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ORIGINAL RESEARCH

Vulnerable Plaques Producing an Acute Coronary Syndrome Exhibit a Different CT Phenotype than Those That Remain Silent

Răzvan-Andrei Licu[1], Emanuel Blîndu[1], Diana Opincariu[1,2], Theodora Benedek[1,2,3]

[1] Emergency Clinical County Hospital, Târgu Mureș, Romania
[2] "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[3] Center of Advanced Research in Multimodality Cardiac Imaging, CardioMed Medical Center, Târgu Mureș, Romania

ABSTRACT

Background: All plaques that trigger acute coronary syndromes (ACS) present various characteristics of vulnerability. However, not all vulnerable plaques (VP) lead to an ACS. This raises the question as to which of the established CT vulnerability features hold the highest probability of developing ACS. **Aim:** To identify the distinct phenotype of VP that exposes the unstable atheromatous plaque to a higher risk of rupture. **Material and Methods:** In total, 20 patients in whom cardiac computed tomographic angiography (CCTA) identified the presence of a vulnerable plaque and who developed an ACS within 6 months after CCTA examination were enrolled in the study, and compared to 20 age- and gender-matched subjects with VPs who did not develop an ACS. All included patients presented VPs at baseline, defined as the presence of minimum 50% degree of stenosis and at least one CT marker of vulnerability (low attenuation plaques [LAP], napkin-ring sign [NRS], positive remodeling [PR], spotty calcifications [SCs]). **Results:** The two groups were not different in regards to age, gender, cardiovascular risk factors, and comorbidities. Patients who developed an ACS at six months presented higher volumes of lipid-rich ($p = 0.01$) and calcified plaques ($p = 0.01$), while subjects in the control group presented plaques with a larger fibrotic content ($p = 0.0005$). The most frequent vulnerability markers within VPs that had triggered ACS were LAPs ($p < 0.0001$) and PR ($p < 0.0001$). Multivariate analysis identified LAP as the strongest independent predictor of ACS at 6 months in our study population (OR 8.18 [1.23-95.08], $p = 0.04$). **Conclusions:** VPs producing an ACS exhibit a different phenotype compared to VPs that remain silent. The CCTA profile of VPs producing an ACS includes the presence of low attenuation, positive remodeling, and lipid-rich atheroma. The presence of these features in VPs identifies very high-risk patients, who can benefit from adapted therapeutic strategies in order to prevent an ACS.

Keywords: acute coronary syndrome, risk prediction, vulnerable plaques, culprit lesions

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CORRESPONDENCE

Diana Opincariu
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: diana.opincariu@yahoo.ro

Răzvan-Andrei Licu: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 372 653 100, E-mail: licu.razvan@yahoo.com
Emanuel Blîndu: Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureș, Romania. Tel: +40 265 372 653 100, E-mail: emi.blindu@yahoo.com
Theodora Benedek: Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: theodora.benedek@gmail.com

BACKGROUND

Acute coronary syndromes (ACS) are still associated with high morbidity and mortality despite significant advances in treatment modalities.[1] According to the American Heart Association, the United States (US) had 1,413,000 hospital discharges in 2005, most of the patients suffering from non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) and just over 20% being hospitalized with ST-segment elevation myocardial infarction (STEMI).[2] In addition, ACS has a high impact over the US economy, costing Americans over 150 billion dollars annually, half of which is being used on pharmacological therapies.[3] Also, in the United Kingdom, more than 250,000 people develop one form of ACS each year, imposing significant costs on the National Health Service (NHS).[4]

ACSs are the most severe consequence of coronary atherosclerosis, being most frequently triggered by the rupture of a plaque that becomes unstable under various conditions. Coronary plaque rupture has been identified as the pathophysiological mechanism of more than 75% of fatal myocardial infarctions (MI).[5] Plaques that rupture are typically characterized by a large necrotic core, with high lipid content and a thin fibrotic cap – defined as thin-cap fibroatheroma.[6] However, approximately 25–40% of patients with STEMI present plaques with an intact fibrous cap. These lesions generally contain a smaller necrotic lipid core, with an intact, thick fibrotic cap.[7] Three distinct pathophysiological mechanisms have been described in the process of plaque destabilization: plaque rupture (65%), plaque erosion (30%), and nodular calcifications (5%).[8] A study based on intracoronary imaging has shown that plaque rupture had triggered STEMI in 72% and NSTEMI in 32% of cases, while plaque erosion had caused STEMI in 28% versus NSTEMI in 48% of patients. In the remainder 20% of NSTEMI cases, the culprit lesion was characterized by nodular calcifications, with no signs of rupture or erosions.[9] Therefore, an important question still remains regarding the reason why a coronary plaque suddenly becomes unstable and ruptures, thus causing an acute event. The identification of atherosclerotic lesions that are at high risk for rupture is of utmost importance as they can guide timely therapeutic interventions and the prevention of acute coronary events that can be possibly fatal.

