

LISTA LUCRĂRILOR PUBLICATE

ARTICOLE PUBLICATE IN EXTENSO

1. ARTICOLE PUBLICATE IN REVISTE COTATE ISI, CU FACTOR DE IMPACT

Vasile-Bogdan Halatiu, Imre Benedek, Ioana-Patricia Rodean, Liliana-Oana Cojocariu, **Theofana Mihăilă**, Emanuel Blîndu, Aurelian Roșca, Botond-Barna Mátyás, Renata Gerculy, Florin Buicu and Theodora Benedek, Coronary Computed Tomography Angiography-Derived Modified Duke Index Is Associated with Peri-Coronary Fat Attenuation Index and Predicts Severity of Coronary Inflammation, *Medicina* 2024

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Botond Barna Matyas, **Theofana Mihăilă**, Theodora Benedek et al Assessing the Impact of Long-Term High-Dose Statin Treatment on Pericoronary Inflammation and Plaque Distribution-A Comprehensive Coronary CTA Follow-Up Study 2024, *Int. J. Mol. Sci.* 2024

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Emanuel Blîndu, Imre Benedek, Ioana-Patricia Rodean, Vasile-Bogdan Halatiu, Nora Raț, Constantin Țolescu, **Theofana Mihăilă**, Aurelian Roșca, Botond-Barna Mátyás, Evelin Szabó, Renáta Gerculy, Dan Păsăroiu, Florin Buicu and Theodora Benedek „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” | Dec 10, 2023; *Journal of Cardiovascular Emergencies*; Volume 9 (2023): Issue 4 (December 2023)

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Evelin Szabo, Lehel Bördi, **Theofana Mihaila**, Cristian Tolescu and Imre Benedek, Cardiac Magnetic Resonance Features Associated with the Risk of Cardiac Arrest in Patients with Acute Myocardial Infarction | Jan 27, 2023; *Journal of Cardiovascular Emergencies* Volume 8 (2022): Issue 3 (September 2022)

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Theofana Mihăilă, Aurelian Roșca, Bianca Ion - Double Trouble: Interrupting DAPT and COVID-19- revista *Journal of Cardiovascular Emergencies* 2022 DOI: 10.2478/jce-2022-0007

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Theofana Mihăilă, Aurelian Roșca, Bianca Ion -Acute Thrombosis of the Left Main on the Tennis Court in a Young Patient – a Case Report- revista *Journal of Cardiovascular Emergencies* 2022-DOI: 10.2478/jce-2022-0008

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2. ARTICOLE PUBLICATE IN REVISTE INTEXATE BDI

Aurelian Roșca, **Theofana Mihăilă**, Bianca Ion -ESC Guidelines 2022 – a Pragmatic Tool for the Practicing Cardiologist?; *Journal of Interdisciplinary Medicine* 2022;7(3):67-68

Aurelian Roșca, **Theofana Mihăilă**, Bianca Ion -Elevated Lipoprotein(a) Linked to Recurrent Cardiovascular Events – A Case Report; *Journal of Interdisciplinary Medicine* 2022;7(3):78-80



REZUMATE PUBLICATE

T Mihaila, I Benedek, A Rosca, V B Halatiu, I P Rodean, B B Matyas, B N Ion, T Benedek, Myocardial edema at CMR imaging end evolution of ventricular function following COVID-19 myocarditis - insights from the CARDIOCOV study European Heart Journal - Cardiovascular Imaging, Volume 24, Issue Supplement_1, June 2023, jead119.251, <https://doi.org/10.1093/ehjci/jead119.251>Published: 19 June 2023

Theofana Mihaila, Ioana Patricia Rodean, Vasile Bogdan Halatiu, Imre Benedek, Theodora Benedek, FACTORS ASSOCIATED WITH MYOCARDIAL EDEMA AT CARDIAC MAGNETIC RESONANCE IN POST COVID PATIENTS; BOOK of ABSTRACTS George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures University Days December 11 - 15, 2023, Targu Mures; Scientific Session of University Academic Staff International Conference of PhD Students and Young Doctors; No. 6/2023

Article

Coronary Computed Tomography Angiography-Derived Modified Duke Index Is Associated with Peri-Coronary Fat Attenuation Index and Predicts Severity of Coronary Inflammation

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Abstract: *Background and Objectives:* The modified Duke index derived from coronary computed tomography angiography (CCTA) was designed to predict cardiovascular outcomes based on the severity of coronary stenosis. However, it does not take into consideration the presence or severity of peri-coronary inflammation. The peri-coronary fat attenuation index (FAI) is a novel imaging marker determined by CCTA which reflects the degree of inflammation in the coronary tree in patients with coronary artery disease. To assess the association between the modified Duke index assessed by CCTA, cardiovascular risk factors, and peri-coronary inflammation in the coronary arteries of patients with coronary artery disease. *Materials and Methods:* One hundred seventy-two patients who underwent CCTA for typical angina were assigned into two groups based on the modified Duke index: group 1—patients with low index, ≤ 3 ($n = 107$), and group 2—patients with high index, > 3 ($n = 65$). Demographic, clinical, and CCTA data were collected for all patients, and FAI analysis of coronary inflammation was performed. *Results:* Patients with increased values of the modified Duke index were significantly older compared to those with a low index (61.83 ± 9.89 vs. 64.78 ± 8.9 ; $p = 0.002$). No differences were found between the two groups in terms of gender distribution, hypertension, hypercholesterolemia, or smoking history (all $p > 0.5$). The FAI score was significantly higher in patients from group 2, who presented a significantly higher score of inflammation compared to the patients in group 1, especially at the level of the right coronary artery (FAI score, 20.85 ± 15.80 vs. 14.61 ± 16.66 ; $p = 0.01$ for the right coronary artery, 13.85 ± 8.04 vs. 10.91 ± 6.5 ; $p = 0.01$ for the circumflex artery, 13.26 ± 10.18 vs. 11.37 ± 8.84 ; $p = 0.2$ for the left anterior descending artery). CaRi-Heart[®] analysis identified a significantly higher risk of future events among patients with a high modified Duke index ($34.84\% \pm 25.86\%$ vs. $16.87\% \pm 15.80\%$; $p < 0.0001$). ROC analysis identified a cut-off value of 12.1% of the CaRi-Heart[®] risk score for predicting a high severity of coronary lesions, with an AUC of 0.69. *Conclusions:* The CT-derived modified Duke index correlates well with local perilesional inflammation as assessed using the FAI score at different levels of the coronary circulation.

Keywords: CariHeart; cardiac computed tomography; coronary stenosis; fat attenuation index; inflammation

1. Introduction

Cardiac computed tomography angiography (CCTA) has emerged in the latest years as a first-line option to investigate coronary artery disease (CAD) [1]. Besides providing accurate anatomic information regarding coronary arteries via a non-invasive route, it can reliably identify features of increased vulnerability in the coronary circulation. Various studies investigated the association between these features and different cardiovascular pathologies, such as acute coronary syndromes (ACSs), atrial fibrillation, or heart failure [2,3].

Several CCTA-derived scores have been proposed to characterize the severity of coronary stenoses in an attempt to better stratify the risk of cardiovascular events and restrict invasive coronary imaging to those who really need it. For instance, the modified Duke index derived from CCTA was designed to predict the cardiovascular outcome based on the severity of coronary stenosis. An increased Duke index was proved to be associated with a higher risk of fatal events, validating the role of CCTA as a reliable tool for predicting cardiovascular risk [4].

However, the Duke CAD index does not take into consideration the presence or severity of peri-coronary inflammation. An increased level of inflammation at this level may trigger plaque vulnerabilization, ultimately leading to plaque rupture and acute myocardial infarction [5].

It is well-known that not all unstable plaque progresses to rupture. However, persistently high inflammation at the level of the epicardial fat may lead to plaque progression with high potential for vulnerabilization and rupture in a close future [6,7]. Therefore, assessment of coronary inflammation may have a strong clinical impact, contributing to a superior evaluation of plaque-associated risk. It has been suggested that inflammation may be different at various levels of the coronary circulation, underlining the role of regional flow hemodynamic and shear stress in the complex process of plaque vulnerabilization [8]. In light of this, in addition to the traditional risk factors for CAD, pathologies that cause an increased inflammatory state in the body have recently been identified as risk factors for CAD, emphasizing the major role of inflammation in the progression to ACS. [9,10]. Thus, increased attention should be paid to patients whose associated comorbidities imply an increased inflammatory syndrome.

Nowadays, inflammation may be measured at the level of epicardial fat surrounding coronary arteries using a novel technology patented by Caristo (Oxford, UK) which measures the computed tomography attenuation gradient, which is in direct relationship with the inflammation-mediated change in adipocyte composition and phenotype. This technique measures the peri-coronary fat attenuation index (FAI) validated as a novel imaging marker determined by CCTA which reflects the degree of inflammation in the coronary tree in patients with CAD [11]. A recent analysis published in 2022 indicated that the FAI is associated not only with coronary stenosis, where a stenosis with a diameter $\geq 50\%$ had significantly higher FAI values compared to those with a diameter $< 50\%$, but also with vulnerable plaque features [12].

While the association between the severity of coronary lesions and cardiovascular risk is well-known, there are very few data so far regarding the role of inflammation in the progression of coronary lesions towards a higher severity.

The aim of this study was to investigate the association between two CCTA-derived scores associated with increased cardiovascular risk: peri-coronary inflammation at the level of epicardial fat expressed by CaRi-Heart[®] analysis and severity of coronary lesions expressed by the Duke CAD index in patients with CAD.

2. Materials and Methods

2.1. Study Population

This single-center retrospective analysis included 172 adult patients aged over 18 who underwent CCTA at the Center of Advanced Research in Multimodality Cardiac Imaging, Cardiomed Târgu Mureș, Romania, for typical chest pain and a low-to-intermediate likelihood of CAD. Patients with a history of coronary artery disease or non-cardiac chest pain were excluded. Demographic data and risk factors related to coronary artery disease (hypertension, hyperlipidemia, smoking, and diabetes) were obtained prior to the CCTA examination.

Based on the modified Duke index assessed on CCTA, the study population was divided into two groups as follows: group 1—patients with a modified Duke index ≤ 3 ($n = 107$), and group 2—patients with a modified Duke index > 3 ($n = 65$).

All the study procedures were carried out in compliance with the Declaration of Helsinki, with the prior approval of the local ethics committee of the Emergency Clinical County Hospital Târgu Mureș (Ad. 26884/10.11.2021) and the George Emil Palade University of Medicine, Pharmacy, Science and Technology Târgu Mureș (1515/09.12.2021).

2.2. Coronary Computed Tomography Angiography Acquisition

Image acquisition was performed using a 128-slice high-definition scanner (Siemens Healthcare, Erlangen, Germany) before and after intravenous administration of iodinated contrast according to the patient's weight (60 to 100 mL). The images were obtained under continuous ECG monitoring in the three bipolar limb leads and after prior determination of blood pressure, heart rate, and O_2 saturation. Oral metoprolol tartrate was previously administered when needed to achieve a target heart rate below 65 bpm.

2.3. Image Analyses

The obtained images were analyzed independently by two randomly selected CCTA interpreters blinded to the clinical data in order to obtain the modified Duke index using a dedicated software (Syngo.via Frontier, Siemens Healthcare, Erlangen, Germany). Based on the atherosclerotic burden, the patients were classified according to the modified Duke index, a coronary plaque severity score for predicting 5-year cardiovascular survival. Calculation of the Duke index has been described previously [4] (Table 1).

Table 1. Modified Duke prognostic coronary artery disease index based on coronary computed tomography angiography findings [4].

| Modified Duke Prognostic CAD Index | CCTA Findings |
|------------------------------------|---|
| 1 | Stenosis $< 50\%$ |
| 2 | At least two non-obstructive stenoses (including a coronary artery with proximal stenosis or a stenosis of 50–69%) |
| 3 | Two coronary arteries with 50–69% stenosis or one coronary artery with 70% stenosis |
| 4 | Trivascular disease with 50–69% stenoses, or bivascular disease with 70% stenosis, or proximal LAD stenosis of at least 70% |
| 5 | Trivascular disease with stenoses of at least 70% or bivascular disease with at least 70% stenoses involving proximal LAD |
| 6 | Left main stenosis of at least 50% |

CAD—coronary artery disease; CCTA—coronary computed tomography angiography; LAD—left anterior descending artery.

All the images were subsequently transferred to the Centre of CARISTO Diagnostics, Oxford, United Kingdom, for assessment of perivascular adipose tissue (PVAT) and related inflammation. Using artificial intelligence algorithms, the PVAT-fat attenuation index

(PVAT-FAI) reckons attenuation measurements of perivascular adipose tissue surrounding the coronary arterial wall with high accuracy [13,14]. The FAI HU, FAI score, and FAI score centile were assessed for each of the major coronary arteries. Further, the CaRi-Heart® risk, a score validated to predict a fatal cardiac event within the next 8 years, was assessed for each patient.

2.4. Statistical Analysis

The GraphPad InStat 3.10 software (GraphPad Software Inc., San Diego, CA, USA) was used to conduct statistical analysis. Prior to statistical analysis, all the data underwent normality tests. All the data are reported as the absolute values and percentages, or as the medians and standard deviations. For numerical data, unpaired *t*-test or ANOVA test was used for between-group comparisons, and chi-squared test was used for categorical data. Pearson correlation analysis was performed to investigate the association between the modified Duke index and PVAT-FAI. Afterwards, receiver operating characteristic (ROC) analysis was employed to evaluate the ability of the CaRi-Heart® risk to predict a high modified Duke index. The α -value was set at 0.05 for statistical significance.

3. Results

3.1. Baseline Characteristics of the Study Population

The baseline characteristics of the study population and the differences between the low and high modified Duke index groups are presented in Table 2. The patients with a Duke index > 3 were significantly older (64.78 y.o. vs. 60.03 y.o.; $p = 0.002$) and were more frequently diabetic (36.96% vs. 21.50%; $p = 0.02$). There were no significant differences between the two groups in terms of gender distribution, hypertension, hyperlipidemia, and smoking status (all $p > 0.05$).

Table 2. Baseline characteristics of the study population.

| | All n = 172 | Group 1 n = 107 | Group 2 n = 65 | OR | p-Value |
|-------------------|------------------|--------------------|-------------------|------|---------|
| Age (years) | 61.83 \pm 9.89 | 60.03 \pm 10.08 | 64.78 \pm 8.90 | N/A | 0.002 * |
| Gender (male) | 119 (69.18%) | 70 (58.82%) | 49 (41.18%) | 0.61 | 0.17 ^ |
| Hypertension | 147 (85.46%) | 89 (83.18%) | 58 (89.23%) | 0.59 | 0.27 ^ |
| Hyperlipidemia | 90 (52.32%) | 54 (50.47%) | 37 (56.92%) | 0.77 | 0.43 ^ |
| Smoker | 31 (18.02%) | 17 (15.89%) | 14 (21.54%) | 0.68 | 0.34 ^ |
| Diabetes mellitus | 47 (27.32%) | 23 (21.50%) | 24 (36.92%) | 0.46 | 0.02 * |
| HbA1c (%) | 5.76 \pm 0.87 | 5.70 \pm 0.84 | 5.94 \pm 0.82 | N/A | 0.06 * |

The values are expressed as the means \pm standard deviation and as absolute values and percentages, respectively; * *p*-values refer to between-group comparisons based on the unpaired *t*-test; ^ *p*-values refer to between-group comparisons based on the chi-squared test. OR—odds ratio.

3.2. Coronary Inflammation and CT-Derived Duke Index

Table 3 summarizes the differences between the two groups in terms of peri-coronary inflammation magnitude and derived risk using standard adipose tissue CT density and percentile curves for the FAI score for each coronary artery analyzed. Based on the standard adipose tissue Hounsfield units (HU), which ranged between -190 to -30 HU, the coronary FAI index values did not differ significantly between the patients with low or high modified Duke index in any of the three coronary arteries analyzed: left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA).

Table 3. PVAT-FAI values in the low and high modified Duke index patients.

| | | Group 1 n = 107 | Group 2 n = 65 | p-Value |
|-------------------|-----|--------------------|-------------------|-------------|
| FAI HU | LAD | -75.31 ± 7.65 | -77.23 ± 7.30 | 0.10 |
| | LCX | -70.87 ± 7.28 | -71.50 ± 7.88 | 0.59 |
| | RCA | -73.10 ± 9.03 | -72.72 ± 9.07 | 0.79 |
| FAI score | LAD | 11.37 ± 8.84 | 13.26 ± 10.18 | 0.20 |
| | LCX | 10.91 ± 6.56 | 13.85 ± 8.04 | 0.01 |
| | RAD | 14.61 ± 16.66 | 20.85 ± 15.83 | 0.01 |
| FAI score centile | LAD | 0.64 ± 0.27 | 0.55 ± 0.29 | 0.06 |
| | LCX | 0.72 ± 0.24 | 0.68 ± 0.29 | 0.29 |
| | RCA | 0.70 ± 0.29 | 0.70 ± 0.30 | 0.97 |

The values are expressed as the means \pm standard deviation; *p*-values refer to between-group comparisons based on the unpaired *t*-test. FAI—fat attenuation index; HU—Hounsfield units; LAD—left anterior descending artery; LCX—left circumflex artery; RCA—right coronary artery.

