Morphological and Tissue Characterization of Culprit Lesions in Patients with ST-Segment Elevation Myocardial Infarction After Thrombolytic Therapy. Analysis with Grayscale Intravascular Ultrasound and iMAP™ Technology

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ABSTRACT

Background: Currently, there is a great debate about the pathophysiology of acute myocardial infarction and tissue composition and morphology of lesions responsible for ischemic events. However, few studies have investigated the applicability of tissue characterization using iMAP™ technology in these patients. We evaluated patients with ST-segment elevation myocardial infarction after thrombolytic therapy with grayscale intravascular ultrasound and iMAP™ technology to describe the tissue composition of the culprit lesions. Methods: Twenty-five ST-segment elevation myocardial infarction patients with successful reperfusion had the three major epicardial coronary arteries evaluated by grayscale intravascular ultrasound and iMAP™ technology. Results: Mean age was 51 ± 11.5 years with a prevalence of males (72%). The artery most often involved was the right coronary artery (48%). Intravascular ultrasound showed that the culprit lesions were long (mean extension 31.0 ± 17.2 mm) with a high percent of plaque volume (58.5 ± 5.1%). At the point of highest obstruction (minimal luminal area), the plaque burden was 82.5 ± 7.5%. Furthermore, the mean remodeling index was 1.4 ± 1.0, indicating positive remodeling. iMAP™ analysis of the lesion and minimal luminal area showed a prevalence of fibrotic and necrotic components when compared to other components. Conclusions: In ST-segment elevation myocardial infarction patients, the culprit lesion showed a prevalence of positive arterial remodeling and the necrotic core component in the composition of the culprit plaque corroborating in vivo the main pathophysiology of acute atherosclerotic disease.

Acutely myocardial infarction (AMI) is a clinical entity normally resulting from partial (non-ST-segment elevation MI – NSTEMI) or total thrombotic obstruction (ST-segment elevation MI – STEMI) of an epicardial coronary artery. Pathological studies have shown that the triggering event in thrombus formation and subsequent vessel occlusion results from the rupture of atherosclerotic fibrous cap in 60% of cases, from plaque erosion in 30 to 35%, and from a thrombus formation superimposed on calcium nodules in 5 to 10%.

However, much is still debated about the composition of atherosclerotic plaques that develop from a condition considered stable to a situation of instability, with consequent outbreak of thrombotic events and acute coronary ischemia. In this situation, intravascular ultrasound (IVUS) is an important tool in the identification and characterization of the morphology of atherosclerotic plaques related to AMI, although it is not possible to identify plaque erosion due to limitations in spatial resolution, a problem that can be overcome using optical coherence tomography (OCT). The IVUS identifies plaque and calcium nodule rupture with high sensitivity and specificity. Additionally, several findings at IVUS are characteristic of unstable plaques, such as extensive positive remodeling and the presence of small amounts of calcium with localized and scattered distribution (spotty calcification). Recently, the application of tissue characterization with the iMAP™ technology (Boston Scientific, Santa Clara, United States) made further progress in the identification of atherosclerotic plaque composition, identifying and quantifying the lipidic and necrotic contents, which are directly related to lesion instability. Unlike the VH-IVUS® technology (Volcano Corporation, San Diego, United States), there have been few clinical studies assessing the accuracy of iMAP™ in the characterization of atherosclerotic plaques involved in STEMI. Even scarcer are the studies of patients submitted to thrombolytic therapy, in whom IVUS can be performed in vessels without any type of previous intervention (pre-dilation and/or thrombus aspiration).

The present study aimed to describe the quantitative, morphological tissue findings and using IVUS with greyscale analysis and iMAP™ technology of culprit lesions in STEMI patients treated with fibrinolytic therapy.

**METHODS**

**Patients and study design**

From September 2011 to May 2012, 25 patients with clinical and electrocardiographic diagnosis of STEMI treated with fibrinolytic therapy were prospectively included in the study iWonder (Imaging WhOle vessel coroNary tree with intravascular ultrasounD and iMap in patiEnts with acute myocarDial infarction). This study included 100 patients with NSTEMI or STEMI, whether or not treated with fibrinolytic therapy, and analyzed, through IVUS, three epicardial coronary arteries, in greyscale and iMAP™, regarding the phenotypic and tissue characteristics of culprit and non-culprit lesions. The project was conducted in the Hemodynamics and Interventional Cardiology Division of the Hospital São Paulo, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil, having been previously approved by the Research Ethics Committee of the institution (project 0889/11, August 5, 2011) and registered in ClinicalTrials.org under number NCT01437553. All patients or their legal guardians were informed about the objectives and risks of study-related procedures, and signed an informed consent form prior to the diagnostic procedure.