The concept of vulnerable plaque (VP) has been introduced almost 30 years ago, referring to plaques that are hemodynamically insignificant, but are prone to rupture.[10] Today, after the identification of other etiologies for intravascular thrombosis, the definition of VPs has been upgraded to characterize lesions that are not as much prone to rupture, but more prone to causing an acute event. A VP is characterized by having a large lipid core, with an inflamed thin fibrous cap, positive remodeling, neoangiogenesis with intralesional hemorrhage, and also heterogeneous calcium depots.[11]

The identification of VPs has been the foundation for multiple cardiovascular imaging studies. Most of the vulnerability characteristics of coronary plaques can be assessed using intracoronary imaging modalities including intravascular ultrasound and optical coherence tomography.[12,13] However, due to their invasive nature and inability to provide information of the overall coronary vasculature, they have limited use as a first evaluation method of patients presenting with chest pain. Coronary computed tomography angiography (CCTA) has emerged in the last years as the preferred imaging modality for investigating patients with chest pain.[14,15] CCTA can noninvasively provide information regarding the coronary tree, coronary calcifications (coronary calcium score), as well as plaque morphology, composition, and vulnerability degree. CCTA markers indicative for VPs include the napkin-ring sign (NRS), low attenuation plaque (LAP), spotty calcifications (SCs), and positive remodeling (PR).[16-20] The presence of these CT vulnerability markers (VM) has been associated with the risk for future acute coronary events, and various recent meta-analyses have proven their predictive capacity for ACS.[21,22]

All plaques that trigger an acute coronary event present various degrees and characteristics of vulnerability. However, not all vulnerable plaques lead to an ACS. This has been suggested, on the one hand, by a systematic review of several clinical and autopsy studies, which have shown that 11.5% of patients with stable coronary artery disease present subclinical plaque rupture.[23] On the other hand, Motoyama *et al.* (2009) have nicely shown the impact of VMs on the occurrence of ACS during follow-up. In their study cohort, from the 1,059 subjects, 15 patients with ACS had presented two (n = 45) or one (n = 27) vulnerability feature in the future culprit lesions. Despite this, the majority of patients who presented these vulnerability markers did not present an acute event (77.8% with 2 VM and 96.3% with 1 VM, respectively).[24] This raises the question as to which of the established characteristics of plaque vulnerability hold the highest probability of developing acute coronary events, thus preventing possibly catastrophic outcomes.

Therefore, we sought to evaluate VPs that had triggered an ACS in the following several months after diagnosis,

