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Hybrid Imaging to Assess the Impact of Vulnerable Plaque on Post Myocardial Infarction Myocardial Scar

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ABSTRACT

Background: Multimodality imaging improves the accuracy of cardiac assessment in patients with prior myocardial infarction. The aim of this study was to investigate the association between coronary plaque vulnerability (PV) and myocardial viability in the territory irrigated by the infarct-related artery (IRA). Secondary objectives include evaluation of the systemic inflammation but also different cardiac risk scores (SYNTAX score, Duke jeopardy score, or calcium score) using hybrid imaging models of coronary computed tomography angiography (CCTA) and cardiac magnetic resonance (CMR) in patients who have suffered a previous myocardial infarction (MI). **Material and methods:** The study included 45 subjects with documented MI in the 30 days prior to study enrolment, who underwent CCTA and CMR examinations. Computational post-processing of CCTA and CMR images was used to generate fused imaging models. Based on the vulnerability degree of the associated non-culprit lesion located proximally in the IRA, the study population was divided into 3 groups: Group 1 – subjects with no sign of vulnerability (n = 7); Group 2 – subjects with 1 or 2 CT vulnerability features (n = 28); and Group 3 – subjects with >2 features of vulnerability (n = 12). **Results:** CCTA features indicative for the severity of coronary artery disease were not different between groups in terms of calcium scoring (460 ± 501 vs. 579 ± 430 vs. 432 ± 494, p = 0.7) or SYNTAX score (25 ± 9.2 vs. 24.9 ± 8.3 vs. 20.2 ± 11.9, p = 0.4). However, after 1 month, infarct size and the Duke jeopardy score were associated with increased PV (infarct size 8.77 ± 3.4 g in Group 1, compared to 20.87 ± 8.3 g in Group 2 and 27.99 ± 11.8 g in Group 3 (p = 0.007), while the Duke jeopardy score was 4.4 ± 1.6 in Group 1, vs. 7.07 ± 2.1 in Group 2 vs. 7.5 ± 1.73 in Group 3 (p = 0.01). Inflammatory biomarkers were directly associated with coronary plaque vulnerability (p = 0.007 for hs-CRP and p = 0.038 for MMP-9). **Conclusion:** In patients with prior myocardial infarction, the size of myocardial scar was directly correlated with the vulnerability degree of coronary plaques and with systemic inflammation quantified during the acute phase of the coronary event. Hybrid imaging may help to identify the hemodynamically significant plaques with superior accuracy.

Keywords: myocardial infarction, CCTA, MRI, hybrid images, Duke jeopardy score, subtended myocardium, viability

INTRODUCTION

It is well known that cardiovascular diseases have the highest mortality rate worldwide.[1] Innovation in cardiac imaging, mainly based on the cooperation between informatics, cardiology, and radiology, provides learning protocols that improve diagnostic accuracy and offers a wider view on the pathogenesis of different cardiovascular diseases. The concept of hybrid imaging combines more than one imaging methods and offers precious information regarding anatomy and functionality in a spatial view.[2] Multimodality imaging for the assessment of coronary artery disease (CAD), especially myocardial infarction (MI), has become essential for a complex assessment of these patients.[3] Coronary computed tomography angiography (CCTA) is a trustworthy method for the assessment of coronary anatomy and severity of CAD, this noninvasive tool becoming more available in many cardiac centers.

CCTA allows 3D cardiac reconstruction, evaluation of coronary plaques, and also a detailed view on the cardiac geometry with high specificity.[4–9] On the other hand, cardiac magnetic resonance (CMR) is a non-harmful, noninvasive diagnostic tool that provides information regarding functionality, especially kinetics, perfusion, mass, and volume.[10–13] The integration of information from two different imaging tools allows the combination of the provided parameters to obtain a superior analysis of cardiac function and anatomy, but also to have a better view on patient outcomes and risk stratification.