As part of the present subanalysis, the inclusion criteria were age < 75 years; clinical-electrocardiographic diagnosis of STEMI with prior fibrinolytic therapy, with time of evolution < 30 days; identification, through coronary angiography, of the culprit lesion responsible for the clinical picture; and IVUS assessment availability. Exclusion criteria were: STEMI lesion responsible for the clinical picture; and IVUS characterization of coronary lesions after thrombolytic for IVUS and iMAP.
gray scale analysis and morphological characterization by using the iMAP-IVUS® modality (Boston Scientific, Santa Clara, United States). Automatic pullback movements of the ultrasound catheter were performed at a speed of 0.5 mm/s, starting at a 10-mm distal point from the culprit lesion, toward the arterial ostium. For non-culprit arteries, the same routine was performed for analysis of plaques unrelated to the event.

**Intravascular ultrasound image analysis**

All angiography and IVUS images were stored in digital media and copied to an external hard drive for offline analysis at the Intravascular Image Laboratory of the Cardiovascular Research Foundation (New York, United States).

The IVUS analysis was performed in three sequential steps:

1. **Quantitative analysis:** quantitative volumetric analysis was performed according to current guidelines. This phase of the offline IVUS analysis consisted in the definition of the segment to be analyzed in each pullback, including at least 10 mm of extension, distal to the respective vessel ostium. Subsequently, using the Qivus 2.1® software (Medis Medical Imaging Systems, Leiden, the Netherlands) the automatic contours of the vessel and lumen were obtained at every 1 mm within the defined segment. Then, using Simpson’s method, the volumes of the lumen, vessel, and plaque (vessel minus lumen) were computed. The plaque burden was calculated as the ratio of the cross-sectional area of the plaque by the cross-sectional area of the vessel, multiplied by 100. The minimal luminal area (MLA) was defined as the smallest cross-sectional area of the lumen within the lesion. The stenosis area was calculated as the cross-sectional area of the lumen at the MLA divided by the cross-sectional area of reference segment, multiplied by 100. The cross-sectional area of the vessel in the reference segment was defined as the mean proximal and distal cross-sectional area of the vessel, at the point where the vessel had an aspect closest to normal, with the largest lumen and lowest plaque burden. When one of the two reference segments (proximal or distal) could not be measured, the calculation was based on only one of them. If none of the two segments could be measured, variables depending on reference measures were not calculated. The remodeling index was calculated as the cross-sectional area of the vessel at the MLA point divided by the cross-sectional area of reference.

2. **Qualitative analysis:** plaque rupture was defined as an intraplaque cavity in communication with the lumen, in the presence of the fibrous-cap residues or fragments. The plaque was considered as hypoechoic when it was predominantly (> 75%) less bright when compared with the adventitia, and it was considered as hyperechoic when it was brighter (> 75%) than the adventitia. Calcium nodules were defined as a dense, eruptive, irregular surface mass, in contact with and/or near the lumen.

3. **Tissue characterization by iMAP:** iMAP-IVUS® is a type of image that uses radio-frequency spectral analysis to obtain an algorithm to classify the atherosclerotic plaque into four components: fibrotic, lipidic, necrotic, and calcified. The development of this algorithm was based on ex vivo histological analyses, and each component was assigned a color: green for the fibrotic component, yellow for the lipidic component, red for the necrotic component, and white for the calcified component (Figure 1).

Categorical variables were expressed as absolute and percentage frequencies, and continuous variables were expressed as means ± standard deviations.

**RESULTS**

The mean age of patients was 51 ± 11.5 years, with a predominance of male patients (72%). The time between the index event and performance of the IVUS procedure was 7.2 ± 2.1 days. Among the risk factors for coronary artery disease (CAD), a high prevalence of diabetes (40%), hypertension (60%), and smoking (64%) was observed. Moreover, at admission, there were a low proportion of patients using acetylsalicylic acid (ASA), as none had had a previous ischemic event. The other clinical and angiographic characteristics are summarized in Table 1.

In the analysis of the culprit lesion by IVUS with gray scale (Table 2), long lesions (extension of 31.0 ± 17.2 mm) with high plaque volume (58.5 ± 5.1%) were
observed. At the point of maximum obstruction (MLA), the lumen was 2.0 ± 1.0 mm², while the measured plaque burden was 82.5 ± 7.5%. Consistent with the profile of patients studied, the mean rate of remodeling was > 1.05 (1.3 ± 1.0).