Interestingly, FAI scores of coronary inflammation at the level of the RCA and LCX differed significantly between the two studied groups, while this difference was not observed for the LAD. The patients with a Duke index > 3 presented a significantly higher FAI score at the level of the RCA (20.85 ± 15.83 vs. 14.61 ± 16.66 ; $p = 0.02$) and LCX (13.85 ± 8.04 vs. 10.91 ± 6.56 ; $p = 0.02$) compared to the patients with a Duke index ≤ 3 , as showed in Figure 1. However, this was not reflected in an increased risk per coronary artery compared with reference standards for the same age group. FAI score percentiles were not significantly different between the two analyzed groups at any of the three coronary arteries analyzed (all $p > 0.05$).

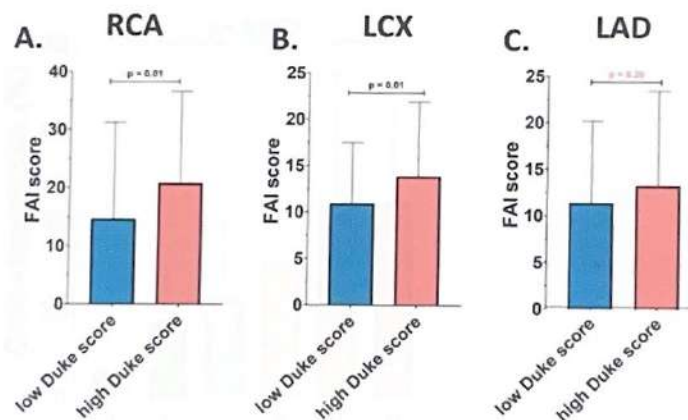


Figure 1. FAI score in the low vs. high modified Duke index patients. (A) FAI score at the level of the right coronary artery (RCA). (B) FAI score at the level of the left circumflex artery (LCX). (C) FAI score at the level of the left anterior descending artery (LAD).

3.3. Coronary Inflammation and Risk of Fatal Cardiac Events as Assessed using the CaRi-Heart® Risk Score

The risk of future fatal cardiac events was determined using the CaRi-Heart® risk score, integrating the global risk, the individual risks related to inflammation at the level of the three coronary arteries, and the risk factors of the patients (smoker status, hypertension, diabetes, and hypercholesterolemia). CaRi-Heart® analysis identified a significantly higher risk of future events among the patients with a high modified Duke index ($34.84\% \pm 25.86\%$ vs. $16.87\% \pm 15.80\%$; $p < 0.0001$) as shown in Figure 2.

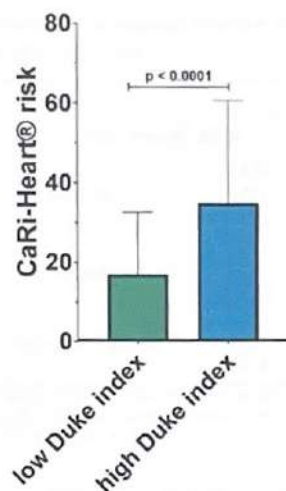


Figure 2. CaRi-Heart® risk in the low vs. high modified Duke index patients.

ANOVA analysis identified a very good association between the CaRi-Heart® risk and the modified Duke index, with higher levels of the CaRi-Heart® score for each superior level of the Duke index ($6.46\% \pm 5.26\%$ for Duke 1; $7.26\% \pm 14.64\%$ for Duke 2; $22.24\% \pm 18.65\%$ for Duke 3; $30.15\% \pm 23.16\%$ for Duke 4; $42.47\% \pm 29.93\%$ for Duke 5; and $42.95\% \pm 28.13\%$ for Duke 6; $p < 0.0001$) (Figure 3.).

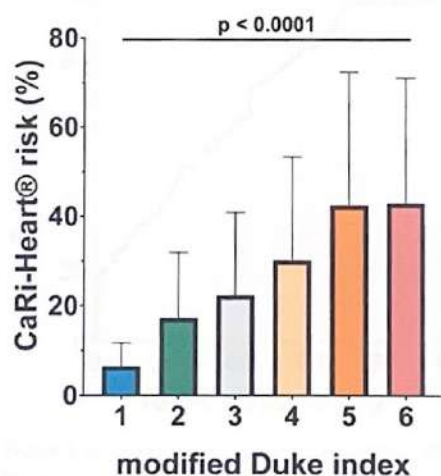


Figure 3. CaRi-Heart® risk in the six classes of the modified Duke index patients.

3.4. Correlation between Coronary Inflammation, Cardiac Computed Tomography Lesion Severity, and the CaRi-Heart® Risk

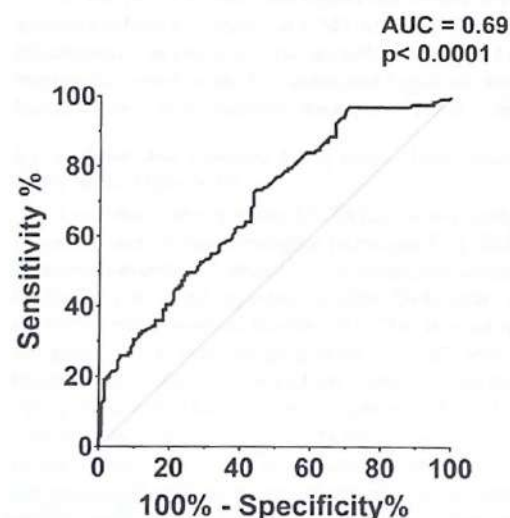
The correlation between the modified Duke index, coronary inflammation, and the CaRi-Heart® risk is presented in Table 4. A high positive correlation was observed between the modified Duke index and the CaRi-Heart® risk as revealed by the Pearson correlation coefficient of 0.75. Weak but significant correlations were also observed between the modified Duke index and the FAI score at the level of all three coronary vessels (all $p < 0.05$).

Table 4. Correlations between the modified Duke index and the PVAT-FAI values, score, and the CaRi-Heart® risk.

| | | <i>R</i> | 95% Confidence Interval | <i>p</i> -Value |
|-------------------|-----|----------|-------------------------|-----------------|
| CaRi-Heart® Risk | | 0.75 | 0.70–0.82 | <0.0001 |
| FAI HU | LAD | −0.15 | −0.29–0.00 | 0.04 |
| | LCX | −0.12 | −0.26–0.03 | 0.11 |
| | RCA | 0.03 | −0.11–0.18 | 0.65 |
| FAI score | LAD | 0.15 | 0.00–0.29 | 0.04 |
| | LCX | 0.23 | 0.08–0.37 | 0.002 |
| | RAD | 0.19 | 0.04–0.34 | 0.01 |
| FAI score centile | LAD | −0.12 | −0.27–0.02 | 0.09 |
| | LCX | −0.15 | −0.30–0.00 | 0.04 |
| | RCA | 0.05 | −0.09–0.20 | 0.46 |

Note: *p*-values refer to Pearson correlation analysis; *R*—Pearson correlation coefficient; FAI—fat attenuation index; HU—Hounsfield units; LAD—left anterior descending artery; LCX—left circumflex artery; RCA—right coronary artery.

Receiver operating characteristic (ROC) curve analysis (Figure 4) was used to assess the CaRi-Heart® risk's ability to predict a modified Duke index above 3. The CaRi-Heart® risk's optimal cut-off value for predicting a high Duke index was set at 12.1%, with a sensitivity of 61.83% and a specificity of 61.65%, with an AUC of 0.69.

**Figure 4.** ROC analysis for the accuracy of the CaRi-Heart® risk in predicting a high modified Duke index. AUC = area under the curve.

Based on this cut-off value, the mean modified Duke index was calculated in the patients with a high CaRi-Heart® risk (below 12.1%) and in the patients with a high CaRi-Heart® risk >12.1%. The mean modified Duke index was significantly higher in the group with CaRi-Heart® risk >12.1% (2.42 ± 1.22 vs. 3.46 ± 1.28 ; $p < 0.0001$), indicating a very strong association between high inflammation, lesion severity, and future risk of fatal cardiovascular events (Figure 5).

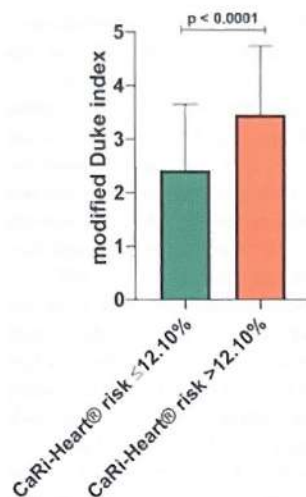


Figure 5. Modified Duke index in the low vs. high CaRi-Heart® risk patients.

4. Discussion

In the present study, we report the results of a CCTA study in patients with a low-to-intermediate likelihood of CAD. Our study is focused on the importance of coronary inflammation in predicting the severity of CAD and indicates that both high inflammatory burden expressed by the FAI index and high CaRi-Heart® risk are associated with coronary lesion severity as revealed by the modified Duke index assessed on the CCTA.

4.1. Modified Duke Coronary Artery Disease Index Assessed Using Coronary Computed Tomography Angiography

Over the past ten years, CCTA has become established clinical medicine more than any other non-invasive imaging technique [15]. To identify patients who are at high risk of adverse events, a number of composite risk scores based on CCTA has been proposed lately. The previously reported modified Duke index and prognostic CAD index are used to assess the atherosclerotic burden on CCTA. According to the original Duke index, patients are given a risk score ranging from 0 to 100, which takes into account the severity of stenoses and both the proximal LAD stenosis and the left main stenosis [16]. In a study of 1127 people with a low-to-intermediate risk of CAD, the Duke index was highly correlated with the risk of all-cause mortality [4]. According to data from the ISCHEMIA trial which included over 5000 patients, the severity of ischemia determined by functional tests was not associated with an increased risk of adverse outcomes, while the severity of coronary lesions assessed using the CCTA Duke CAD index was associated with an increased risk of mortality, underlining the significance of this score in the prediction of a poor outcome [17]. A study conducted in China on a population of over 9500 patients with CAD which reported a mortality rate of more than 5% after 4 years found that the risk of death from any cause was proportional to the Duke CAD index [18].

However, the Duke CAD index only includes CCTA-derived information and no information on patients' risk factors or peri-coronary inflammation. For a better clinical decision and improved outcomes, developing risk scores in combination with the patient's history and data regarding peri-coronary inflammation are of great importance.

4.2. Coronary Inflammation and the Severity of Lesions Expressed by the Duke Index

In the present study, several important findings arise regarding the association between coronary inflammation and the severity of coronary lesions, as indicated by the modified Duke index. Demographic characteristics reveal that individuals with a higher Duke index, indicating more severe coronary lesions, tend to be of older age and have a higher

prevalence of diabetes. This aligns with the existing literature, which suggests that both age and diabetes are risk factors of more severe CAD [19,20].

The study's analysis of peri-coronary inflammation as measured by the FAI using CT imaging reveals nuanced insights. The FAI scores indicative of the degree of inflammation were significantly higher in the RCA and LCX in the patients with a Duke index > 3 compared to those with a lower score. This suggests a correlation between the severity of coronary lesions and the level of inflammation in these specific arteries. However, the LAD did not show this trend, indicating that the relationship between coronary inflammation and lesion severity might be artery-specific, as suggested by previous studies [21,22].

The lack of a significant difference in the FAI score percentiles between the two groups across all three coronary arteries despite the observed differences in the FAI scores suggests that while inflammation is indeed higher in patients with more severe lesions, it may not exceed the expected range for their age group. This could imply that the extent of inflammation in CAD might be more related to individual patient characteristics rather than the severity of the disease itself [23].

The CaRi-Heart[®] risk score, which integrates the risks associated with coronary arteries and patient-specific risk factors, showed a significantly higher risk of future fatal cardiac events in patients with a high Duke index. This finding underscores the importance of comprehensive risk assessment in patients with CAD considering not just the anatomical severity of the disease, but also the inflammatory milieu and other patient-related factors.

ROC curve analysis for the CaRi-Heart[®] risk in predicting a high Duke index establishes a specific cut-off value with moderate sensitivity and specificity. This indicates the potential utility of the CaRi-Heart[®] risk score in clinical settings for predicting lesion severity. Moreover, the significantly higher mean Duke index in the patients with a CaRi-Heart[®] risk above the cut-off point solidifies the link between higher inflammation, more severe coronary lesions, and an increased risk of fatal cardiac events.

4.3. Coronary Inflammation and Cardiovascular Risk

CAD, recognized as the primary contributor to global morbidity and mortality rates [24], is now comprehensively perceived as a process characterized by multiple steps and factors, with chronic inflammation playing a crucial role at each phase [25]. The diverse clinical presentations of CAD, spanning from initial atherosclerotic changes to the advancement of plaques and sudden coronary incidents, highlight the disease's intricate nature. This underscores the necessity for all-encompassing evaluation methods that prioritize inflammation as the central element, especially in the onset of ACSs via triggering cardioembolic events [26,27].

Recent progress in precision medicine for cardiovascular disease has been marked by significant enhancements in risk assessment methodologies. Contemporary models integrating a range of biomarkers, including those related to inflammation, have improved the accuracy and subtlety of cardiovascular risk predictions. Notably, a link has been established between various inflammatory biomarkers such as fibrinogen, interleukin 6 (IL-6), C-reactive protein (CRP), and galectin-3 and the onset of CVD [28].

A separate meta-analysis investigating the role of vascular inflammation biomarkers in cardiovascular risk prediction further supports this trend. The analysis found that incorporating these biomarkers alongside traditional clinical risk factors significantly improves the prediction of cardiovascular events. This finding accentuates the critical role of inflammation markers in both the evaluation and management of the CVD risk [29]. Additionally, contemporary research is reshaping the understanding of atherosclerosis. New findings challenge the established beliefs and bring to light a range of non-conventional risk factors and intricate biological mechanisms underlying the disease. This evolving perspective emphasizes the complexity of atherosclerosis and the necessity for advanced diagnostic and management strategies in cardiovascular medicine [30].

An emerging focus in cardiovascular research is the measurement of the FAI which carries important clinical implications. Recent investigations have underscored the FAI's significance as an innovative biomarker for evaluating cardiovascular risk [31,32]. The FAI score, recognized as a proprietary biomarker and a key component of the CaRi-Heart® report, plays a pivotal role in quantifying coronary inflammation. It also serves to gauge an individual's risk in comparison to a similar demographic group [13].

The development of the peri-coronary FAI as a biomarker for imaging coronary inflammation represents a significant advance in the field. Utilized in conjunction with standard CTA, the FAI plays a crucial role in detecting vulnerable plaques, key indicators for predicting and managing cardiovascular risks [33]. Beyond plaque identification, the FAI's standardized application in CTA allows for non-invasive monitoring of coronary artery inflammation. This method involves analyzing spatial variations in the composition of perivascular fat, thus offering deeper insights into the inflammatory processes central to CAD [11]. Additionally, this approach enhances prognostic accuracy beyond what traditional risk factors provide, highlighting the critical role of inflammation in comprehensive cardiovascular risk evaluation [34]. Beside inflammation, we should also take into account that CAD displays some differences regarding risk factors and pharmacological treatment, which may influence the outcome [35,36].

The results of the current study must also be seen from the perspective of some limitations. The present study is an observational one; while it can identify associations, establishing a direct cause-and-effect relationship is challenging due to the potential influence of confounding variables. Another limitation of the study is the lack of follow-up data, which would have been of great importance in monitoring the relationship between the imaging markers studied and the cardiovascular outcome.

The present study indicates a correlation between the modified Duke index and perilesional inflammation as assessed by the FAI score. The more pronounced inflammation observed in patients with a modified Duke score >3 should lead to a more aggressive strategy regarding statin treatment as a secondary prevention measure and to reduce mortality in this category of patients. Quantifying both, the modified Duke score and peri-coronary inflammation using the FAI could guide the decision of revascularization strategy for some borderline lesions which present a high degree of inflammation and consequently constitute lesions with an increased vulnerability. The current study emphasizes the additive role of the FAI in the modified Duke score in making an optimal therapeutic decision.

5. Conclusions

The CT-derived modified Duke index correlates well with local perilesional inflammation as assessed by the FAI score at different levels of the coronary circulation. The CCTA assessment of coronary inflammation may identify dangerous plaques and reveal increased inflammation in the coronary tree of patients with a low-to-intermediate likelihood of CAD and consequently guide the therapeutic decision.

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Article

Assessing the Impact of Long-Term High-Dose Statin Treatment on Pericoronary Inflammation and Plaque Distribution—A Comprehensive Coronary CTA Follow-Up Study

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Abstract: Computed tomography angiography (CTA) has validated the use of pericoronary adipose tissue (PCAT) attenuation as a credible indicator of coronary inflammation, playing a crucial role in coronary artery disease (CAD). This study aimed to evaluate the long-term effects of high-dose statins on PCAT attenuation at coronary lesion sites and changes in plaque distribution. Our prospective observational study included 52 patients (mean age 60.43) with chest pain, a low-to-intermediate likelihood of CAD, who had documented atheromatous plaque through CTA, performed approximately 1 year and 3 years after inclusion. We utilized the advanced features of the CaRi-Heart[®] and syngo.via Frontier[®] systems to assess coronary plaques and changes in PCAT attenuation. The investigation of changes in plaque morphology revealed significant alterations. Notably, in mixed plaques, calcified portions increased ($p < 0.0001$), while non-calcified plaque volume (NCPV) decreased ($p = 0.0209$). PCAT attenuation generally decreased after one year and remained low, indicating reduced inflammation in the following arteries: left anterior descending artery (LAD) ($p = 0.0142$), left circumflex artery (LCX) ($p = 0.0513$), and right coronary artery (RCA) ($p = 0.1249$). The CaRi-Heart[®] risk also decreased significantly ($p = 0.0041$). Linear regression analysis demonstrated a correlation between increased PCAT attenuation and higher volumes of NCPV ($p < 0.0001$, $r = 0.3032$) and lipid-rich plaque volume ($p < 0.0001$, $r = 0.3281$). Our study provides evidence that high-dose statin therapy significantly reduces CAD risk factors, inflammation, and plaque vulnerability, as evidenced by the notable decrease in PCAT attenuation, a critical indicator of plaque progression.