In order to evaluate the impact of a coronary artery stenosis on myocardial function and structure, many scientists have developed different scores that were difficult to apply in clinical practice sometimes, but their effectiveness on risk prediction has been proven on patients with known CAD or with history of acute myocardial infarction (AMI), including the SYNTAX Score, coronary calcium score, or a more complex assessment – the residual SYNTAX score. However, in the age of advanced technology and artificial intelligence, there are machine learning algorithms that can automatically evaluate the myocardial mass subtended by a coronary lesion.[14] Also, there are relatively simple methods, such as calculating the Duke jeopardy score, in order to estimate the percentage of affected myocardium in ischemic heart disease.[15] This cardiac score is used for calculating the percentage of myocardial tissue at risk, based on the location of a coronary artery stenosis.[16] For calculating this score, the coronary artery tree is divided into 6 segments, and each segment presenting stenosis of more than 75% is attributed 2 points. Therefore, the maximum Duke jeopardy score can be 12 points.[15] Investigation of the impact of CAD on myocardial function and structure may provide details regarding myocardial viability. This is compulsory for evaluating the ability of recovering an ischemic myocardial territory through coronary revascularization. It is well known that the gold standard method for appraisal of myocardial viability is fluorodeoxyglucose positron emission tomography (F-FDG PET).[17–20] Due to high costs and radiation exposure, which may range from 7 to 9 mSV, its availability is still low. This imaging procedure allows the investigation of cardiac function, while simultaneously providing information regarding myocardial metabolism and perfusion.[21] Nevertheless, CMR evaluation, especially using late gadolinium enhancement sequences (LGE), allows the differentiation of viable from non-viable myocardium, in contrast to nuclear scintigraphy which allows only indirectly evaluation of the viable myocardium.[22] Viability evaluation prior to revascularization of stenotic coronary lesions is advantageous for guiding the right treatment, and mostly to predict functional recovery after blood flow restauration through coronary revascularization. From this point of view, it is also important to mention the animal study conducted by Force *et al.*, which developed the concept of tethering myocardium, i.e. the viable myocardium juxtaposed to cicatricial regions which might not heal after proper blood flow restaurantion.[23]

OBJECTIVES

The main objective of the study was to generate fused models based on hybrid CCTA/CMR imaging for the complex evaluation of myocardial viability and vulnerable coronary plaques after an acute myocardial infarction, and to investigate its reliability in assessing the association between non-culprit plaque vulnerability and myocardial function in the territory irrigated by the coronary artery presenting with vulnerable plaques. Secondary, we aimed to investigate a possible relation between systemic inflammation and the amount of myocardial fibrosis reflected by infarct size, mass, and percentage in patients with vulnerable coronary plaques.

MATERIAL AND METHODS

Study Population

This original research was a prospective observational study conducted in the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center in Târgu Mureş, Romania. We included 45 subjects with documented MI 30 days prior to study enrollment.

All subjects gave signed consent, and all study procedures were approved by the ethics committee of the institution and were in line with the principles stipulated in the Declaration of Helsinki.

We excluded subjects with any malignancy, renal diseases with abnormal levels of creatinine or known allergy to iodine contrast, as well as pregnant patients. Venous blood samples were collected in order to determine the level of inflammatory biomarkers at day 1 following the acute event: highly-sensitive C reactive protein (hs-CRP) and matrix metalloproteinase 9 (MMP-9), and also complete blood count and CK-MB levels. During initial hospitalization for infarction, all subjects underwent invasive coronary angiography and cardiac ultrasound. At one month after the acute event, all patients underwent CCTA and CMR assessment.

CCTA acquisition protocol and image post-processing

All CCTA examinations were performed using a Siemens Somatom Definition 128-slice scanner (Siemens Healthcare GmbH, Erlangen, Germany). All CCTA images were examined by two experienced investigators.

Prior to examination, the heart rate was recorded in all subjects, and those who had a heart rate higher than 65 bpm received beta-blockers in order to decrease the heart rate to 60 bpm.