The lesion tissue analysis by iMAP™ showed a predominance, in percentage terms, of fibrotic and necrotic components, when compared to the others, demonstrating greater vulnerability and instability of these lesions. This finding was similar to that observed at the point of maximum obstruction (MLA), also with a predominance of fibrotic and necrotic components.

Finally, the IVUS morphological analysis showed that the triggering event for thrombosis was coronary plaque rupture in 36% of cases (9/25), while calcium nodules were observed in only 4% of patients (1/25).
DISCUSSION

The present study evaluated 25 patients with STEMI undergoing fibrinolytic therapy referred for coronary angiography and submitted to IVUS of all three epicardial coronary arteries. The main findings were: (1) culprit lesions showed findings consistent with a vulnerable plaque, such as large necrotic core (> 20%) and reduced calcified content; (2) plaque rupture was the underlying event for coronary thrombosis in 36% of cases; and (3) positive arterial remodeling was present in almost all the lesions. The present study provides, for the first time in literature, the description of the morphological characteristics of the plaque responsible for STEMI in patients after the use of fibrinolytic therapy using the iMAP™ tissue characterization technology. A potential advantage of this analysis when compared to previous studies lies in the fact that the IVUS analysis was performed after successful fibrinolytic therapy, minimizing the risk of thrombus interference in image interpretation.

Recent pathological studies have described the evolution stages of the atherosclerotic plaque, from the stable, incipient, and benign state, to more advanced stages of instability, leading to acute coronary events. In the early stages of intimal thickening and intimal xanthoma, the atherosclerotic plaque is constituted mainly of focal accumulation of smooth muscle cells with extracellular matrix rich in proteoglycans, without signs of inflammation. From this stage onwards, atherosclerosis progression occurs with marked inflammatory component, represented mainly by macrophage infiltrates in the lipid core, and a decrease in proteoglycan and collagen in the fibrous cap. In the last phase of the natural course of atherosclerosis, this evolution process results in the formation of the so-called vulnerable plaque, represented by thin-cap fibroatheroma (TCFA), whose diagnostic findings are a large necrotic core (usually ≥ 25% of plaque area) surrounded by a thin fibrous cap (≤ 65 μm) and richly infiltrated by macrophages with reduced amount of smooth muscle cells.

One of the most often studied findings associated with plaque vulnerability is arterial remodeling. Initially described by Glagov et al. in 1987, the positive arterial remodeling has been observed in atherosclerotic plaques responsible for acute coronary events and associated with the increase in CK-MB after PCI, no-reflow phenomena during primary PCI, recurrent ischemia after PCI, major cardiovascular events in patients with unstable angina undergoing any form of revascularization, and intimal hyperplasia after PCI with bare-metal and drug-eluting stents. In the present study, the mean arterial-remodeling index was 1.4 ± 1.0, greater than 1.05, thus characterizing the predominance of positive arterial remodeling and corroborating the aforementioned literature.

In addition to arterial remodeling, other data from the quantitative analysis of the IVUS in grayscale are noteworthy. One is the quantification of the plaque burden, of the atheroma that has been previously shown to be directly associated with distal embolization. Furthermore, in the VH-IVUS in Vulnerable Atherosclerosis (VIVA) study, in which 170 patients with stable angina or acute coronary syndrome with troponin elevation were evaluated through IVUS of three vessels, one of the predictors of major adverse cardiovascular event during a mean follow-up of 625 days was the presence of plaque burden > 70%. Similarly, in the PROSPECT study, which assessed 697 patients with acute coronary syndrome submitted to IVUS of the three arteries, one of the most significant predictors of major cardiovascular adverse event associated with non-culprit lesions during 3 years of follow-up was plaque burden > 70% (the other variables were the presence of TCFA and MLA ≤ 4.0 mm²). In the present analysis, involving only patients with STEMI, the plaque burden found in the culprit lesion was 82.5 ± 7.5%. A recent subanalysis of the PROSPECT study demonstrated that diabetic patients had even more significant findings related to plaque burden when compared to those without diabetes (56.8 vs. 55.0%; p = 0.0006). In the present study, in an exploratory comparison, a similar numerical trend was observed, with the diabetic population showing higher plaque burden (84.4 ± 9.0%) when compared to non-diabetic patients (81.5 ± 6.4%), but without reaching statistical significance (p = 0.77).