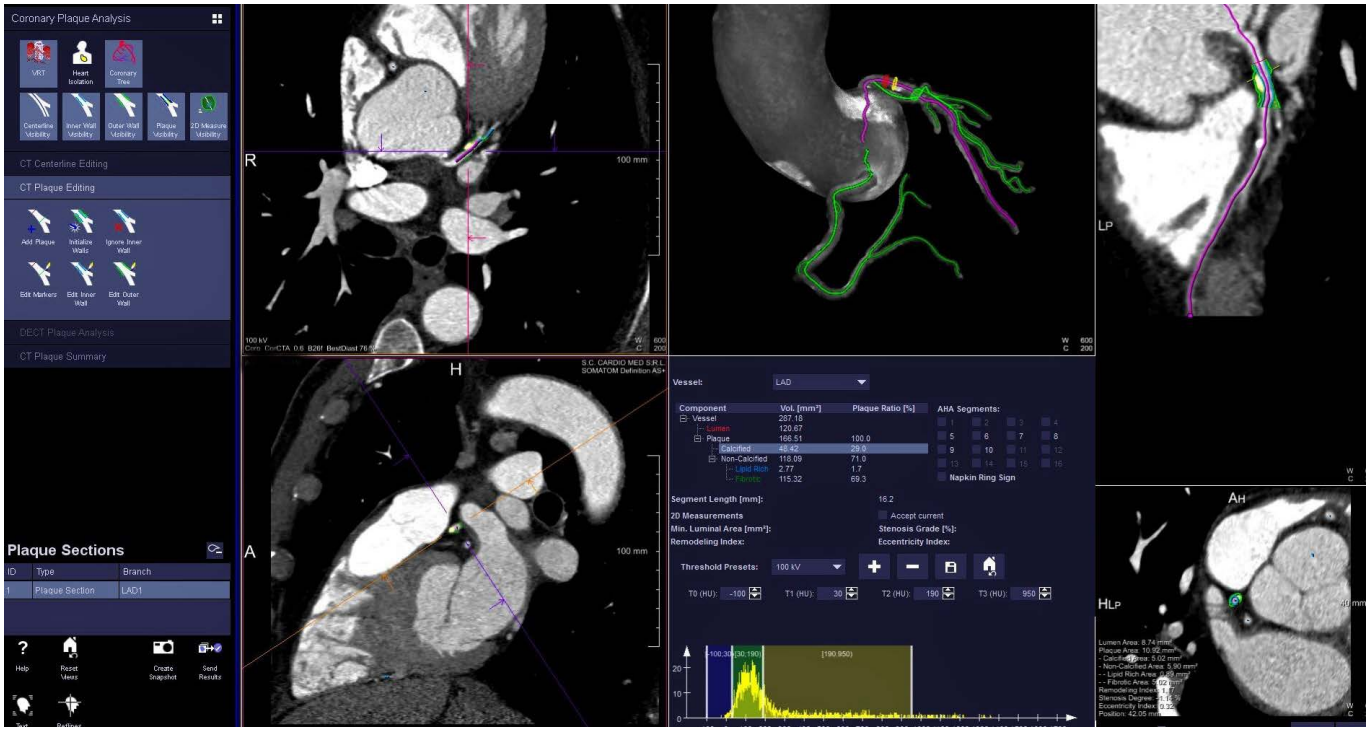

FIGURE 1. Example of a coronary plaque analysis using Syngo.via frontier software. The components of the atheromatous plaques are automatically quantified, and their volumes are displayed on the screen.

in comparison to VPs that did not cause an acute event, in patients who had undergone CCTA for chest pain. The aim of the study was to identify the distinct phenotype of VP which exposes the unstable atheromatous plaque to a higher risk of rupture.

MATERIAL AND METHODS

The study included 20 patients in whom 128-slice CCTA performed for chest pain revealed the existence of a VP and who developed an ACS in the following 6 months after the examination, as well as 20 age- and gender-matched controls. The exclusion criteria included ACS at baseline (requiring urgent hospitalization), contraindication of administration of iodine contrast agents (acute thyroiditis, allergies), acute renal failure, or severe renal failure. Follow-up was performed by telephone, using the national healthcare database for emergency admissions. All the study procedures were performed according to good clinical practice guidelines, and the Declaration of Helsinki. Ethical approval was acquired from the institution where the study was conducted and from Ethics Committee of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania. Written informed consent was obtained from all study subjects, prior to enrollment.

CCTA was performed using a 128-slice dual source CT (Somatom Definition, Siemens Healthcare, Germany), described in a previous study published by the research group.25 The following scan parameters were used: 120 kV tube voltage, gantry rotation time of 0.33 s, 128 × 0.6 collimation, with patients in inspiratory breath-hold position, following the same protocol. All examinations were performed at a stable heart rate below 60 beats/minute