The first image acquisition was performed in a frontal plane topogram, followed by a native acquisition and dynamic contrast administration, using venous right antecubital approach and an automatic syringe, with a rate of contrast administration of 5 mL/s, followed by 50 mL saline flush administration.

The following CCTA features of plaque vulnerability were assessed: positive remodeling (PR), spotty calcifications (SC), low-attenuation plaque (LAP), and napkin-ring sign (NRS).23–28 All coronary plaques were evaluated by two experienced radiologists, and for each plaque we calculated a vulnerability score based on CCTA markers. The presence of each marker was assigned 1 point. We considered only vulnerable plaques located upstream of the culprit lesion that irrigated the infarcted subtended myocardium. Based on this vulnerability score, the study population was divided into three groups: Group 1, consisting of 7 patients without vulnerable plaques; Group 2, consisting of 28 patients with moderate plaque vulnerability (1 or 2 vulnerability markers); and Group 3, consisting of 12 patients with high vulnerability degree plaques (more than 2 CCTA-based vulnerability markers). We calculated the Duke jeopardy score, the SYNTAX score, and the calcium score based on CCTA image acquisition in all patients.

CMR acquisition protocol

In all patients, the applied CMR acquisition protocol focused on the delayed enhancement sequences and used a 1.5T Siemens Magnetom Aera equipment. All myocardial segments were examined during late gadolinium enhancement, and all CMR images were reviewed by two experienced radiologists, who assessed the presence and extension of ischemic lesions, possible edema in T2 sequences, ejection fraction, myocardial mass, volumes, and contractility.

All subjects underwent invasive coronary angiography during the acute coronary event using a Siemens biplane system, and coronary lesions located contiguous to the infarcted area were mapped by retrospective analysis of the recorded examinations.

Computational CCTA/CMR image post-processing

Computational CT post-processing was performed using Siemens SyngoVia software (Siemens Medical Solutions, Erlangen, Germany). The 3D reconstruction of the coronary arteries was performed, and coronary arteries were individually reconstructed around their axis.

Advanced analysis of coronary plaques was performed using a semi-automatic image algorithm which detects the vascular contour, on the same research software and using the platform dedicated to coronary analysis (SyngoVia Frontier Coronary Plaque Analysis, Siemens, Erlangen, Germany).

The CMR images were processed using a dedicated MR software for the quantification of myocardial fibrosis (Q-mass, Medis Suite MR, Leiden, the Netherlands). In order to calculate the myocardium mass and infarct size volume, the transmural extent of the infarction was calculated by manually drawing the endocardial and epicardial contours in each slice of the late enhancement series. Then, the software calculated the myocardium mass automatically, differentiating the healthy myocardium from the non-viable one.

The CCTA image was opened in MM Reading mode with an established research software (SyngoVia Frontier, Siemens). The Coronary 0.6 slices were selected, and then a CMR image of the same subject was added. The software was designed to recognize if the imaging method belongs to the same subject, using anatomical particularities. From the CMR images, late enhancement sequences were chosen and then fused with CCTA images, thus obtaining a