Keywords: pericoronary adipose tissue inflammation; computed tomography angiography; fat attenuation index score; atherosclerosis; coronary artery disease; high-dose statin



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1. Introduction

Coronary artery disease (CAD) is a major global health challenge and the leading cause of death worldwide, responsible for over nine million deaths in 2019 [1,2]. It manifests in various forms, such as stable and unstable angina, myocardial infarction (MI), and sudden cardiac death [3]. Significantly, a quarter of MI patients develop heart failure, which has a high five-year mortality rate of 50%, placing considerable strain on healthcare systems [4].

Pericoronary adipose tissue (PCAT) is a specific type of epicardial adipose tissue (EAT) that surrounds the coronary arteries, with distinct morphological and functional characteristics despite its close proximity to EAT [5,6]. Emerging research suggests that PCAT

plays a unique role in cardiovascular diseases, making both its quantitative and qualitative assessment crucial for evaluating an individual's risk of cardiometabolic disorders [5,7,8]. Vascular inflammation within PCAT is a hallmark of unstable "vulnerable" coronary plaques and a key contributor to the progression of coronary atherosclerosis [9–11]. Utilizing computed tomography angiography (CTA) to measure the fat attenuation index (FAI) has become clinically important for identifying high-risk patients [12,13] and assessing the impact of anti-inflammatory treatments, such as how statins have been shown to reduce the CT attenuation in EAT, indicating their therapeutic effect [14].

CTA serves as a noninvasive method for evaluating PCAT, using the FAI to monitor changes in PCAT and track coronary plaque progression. An increase in PCAT density often signifies various stages of CAD [13] and is associated with vulnerable plaque characteristics, predictors of clinical incidents [15,16], especially in acute coronary syndrome [17]. However, the study of PCAT's role in plaque progression is still emerging, limited by patient numbers and follow-up duration, leaving the full impact of PCAT density changes on plaque progression yet to be fully understood [18,19].

Statin therapy plays a crucial role in stabilizing plaques in CAD, mainly by reducing low-density and fibro-fatty plaque volumes and increasing denser, calcium-rich plaques. This increase in calcium in heart arteries further lowers plaque detachment risk [20]. Statins work through various mechanisms, including reducing lipid accumulation in plaques, decreasing inflammation, and enhancing endothelial function [21,22]. They effectively decrease plaque and external elastic membrane volumes without impacting the lumen volume, primarily due to their anti-inflammatory properties. However, there are some associated risks with intensive statin use [23].

Against this backdrop, our objective was to investigate the effects of extended high-dose statin therapy on the FAI of PCAT at coronary lesion sites. Additionally, we sought to assess alterations in plaque distribution over time, utilizing a 128-slice contrast-enhanced CTA during follow-up appointments.

2. Results

2.1. Baseline Characteristics of the Study Population

In this study, we enrolled 52 participants who met all the previously outlined inclusion criteria. The average age of these patients at the initial scan was 60.43 ± 9.21 years, with males constituting 65.38% ($n = 34$) of the cohort. The cohort had a high prevalence of traditional risk factors for CAD, with hypertension being the most prevalent at 84.61% ($n = 44$). Additionally, 63.46% ($n = 33$) of the patients had hyperlipidemia, while diabetes mellitus and smoking were present in 26.92% ($n = 14$) and 17.30% ($n = 9$) of the patients, respectively. A considerable number of patients, accounting for 42.30% ($n = 22$), indicated a family history of CAD, underscoring the hereditary aspect of the disease in their familial background. The composition of plaque types within the selected coronary arteries was categorized as follows: 54.06% ($n = 80$) were calcified plaques, 4.73% ($n = 7$) were non-calcified plaques, and 41.21% ($n = 61$) were mixed plaques featuring both calcified and non-calcified components. The mean calcium score among the participants was 127.5 ± 72.96 . The distribution across different calcium score ranges was as follows: scores < 10 were observed in 5.77% ($n = 3$), scores ranging from 10 to 400 comprised the majority at 69.23% ($n = 36$), and scores > 400 were found in 25.00% ($n = 13$). These findings are presented in Table 1.

Table 1. Clinical characteristics, comorbidities, and risk factors of the study population at baseline.

| Parameters | |
|---|-------------------|
| Age at time of scan, year, mean \pm SD | 60.43 ± 9.21 |
| Male gender, n (%) | 34 (65.38) |
| Body mass index (kg/m^2), mean \pm SD | 28.57 ± 4.36 |
| Time until the second CTA scan (days), mean \pm SD | 372.4 ± 68.06 |
| Time until the last CTA scan (days), mean \pm SD | 1103 ± 108.4 |
| LVEF ¹ (%), mean \pm SD | 48.21 ± 5.37 |

Table 1. Cont.

| Parameters | |
|---|-------------------|
| Cardiovascular risk factors: | |
| Hypertension, <i>n</i> (%) | 44 (84.61) |
| Hypercholesterolemia, <i>n</i> (%) | 33 (63.46) |
| Diabetes mellitus, <i>n</i> (%) | 14 (26.92) |
| Smoking, <i>n</i> (%) | 9 (17.30) |
| Familial history of CAD ² , <i>n</i> (%) | 22 (42.30) |
| Plaque types: | |
| Calcified plaque, <i>n</i> (%) | 80 (54.06) |
| Non-calcified plaque, <i>n</i> (%) | 7 (4.73) |
| Mixed plaque, <i>n</i> (%) | 61 (41.21) |
| Lesion location: | |
| LAD ³ , <i>n</i> (%) | 87 (58.78) |
| LCX ⁴ , <i>n</i> (%) | 16 (10.81) |
| RCA ⁵ , <i>n</i> (%) | 45 (30.41) |
| Calcium score, mean \pm SD | 127.5 \pm 72.96 |
| <10, <i>n</i> (%) | 3 (5.77) |
| 10–400, <i>n</i> (%) | 36 (69.23) |
| >400, <i>n</i> (%) | 13 (25.00) |

¹ LVEF—left ventricular ejection fraction; ² CAD—coronary artery disease; ³ LAD—left anterior descending artery;

⁴ LCX—left circumflex artery; ⁵ RCA—right coronary artery.

2.2. Serial Changes in the Lipid Panel Outcomes during Follow-Up

After commencing statin therapy, the blood tests conducted during the first-year follow-up revealed significant changes in lipid profiles. The average total cholesterol levels decreased significantly from 194.3 ± 66.76 to 145.2 ± 34.7 ($p = 0.0003$). Notable alterations were also observed in LDL-Cho and HDL-Cho levels, with LDL-Cho decreasing from 105.9 ± 33.97 to 87.69 ± 32.99 ($p < 0.0001$) and HDL-Cho increasing from 38.11 ± 8.72 to 47.10 ± 7.97 ($p < 0.0001$).

Long-term analysis at the time of the last visit revealed persistent significant differences in these parameters when comparing initial and final visits, with total cholesterol ($p < 0.0001$), LDL-Cho ($p < 0.0001$), and HDL-Cho ($p < 0.0001$) all showing notable differences. Triglyceride levels also changed significantly after one year and showed a significant long-term decrease from 188.7 ± 66.01 to 171.9 ± 53.76 ($p < 0.0001$), reflecting effective anti-triglyceride therapy. These findings are detailed in Table 2.

Table 2. Comparison of lipid panel outcomes across various follow-up appointments.

| Lipid Profile Parameters | 1st Visit | 2nd Visit | <i>p</i> -Value * | Last Visit | <i>p</i> -Value |
|---|------------------------------------|------------------------------------|-------------------|------------------------------------|-----------------|
| T-Cho ¹ (mg/dL), mean \pm SD, [95% CI] | 194.3 \pm 66.76 [176.1–212.5] | 145.2 \pm 34.7 [129.1–164.4] | 0.0003 | 150.7 \pm 48.92 [137.3–164.0] | <0.0001 |
| LDL-Cho ² (mg/dL), mean \pm SD, [95% CI] | 105.9 \pm 33.97 [96.41–115.3] | 87.69 \pm 32.99 [78.50–96.87] | <0.0001 | 84.07 \pm 32.16 [75.12–93.03] | <0.0001 |
| HDL-Cho ³ (mg/dL), mean \pm SD, [95% CI] | 38.11 \pm 8.72 [35.68–40.53] | 47.10 \pm 7.97 [44.88–49.32] | <0.0001 | 50.01 \pm 6.46 [48.21–51.81] | <0.0001 |
| TGs ⁴ (mg/dL), mean \pm SD, [95% CI] | 188.7 \pm 66.01 [170.3–207.1] | 179.4 \pm 59.49 [162.9–196.0] | <0.0001 | 171.9 \pm 53.76 [156.9–186.9] | <0.0001 |

¹ T-Cho—total cholesterol; ² LDL-Cho—low-density lipoprotein cholesterol; ³ HDL-Cho—high-density lipoprotein cholesterol; ⁴ TGs—triglycerides. * see the description in the statistical analysis section of Section 4.

2.3. Serial Changes of Plaque Features before and after Statin Treatment

Subsequently, we examined the morphological changes in plaque features during the follow-up period. However, due to the minimal changes experienced during the short (1 year) follow-up and the very time-consuming evaluation procedure, we only performed

plaque analysis on the baseline CTA scans and the last multi-year control scans. The study observed an overall increase in the volume of calcified plaques, though this change was not statistically significant between the initial and final follow-up CTA scans ($p = 0.0773$). Regarding non-calcified plaques, changes were also noted, highlighting the dynamic and variable nature of plaque morphology. However, only seven plaques were analyzed in this category, and a significant transformation was observed solely in the CPV over a period of 3 years.

Figure 1 presents the TPV values for each plaque type, illustrating the shifts in plaque morphology during the follow-up period. However, these changes were not statistically significant.

In our longitudinal analysis of plaque morphology, we found the mixed plaques particularly intriguing due to their dynamic changes. Specifically, the CPV within these plaques significantly increased from $53.92 \pm 31.29 \text{ mm}^3$ to $87.42 \pm 43.48 \text{ mm}^3$ ($p < 0.0001$). In contrast, the NCPV significantly decreased from $180.5 \pm 66.81 \text{ mm}^3$ to $155.4 \pm 59.51 \text{ mm}^3$ ($p = 0.0209$). Although the TPV increased, this change was not statistically significant, moving from $237.4 \pm 70.0 \text{ mm}^3$ to $256.9 \pm 79.84 \text{ mm}^3$ ($p = 0.1454$). Further analysis of the NCPV showed an increase in the volume of fibrotic plaques from $154.8 \pm 63.04 \text{ mm}^3$ to $179.8 \pm 63.46 \text{ mm}^3$ ($p = 0.0324$), while lipid-rich plaques significantly decreased from $20.94 \pm 9.93 \text{ mm}^3$ to $16.62 \pm 7.69 \text{ mm}^3$ ($p = 0.0057$). In summary, during the follow-up period, there was a decrease in NCPV with significant changes in the FPV and LRPV, alongside a significant increase in CPV in mixed plaques. These findings are further detailed in Table 3 and Figure 2.

The findings we have discussed are best validated by a specific instance from our patient pool, which is depicted in detail in Figure 3. This illustration provides a clear view of how statin therapy contributes to the reduction in FAI score and the alteration of plaque characteristics, showcasing the changes in a patient over the course of treatment.

Table 3. Comparison of plaque changes at the baseline and final follow-up appointments.

| Serial Changes of Plaque Components | 1st Scan | Last Scan | p-Value |
|--|------------------------------------|------------------------------------|---------|
| Calcified plaques ($n = 80$) | | | |
| ¹ TPV (mm^3), mean \pm SD, [95% CI] | 185.1 ± 78.70 [167.5–202.5] | 206.8 ± 86.03 [187.7–226.0] | 0.0773 |
| Non-calcified plaques ($n = 7$) | | | |
| TPV (mm^3), mean \pm SD, [95% CI] | 57.23 ± 26.96 [32.30–82.16] | 55.51 ± 24.25 [33.09–77.94] | 0.9122 |
| ² FPV (mm^3), mean \pm SD, [95% CI] | 47.36 ± 31.04 [18.65–76.06] | 49.70 ± 25.14 [26.45–72.95] | 0.8859 |
| ³ LRPV (mm^3), mean \pm SD, [95% CI] | 5.14 ± 2.65 [2.68–7.60] | 4.70 ± 3.34 [1.60–7.79] | 0.2070 |
| ⁴ CPV (mm^3), mean \pm SD, [95% CI] | 0 | 2.47 ± 1.89 [0.71–4.22] | 0.0137 |
| Mixed plaques ($n = 61$) | | | |
| TPV (mm^3), mean \pm SD, [95% CI] | 237.4 ± 70.0 [219.5–255.4] | 256.9 ± 79.84 [236.5–277.4] | 0.1454 |
| ⁵ NCPV (mm^3), mean \pm SD, [95% CI] | 180.5 ± 66.81 [163.3–197.6] | 155.4 ± 59.51 [140.1–170.6] | 0.0209 |

¹ TPV—total plaque volume; ² FPV—fibrotic plaque volume; ³ LRPV—lipid-rich plaque volume; ⁴ CPV—calcified plaque volume; ⁵ NCPV—non-calcified plaque volume.

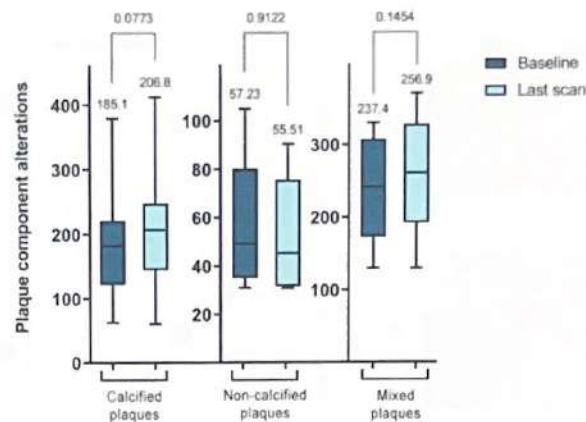


Figure 1. Serial changes of total plaque volume (TPV) for each plaque type.

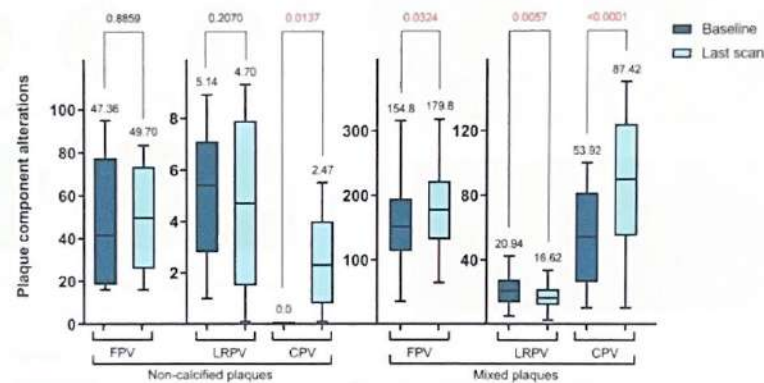


Figure 2. Serial changes of plaque components in the non-calcified and mixed plaque types (FPV—fibrotic plaque volume; LRPV—lipid-rich plaque volume; CPV—calcified plaque volume).

2.4. Serial Changes of Lesion-Specific PCAT-FAI before and after Statin Treatment

For all lesions across the coronary arteries, follow-up data revealed that high-dose statin therapy significantly altered the lesion-specific PCAT-FAI after nearly one year, with a general trend of gradual decrease remaining thereafter at the last scan. Figure 4 displays the diagrams that break down the data into the two specific follow-up intervals: 1 year and over 3 years. The specific details for all the PCAT-FAI parameters are outlined separately.

It is important to note that the traditionally measured FAI in HU units showed a significant decrease only in the LAD at the one-year follow-up (-68.94 ± 6.88 vs. -72.83 ± 6.29 , $p = 0.0061$). This reduction remained consistent up to the final scans (-68.94 ± 6.88 vs. -71.75 ± 8.07 , $p = 0.0138$).

Regarding specific FAI scores, there was an overall decrease across all three coronary arteries at the one-year mark compared to initial measurements. This decrease was significant for the total score (16.78 ± 8.76 vs. 12.05 ± 7.88 , $p < 0.0001$), LAD (15.93 ± 9.22 vs. 11.75 ± 7.35 , $p = 0.0109$), LCX (14.78 ± 7.35 vs. 10.80 ± 7.27 , $p = 0.0029$), and RCA (19.60 ± 8.99 vs. 13.13 ± 8.34 , $p < 0.0001$). Although these values started to increase slightly by the time of the last CTA, a significant difference was maintained for the total score (16.78 ± 8.76 vs. 13.64 ± 8.00 , $p = 0.0007$), LAD (15.93 ± 9.22 vs. 12.03 ± 6.27 , $p = 0.0142$), and LCX (14.78 ± 7.35 vs. 12.15 ± 7.51 , $p = 0.0513$). However, for the RCA, after 3 years, the FAI score increased to the point where the difference was no longer significant (19.60 ± 8.99 vs. 16.73 ± 9.17 , $p = 0.1249$).