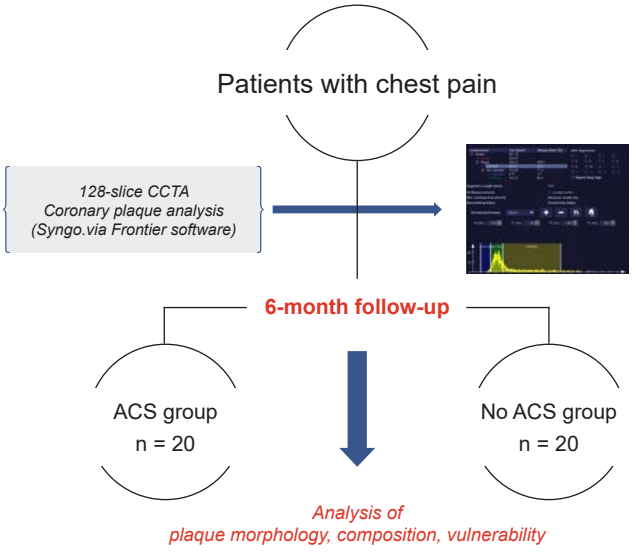

FIGURE 2. Diagram of the study protocol

TABLE 1. Baseline characteristics of the study groups

	ACS group n = 20	No ACS group n = 20	p value
Age, yrs (median)	65.9	62.35	
Males, n (%)	13 (65%)	15 (75%)	0.16
Hypertension, n (%)	18 (90%)	18 (90%)	1
Diabetes, n (%)	11 (55%)	9 (45%)	0.2
Dyslipidemia, n (%)	18 (90%)	17 (85%)	0.39
Smoking, n (%)	4 (20%)	5 (25%)	0.49

after the administration of an oral beta-blocker. Agatston coronary artery calcium score (CAC) was assessed during the pre-contrast scan, and a CAC >2,000 was considered exclusion criteria, as intense calcifications alter CCTA acquisitions. During an inspiratory breath-hold, 80–100 mL of iodinated contrast agent (Ultravist 370 mgI/mL, Bayer Healthcare, Germany) was administered according to the patient's body weight, with a flow rate of 5.5 mL/s, followed by 50 mL of 0.9% saline solution at the same flow rate.

The CCTA images were post-processed for plaque analysis of morphology, composition, and detection of four CT vulnerability markers (LAP, NRS, PR, SCs). The following parameters characterizing plaque phenotypes were analyzed: stenosis (%), plaque length (mm), volume (mm3), remodeling and eccentricity indexes, as well as plaque components (calcified, non-calcified, fibrotic, lipid-rich volumes and %). Image post-processing was performed on an offline workstation with the use of Syngo.via Frontier software (Siemens Healthineers, Erlangen Germany) (Figure 1).

All included patients had presented vulnerable plaques as assessed at the baseline CCTA examination, defined as the presence of minimum 50% degree of stenosis and at least one CT vulnerability marker (LAP, NRS, PR, SCs).

A diagram of the study protocol is shown in Figure 2.

RESULTS

From the total number of patients included in the study, 20 patients presented an ACS during the 6-month follow-up, which were matched with 20 subjects that did not present ACS (n = 20). The baseline characteristics of the study population are listed in Table 1.

There were no significant differences between groups in regards to the cardiovascular risk factors and comorbidities.

The CCTA analysis of plaque morphology and composition revealed that lesions that had triggered an acute event at 6 months presented a significantly higher remodeling index (1.13 ± 0.35 vs. 0.98 ± 0.19, p = 0.04), and higher calcified (59.99 ± 77.2 mm^3 vs. 35.45 ± 77.1 mm^3, p = 0.01) and lipid-rich (9.86 ± 10.8 mm^3 vs. 2.68 ± 1.0 mm^3, p = 0.01) volumes. Conversely, patients who did not exhibit an ACS had significantly larger fibrotic content in the analyzed lesions (64.34 ± 20.43% vs. 83.29 ± 21.31%, p = 0.0005) (Table 2).

When analyzing the vulnerability degree of coronary lesions, we found that patients presenting acute coronary events had a significantly higher rate of LAP (45% vs. 10%, p <0.0001) and PR (50% vs. 15%, p <0.0001). However, the incidence of SCs was significantly lower in patients with ACS (50% vs. 65%, p = 0.04). The frequency of NRS (25%

TABLE 2. CCTA evaluation of plaque morphology and composition

	ACS group n = 20	No ACS group n = 20	p value
Degree of stenosis (%)	53.11 ± 10.32	55.55 ± 8.31	0.41
Plaque length (mm)	17.19 ± 5.94	16.95 ± 3.44	0.95
Plaque volume (mm)	188.1 ± 104.7	186.4 ± 90.74	0.95
Remodeling index	1.13 ± 0.35	0.98 ± 0.19	0.04
Eccentricity index	0.29 ± 0.19	0.3 ± 0.12	0.87
Calcified volume (mm^3)	59.99 ± 77.2	35.45 ± 77.1	0.01
Calcified %	27.24 ± 22.9	15.03 ± 21.4	0.02
Non-calcified volume (mm^3)	145.5 ± 104.4	151.0 ± 73.59	0.84
Non-calcified %	72.77 ± 22.98	84.99 ± 21.45	0.02
Lipid-rich volume (mm^3)	9.86 ± 10.8	2.68 ± 1.0	0.01
Lipid-rich %	8.42 ± 11.8	1.69 ± 0.9	0.02
Fibrotic volume (mm^3)	2.92 ± 0.23	2 ± 0.36	0.32
Fibrotic %	64.34 ± 20.43	83.29 ± 21.31	0.0005