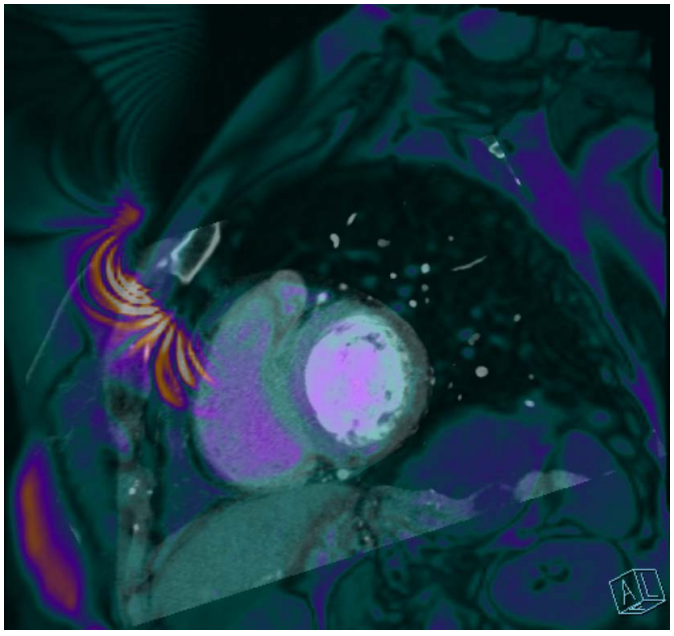

FIGURE 1. Hybrid CCTA/CMR image with CMR reconstruction superposed on the CT image, revealing antero-lateral myocardial ischemia with myocardial scar

hybrid cardiac CCTA\CMR image, as the one exemplified in Figure 1.

Data analysis

All data were recorded, archived in a dedicated database, and analyzed using Graph Pad Prism 8 software. ANOVA test was used for comparison of quantitative variables between groups, and the Chi square test and its variants were used to evaluate the association between groups in regard to qualitative data. A p value of 0.05 was considered statistically significant.

RESULTS

In total, 45 patients were included in the study, with a mean age of 60 years (ranging from 41 to 86 years), 77% of them being males. General characteristics of the included patients are listed in Table 1. From the total population of the study, 93.3% suffered from hypertension, 28.8% had type 2 diabetes mellitus, 40% were active smokers, and 37.7% were diagnosed with dyslipidemia. Location of the AMI was in the inferior territory in 46.6% of the subjects, and 55.5% had multivessel CAD. There were no statistically significant differences between the three groups regarding left ventricular ejection fraction (p = 0.5), the presence of diabetes mellitus (p = 0.8), or tobacco use (p = 0.6).

The amount of myocardial necrosis at presentation in the emergency department was not significantly different between the groups, as highlighted by similar levels of CK-MB: 1.153 ± 1.868 IU/L in Group 1, 498.3 ± 428.8 IU/L in Group 2, and 2.131 ± 1.832 IU/L in Group 3 (p = 0.08). However, after 1 month, the infarct size and the Duke jeopardy score were both significantly higher in patients with vulnerable plaques. Infarct size at one month was 8.77 ± 3.4 g in Group 1, compared to 20.87 ± 8.3 g in Group 2 and 27.99 ± 11.8 g in Group 3 (p = 0.007), as shown in Figure 2, while the Duke jeopardy score was 4.4 ± 1.6 in Group 1, 7.07 ± 2.1 in Group 2 and 7.5 ± 1.73 in Group 3 (p = 0.01) (Figure 3).

Inflammatory biomarkers were directly associated with non-culprit coronary plaque vulnerability (Figure 4). Hs-

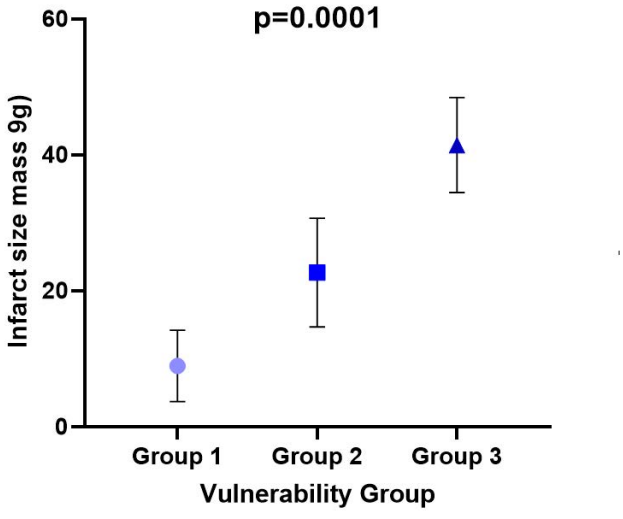

FIGURE 2. Infarct size by CMR and degree of vulnerability by CCTA. The infarct size mass was significantly higher in patients with the highest vulnerability degree of the non-culprit plaque located on the infarct-related artery.