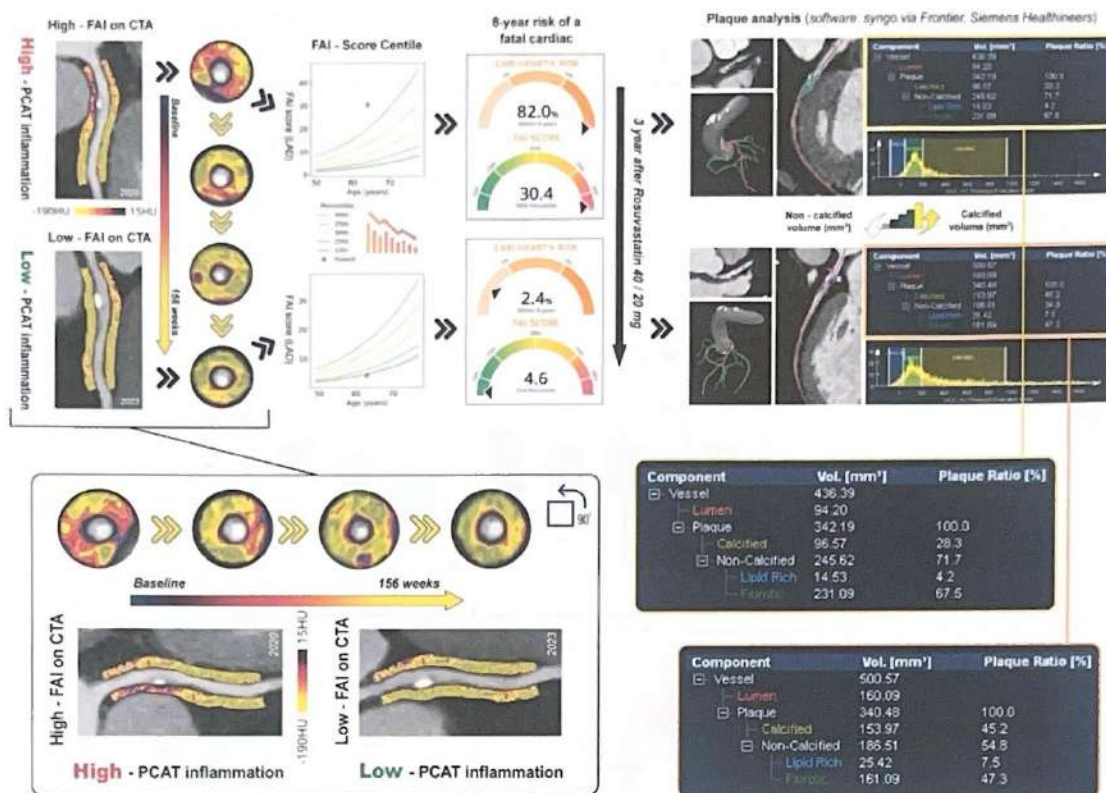


Figure 3. A schematic illustration of a patient case showing a high baseline FAI score with subsequent reduction in vascular inflammation after three years of therapy, along with an analysis of changes in plaque composition over the same follow-up period (PCAT—pericoronary adipose tissue; FAI—fat attenuation index; CTA—computed tomography angiography; HU—Hounsfield units; LAD—left anterior descending artery).

The FAI scores for the LAD, LCX, and RCA were plotted on percentile curves for different age and sex groups, with their predictive value assessed using Cox proportional hazards models. These models were adjusted for risk factors such as hypertension, diabetes, smoking, hyperlipidemia, high-risk plaque features, and the modified Duke CAD prognostic index [24].

Concurrently, a notable shift in the PCAT-FAI score percentiles was observed, indicating a significant decrease across all three coronary arteries when comparing baseline scans with subsequent scans. For the LAD, scores decreased from 72.88 ± 16.22 to 64.96 ± 24.45 ($p = 0.0526$) and further to 61.91 ± 17.96 ($p = 0.0044$). The LCX scores dropped from 73.56 ± 15.60 to 63.85 ± 16.32 ($p = 0.0120$) and then to 60.18 ± 18.07 ($p < 0.0001$). For the RCA, the scores went from 81.73 ± 13.61 to 70.73 ± 18.98 ($p = 0.0001$) and subsequently changed to 71.72 ± 19.21 ($p = 0.0041$).

There was a notable reduction in the CaRi-Heart® Risk score between the initial and second scans (33.20 ± 22.07 vs. 17.78 ± 13.41 , $p = 0.0001$). Although there was an increase in the score at the time of the last visit, it still remained significantly lower compared to the initial value (33.20 ± 22.07 vs. 20.65 ± 16.14 , $p = 0.0041$), as depicted in Figure 5. The CaRi-Heart® analysis takes into account age and gender to assess coronary inflammation and predicts the 8-year risk of a fatal cardiac event. This evaluation includes the FAI Score, plaque burden, and various clinical risk factors.

2.5. Relationship between the PCAT-FAI Assessment and Plaque Component Morphology

Considering the individual PCAT-FAI score values for each plaque, we conducted a linear regression analysis based on the baseline CTA scans. Intriguingly, this shed light on what the literature has previously speculated but not studied with FAI scoring: an increase in FAI score correlates with an increase in TPV ($p = 0.0569$, $r = 0.0600$), NCPV ($p < 0.0001$, $r = 0.3032$), and significantly, with an increase in LRPV ($p < 0.0001$, $r = 0.3281$). However, such a correlation was not found between the FAI score and the TPV of calcified plaques ($p = 0.4277$), nor in the CPV ($p = 0.2021$) or FPV ($p = 0.9992$) of mixed plaques (Figure 6).

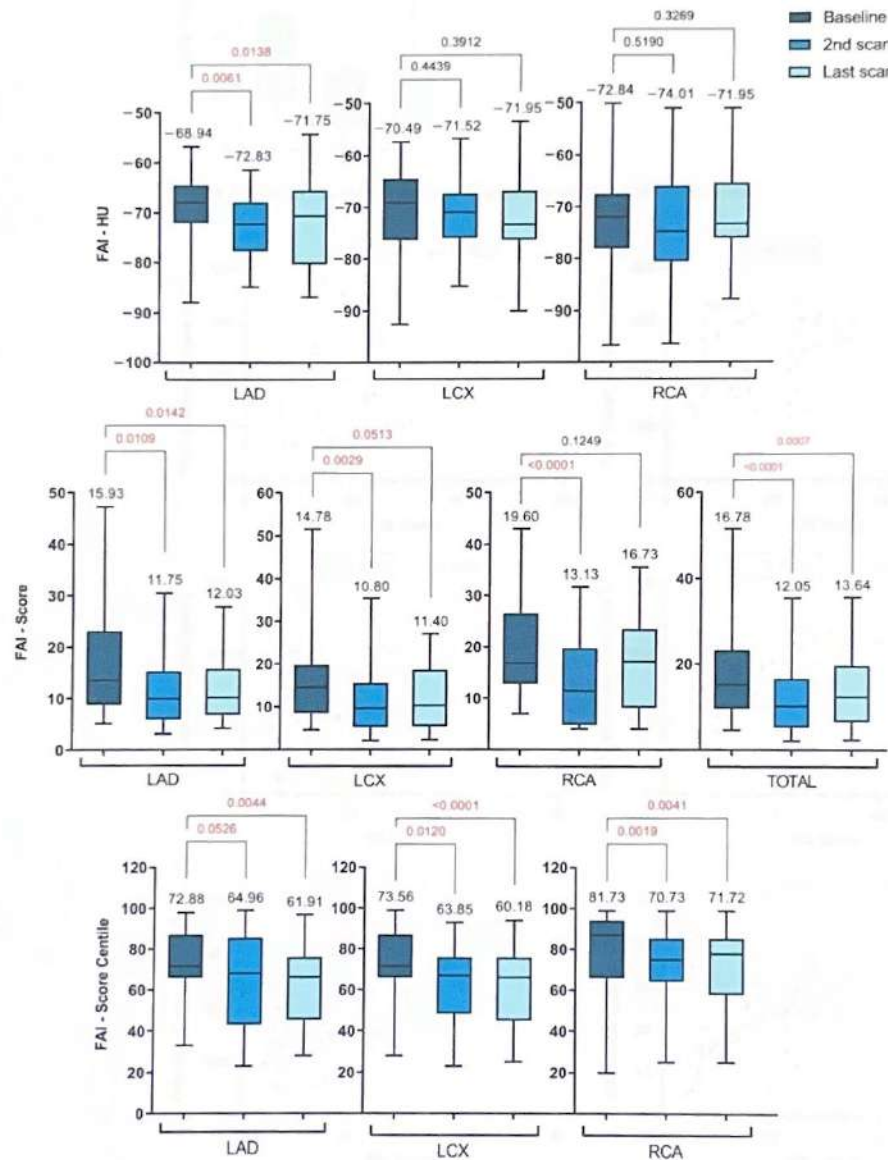


Figure 4. Serial changes of PCAT-FAI before and after statin treatment during the scans (FAI—fat attenuation index; HU—Hounsfield units; LAD—left anterior descending artery; LCX—left circumflex artery; RCA—right coronary artery).

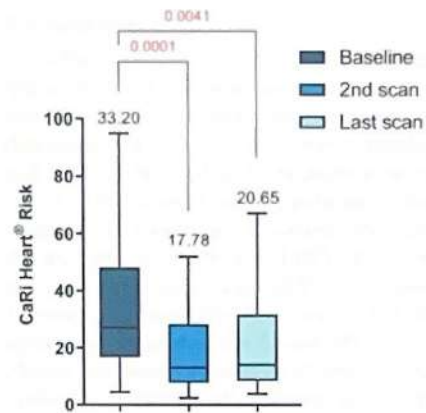


Figure 5. Personalized CaRi-Heart® cardiovascular risk assessment.

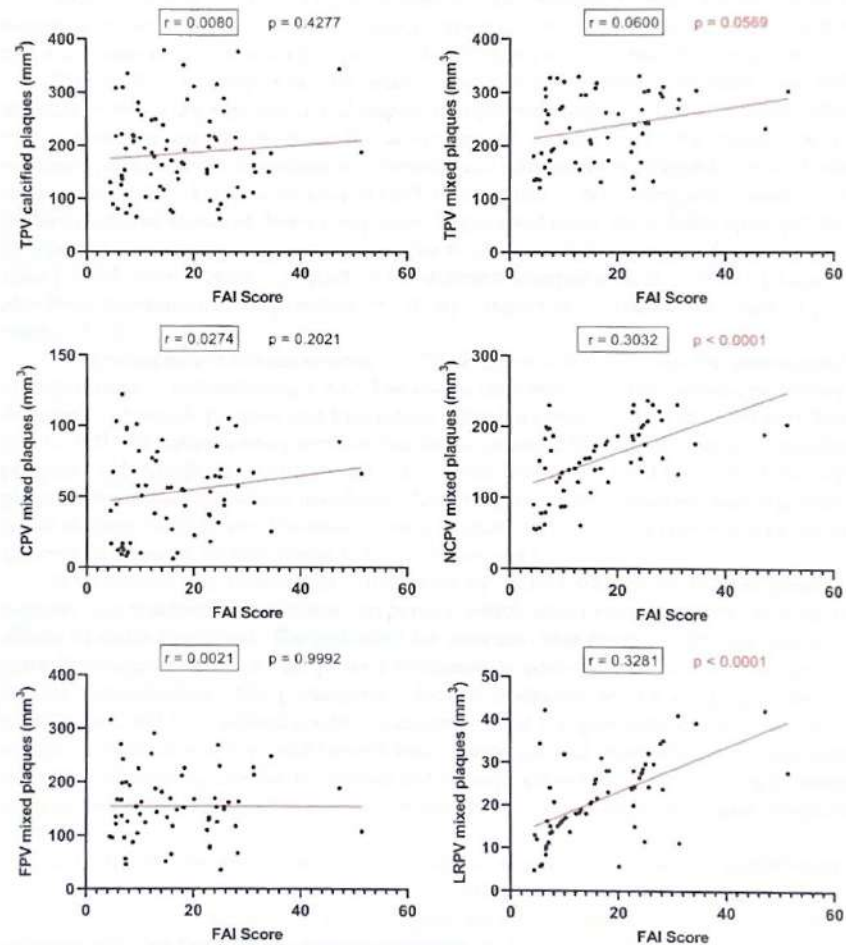


Figure 6. Analyzing PCAT-FAI score in relation to plaque components using linear regression (TPV—total plaque volume; CPV—calcified plaque volume; FPV—fibrotic plaque volume; NCPV—non-calcified plaque volume; LRPV—lipid-rich plaque volume; FAI—fat attenuation index).

3. Discussion

Our study's main outcome strongly supports the benefits of statin therapy in reducing risk factors and inflammation associated with CAD. The data from our participant cohort, demonstrating significant reductions in lipid levels, plaque-specific inflammation, and changes in plaque structure, indicate that high-dose statin therapy has a positive impact on both the biochemical and structural aspects of CAD pathology.

The FAI score correlates with the vulnerable component of plaque, a topic that recent studies have investigated, particularly examining the relationship between PCAT-FAI and the increase in NCPV and LRPV. These studies have focused on the predictive power of PCAT attenuation and NCPV concerning MI. Research has demonstrated that PCAT attenuation around the RCA can predict MI occurrence, making it a significant predictive marker for assessing the 5-year MI risk [25]. Additionally, the combination of FAI and plaque assessments has been shown to more effectively distinguish ischemia compared to evaluations based solely on stenosis. This highlights the significance of FAI as a marker for the risk of coronary atherosclerosis, supporting its strong association with the development of coronary atherosclerosis and plaque vulnerability [26,27].

Statins not only improved lipid profiles but also seemed to induce a shift in plaque morphology, with increases in CPV suggesting a move towards more stable plaque forms, and a decrease in NCPV reflecting potential reductions in vulnerability to rupture.

This study's findings resonate with existing research that links statin use with a slowdown in CAD progression and improved lipid regulation [28]. It is well-established that statins can notably decrease the advancement of atherosclerotic plaques and the incidence of MACE, despite increasing coronary calcium, which may be indicative of plaque stabilization [29–31]. The relevance of high-dose statins in delivering additional vascular protection above standard doses is supported by clinical trials, though the appropriateness of this therapy remains patient-specific due to the variability in clinical conditions and risks [32,33]. Such therapy's impact on the different components of coronary plaques has also been substantiated, supporting the study's report of differential changes in plaque types [19,34].

Integrating recent advancements in CTA into our study enriches the understanding of statin therapy in combating CAD. The use of radiomics and radio-transcriptomics for detecting vulnerable plaques and forecasting potential cardiac events in both heart disease and COVID-19 patients complements our findings about the role of statins in stabilizing plaques. This highlights statins' dual role in both managing lipid levels and modifying plaque composition to reduce instability. Adopting these sophisticated imaging methods could deepen insights into the effectiveness of statin treatment, paving the way for more tailored therapeutic approaches in CAD management [35,36].

Nonetheless, this research is constrained by factors such as its limited participant number and relatively brief follow-up period, which may not fully reflect the long-term effects of statin treatment. The potential for selection bias given by the sole use of CTA scans for plaque evaluation also poses a limitation, as some plaques may not be detectable by this method alone. The participant selection, characterized by a high prevalence of traditional CAD risk factors, could additionally limit the generalizability of the study's results. Future research would benefit from a broader and more diverse cohort and an extended monitoring timeline to validate the findings presented here. Utilizing a variety of imaging techniques could offer a more nuanced view of the changes in plaque composition over time.

In summary, the clinical implications of this study are significant, underlining the importance of high-dose statin therapy in the management and potential modification of CAD. The evidence of statin efficacy in improving lipid profiles, reducing plaque-specific inflammation, and stabilizing plaque morphology holds considerable promise for CAD treatment strategies. Although the study's limitations indicate a need for ongoing research, they do not undermine the current clinical application of its findings. Future studies,

addressing these limitations, could provide even stronger support for the use of statins in CAD management and prevention strategies.

4. Materials and Methods

4.1. Study Design and Population

In our single-center, longitudinal, prospective, observational, nonrandomized study, 109 patients with chest pain and a low to intermediate risk of CAD were recruited. These participants underwent a detailed examination of their coronary anatomy, atherosclerotic changes, FAI scoring, and plaque analysis using 128-slice CTA. The study was designed to monitor the same group of individuals over time to observe any developments in their condition. Follow-up periods were divided into two intervals: one spanning approximately one year, and another extending beyond three years.

Our study applied the following inclusion criteria: (1) the initial CTA had to show at least one lesion with a luminal stenosis of 25–49% in any major coronary artery with a diameter of ≥ 2 mm, below CAD-RADS category 3; (2) participants had to be new to statin therapy and free from any other lipid-lowering medications at the time of their baseline scan. The following exclusion criteria were applied: (1) patients whose coronary CTA results were not clear enough for quantitative assessment ($n = 23$) or PCAT density analysis ($n = 15$) at either the initial or follow-up scans, precluding good quality analysis; (2) patients who had clinical incidents leading to coronary revascularization in the interval between their CTAs ($n = 19$). After applying these exclusion criteria, the final analysis included 148 lesions from 52 patients (as shown in Figure 7).