TABLE 3. Multivariate analysis of CT vulnerability markers as predictors of ACS at 6 months

Variable	OR (95% CI)	p value
PR	6.44 (1.07–1.97)	0.0591
NRS	1.74 (0.25–15.33)	0.8242
LAP	8.18 (1.23–95.08)	0.0434
SCs	0.95 (0.17–5.08)	0.7793

vs. 30%, p = 0.52) was not different among the two study groups (Figure 3).

Multivariate analysis for CT vulnerability markers identified the presence of LAP as the only independent predictor for ACS (OR 8.18 [1.23–95.08], p = 0.04).

DISCUSSIONS

The present study aimed to evaluate which vulnerability feature is most likely to cause an ACS in patients with chest pain who present VPs at the baseline CCTA evaluation. The premise of the study was not to validate the established influence of plaque vulnerability on the risk for future acute coronary events, but rather to investigate which vulnerable plaque features are more prone to trigger an ACS. This hypothesis has been suggested by previous studies that have shown a clear connection between VPs and ACS, but a large number of unstable plaques, as depicted by CCTA, did not lead to an acute event.[23,24] For this, we performed an analysis of patients with chest pain and VPs (defined as the presence of at least one established CCTA VM) who presented ACS, and who were matched with subjects presenting VPs at baseline, but without acute events during a 6-month follow-up period.

VPs that had triggered an acute event presented a significantly higher remodeling index. The vascular remodeling pattern at the site of an atherosclerotic lesion has shown a pivotal influence on the natural course of atherosclerosis. Outward PR is responsible for acute coronary events, while negative inward remodeling has been associated with progression of stenosis in patients with stable coronary artery disease.[26,27] An increased remodeling index (>1.1) indicates the presence of PR, which is a feature of vulnerability that has been associated with other markers responsible for plaque destabilization (e.g., thin-cap fibroatheroma), and also with the risk for future cardiac events. In addition, coronary plaques that exhibit PR are more likely to have larger necrotic cores, inflamed thin fibrous caps, heterogeneous calcifications, and intralesional hemorrhages.[19,28,29]

Future culprit plaques exhibited higher calcified and lipid-rich content compared to plaques that remained clinically silent. On the other hand, subjects in the control