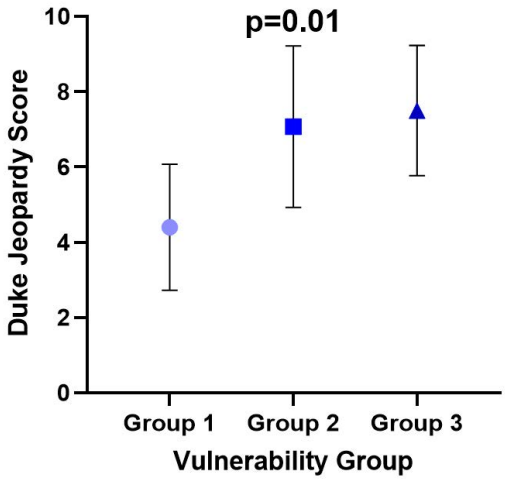

FIGURE 3. The Duke jeopardy score and degree of vulnerability

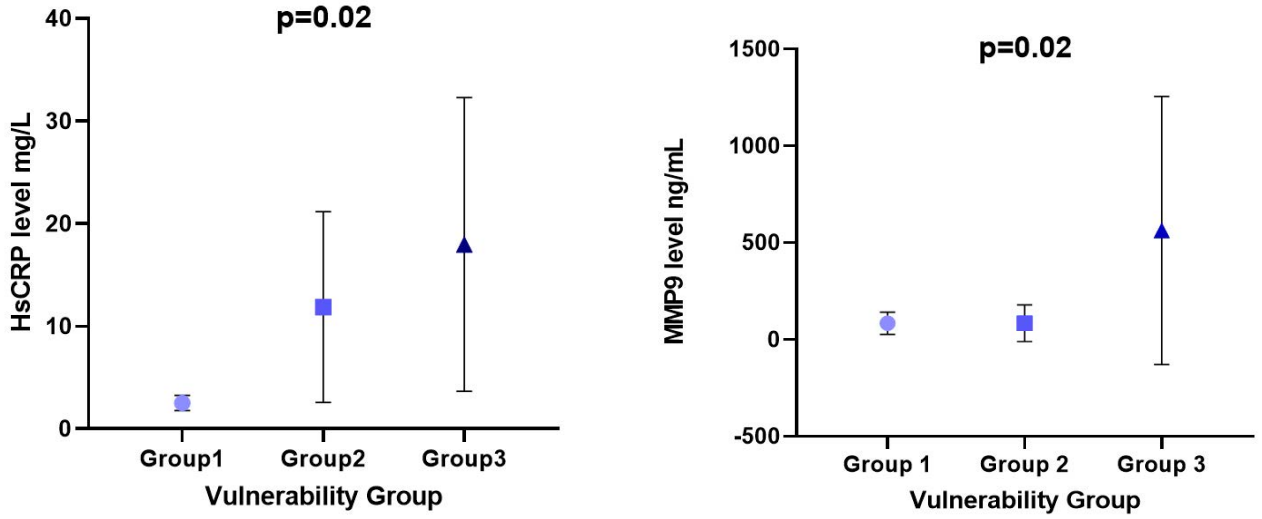

FIGURE 4. Systemic biomarkers associated with increased inflammation (hsCRP and MMP-9) and plaque vulnerability. The highest serum levels of inflammatory biomarkers were observed in patients with the highest plaque vulnerability degree.

CRP was 2.5 ± 0.7 mg/L in Group 1 vs. 11.86 ± 9.3 mg/L in Group 2 and 17.98 ± 14.31 mg/L in Group 3 (p = 0.02). MMP-9 was significantly higher in patients with advanced vulnerability of the coronary plaques (563.2 ± 691.6 ng/mL in Group 3 vs. 83.71 ± 94.47 ng/mL in Group 2 and 84.4 ± 57.56 ng/mL in Group 1, p = 0.02) (Table 2).