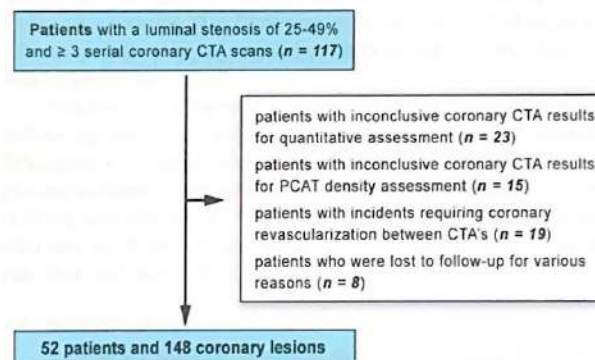


Figure 7. Patient recruitment flowchart (CTA—computed tomography angiography; PCAT—pericoronary adipose tissue).

At each visit, comprehensive lipid profiles, including measurements of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-Cho), and high-density lipoprotein cholesterol (HDL-Cho) levels, were collected. Additionally, we meticulously recorded demographic data, other laboratory test results, cardiovascular risk factors, and any new or progressing symptoms for each participant.

4.2. Coronary CTA Acquisition Protocol

All study procedures utilized a 128-slice scanner (Somatom Definition AS, Siemens Healthineers, Erlangen, Germany) for conducting CTA scans on all study participants. Patients with heart rates under 65 bpm underwent scans with retrospective gating and specific technical settings. If heart rates exceeded 65 bpm, beta-blockers were used to achieve the target heart rate, with continuous blood pressure monitoring. The procedure included a non-contrast coronary calcium scan, followed by an iodine contrast injection and a saline flush, with patients holding their breath. The scans were systematically archived in

a specialized electronic imaging database, which facilitated offline image post-processing and cloud-based distribution.

4.3. Pericoronary Adipose Tissue FAI and Plaque Analysis

Images obtained from the scans were converted to DICOM format, anonymized, and then securely sent to our collaborative research facility, the Centre of Caristo Diagnostics in Oxford, UK, for post-processing. This process involved analyzing inflammation in the PCAT for each coronary artery. Utilizing advanced artificial intelligence (AI) algorithms from CaRi-Heart[®] by Caristo Diagnostics (Centre of Caristo Diagnostics, Oxford, UK), the PCAT-FAI and AI-based FAI scores were accurately calculated for each major coronary artery across all patients.

The AI algorithms enhance the precision of the PCAT-FAI by measuring attenuation in 3D layers, each 1 mm thick, around the coronary arteries [6,37]. These algorithms perform a series of complex operations, including segmenting cardiac structures and evaluating the PCAT. They adjust for a range of scan-related variables to ensure that the PCAT-FAI is a reliable marker of coronary inflammation, distinct from standard CT attenuation values [38].

To clarify, the distinctions between FAI, FAI score, and CaRi-Heart[®] risk are as follows: (1) FAI, measured in Hounsfield units (HU), offers an unmodified graphical depiction of inflammation levels in the three primary epicardial coronary arteries; (2) FAI score provides a customized evaluation, quantifying coronary inflammation in these arteries while incorporating age and gender, and is expressed as a relative risk; (3) CaRi-Heart[®] risk represents the absolute risk of experiencing a fatal cardiac event within the next eight years. This risk assessment is based on individualized FAI score values, the extent of coronary atherosclerotic plaque, and other clinical risk factors (diabetes, smoking, hyperlipidemia, and hypertension) [39].

For the assessment of plaque characteristics and components at baseline and during follow-up visits, we utilized the Syngo.via Frontier[®] (Syngo.Via, Siemens Healthineers, Erlangen, Germany) offline workstation. This enabled us to measure various types of plaque volumes, including total (TPV), calcified (CPV), non-calcified (NCPV), lipid-rich (LRPV), and fibrotic (FPV) plaques. Furthermore, we visually categorized all target lesions into one of three predefined types: calcified, non-calcified, or mixed (containing both calcified and non-calcified components).

4.4. Statistical Analysis

Following the calculation of the PCAT-FAI for each coronary artery, the results were transmitted to our institution and cataloged in a Microsoft Excel electronic database. For statistical evaluation, we used GraphPad Prism 9.5 software (GraphPad Software, Inc., San Diego, CA, USA). Our analysis encompassed PCAT-FAI measurements across 148 coronary arteries, including 50 from the LAD, 48 from the LCX, and 50 from the RCA. We also calculated the CaRi-Heart[®] risk scores for each participant.

Data from various follow-up periods were comparatively analyzed. We displayed categorical data as counts and percentages, applying the Chi-square test or Fisher's exact test for analysis, contingent on dataset dimensions. For continuous data, we provided means \pm standard deviations, employing the paired Student's *t*-test for normally distributed datasets, or the Wilcoxon signed-rank test for those with skewed distributions. To explore the association between shifts in PCAT-FAI values and alterations in plaque attributes, Pearson's correlation was used for normally distributed variables, while Spearman's rank correlation was utilized for others. A $p < 0.05$ was used to denote statistical significance.

5. Conclusions

Our study validates the efficacy of high-dose statin therapy in diminishing risk factors, inflammation, and plaque vulnerability in CAD. It demonstrates that a high FAI score,

indicative of inflamed PCAT and vulnerable plaque morphology, is significantly reduced following high-dose statin treatment. This underscores the significance of the FAI score as a predictive marker for the progression and evolution of CAD.

Author Contributions: Conceptualization, B.B.M., I.B. and T.B.; methodology, T.B. and I.B.; validation, B.B.M., I.B., E.B., N.R., Z.P. and T.B.; formal analysis, I.B., T.M. and Z.P.; investigation, B.B.M., E.B. and T.B.; resources, I.B.; data curation, N.R. and T.M.; writing—original draft preparation, B.B.M. and T.B.; writing—review and editing, B.B.M. and T.B.; visualization, B.B.M., E.B., N.R. and T.B.; supervision, I.B.; project administration, I.B. and T.B.; funding acquisition, I.B. and T.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The research procedures followed good clinical practice guidelines and adhered to the Declaration of Helsinki. Institutional ethics approval was obtained from the ethics committee (26884/10 November 2021) and from the Scientific Research Ethics Committee at the “G. E. Palade” University of Medicine, Pharmacy, Science, and Technology in Târgu Mureș (1513/9 December 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

Acknowledgments: Preliminary findings from this study were presented at the 2023 ESC Congress of the European Society of Cardiology in Amsterdam [40]. This paper also constitutes a component of the first author’s doctoral thesis at the University of Medicine, Pharmacy, Science, and Technology ‘G. E. Palade’ of Târgu-Mureș, as part of the Doctoral School of Medicine and Pharmacy, and has received the endorsement of all contributing authors.

Conflicts of Interest: The authors report no conflicts of interest. Furthermore, the funding bodies were not involved in any aspect of this study’s design, nor in the gathering, analysis, or interpretation of data. They also did not contribute to the manuscript’s composition or influence the decision to publish the findings.

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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, CaRI-Heart 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,^{3,4} 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 $\text{TNF-}\alpha$, IL-6, and $\text{IFN-}\gamma$) 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-

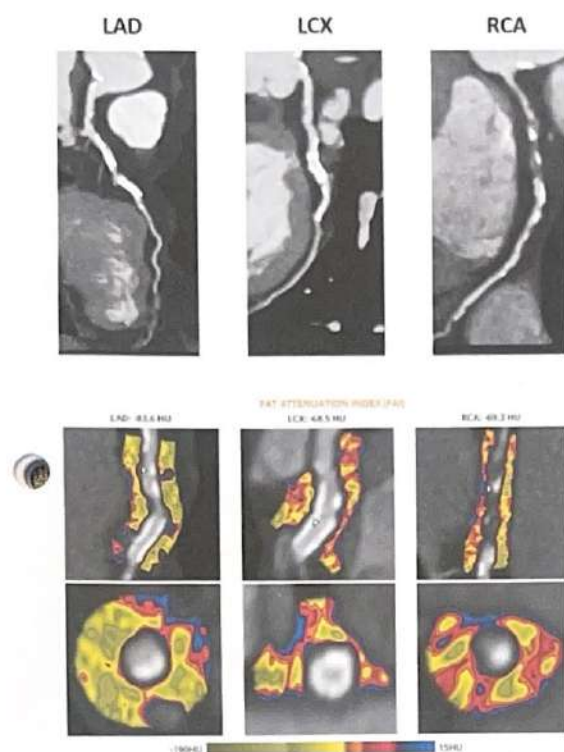


FIGURE 1. CCTA image of the three major coronary arteries and a color representation of FAI analysis for the same patient. Yellow areas represent zones with low inflammation, while red and blue areas represent zones with high inflammation.

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).

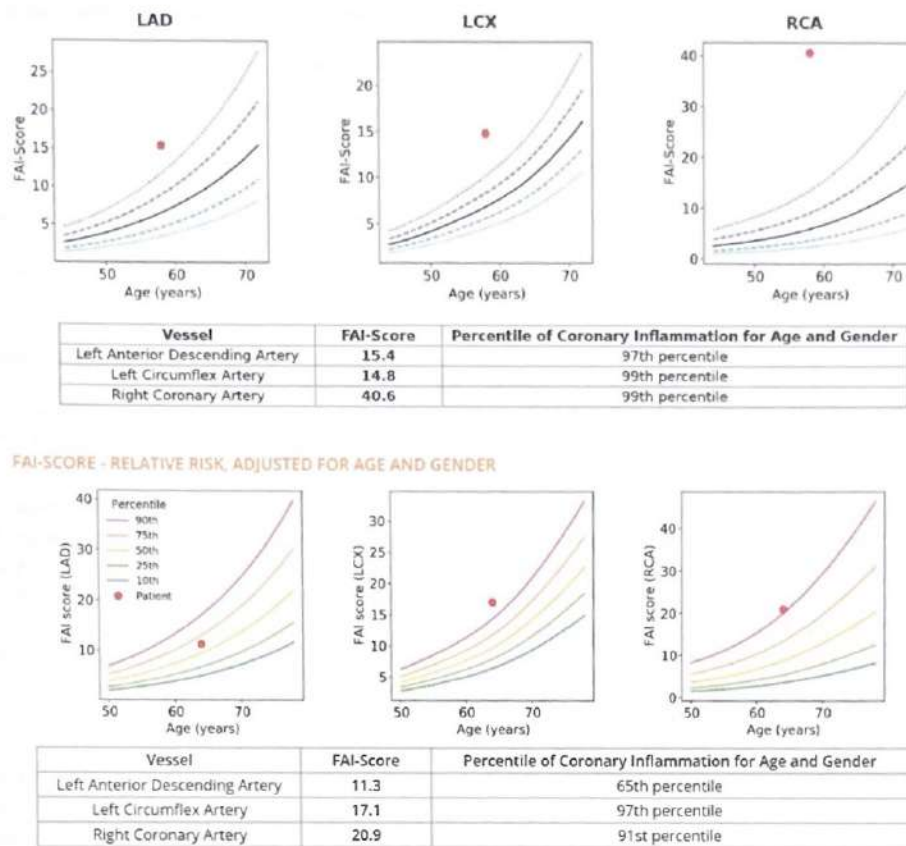


FIGURE 2. FAI score percentiles in two patients with different inflammation levels. **A** – FAI analysis in a patient with high inflammation. There is a high FAI score percentile in all three coronary arteries, but more expressed in the RCA. **B** – FAI analysis in a patient with moderate inflammation. 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. $12.3 \pm$

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 (4%) | 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 |

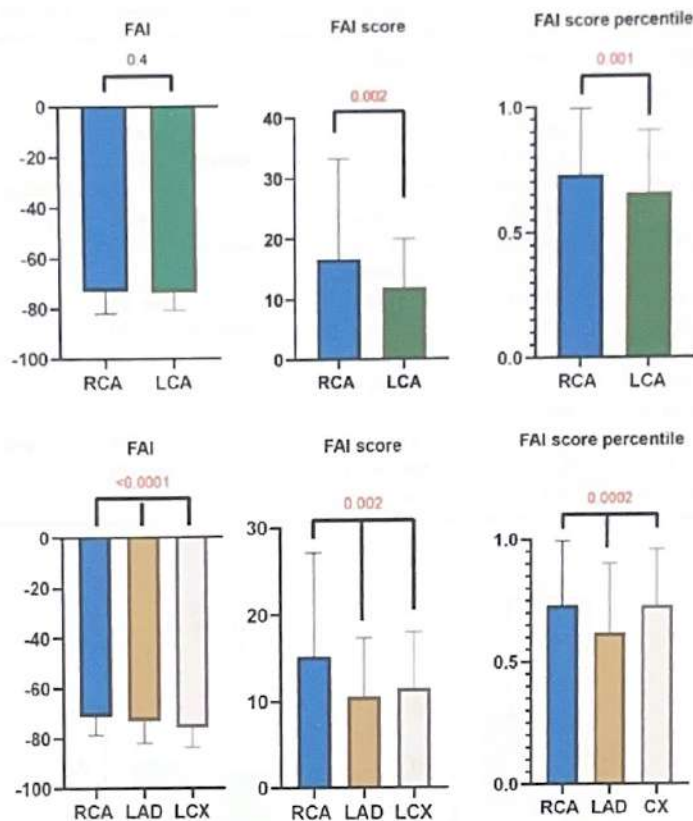


FIGURE 3. FAI assessment of coronary inflammation in the three coronary arteries, based on FAI, FAI score, and FAI score percentiles. **A** – comparison between the left and right coronary system; **B** – comparison between the three coronary arteries individually.

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- β 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-

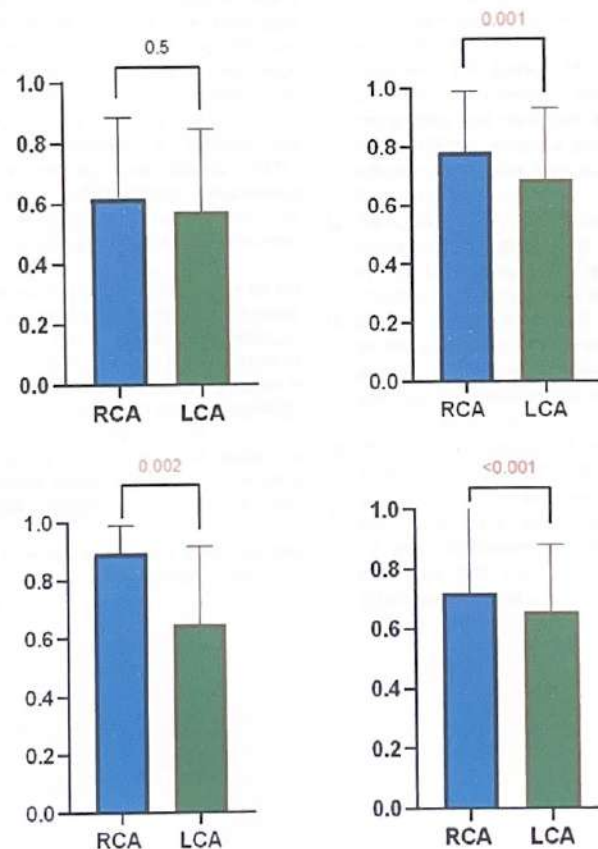
tablished the idea that local hemodynamic factors, such as blood flow patterns and wall shear stress, might contribute to the onset of atherosclerosis and, crucially, its advancement.¹⁶

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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ORIGINAL RESEARCH

Cardiac Magnetic Resonance Features Associated with the Risk of Cardiac Arrest in Patients with Acute Myocardial Infarction

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ABSTRACT

Background: Cardiac arrest (CA) is the most severe complication of acute myocardial infarction (AMI). Besides the location and severity of coronary occlusion, different factors may have significant role in the pathogenesis of AMI-related cardiac arrest (CA), but their contribution is still under investigation. The aim of the study was to investigate the cardiac magnetic resonance (CMR) features of myocardial injury associated with a higher risk of CA accompanying an AMI. **Methods:** In total, 918 myocardial segments from 54 post-AMI patients undergoing CMR imaging with delayed gadolinium enhancement were enrolled in the study, of which 18.54% presented CA during the acute phase of AMI. In all patients, infarct mass, the proportion of high transmural extent, and scar mass at different myocardial segments were calculated using QMap software (Medis BV). **Results:** Compared to patients without CA, those with CA had a significantly higher infarct size ($p = 0.03$) and a higher degree of transmural extent (29.28% vs. 14.1%, $p = 0.01$). The risk of CA during the acute phase was significantly higher in patients in whom the location of myocardial injury was at the level of latero-apical, antero-lateral, and basal anterior segments. Group 1 presented a larger infarct size at the level of the latero-apical (33.9 ± 30.6 g vs. 13.6 ± 17.3 g, $p = 0.02$), anterolateral (26.5 ± 29.0 g vs. 8.9 ± 12.8 g, $p = 0.02$), and anterobasal segment (20.1 ± 21.5 g vs. 7.8 ± 14.7 g, $p = 0.02$). **Conclusions:** CMR imaging identified infarct mass, high transmural extent, and large myocardial injury as features associated with an increased risk of CA in the acute phase of AMI, especially at the level of anterolateral segments.

Keywords: cardiac arrest, acute myocardial infarction, cardiac magnetic resonance, infarct size, infarct location

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INTRODUCTION

Despite significant advances in cardiology over the past few decades, sudden cardiac arrest (SCA) remains a major challenge in cardiovascular medicine. The identification of clinical characteristics associated with SCA may have a strong impact on patient management, in the attempt to reduce all-cause mortality in these critical cases.¹

Cardiac magnetic resonance (CMR) has the ability to noninvasively characterize the structure of the heart muscle tissue in a unique way, in parallel with measurement of the volumes and size of the replacement fibrosis.^{2,3} CMR is the gold-standard modality for structural and functional myocardial evaluation, being also able to provide extremely accurate information about tissue characterization. Late gadolinium enhancement (LGE) for replacement fibrosis, T1 imaging for interstitial fibrosis, and T2 imaging for myocardial edema/inflammation are the most frequently used methods in CMR imaging for the complex evaluation of post-myocardial patients.^{4,5}

CMR imaging is an important part of a diagnostic test in patients who have survived SCA.⁶ At the same time, CMR is important for risk assessment, treatment strategy, and long-term follow-up of patients with ischemic heart disease, including those with ST-elevation myocardial infarction (STEMI) to visualize and quantify permanent myocardial injury.⁷

It is well known that in patients with AMI, the size of myocardial necrosis and the transmural degree depends on many factors including the presence of collateral blood flow, the time between the first symptoms and completion of revascularization, and the effectiveness of revascularization.