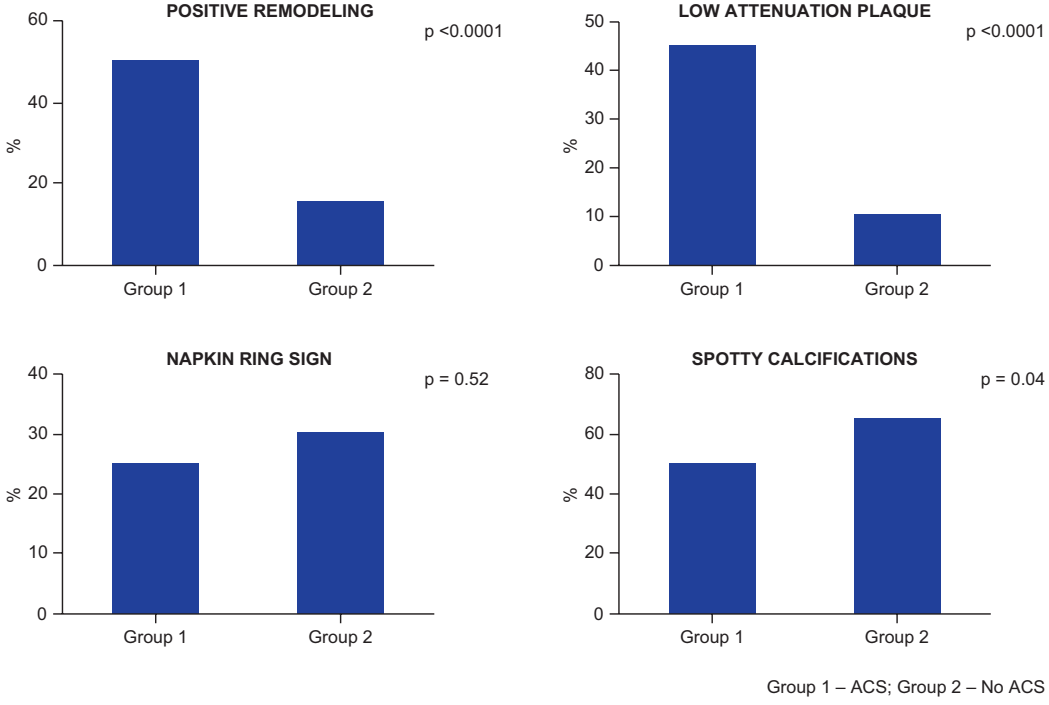

FIGURE 3. Vulnerability features present in the study groups, indicating that once identified in a coronary plaque, positive remodeling, low attenuation, and spotty calcium are associated with a higher risk for early development of an acute coronary syndrome

group exhibited a higher fibrotic content within the analyzed plaques, which has been proven to predict plaque stability by previous studies. The study of plaque composition has led to a CCTA classification of coronary lesions into calcified, partially calcified, and non-calcified lesions.[15,30] Typically, a VP has been described as a non-calcified lesion, with a large necrotic core and high lipidic content. The lipidic content of VPs is inversely correlated with the thickness of the fibrous cap, thus predicting the presence of a thin-cap fibroatheroma as evaluated via intracoronary imaging modalities. The large necrotic core (>10%) is depicted as having a low attenuation in the CCTA examination, less than 30 Hounsfield units.[16,20,31]

Results in the present study indicating that future culprit plaques exhibit a higher calcified volume compare to lesions that remained clinically silent, could be considered controversial. The process of plaque mineralization is one of the final acts in the evolution of atherosclerosis, leading to plaque stabilization. However, coronary calcifications have been associated with an increased rate of adverse events by earlier CCTA studies that had focused on evaluation of coronary calcium scoring. A high calcium content may be indicative for an increased plaque burden and longer evolution of the atherosclerotic process.[32,33] Despite this, a 13-month follow-up study showed that partially (HR = 86.96, p = 0.002) or non-calcified (HR = 58.06, p = 0.005) plaques were associated with higher rates of major adverse cardiovascular events (MACE) compared to calcified lesions (HR = 32.94, p = 0.02).[34] Conversely, another study found that mixed and calcified lesions were more likely to predict the two-year all-cause mortality (p <0.0001).[35] The divergent role of calcium may stem from the architectural deposition of calcifications within the lesion. Microcalcifications (<3 mm) are considered as the initial marker indicating the mineralization process. Typically, these speckle-like calcium depots are actually the spotty calcifications that have been established as a CCTA feature for VP. Macrocalcifications result in sheet-like deposits (>3 mm), which are usually characteristic for progression and stabilization of coronary lesions. Many imaging modalities have shown that spotty calcifications predict unstable plaques, while extensive, sheet-like calcium depots predict plaque stabilization.[36]

Coronary plaques that exhibit a higher fibrotic content and a thicker fibrous cap, are considered stable. A fibroatheroma is defined as having a lipidic pool of at least one quadrant, and if the necrotic lipidic core surpasses two quadrants, it is typically referred to as a thin-cap fibroatheroma. On the other hand, the cut-off value of 65 μm is accepted for the definition of thick and thin-cap fibroatheromas, respectively.[6] Vergallo *et al.* found that non-culprit lesions present smaller lipidic pools with thicker fibrous caps compared to culprit lesions that had ruptured.[37] The results of our study are concurrent with the observations according to which the fibrotic content is directly proportional with the stability of the plaque.

The increasing use of CCTA in cardiovascular research and also in the management of patients with chest pain and suspected coronary artery disease has led to the identification of specific high-risk criteria for VPs. The predefined CCTA features for plaque destabilization include the presence of low-attenuation plaque, spotty calcification, positive remodeling, and napkin-ring sign.[16–20] Their predictive capacity for coronary risk has been nicely illustrated in a meta-analysis conducted by Nereklar *et al.*, in which the isolated presence of each marker was associated with MACE rates (LAP: HR −2.95, p <0.001; PR: HR −2.58, p <0.001; SCs: HR 2.25, p = 0.006; NRS: HR 5.06, p <0.001). Moreover, the presence of more than two high-risk features showed additional risk in several studies, thus indicating that the more VMs are present in a coronary plaque, the higher will the risk be for presenting an ACS on the short and long term.[21,22,24]

Our results found that VPs that had triggered an acute event exhibited a significantly higher number of low attenuation plaques and positive outward vascular remodeling. LAP maintained its predictive capacity even after adjustments for other vulnerability markers were performed.