Interestingly, CCTA characteristics associated with the severity of CAD were not significantly different between groups in terms of calcium score (460 ± 501 vs. 579 ± 430 vs. 432 ± 494, p = 0.7) or SYNTAX score (25 ± 9.2 vs. 24.9 ± 8.3 vs. 20.2 ± 11.9, p = 0.4) (Figure 5).

DISCUSSIONS

This manuscript is part of the FUSE-HEART study, a complex research based on imaging markers, which aims to provide more information regarding myocardial viability, coronary plaques, and inflammation in patients who have suffered an AMI. The present study aimed to investigate possible correlations between inflammation status, myocardial viability assessed by CMR, and coronary plaque vulnerability of non-culprit lesions located on the infarct related artery, as assessed by CCTA.

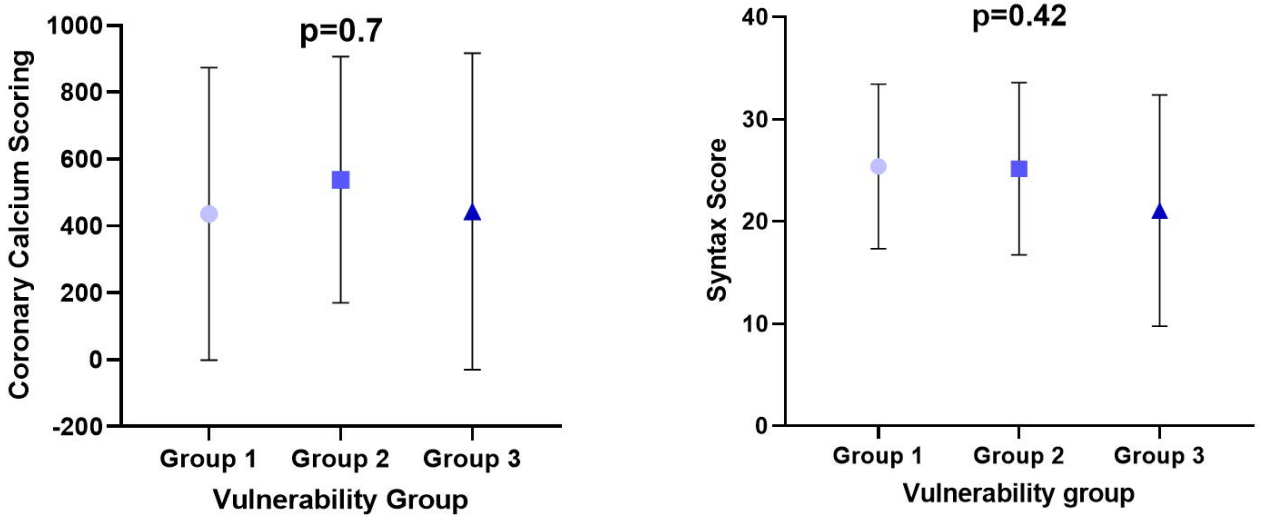

FIGURE 5. CT markers of atherosclerosis severity in the study population: coronary calcium score and SYNTAX score – comparative analysis between the three plaque vulnerability groups

TABLE 1. Clinical and echocardiographic characteristics in the population of the study. All values are expressed as mean (SD).

	Group 1	Group 2	Group 3
Age, years	61 (7.35)	62.14 (10.72)	58.08 (10.18)
Weight, kg	85 (15.3)	84.50 (15.18)	79.50 (8.90)
Leukocyte no., cells/μL	8001 (1923)	8066 (1682)	9288 (1961)
Ejection fraction, %	48 (2.19)	46.41 (4.77)	47 (4.56)
End-diastolic left ventricle diameter, mm	50.8 (4.15)	52.92 (5.36)	54.56 (4.48)

