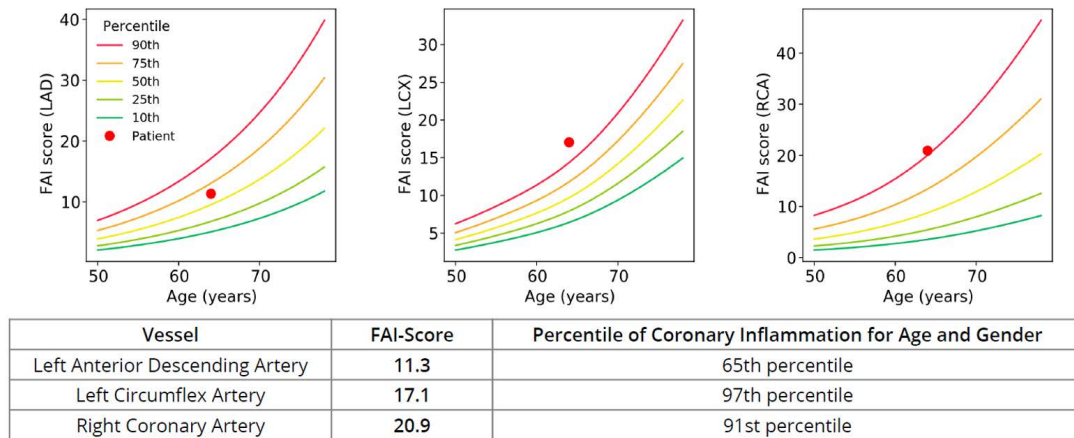


FIGURE 2. FAI score percentiles in two patients with different inflammation levels. **A** – FAI analysis in a patient with high inflammation. There is a high FAI score percentile in all three coronary arteries, but more expressed in the RCA. **B** – FAI analysis in a patient with moderate inflammation. There is a moderate FAI score percentile in all three coronary arteries.

Subgroup analysis in the four CSs comparing RCA vs. LCA revealed the following:

- in CS 1, no statistical difference was observed between the RCA and LCA regarding FAI (-74.57 ± 8.8 vs. -74.54 ± 7.2 , $p = 0.7$), FAI score (14.83 ± 10.19 vs. 12.54 ± 6.7 , $p = 0.3$), or FAI score percentiles (0.62 ± 0.26 vs. 0.57 ± 0.27 , $p = 0.5$) (Figure 4A);
- in CS 2, the RCA exhibited a significantly higher FAI score compared to the LCAs (16.86 ± 14.9 vs. 11.29 ± 8.1 , $p = 0.006$) and higher FAI score percentiles (0.71 ± 0.2 vs. 0.68 ± 0.24 , $p = 0.001$), without a statistical difference in the FAI measured as HU (Figure 4B);
- in CS 3, the RCA coronary artery showed a higher FAI score compared to the LCAs (20.98 ± 16.2 vs. 12.3 ± 6.7 , $p = 0.04$) and larger FAI score percentiles (0.74 ± 0.3 vs. 0.64 ± 0.26 , $p = 0.002$) (Figure 4C);
- in CS 4, a significant difference was observed in the RCA regarding the FAI score percentiles (0.71 ± 0.31 vs. 0.65 ± 0.2 , $p < 0.001$), while the FAI score did not show statistical differences among the coronary arteries (Figure 4D).

DISCUSSION

We conducted an observational, single-center study to assess differences in topography of inflammation in the right vs. the left coronary arterial system in patients who underwent clinically indicated CCTA.

Our findings indicate significant variations in fat attenuation measurements, suggesting different degrees

TABLE 1. Patient characteristics, main biochemistry results and imaging data in the study groups