The aim of this study was to investigate the CMR features of myocardial injury associated with a higher risk of cardiac arrest (CA) accompanying an acute myocardial infarction (AMI).

MATERIAL AND METHODS

STUDY POPULATION

This single-center, non-randomized, observational study was conducted in the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center, Târgu Mureș, Romania. In total, 54 patients with recent AMI were enrolled in the study. All patients underwent post-AMI CMR imaging with LGE, performed one month after the infarction to evaluate the infarct size and transmural index.

STUDY GROUPS

The study population was divided into two groups: group 1 – 8 patients who survived a CA in the acute phase of an AMI, and group 2 – 46 patients, matched for age and gender, with AMI but without CA. In all patients, infarct mass, the proportion of high transmural extent, and scar mass at different myocardial segments were calculated using Medis Suite 2.1 with the Qmass 8.1 application. The study protocol is illustrated in Figure 1.

CMR IMAGING AND LEFT VENTRICULAR ASSESSMENT

All CMR examinations were performed with commercially available 1.5 T Siemens Magnetom Aera MRI equip-

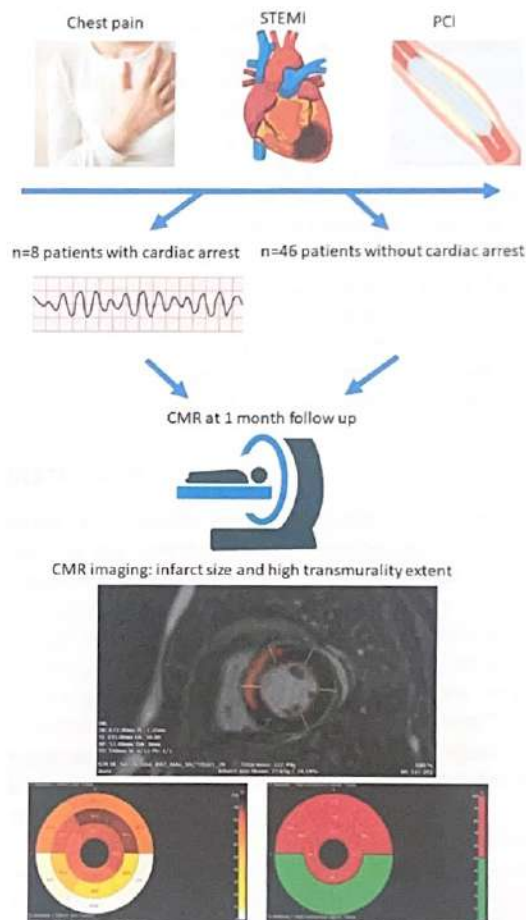


FIGURE 1. Diagram of the study protocol

ment (Siemens, Erlangen, Germany). CMR image series were used to calculate indexed left ventricular (LV) mass, LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and cardiac output (CO). Image post-processing was performed with Medis QMass 8.1 software (Medis, Leiden, the Netherlands). LGE image processing and delayed signal intensity (DSI) analysis were performed in 10–12 consecutive short-axis LGE images. For segmentation, full width at half maximum automated thresholding with hyperenhancement on LGE was used. Epi- and endocardial contours were drawn manually in short-axis images (excluding papillary muscles). The transmural threshold was set to 50%. The following CMR-derived parameters were determined: LV myocardium volume (mL), myocardium mass (g), infarct size volume (mL), infarct size mass (g), infarct size percentage (%), high transmural extent (mL), and high transmural extent (g).

STATISTICAL ANALYSIS

The collected data was statistically analyzed with Graph Pad InStat 3.10 software (GraphPad Software, Inc., San Diego, USA). Quantitative variables were expressed as mean \pm standard deviation, and binary variables as integer values and percentages. Unpaired Student's t-test and the Mann-Whitney test were used for comparison of continuous variables between groups, and Fischer's exact test was used for the comparison of categorical variables. The threshold for statistical significance was set at $p \leq 0.05$, and all statistical tests were two-sided.

ETHICS

The study protocol has been approved by the ethics committee of Cardio Med center and of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology. All study subjects provided written informed consent, and study procedures were carried out in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki.

RESULTS

CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

The clinical characteristics of the study population are presented in Table 1. There were no significant differences between CA and non-CA groups regarding age ($p = 0.8$), female gender ($p = 0.24$), and comorbidities such as hy-

TABLE 1. Clinical characteristics of the study population

| | Group 1 CA group (n = 8) | Group 2 Non-CA group (n = 46) | p value |
|------------------------|--------------------------------|-------------------------------------|---------|
| Age, years | 55.6 \pm 15.5 | 56.7 \pm 11.63 | 0.8 |
| Gender, female, n (%) | 4 (50%) | 13 (28.26%) | 0.24 |
| Hypertension, n (%) | 4 (50%) | 36 (78.26%) | 0.18 |
| Current smoking, n (%) | 4 (50%) | 21 (45.6%) | >0.9 |
| Diabetes, n (%) | 1 (12.5%) | 10 (21.7%) | >0.9 |

pertension ($p = 0.18$), smoking status ($p = 0.9$), and diabetes mellitus type 2 ($p = 0.9$).

CMR DATA IN THE STUDY POPULATION

The CMR data in this study population are presented in Table 2. Compared to patients without CA, those with CA had a significantly higher infarct mass (47.9 ± 38 g vs. 23.3 ± 17.8 g, $p = 0.03$), infarct mass % ($26.9 \pm 17.3\%$ vs. $15.1 \pm 8.6\%$, $p = 0.02$), and a higher degree of transmurality ($29.28 \pm 20.2\%$ vs. $14.1 \pm 9.2\%$, $p = 0.01$) (Figure 2). The CMR results indicate that the risk of CA during the acute phase was significantly higher in patients in whom the location of myocardial injury was at the level of latero-apical, anterolateral, and anterobasal segments. Group 1 presented a larger infarct size at the level of the latero-apical (33.9 ± 30.6 g vs. 13.6 ± 17.3 g, $p = 0.02$), anterolateral (26.5 ± 29.0 g vs. 8.9 ± 12.8 g, $p = 0.02$), and anterobasal segment (20.1 ± 21.5 g vs. 7.8 ± 14.7 g, $p = 0.02$) (Figure 3).

DISCUSSION

Among the available imaging methods, CMR is considered the gold standard for determining infarct size and transmural extent in STEMI patients.⁸ LGE CMR is the recommended approach to quantify infarct dimensions.⁹ In the case of AMI, the rupture of the heart muscle cells allows the diffusion of gadolinium-based agents into the intracellular space. This results in "hyperenhancement" of the infarcted area compared to healthy myocardium.¹⁰ The prognostic validity of CMR-determined acute infarct size is associated with other established clinical risk factors such as LVEF.

CMR markers are superior to clinical risk scores in assessing the presence or risk of LV dysfunction.¹¹ Therefore, infarct size assessment performed with LGE-CMR offers the possibility of more accurate clinical risk prediction in STEMI patients. Previous studies have confirmed that STEMI patients with myocardial injury at the level of

TABLE 2. CMR data in the study population

| | Group 1 CA group (n = 8) | Group 2 Non-CA group (n = 46) | p value |
|--------------------------------------|--------------------------------|-------------------------------------|---------|
| Left ventricle myocardium mass (g) | 164 ± 41 | 144 ± 40 | 0.2 |
| Infarct size mass (g) | 47.9 ± 38 | 23.3 ± 17.8 | 0.03 |
| Infarct size percentage (%) | 26.9 ± 17.3 | 15.1 ± 8.6 | 0.02 |
| High transmural extent (g) | 52.2 ± 45.2 | 21.9 ± 18.7 | 0.02 |
| High transmural extent (%) | 29.28 ± 20.2 | 14.1 ± 9.2 | 0.01 |
| Infarct mass septal apical (g) | 30.92 ± 35.5 | 32.18 ± 35.12 | 0.89 |
| Infarct mass antero-apical (g) | 30.13 ± 25.66 | 25.66 ± 28.47 | 0.69 |
| Infarct mass latero-apical (g) | 33.9 ± 30.6 | 13.6 ± 17.3 | 0.02 |
| Infarct mass infero-apical (g) | 25.8 ± 26.6 | 18.1 ± 23.7 | 0.39 |
| Infarct mass mid anteroseptal (g) | 32.9 ± 36.6 | 21.24 ± 25.1 | 0.6 |
| Infarct mass mid anterior (g) | 28.7 ± 35.5 | 12.8 ± 20.2 | 0.3 |
| Infarct mass mid anterolateral (g) | 26.5 ± 29 | 8.9 ± 12.8 | 0.02 |
| Infarct mass mid inferolateral (g) | 27.7 ± 30.02 | 18.9 ± 25.2 | 0.36 |
| Infarct mass mid inferior (g) | 21.5 ± 25.28 | 14.86 ± 20.4 | 0.84 |
| Infarct mass mid inferoseptal (g) | 22.3 ± 27.9 | 12.9 ± 17.16 | 0.36 |
| Infarct mass basal anteroseptal (g) | 18.25 ± 21.1 | 15.01 ± 17.08 | 0.77 |
| Infarct mass basal anterior (g) | 20.1 ± 21.5 | 7.8 ± 14.7 | 0.03 |
| Infarct mass basal anterolateral (g) | 18.6 ± 27.4 | 7.3 ± 14.3 | 0.47 |
| Infarct mass basal inferior (g) | 18.5 ± 25.3 | 15.4 ± 22.7 | 0.48 |
| Infarct mass basal inferoseptal (g) | 17.4 ± 20.06 | 18.8 ± 20.5 | 0.96 |

the anterior wall are at increased risk of adverse left ventricular remodeling, heart failure, and death.¹² However, it has not been clarified whether the worse outcome can be attributed to the specific characteristics of the infarct site alone in patients with anterior wall STEMI, or whether only these patients have a larger infarct size and transmural extent.¹³ Our study indicates that there are several locations of myocardial necrosis which seem more prone to produce a CA, and these are located especially at the level of anterior and lateral segments.

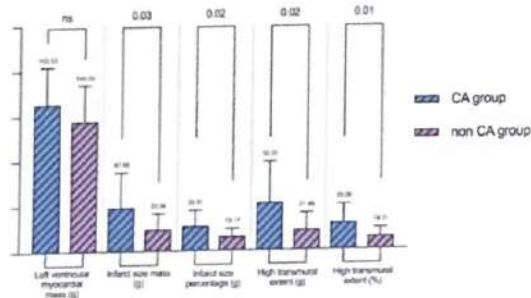


FIGURE 2. Comparative analysis of LV mass, infarct size, and transmural extent between study groups

The injection of stem cells in the ventricular myocardium of post-MI patients had a significant limitation resulting from the pro-arrhythmogenic effect of the stem cells, especially when intra-myocardial route is selected for injection instead of intra-arterial way.^{14,15} In light of the current study, if different myocardial segments have different arrhythmogenic potential, it can be speculated that the pro-arrhythmogenic effect of stem cells at the

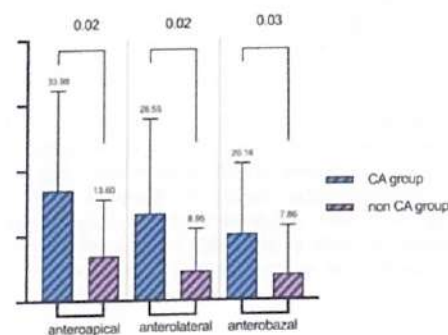


FIGURE 3. Patients with myocardial injury located in the antero-apical, latero-apical, and anterior segments were more prone to develop cardiac arrest during the acute phase of AMI.

level of myocardial tissue may be avoided if the location of the injection is selected in areas less predisposed to CA.

In our study, patients with a large myocardial scar in the anterolateral segments had a higher incidence of CA in the acute phase, suggesting the existence of a causal relationship between necrosis location and the risk of sudden death. This may explain why patients with myocardial infarction of limited severity may develop CA if the location of the myocardial necrosis is in an area predisposed to arrhythmic complications.

CONCLUSION

Myocardial mass, high transmural extent at CMR imaging, and a large myocardial injury identified by CMR at the anterior and lateral ventricular segments level seem to be associated with an increased risk of CA in the acute phase of AMI.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

Double Trouble: Interrupting DAPT and COVID-19

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ABSTRACT

Cardiovascular disorders have been described as relevant risk factor for severe COVID infection. Stent thrombosis is a life-threatening complication that may occur subacutely. We present an interesting case of a middle-aged woman who developed acute stent thrombosis while interrupting dual antiplatelet therapy (DAPT) ticagrelor, during an episode of coronavirus disease (COVID-19). In our case, the patient's not-compliance to DAPT, associated with COVID-19 infection and a hyperinflammatory and hypercoagulable state associated with it played a major role in the development of stent thrombosis. The hypercoagulable and hyperinflammatory state associated with COVID-19 has important implications for cardiac patients, especially those undergoing complex coronary intervention, predisposing them to an increased risk of post-PCI complications.

Keywords: COVID-19, stent thrombosis, dual antiplatelet therapy, hypercoagulability

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INTRODUCTION

The COVID-19 pandemic has adversely affected the management of the entire spectrum of noncommunicable diseases. It also had a very strong effect on delivery of healthcare for cardiovascular disease, which remains the leading cause of death worldwide.¹⁻³

COVID-19 was associated with a significant and abrupt reduction in cardiovascular diagnostic tests across the globe. At the same time, SARS-CoV-2 infection was associated with a significantly longer hospital stay and ventilation time, higher mortality rates, and various postoperative complications.^{1,4}

Cardiovascular disorders have been described as relevant risk factors for severe COVID infection. On the other hand, COVID infection has also been associated with new-onset cardiovascular injuries.²⁻⁵

Coronary artery disease is considered a high-risk comorbidity of COVID-19 infection. The treatment of patients with acute coronary syndromes (ACS) routinely involves percutaneous coronary intervention (PCI) and the use of intracoronary stents. Stent thrombosis is a life-threatening complication that may occur acutely (in the first 24 hours), subacutely (from 24 hours to 30 days), or late after stent placement.^{4,6}

The development and clinical use of drug-eluting stents (DES) in the 2000s was a major breakthrough in the field of interventional cardiology. First-generation DES remarkably reduced the rates of in-stent restenosis and consequent target-lesion revascularization compared to bare-metal stents. However, a major safety concern regarding stent thrombosis emerged with the use of first-generation DES, with its attendant high rates of myocardial infarction (MI) and mortality.^{2,4}

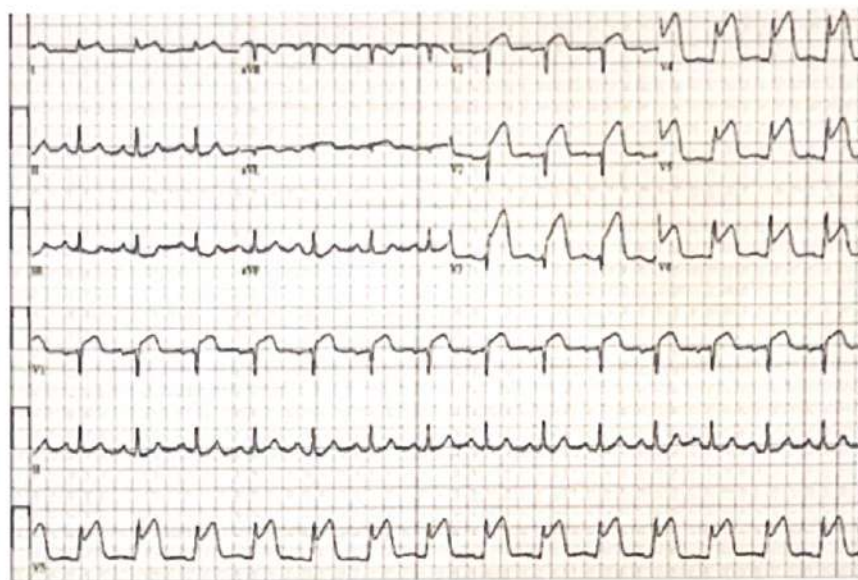


FIGURE 1. Pre-interventional ECG – first presentation

Ticagrelor is a reversible nonthienopyridine oral P2Y₁₂ antagonist that provides more potent and consistent platelet inhibition with faster onset and offset of action than clopidogrel.^{6,7}

We present an interesting case of a middle-aged woman who developed acute stent thrombosis while interrupting dual antiplatelet therapy (DAPT) ticagrelor, during an episode of coronavirus disease (COVID-19).⁷⁻⁹

CASE PRESENTATION

A 54-year-old hypertensive, actually ex-smoker but habitual smoker, dyslipidemic woman was hospitalized two times in a month in our clinic. At the first presentation, the patient was admitted with cardiogenic shock due to multiple episodes of successfully resuscitated ventricular fibrillation, preceded by angina. The onset of anginal