The concept of vulnerable patients and vulnerable coronary plaques was first described several years ago. In 1989, Muller *et al*. used the terminology of vulnerable plaques for the first time, to identify atherosclerotic coronary plaques responsible for most cardiovascular sudden events due to rupture.[24,25] In this regard, in 2003, Morteza *et al*. provided a more detailed definition of the vulnerable plaque: a plaque that has a high probability of rupture, with subsequent thrombosis, one that can become a culprit lesion in the near future.[26] Most of the major criteria that define this type of plaque are based on histological and intravascular imaging studies, which indicate the presence of active inflammation expressed by monocytes, macrophage and T-cell infiltration, or the aspect of plaque with a thin cap with rich lipid core.[27,28] There are also noninvasive characteristics of vulnerable coronary plaques that can be evaluated using CCTA. These features include positive remodeling, spotty calcifications, low attenuation, and the napkin-ring sign.[29–34] However, cardiovascular risk stratification involves more than the presence of vulnerable coronary plaques; it also includes the concepts of vulnerable blood and vulnerable myocardium. Together with documented systemic inflammation, all these meet the criteria to define the vulnerable patient, who presents a high probability to develop an acute coronary syndrome or sudden cardiac death.[26]

Many imaging procedures have improved in the last decades, in order to achieve a better diagnostic accuracy and for evaluating the vulnerable patient in order to predict the risk of major adverse cardiovascular events (MACE).

Our study aimed to demonstrate how inflammation and myocardial fibrosis influence the coronary plaques located in proximity of culprit lesions that have already caused an AMI. The identified associations have highlighted that even in the absence of any statistically significant difference between the groups in terms of myocardial necrosis, systemic inflammatory biomarkers (MMP-9 or hs-CRP) were significantly higher in the group of subjects with a higher vulnerability degree of non-culprit coronary plaques located in the infarct-related artery. This association shows the detrimental effect of inflammation on coronary plaque vulnerability. Moreover, we found that the infarct size mass expressed in grams was more increased in the group with the highest degree of plaque vulnerability, which suggests that pancoronary vulnerability may influence myocardial healing following an acute coronary event, after proper revascularization.

According to our knowledge, this is the first study to use hybrid imaging and fused reconstructions of CCTA and CMR images to demonstrate the correlation between infarct size and non-culprit plaque vulnerability. First, we developed a protocol for obtaining fused images, then we

TABLE 2. Multimodality imaging characteristics and systemic biomarkers in the study groups. All values are expressed as mean (SD).

	Group 1	Group 2	Group 3	p value
Infarct size mass, g	8.94 (5.25)	22.70 (7.9)	41.45 (6.9)	0.0001
SYNTAX score	25.40 (8.042)	25.18 (8.4)	21.08 (11.32)	0.4226
Ca score, HU	436 (437.5)	538.3 (368.2)	443.8 (473.5)	0.74
Hs-CRP, mg/L	2.52 (0.74)	9.12 (6.19)	16.36 (11.73)	0.007
Duke jeopardy score	4.4 (1.67)	7.07 (2.14)	7.5 (1.73)	0.01
CK-MB, IU/L	1153 (1868)	498.3 (428.8)	2131 (1832)	0.08
MMP-9, ng/mL	130 (70)	101.3 (52)	477 (329)	0.038

Hs-CRP – high-sensitivity C-reactive protein; CK-MB – creatin kinase MB isoform; MMP9 – matrix metalloprotease 9

tested the prototype in clinical settings, on 45 patients with prior MI. This is the first study of its kind which has successfully demonstrated the role of advanced multimodality imaging in the assessment of patients with CAD and vulnerable coronary plaques.

CONCLUSIONS

In patients with prior myocardial infarction, the size of myocardial scar is directly correlated with the vulnerability degree of non-culprit coronary plaques located on the infarct-related artery and with systemic inflammation evaluated during the acute event. Hybrid imaging may help to identify hemodynamically significant vulnerable plaques with superior accuracy. The integration of hybrid imaging with inflammatory biomarkers may improve risk stratification for major adverse cardiovascular events in the postinfarction period.

CONFLICT OF INTEREST

Nothing to disclose.

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