Variable	Total (n = 153)	CS 1 (n = 26)	CS 2 (n = 72)	CS 3 (n = 18)	CS 4 (n = 37)
Age, years	62 ± 10	66 ± 10	60 ± 10	63 ± 9	62 ± 10
Gender, male, n (%)	104 (68%)	14 (63%)	45 (63%)	14 (77%)	29 (78%)
Hypertension, n (%)	129 (84%)	25 (96%)	58 (80%)	16 (88%)	30 (81%)
Diabetes mellitus, n (%)	42 (27%)	11 (42%)	18 (25%)	6 (33%)	7 (18%)
Hypercholesterolemia, n (%)	77 (50%)	19 (73%)	30 (42%)	8 (44%)	20 (54%)
Atrial fibrillation, n (%)	32 (20%)	4 (15%)	17 (23%)	1 (5%)	10 (26%)
Chronic kidney disease, n (%)	14 (9%)	3 (11%)	4 (14%)	2 (11%)	5 (13%)
Heart failure, n (%)	118 (77%)	21 (80%)	56 (77%)	17 (94%)	24 (64%)
Serum cholesterol, mean ± SD (mg/dL)	167.6 ± 47	166.3 ± 40	163 ± 44	168.9 ± 59	171.9 ± 50
Ejection fraction, mean ± SD (%)	46 ± 6.6	47 ± 6	46 ± 7	45 ± 5	48 ± 5
Creatinine, mean ± SD (mg/dL)	0.96 ± 0.2	0.92 ± 0.2	0.92 ± 0.2	0.89 ± 0.2	1 ± 0.3
Calcium score, mean ± SD	164 ± 138	98 ± 37	198 ± 176	138 ± 53	154 ± 95

of inflammation within the different coronary territories. We found regional differences in fat attenuation measurements and FAI scores between the RCA and the other coronary arteries in each scenario. This suggests variations in the composition and characteristics of atheromatous plaques within the different coronary arteries, highlighting the importance of considering the specific artery involved in the assessment of coronary artery disease. Such differences provide valuable insights into the distribution and composition of atheromatous plaques across the coronary vasculature.

It is important to note that the FAI value is not static and can be affected by various treatments, such as statins, anti-inflammatory medications, and disease-modifying therapies. In a detailed analysis of the CRISP-CT study, it

was noted that FAI has lost its significant predictive value for future adverse events in patients who started taking statins or aspirin after their coronary CCTA.¹³ This observation aligns with findings from other research groups, who demonstrated that perivascular FAI is a dynamic marker, responsive to statin therapy. They observed a notable reduction in PCAT-FAI around noncalcified and mixed plaques, although this effect was not seen with calcified plaques. This reduction may be due to the role of statins in stabilizing vulnerable plaques by shrinking the necrotic core.¹⁴

While systemic risk factors have a key role in the development of CAD, the site-specific emergence of atherosclerotic lesions depends on local hemodynamical parameters. The difference in inflammation levels between

TABLE 2. FAI analysis of coronary inflammation in the right vs. left coronary system for each CS

CS		RCA	LCA	p value
Total	FAI	-71.25 ± 7.4	-73.71 ± 6.9	0.46
	FAI score	15.23 ± 11.97	11.93 ± 8.06	0.002
	FAI score percentile	0.7 ± 0.2	0.65 ± 0.2	0.001
CS 1 – ACS in the follow-up period	FAI	-74.57 ± 8.8	-74.54 ± 7.2	0.77
	FAI score	14.83 ± 10.1	12.54 ± 6.7	0.3
	FAI score percentile	0.62 ± 0.2	0.57 ± 0.2	0.5
CS 2 – post-COVID	FAI	-72.89 ± 9.4	-73.39 ± 7.1	0.7
	FAI score	16.86 ± 14.9	11.29 ± 8.1	0.006
	FAI score percentile	0.71 ± 0.2	0.68 ± 0.2	0.001
CS 3 – high-risk residual lesions	FAI	-73.65 ± 8.2	-75.71 ± 4.7	0.3
	FAI score	20.98 ± 16.2	12.3 ± 6.7	0.04
	FAI score percentile	0.74 ± 0.3	0.64 ± 0.2	0.002
CS 4 – high-risk, native vessels	FAI	-71.89 ± 8.5	-72.75 ± 7.1	0.6
	FAI score	15.26 ± 22.6	12.58 ± 9.5	0.5
	FAI score percentile	0.71 ± 0.3	0.65 ± 0.2	<0.001