Low attenuation plaques, indicative for a large lipidic content, overlapped by a thin fibrous cap, have been shown to predict the rate of MACE. In the SCOT-HEART trial, LAP was the best predictor for subsequent MI in patients with chest pain (HR = 1.6 per doubling, 95% CI 1.1–2.43) over a follow-up of 4.7 years.[38] A study characterizing 848 coronary plaques in 311 patients with clinical indication for CCTA has found that the total LAP volume was significantly higher in patients that had presented the composite end-point of all-cause mortality, MI, and coronary revascularization during a median follow-up of 3.2 years (315 ± 211 mL vs. 182 ± 139 mL, p = 0.005).[39] Moreover, a per plaque analysis on patients with ACS revealed that LAPs were present in 67.4% of culprit lesions versus only 29.03% of non-culprit lesions (p = 0.0001).[20]

The process of outward remodeling, despite having a pivotal role in maintaining the coronary lumen unobstructed, has been linked to an increased rate of adverse events. In addition, the presence of this VM is usually accompanied by other high-risk plaque features, with incremental increase of the associated coronary risk.[40] Several large clinical trials have found that a significant propor-

tion of patients presenting with ACS did not present a hemodynamically significant stenosis at the level of the culprit lesion, which is explained by the presence of positive remodeling.[41–43]

Interestingly, the presence of the napkin-ring sign was not significantly different between VPs that led to an acute event compared to those who remained clinically silent. Spotty calcifications were more frequent in plaques that did not trigger an ACS. NRS has been found as the best predictor for long-term adverse events (HR 3.85, 95% CI 1.7–8.6, p <0.0001), together with LAP <60 HU (HR 4.96, 95% CI 2.0–12.2, p <0.0001), even after adjustments for stenosis severity or plaque composition were made. However, SCs presented a lower predictive capacity, which was not maintained after adjustments were done.[44] In a very recent study, 318 patients with mild coronary stenosis who underwent CCTA were followed up for the occurrence of MACE over a 24-month period. The results showed that both NRS (p = 0.001) and SCs (p = 0.027) were predictive for the study end-point on the univariate analysis. However, the predictive capacity of these two high-risk features was not maintained in the multivariate analysis of factors influencing the adverse events (NRS: p = 0.608, SCs: p = 0.374).[45] Their results are similar to the findings of our study, but the present analysis indicated that NRS and SCs were not associated with the occurrence of ACS at six months, both in the univariate and multivariate analysis.

The most predictive CT vulnerability feature for future ACS was the presence of LAP, indicative for a large necrotic core, which typically signals the presence of a thin-cap fibroatheroma. In addition to intrinsic characteristics of the vulnerable plaques, there are other factors that influence the transformation of a VP into a culprit plaque. Several other extrinsic factors of vulnerability, including inflammation and hemodynamics, have been shown to influence plaque evolution.[11,46–49] Therefore, the detection of other extrinsic markers for plaque culpability (coronary shear stress, markers of local coronary inflammation) in patients presenting VPs could improve risk prediction.

STUDY LIMITATIONS AND FUTURE PERSPECTIVES

The main limits of the present study derive from the relatively low number of patients. Future patient enrollment and extension of the follow-up period could offer a better characterization of vulnerable plaques that actually lead to an acute event. This could impact the clinical approach of patients presenting with chest pain who undergo CCTA, as it can influence the therapeutic management, and thus improve outcomes, in terms of both individual patient care and quality of life, and also in terms of healthcare costs.

CONCLUSIONS

Vulnerable plaques producing an ACS exhibit a different phenotype compared to unstable plaques that remain silent. The CCTA profile of atheromatous plaques producing an ACS includes the presence of low attenuation, positive remodeling, and lipid-rich atheroma. The presence of these features in high-risk coronary plaques identifies very high-risk patients, who can benefit from adapted therapeutic strategies in order to prevent the development of an ACS.

CONFLICT OF INTEREST

None declared.

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