In relation to the event triggering the thrombosis and subsequent coronary-artery occlusion, it is well established in the literature that plaque rupture is responsible for most cases (60%). In a recent study using OCT and comparing 80 patients with asymptomatic CAD and NSTEMI, Shimamura et al. demonstrated that symptomatic plaque rupture, i.e., associated with acute ischemic events, showed a higher number of plaques rich in lipids and thrombus, as well as lower MLA of the lesion and MLA at the peak of rupture. Of the 25 culprit lesions analyzed in this study, plaque rupture was identified in 9 (36%) (Figure 2). This percentage, lower than that usually described, may have been a result of the long period of time between the index event and the performance of IVUS in some cases (mean time between index event and IVUS procedure: 7.2 ± 2.1 days). Thus, it is possible that some ruptured plaques scarred, or that the cavity was filled by a thrombus, thus hindering their identification through IVUS. Recently, calcium nodules, also identifiable by IVUS, were associated with acute coronary syndrome in 5 to 10% of cases. The mechanism by which calcium nodules result in coronary thrombosis is still unknown. In the present cohort, only one patient (4%) had a calcium nodule identified by IVUS (Figure 3), similar to the prevalence reported in previous studies.

When using tissue characterization through iMAP™, the characteristic finding of unstable plaques consists in the large amount of necrotic core. In a study by Missel
et al. using virtual histology, a correlation was found between a large necrotic core and reduced calcified component, with increased CK-MB release in patients with acute coronary syndrome. In this study, the volume of the necrotic core was found to be 19.2 ± 18.0 mm³, while the calcified component volume was 1.4 ± 13.9 mm³. Moreover, the authors demonstrated that higher-risk patients (those with CK-MB release and ST segment depression on ECG) presented high necrotic core/dense calcium ratio (NC/DC = 1.83, interquartile range, 1.27 to 2.76) as a risk predictor. In the present study, which differed from the above mentioned study by evaluating patients at higher risk (STEMI) and with different tissue characterization technology, a necrotic core volume of 60.0 ± 65.6 mm³ and calcified component of 6.12 ± 8.34 mm³ were observed, and the NC/DC ratio was 10.6 ± 13.9. This demonstrates that there may be a correlation between a profile of more severe patients, represented by STEMI, and a larger number of necrotic components in culprit lesions.

In a contemporary study comparing patients with AMI with or without ST-segment elevation, the mean percentage of necrotic component was found to be 37% in the STEMI group, while the calcified component was only 3%. In the present study, the mean percentage of the necrotic component was 23.4 ± 9.2%, and the calcified component was 2.17 ± 1.76%. These findings are similar when the full extent of the lesion or only the MLA are analyzed. In the present analysis, at the point of MLA, the mean percentage of necrotic component was 23.6 ± 14.8% and the calcified component was 1.62 ± 1.70%.

Finally, the results demonstrated using iMAP™ in patients with STEMI were similar to those previously published with VH-IVUS®, demonstrating its potential applicability in clinical practice.

**Limitations**

The present study has several limitations; the main ones are related to the low spatial resolution of IVUS, especially when compared to OCT. This can result in difficulty in the identification and quantification of the thrombotic component, which may be mistakenly classified as fibrotic component by iMAP™. However, unlike the OCT, the IVUS has greater wave penetration, allowing for the quantification of arterial remodeling.

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**Figure 2** – Intravascular ultrasound cross-sectional images in three different patients, showing examples of ruptured plaque (arrow) as the event that triggered the coronary thrombosis.

**Figure 3** – Intravascular ultrasound of the right coronary artery showing compatibility with calcium nodule (dense, eruptive mass, with irregular surface, in contact with and/or near the lumen, as indicated by the arrow).
for instance. Additionally, the guidewire artifact, while interfering minimally in image generation, may have been included in this analysis as necrotic component, thus overestimating its quantification. The findings of the present study are reserved only for patients with STEMI after fibrinolytic therapy, thus limiting the external validity of the findings.

CONCLUSIONS

In this study, involving a small number of patients with STEMI, morphological characterization through intravascular ultrasound in grayscale and tissue US with iMAP™ technology, showed that there is a predominance of positive arterial remodeling and necrotic component in the composition of the culprit plaque, which supports the pathophysiology of atherosclerotic disease. The presence of plaque rupture, however, was prevalent in only 40% of cases. Future studies using new invasive imaging technologies with higher spatial resolution are needed to attain a better comprehension of the pathophysiology and better treatment promotion for patients with acute myocardial infarction with ST-segment elevation.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES