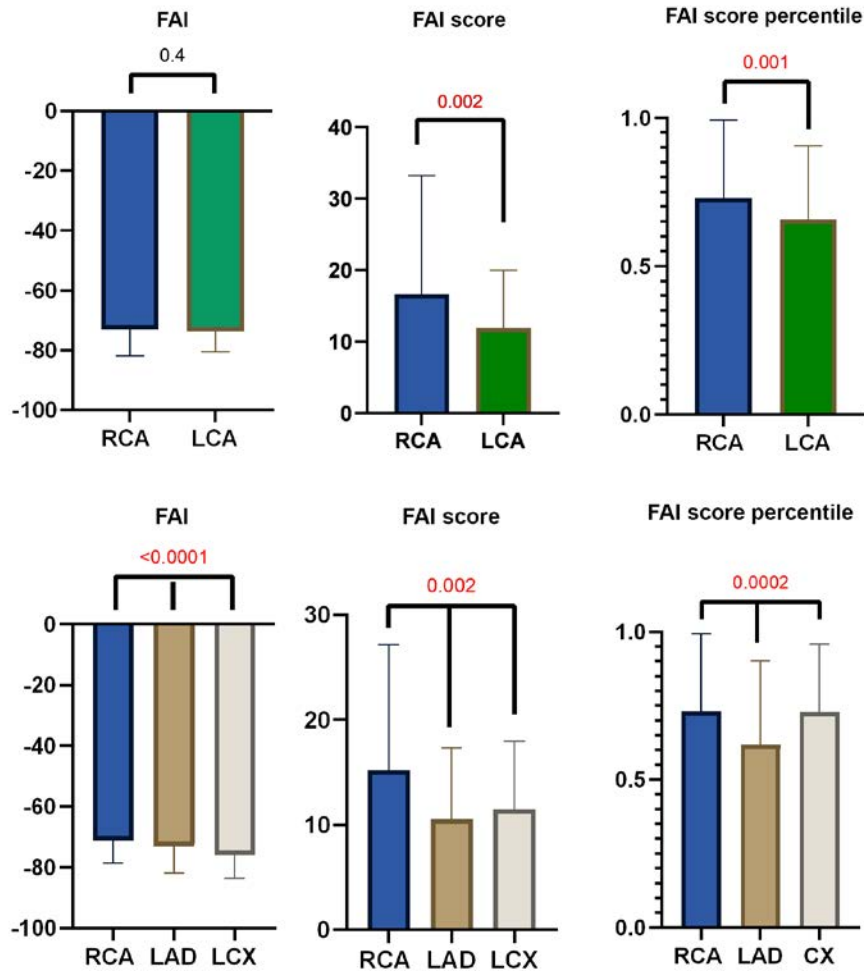


FIGURE 3. FAI assessment of coronary inflammation in the three coronary arteries, based on FAI, FAI score, and FAI score percentiles. **A** – comparison between the left and right coronary system; **B** – comparison between the three coronary arteries individually.

coronary areas may be due to varying blood flow patterns. Endothelial cells react to wall shear stress, a force from blood flow, by regulating gene and protein expression. This regulation affects vascular development and maintenance. High, steady shear stress keeps these cells dormant, but low or irregular stress activates them, leading to inflammation. Interactions between shear stress and pro-inflammatory cytokines like tumor necrosis factor and interleukin- 1β are also important. These cytokines induce inflammation, with high shear stress reducing their activation effect on endothelial cells, while low stress enhances it.¹⁵

Many studies have examined the distribution of atherosclerotic plaques in the human arterial system, often finding that these plaques are commonly located in areas where arteries have complex geometries, leading to irregular blood flow. These findings have widely es-

tablished the idea that local hemodynamic factors, such as blood flow patterns and wall shear stress, might contribute to the onset of atherosclerosis and, crucially, its advancement.¹⁶

CONCLUSION

Plaques located in different coronary territories exhibit different vulnerability patterns and different levels of inflammation. The RCA seems to have a more pronounced susceptibility to inflammation, right coronary plaques exhibiting higher inflammation scores in the territories surrounding coronary plaques. These findings highlight regional differences in fat attenuation measurements and FAI scores, particularly between the RCA and the other coronary arteries within each scenario. It indicates variations in the composition and characteris-

TABLE 3. FAI, FAI score and FAI score percentiles for each CS in each coronary artery

CS		RCA	LAD	LCX	p value
Total	FAI	-71.25 ± 7.4	-73.04 ± 8.9	-76 ± 7.6	<0.0001
	FAI score	15.23 ± 11.9	10.55 ± 6.7	11.48 ± 6.5	0.02
	FAI score percentile	0.73 ± 0.2	0.6 ± 0.2	0.72 ± 0.2	0.0001
CS 1 – ACS in the follow-up period	FAI	-74.57 ± 8.8	-76.13 ± 6.69	-71.92 ± 8.43	0.89
	FAI score	14.83 ± 10.1	12.79 ± 8.09	12.92 ± 6.01	0.18
	FAI score percentile	0.62 ± 0.2	0.57 ± 0.28	0.61 ± 0.30	0.78
CS 2 – post-COVID	FAI	-72.89 ± 9.4	-75.49 ± 7.62	-72.89 ± 9.40	0.206
	FAI score	16.86 ± 14.9	9.47 ± 6.02	10.48 ± 6.24	0.0101
	FAI score percentile	0.71 ± 0.2	0.65 ± 0.28	0.78 ± 0.20	0.003
CS 3 – high-risk residual lesions	FAI	-73.65 ± 8.2	-78.76 ± 6.01	-73.65 ± 8.28	0.0303
	FAI score	20.98 ± 16.2	11.77 ± 7.68	12.83 ± 6.47	0.008
	FAI score percentile	0.74 ± 0.3	0.59 ± 0.29	0.73 ± 0.22	0.005
CS 4 – high-risk, native vessels	FAI	-71.89 ± 8.5	-75.55 ± 8.9	-71.89 ± 8.56	0.445
	FAI score	15.26 ± 22.6	10.56 ± 7.28	11.87 ± 7.3	0.018
	FAI score percentile	0.71 ± 0.3	0.59 ± 0.28	0.74 ± 0.20	0.0012

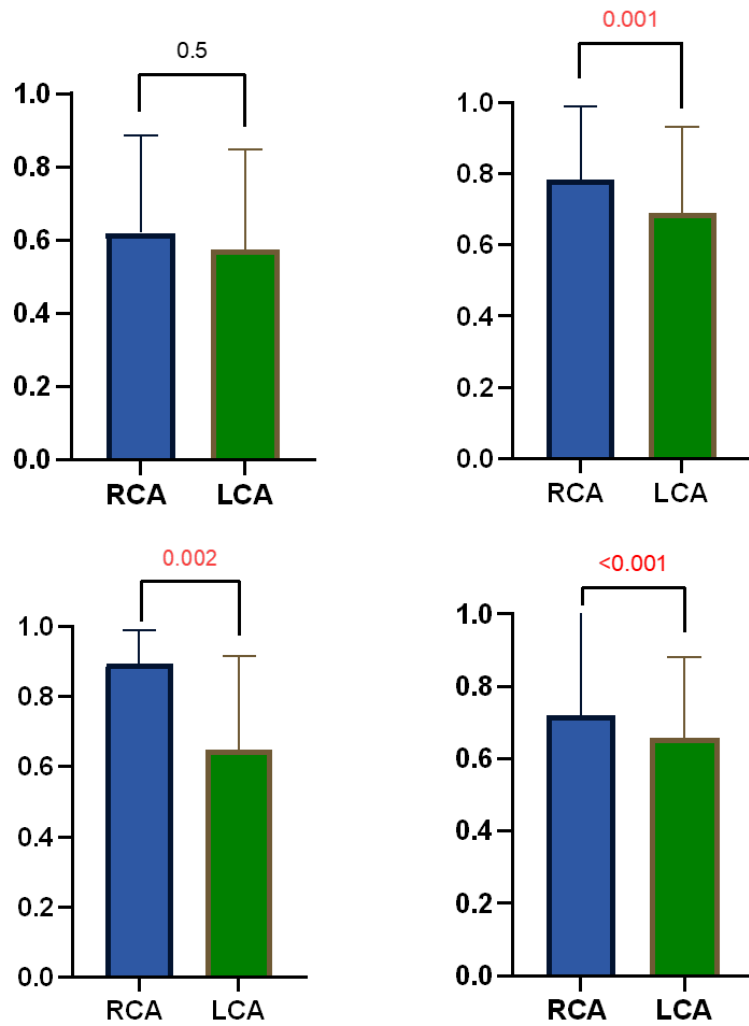


FIGURE 4. FAI assessment of coronary inflammation in the four clinical scenarios, based on FAI score percentiles. **A** – CS 1; **B** – CS2; **C** – CS3; **D** – CS4.

tics of atheromatous plaques across different coronary arteries, emphasizing the importance of considering the specific artery involved in the assessment of coronary artery disease.

CONFLICT OF INTEREST

Nothing to declare.

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