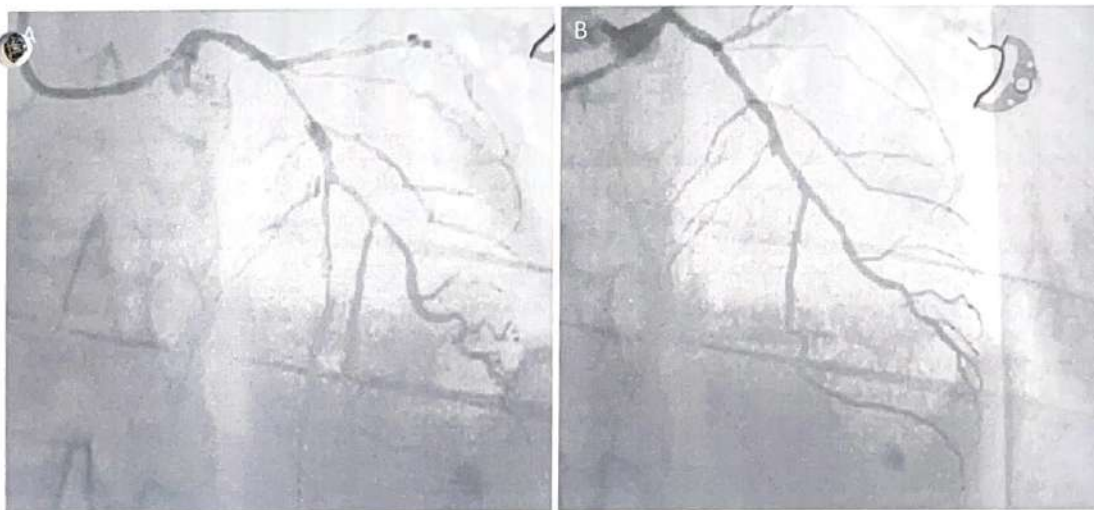


FIGURE 2. Interventional aspects. A – Pre-interventional aspect of LAD; B – Post-interventional aspect of LAD after stenting

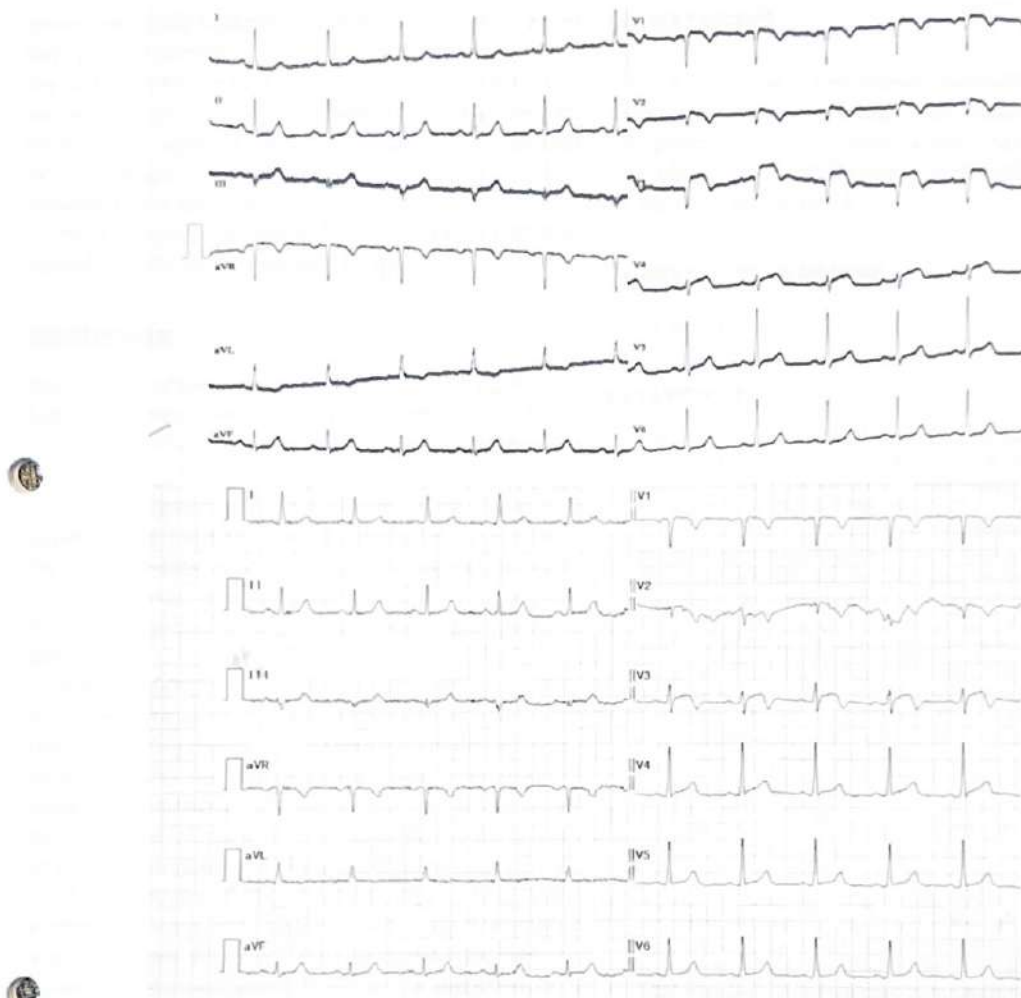


FIGURE 3. Pre- and post-interventional ECG – second presentation

pain was seven hours before admission. As this case was performed at the peak of a COVID-19 wave in the region, a COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) was performed prior to the procedure, as mandated by the institutional protocol, and it was found to be negative. The electrocardiography (ECG) revealed ST elevation of 5–7 mm in V1 to V6 and DI, as well as ST-depression in DII and aVF, and she had elevated levels of high-sensitivity cardiac troponin I (hs-cTnI) (3,231 ng/L) and mildly elevated levels of CK-MB. The echocardiographic investigation revealed global akinesia with left ventricular ejection fraction (LVEF) of 35%.

The patient was diagnosed with extensive anterior MI, and after receiving loading doses of aspirin, ticagrelor,

and atorvastatin, she underwent percutaneous coronary angiography which revealed thrombosis of the left anterior descending (LAD) artery treated by thrombectomy and stent implantation. The patient was hemodynamically stable and was discharged home free of angina seven days later, with a LVEF of 40%.

One week after discharge, the patient was returned to the emergency room with anterior MI demonstrated by a new ST-segment elevation in V2 to V4, elevated levels of cardiac enzymes, and anterior wall akinesia with a LVEF of 40%.

Although she was afebrile, had no respiratory symptoms, and had a normal SpO₂, her RT-PCR COVID-19 test turned out to be positive. She reported the occurrence of

generalized body weakness and fatigue since six to seven days prior to presentation, and that she had stopped taking ticagrelor by her own initiative two days prior to presentation. Urgent coronary angiography was performed immediately, which showed stent thrombosis in the LAD near the origin of the diagonal branch, treated with implantation of a new stent.

The patient and the ethics committee of the institution agreed with the publication of the case.

DISCUSSION

In a study conducted by He *et al.* in 2020, myocardial injuries were associated with a poorer prognosis for COVID patients.² However, the exact interaction mechanism between COVID infection and cardiovascular disorders is yet to be understood. Several mechanisms have been hypothesized for SARS-CoV-2-associated cardiovascular involvements, including coronary plaque destabilization, hypoxia, systemic inflammation, T cell cytokine response, myocardial fibrosis, and direct cardiomyocyte damage.⁷

Although COVID-19 usually presents with respiratory signs and symptoms, various cardiovascular manifestations, including myocardial injury/myocarditis, arrhythmias, MI, and thromboembolism, have been reported since the outbreak of the pandemic. The occurrence of various types of stent thrombosis, from acute to very late stent thrombosis, has been reported in patients with COVID-19 illness. Pathophysiologically, a heightened systemic inflammatory response and a hypercoagulable state associated with the COVID-19 illness have been involved as the major causative factors for increased incidence of both arterial and venous thrombosis during this illness. Also, SARS-CoV-2 has been involved in endothelial injury, endothelial dysfunction, and microcirculatory impairment.^{1,5,9}

In our case, the patient's non-compliance to DAPT, associated with COVID-19 infection and a hyperinflammatory and hypercoagulable state associated with it played a major role in the development of stent thrombosis.

CONCLUSIONS

The hypercoagulable and hyperinflammatory state associated with COVID-19 has important implications for cardiac patients, especially those undergoing complex coronary interventions, predisposing them to an increased risk of post-PCI complications.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

Acute Thrombosis of the Left Main on the Tennis Court in a Young Patient – a Case Report

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ABSTRACT

In acute coronary syndromes, timely revascularization of the obstructed artery is crucial. In young patients, acute myocardial infarction can have a very severe evolution and is frequently associated with cardiogenic shock. We present the case of a 36-year-old male patient, smoker with no other apparent risk factors for coronary artery disease, who suffered a cardiac arrest while playing tennis. Emergency coronary angiography revealed acute occlusion of the left anterior descending artery, which was promptly revascularized. The patient had a good clinical evolution and was discharged after six days. The case underlines the importance of a well-functioning emergency system and STEMI network, able to provide life-saving therapy in a timely manner.

Keywords: left main coronary artery thrombosis, young patients, primary PCI

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INTRODUCTION

Acute coronary syndromes are major medical emergencies in which timely revascularization of the obstructed artery is crucial in order to save the viability of the myocardial fibers. The leading cause of death in patients hospitalized for acute myocardial infarction (AMI) is cardiogenic shock (CS).¹ Many studies indicate a significant survival benefit at six months after early revascularization. Especially for patients with AMI complicated by CS, primary percutaneous coronary intervention (PCI) should be strongly considered and may be life-saving.^{2–4}

In very young patients, AMI carries a significant morbidity, being associated with a strong psychological impact and financial burden for the patient and their family.⁵ At the same time, in young patients suffering an AMI, CS is frequently associated, requiring a rapid diagnosis

and supportive therapy.¹ Despite significant advances in device-based and pharmacological therapies for CS, the mortality associated with this critical condition has not improved significantly over the past 20 years.^{5–7} However, an efficient management, consisting in early stabilization and immediate repermeabilization (with fibrinolytic therapy or percutaneous intervention), has been shown to reduce the mortality associated with this severe condition.⁸

At the same time, left main coronary artery thrombosis (LMCAT), identified during coronary angiography, is a rare and challenging condition.^{7–9} Left ventricular dysfunction (LVD) is the most common cause of CS, being reported as the primary cause of CS in 74.5% of patients with acute heart failure.^{2,10}

In young patients aged <35 years, AMI is poorly characterized, although it is estimated to be less than 2%. Fur-

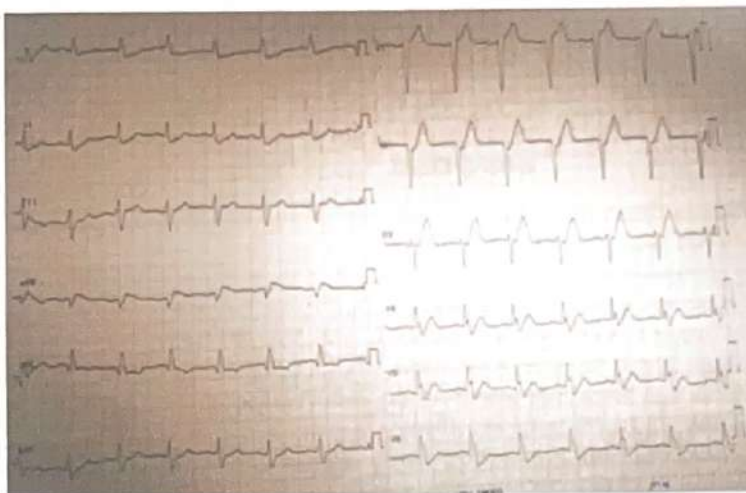


FIGURE 1. ECG of the patient which revealed ST-elevation in anterolateral leads with mirror-image in posteroinferior leads

thermore, its occurrence at a young age affects the productive age group, with a strong socioeconomic impact.¹¹

CASE PRESENTATION

We aim to present the successful treatment of a 36-year-old male patient, smoker, without any history of cardiovascular disease, who had a cardiac arrest while playing tennis. The patient had no significant personal medical history, took no medications, and exercised regularly with no difficulties. Also, family history was not notable for sudden cardiac death or coronary artery disease.

He collapsed on the tennis field in front of his friend and teammate before complaining of developing severe chest pain without any other symptoms. His friend immediately contacted emergency medical services and initiated basic cardiopulmonary resuscitation. The ambulance arrived in 10 minutes, and the patient was transported to the nearest emergency department. Upon arrival, the patient was in ventricular fibrillation, which returned to sinus rhythm after one electric shock of 200 J. He was resuscitated for 20 minutes in total. On presentation at the emergency room, the patient's blood pressure was 90/60 mmHg, heart rate was 101 beats/min, and oxygen saturation was above 97% on oxygen mask. Positive inotropic and vasopressor agents, dobutamine and noradrenaline, were initiated as treatment for hemodynamic instability.

The twelve-lead electrocardiogram (Figure 1) revealed ST segment elevation in antero-lateral leads, which led to the diagnosis of ST-elevation acute coronary syndrome.

Based on the electrocardiogram, elevated cytolytic myocardial enzymes, and primary symptoms, the patient was diagnosed with Killip IV anterior ST-elevated myocardial infarction (STEMI).

The bedside cardiac echocardiography revealed a left ventricular failure with global akinesia, ruling out any aortic aneurysm or dissection.

Afterwards, the patient was transferred for emergency cardiac catheterization, where he developed cardiogenic pulmonary edema which was successfully treated. The coronary angiography was performed using a right transradial approach and revealed an acute thrombosis in the left main, treated with thrombectomy followed by stent implantation in the left main and in the circumflex artery. The revascularization procedure was done at one hour from the onset of cardiac arrest.

The patient was further transferred to the acute cardiac care unit, where he was continuously monitored and stabilized. Immediately after the intervention, the echocardiography revealed severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) of only 25%, akinesia of the apex and severe septal and anterior wall hypokinesia. NT pro-BNP levels was 352 pg/mL. Complex treatment for coronary ischemic disease, heart failure, and arrhythmia was initiated during hospitalization, and no further complications were registered during the acute phase. Before hospital discharge, the patient was instructed to achieve an ideal weight and was counseled for smoke cessation and a diet low in saturated fat and cholesterol.

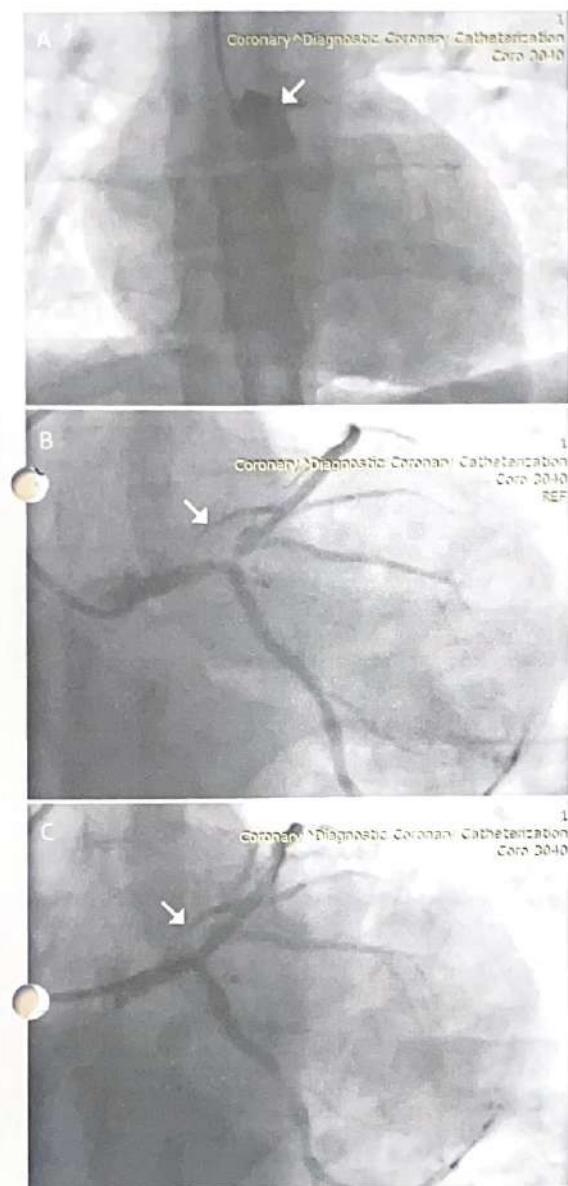


FIGURE 2. Coronary angiography. **A** – LMCAT (arrow); **B** – post-interventional aspect, with residual stenosis (arrow); **C** – post-interventional aspect with no residual stenosis (arrow)

The echocardiography performed at the one-month follow-up revealed a LVEF of 40% with septal and anterior wall hypokinesia. At six months after discharge, the patient was completely asymptomatic, the echocardiography revealed a LVEF of 52% and an NT pro-BNP level of 118 pg/mL.

The patient agreed to the publication of his data and the publication was approved by the institution ethics committee.

DISCUSSION

The particularities of STEMI management in very young patients are not well defined. These patients usually have a poor collateral coronary network, which severely limits the possibility to provide alternative irrigation in case of sudden coronary artery occlusion. Another particular aspect of MI occurring in very young patients is the absence of prodromal symptoms, fact which seems to be more common in younger patients with coronary artery disease.⁴⁻⁶ Consistent with the published data, mortality due to cardiogenic shock in AMI has been found to be significantly lower in hospitals with catheterization laboratory than in hospitals without such facilities.^{7,9} The outcome of PCI is important in determining the survival of patients, and the degree of reperfusion in the infarct-related artery is associated with outcomes.³

In the recent SHOCK trial, the 30-day mortality rate was reduced with successful angioplasty (38%) as compared to patients with unsuccessful angioplasty (79%). However, reperfusion was lower in patients with CS.

Patients with CS have less successful reperfusion rates with PCI in the infarct-related artery compared to patients without shock (54% to 100%). LMCAT is a rare and life-threatening angiographic finding, with an estimated incidence of 0.8–1.7% among patients with STEMI and a dramatic clinical presentation with cardiogenic shock or sudden cardiac death. The usual pathophysiological substrate of LMCAT is fibrous cup rupture of an atherosclerotic plaque, followed by thrombus formation. However, other predisposing factors include hypercoagulable state, post-partum state, embolization of intracardiac masses, cocaine-induced plaque rupture, and vasospasm.

There are two strategies in treating AMI-related CS: medical and invasive. In institutions lacking revascularization facilities, fibrinolytic therapy may represent an alternative. Complete thrombosis of the left main coronary artery is a rare angiographic finding and usually leads to CS. The prognosis of this condition is very dependent on the collateral coronary circulation and the myocardial protection seems to depend on the rapidity of revascularization. Two therapeutic approaches may be envisaged; emergency coronary bypass grafting or percutaneous angioplasty, the natural history being particularly disastrous. However, current guidelines favor an invasive approach. Prognosis is established by the outcome of re-

vascularization regardless of the procedure used, such as PCI or surgery.

CONCLUSION

This case indicates the importance of early diagnosis and revascularization in STEMI, especially in the case of STEMI occurring at a very young age. The patient was lucky to have the cardiac arrest on a tennis field that was close enough to the cathlab, and to have resuscitation started immediately after the onset of the CS. This presentation should draw attention to the importance of going to the closest hospital immediately after the onset of symptoms.

CONFLICT OF INTEREST

Nothing to declare.

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ESC Guidelines 2022 – a Pragmatic Tool for the Practicing Cardiologist?

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Four new guidelines have been launched during the 2022 congress of the European Society of Cardiology (ESC), all of them being extremely complex and providing unique interdisciplinary perspectives on the management of cardiovascular diseases in different clinical scenarios.

For instance, the cardio-oncology guideline is the first ESC guideline dedicated to cardio-oncology, being developed together with the European Society of Hematology, European Society of Radiotherapy, and the International Society of Cardio-Oncology.¹ This guideline includes a large number of recommendations on the diagnosis, treatment, and prevention of cardiovascular toxicity associated with main oncologic treatments, at the same time providing clear recommendations on the management of cardiovascular diseases caused by cancer, directly or indirectly. The guideline underlines the need for a complex interdisciplinary approach and communication between different specialties (cardiologist, oncologist, hematologist) for the optimum management of the large variety of complex conditions that may occur in a patient with cancer.

The guideline includes a very pragmatic algorithm for assessment of the cardiovascular risk of patients scheduled for cytostatic treatment, the recommendation being adapted to each class of drugs used. At the same time, a new international definition of cancer treatment-related cardiovascular toxicity is provided, in which cardiovascular toxicity is classified in four severity groups, according to ECG, physical and metabolic status, and cardiovascular history. An ECG is recommended to all cancer patients, while a cardiologist consultation is recommended in all those with ECG, both indications being class I. It is also recommended that all patients with low risk for cardiovascular toxicity should be referred for immediate initiation of anti-cancer therapy.¹

Echocardiography and biomarker determination have a central role in the assessment of cardiovascular risk. It is recommended that echocardiography and biomarkers to be performed repeatedly at different time intervals according to the specifics of the condition and treatment. Echocardiography remains the first-line option to assess ventricular function, while 3D echocardiography is the method of choice to quantify left ventricular ejection fraction.¹

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Cancer patients who present with neoplasm and Takotsubo syndrome should undergo a computed tomography (CT) angiography examination to exclude an acute coronary syndrome, and a cardiac magnetic resonance imaging (MRI) to exclude myocarditis or myocardial infarction, both indications being class I.

Another group of recommendations refer to anticoagulant treatment in cancer patients with atrial fibrillation or venous thromboembolism, the guideline indicating continuation of non-vitamin K antagonist oral anticoagulants (NOAC) (apixaban, rivaroxaban or edoxaban) in all patients with venous thromboembolism (indication class I).

Among the new recommendations mentioned in the new guideline for the management of patients with ventricular arrhythmia and prevention of sudden cardiac death, a large number refer to the installation of external defibrillators in public spaces, which is hoped to reduce the fatality rate of sudden cardiac death occurring out of hospital.² Another new recommendation is related to the implantation of an implantable cardioverter-defibrillator (ICD) in all patients with coronary artery disease and a left ventricular ejection fraction below 30%, despite an optimum management of minimum three months.

At the same time, several recommendations have been upgraded in comparison with the previous edition of the guideline. Programmed electrical stimulation in patients with prior ST-elevation myocardial infarction (STEMI), as well as the implantation of an ICD in symptomatic patients with long QT became a class I indication. However, several aspects remain unclear, such as the role of cardiac MRI in the stratification of the risk for sudden cardiac death in patients with chronic coronary syndrome, or how can we identify patients with chronic coronary syndrome and extremely low ejection fraction, at risk for sudden cardiac death.

The new guideline for pulmonary hypertension (PH) simplifies the algorithm of diagnosis of pulmonary hypertension in a three-step approach, from PH suspicion to echo-based detection and confirmation using cardiac MRI.³ At the same time, the new guideline introduces new criteria based on MRI and echo for the confirmation of PH diagnosis. The guideline defines the criteria for PH centers, which are extremely complex and should have appropriate infrastructure, human resources, and experience. CT coronary angiography remains a class I indication to establish the etiology of chronic thromboembolic pulmonary hypertension (CTEPH). At the same time, interventional treatment using pulmonary balloon angioplasty for CTEPH is upgraded from class IIb to class I in the new guideline.

The fourth guideline launched by the ESC in 2022 regards the cardiovascular assessment and management of

patients undergoing non-cardiac surgery, which provides extremely useful answers for clinicians.

One of the highest impact recommendations in these guidelines is the indication for coronary CT angiography to exclude coronary artery disease in all patients with low-intermediate probability of coronary artery disease (class IIa indication).⁴ A frequent situation is the one related to discontinuation of antiplatelet treatment prior to a non-cardiac intervention, which can lead to stent obstruction. In these cases, it is recommended to postpone elective interventions to at least 6 months after the elective revascularization or up to 12 months post-acute myocardial infarction. When discontinuation of antiplatelet treatment is mandatory, the guideline recommends that this should be done with 3–5 days prior to intervention for ticagrelor, 5 days prior to intervention for clopidogrel, and 7 days for prasugrel. As for the anticoagulant treatment, immediate discontinuation of NOAC is recommended in the case of urgent surgery, which is recommended to be performed at least 12–24 hours after the last NOAC administration.⁴

In the 2022 edition of this guideline, low-risk patients scheduled for surgery with a low-intermediate risk do not require routine preoperative ECG or biomarker determination, but a preoperative ECG is recommended in all cases with known coronary artery disease, cardiovascular risk factors, or symptoms suggestive for coronary artery disease.

CONFLICT OF INTEREST

Nothing to declare.

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Elevated Lipoprotein(a) Linked to Recurrent Cardiovascular Events – A Case Report

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ABSTRACT

The role of lipoprotein(a) [Lp(a)] in the development of atherosclerosis has been recently recognized, and the current recommendation is to measure Lp(a) once in a lifetime in all individuals, in order to identify those at risk for developing an acute coronary syndrome or recurrent events, even in the absence of other cardiovascular risk factors. We present the case of a middle-aged patient with recurrent cardiovascular events, in whom we identified high levels of Lp(a) as a possible explanation of the recurrent events.

Keywords: atherosclerosis, lipoprotein(a), acute coronary syndromes

INTRODUCTION

Lipoprotein(a) [Lp(a)] is an established and genetically determined risk factor for atherosclerosis, coronary heart disease, stroke, thrombosis, and aortic stenosis. Structurally, it is a variant of LDL-cholesterol. Levels of Lp(a) above 50 mg/dL are correlated with an increased risk of cardiovascular disease. Screening patients to determine their Lp(a) levels could help identify those who need more aggressive lipid therapy and cardiovascular disease risk management.

It has been suggested that Lp(a) could provide a possible explanation for younger patients suffering from coronary artery disease with or without other risk factors. We present the case of a middle-aged patient with elevated Lp(a) levels resulting in multiple cardiovascular events.

CASE PRESENTATION

A 57-year-old hypertensive, diabetic patient with a history of post-inferior myocardial infarction, treated with primary revascularization and implantation of two pharmacologically active stents in the right coronary artery, presented with constrictive chest pain at rest, associated with fatigue and dyspnea, started two weeks prior to presentation and exacerbated on the day of admission. The electrocardiogram showed flattened T waves in V4–V6, DI,

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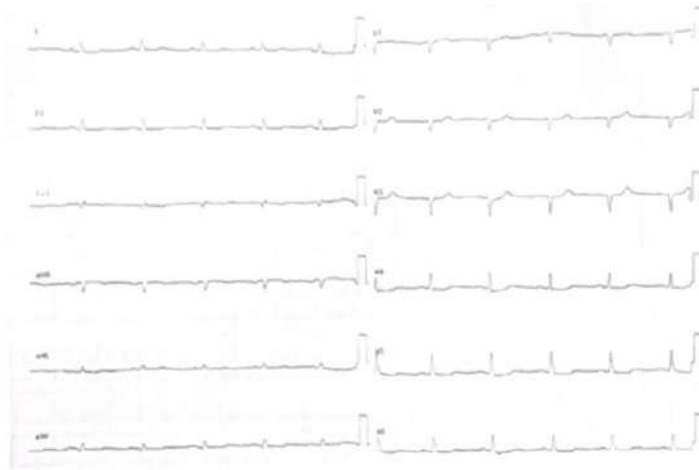


FIGURE 1. ECG at presentation, suggestive for diffuse ischemia

and DII, and amputated R waves in V1–V3. Troponin values were normal.

Transthoracic echocardiography showed slightly impaired systolic function, with basal interventricular septum hypokinesis, a left ventricular ejection fraction of 45%, diastolic dysfunction-type altered relaxation, minor mitral regurgitation, and minor tricuspid regurgitation. Urgent coronary angiography revealed a stenosis of the distal left main coronary artery, extending to the anterior descending artery and to the circumflex artery, and patent stents in the right coronary artery. Taking into account the repeated cardiovascular events of the patient, it was decided to measure Lp(a) levels, which were 0.77 g/L, considered very high.

The patient and the institution agreed with the publication of the case.

DISCUSSION

Lp(a) is considered an independent and unmodifiable risk factor for coronary heart disease, aortic valve stenosis, myocardial infarction, and ischemic stroke. The concentration of Lp(a) is strongly determined genetically, and its resemblance to plasminogen increases its atherogenicity.¹ Moreover, unlike other lipoproteins characterized by constant masses, Lp(a) exhibits various isoforms of different sizes, inversely related to its concentration in plasma. Due to this particular characteristic, its measurement presents many challenges.^{1,2}

The current recommendation is to perform a Lp(a) measurement once in a lifetime in all individuals. Although clinical data highlight the importance of reducing Lp(a) in

order to reduce cardiovascular risk, there is no selective drug approved for Lp(a) hyperlipoproteinemia. Apheresis lowers both Lp(a) and LDL-cholesterol by removing proteins that contain apo-B. However, apheresis of lipoproteins does not reduce Lp(a) permanently and should be repeated every two weeks.³ Researchers are convinced that further international effort is needed in different ethnicities to assess the atherothrombotic risk due to Lp(a) on the one hand and apolipoprotein A on the other.⁴

In light of the introduction of new therapeutic approaches to lower Lp(a), the availability of well-standardized tests that provide comparability of results obtained by different laboratories is indispensable for the selection and classification of high-risk individuals.⁵ The introduction of new therapeutic approaches will require clinical trials to assess the clinical utility of Lp(a) decrease.^{6,7}

CONCLUSIONS

In conclusion, elevated levels of Lp(a), a lipid molecule involved in atherosclerosis development, may be associated with the occurrence of acute coronary syndromes even at a young age, and even in patients with no major cardiovascular risk factors. Lp(a) determination should be performed in all patients presenting with chest pain, especially in those with no reasonable explanation for the acute cardiovascular event.

CONFLICT OF INTEREST

Nothing to declare.

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CERTIFICATE

This is to certify that

Doctor T Mihaila
(Targu Mures - Romania)

has presented an abstract entitled

**Myocardial edema at CMR imaging end evolution of ventricular function following
COVID-19 myocarditis - insights from the CARDIOCOV study**

Authors: T Mihaila (Targu Mures,RO), I Benodek (Targu Mures,RO), A Rosca (Targu Mures,RO), VB Halatiu (Targu Mures,RO), IP Rodean (Targu Mures,RO), BB Matyas (Targu Mures,RO), BN Ion (Targu Mures,RO), T Benedek (Targu Mures,RO)

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Myocardial edema at CMR imaging and evolution of ventricular function following COVID-19 myocarditis - insights from the CARDIOCOV study

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Background: Myocarditis following SARS-COV-2 infection has recently become a subject of concern, being detected in a significant number of post-COVID-19 patients who undergo cardiac magnetic resonance (CMR) examination. While the role of CMR in detecting presence of viral myocarditis has been well established, the CMR features associated with significant alteration of ventricular function in post-COVID patients are not clearly identified yet.

Purpose: The aim of the study was to investigate the role of myocardial edema (ME) at CMR for predicting the evolution of ventricular function in patients with COVID myocarditis.

Methods: In total, 55 patients with CMR signs of viral myocarditis following COVID-19 infection (52.72% males, mean age 36.85±16.29) were enrolled in the study. The delayed gadolinium enhancement phase-sensitive inversion recovery sequences were used for characterization of the myocardial tissue, and inversion recovery images showing high signal intensity were considered suggestive of edematous changes. Patients were divided into 2 study groups, according to the presence of myocardial edema at the moment of CMR evaluation: group 1 (n=18, 32.72%) - patients without ME, and group 2 (n=37, 67.27%) - patients with ME identified by CMR. In all patients, end-diastolic and end-systolic volume indexes (EDVI and ESVI), ejection fraction (EF) and stroke volume (SV) were calculated.

Results: Compared to patients without ME, those with ME present at CMR were older (42.9±14.8 vs. 36.7±16.6, $p=0.145$) and more frequently males (59.4% vs. 38.8%). At the same time, EF was significantly lower in patients with ME (50.9±14.5% in group 2 vs. 58.4±10.2% in group 1, $p=0.03$). Patients from group 2 also exhibited a more pronounced dilatation of ventricular cavities, as reflected by a significant increase of ventricular volumes and especially of the ESVI (109.8±125.9 versus 80.1±14.2, $p=0.02$ for EDVI, and 65.2±109.1 vs. 30.0±11.4, $p=0.02$ for ESVI). Compared to the group without ME, those with ME presented a significantly lower stroke volume index: 44.2±17.3 in group 1 vs. 47.7±7.5, $p=0.03$ in group 2.

Conclusions: In patients with COVID-19 myocarditis, presence of ME at CMR imaging is associated with a worse evolution of the left ventricular function, as reflected by increased ventricular dilatation and decreased cardiac output in the post-COVID period.



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FACTORS ASSOCIATED WITH MYOCARDIAL EDEMA AT CARDIAC MAGNETIC RESONANCE IN POST COVID PATIENTS

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Background: The occurrence of myocarditis after SARS-CoV-2 infection is highly raised during post-COVID period. Cardiovascular magnetic resonance (CMR) has become the primary tool for non-invasive assessment of myocardial inflammation in patients with suspected myocarditis, due to its unique potential for non-invasive identification of the various hallmarks of the inflammatory response, with relevant impact on patient management and prognosis. We investigated the association between the presence of myocardial edema (ME) and cardiovascular risk factors in patients undergoing CMR analysis for post-COVID myocarditis. **Material and methods:** Fifty-seven patients who underwent CMR for myocarditis were assigned into two groups based on the presence of ME: group 1 - patients with ME (n=38) and group 2 - patients without ME (n=19). Data recorded included demography and cardiovascular risk factors: smoking status, obesity, diabetes mellitus, hyperlipidemia, essential hypertension and heart failure. **Results:** Compared to ME-naïve patients, those with ME were older (42.92 ± 15.08 vs. 36.79 ± 17.1 ; $p = 0.14$) and more often males. There were no statistically significant differences between the study groups regarding presence of most CV risk factors (52.6% vs. 57.9% for hypertension, hypercholesterolemia (44.7% vs. 31.6% for hypercholesterolemia and 65.8% vs. 57.9% for obesity, all $p > 0.05$). However, patients with ME presented more frequently heart failure (71.1% vs. 21.1% ; $p = 0.004$), type 2 diabetes (76.3% vs. 47.4% ; $p = 0.02$) and smoking habits (91.9% vs. 38.9% ; $p < 0.001$). **Conclusions:** Our data suggest that in post-COVID patients, the presence of ME on CMR is associated with several features of higher CV risk, such as heart failure, diabetes mellitus and smoking status, suggesting that these factors could influence the evolution of viral myocarditis in COVID patients.

Keywords: myocardial edema, viral myocarditis, CV risk, post COVID