

Factors Associated with Sub-intimal Coronary Artery Dissection in MINOCA Patients with Delayed Washout at Coronary Angiography – Protocol for an Observational, OCT-based Study

Zsolt Parajkó¹, András Mester^{2,3}, Dan Păsăroiu¹, Theodora Benedek^{2,3}, Imre Benedek^{2,3}

¹ Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Târgu Mureș, Romania

² University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

³ Clinic of Cardiology, Emergency Clinical County Hospital, Târgu Mures, Romania

CORRESPONDENCE

András Mester

Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: andras.mester@yahoo.com

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Zsolt Parajkó • Str. 22 Decembrie 1989 nr. 76, 540124
Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail:
parajko.zsolt@gmail.com

Dan Păsăroiu • Str. 22 Decembrie 1989 nr. 76, 540124
Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail:
dan.pasaroiu@yahoo.com

Theodora Benedek • Str. Gheorghe Marinescu nr. 38,
540139 Târgu Mureș, Romania. Tel: +40 265 215 551,
E-mail: theodora.benedek@gmail.com

Imre Benedek • Str. Gheorghe Marinescu nr. 38,
540139 Târgu Mureș, Romania. Tel: +40 265 215 551,
E-mail: imrebenedek@yahoo.com

ABSTRACT

Background: Myocardial infarction (MI) with no obstructive coronary arteries (MINOCA) is a special form of the acute coronary syndrome. The heterogeneous pathophysiology of MINOCA is not well elucidated and includes cardiac and non-cardiac causes. Slow flow phenomenon on coronary angiography can be associated with several possible causes of MINOCA confirmed by optical coherence tomography (OCT). Therefore, the aim of this study is to assess the underlying mechanism of the delayed washout phenomenon on coronary angiography and the potential role of subintimal coronary artery dissection (SD) in the setting of an acute MI. **Methods and design:** This clinical prospective, descriptive research will enroll patients diagnosed with acute MI (STEMI or NSTEMI) identified by coronary angiography, followed by OCT imaging of the coronary arteries at the Emergency Clinical County Hospital of Târgu Mureș, Romania. The enrolled patients will be separated into two groups based on OCT examination, patients with SD and patients with no SD. **Conclusion:** The underlying mechanisms of MINOCA with delayed washout phenomenon on coronary angiography is still poorly understood. Modern invasive imaging techniques are capable to assess the microstructure of the coronary artery wall and are able to offer the much needed information to elucidate the pathophysiological changes which ultimately cause the acute event. The current study offers a new, complex – clinical, invasive and noninvasive imaging, as well as biomarker-based – approach, which may lead to a better understanding and treatment of this pathology.

Keywords: myocardial infarction, no obstructive coronary arteries, optical coherence tomography, subintimal coronary artery dissection

INTRODUCTION

The majority of acute myocardial infarctions (AMI) are caused by an intracoronary thrombus with plaque rupture or erosion, and coronary angiography is the gold standard for the diagnosis of coronary artery disease (CAD).¹ In patients with AMI presenting with ST-segment elevation on the ECG, the immediate coronary angiography shows in almost 90% of the cases an occluded coronary artery. In contrast, in AMI patients with no ST-segment elevation on the ECG, this proportion is only 26% when the coronary angiography is performed in the first 24 hours of symptoms onset. DeWood *et al.* demonstrated that around 10% of patients with AMI had no significant lesions on coronary angiography, and this phenomenon was confirmed by some large AMI registries.^{2,3}

Myocardial infarction with no obstructive coronary arteries (MINOCA) is a special form of acute coronary syndrome (ACS), present in 5–15% of the cases, typically diagnosed under 50 years of age.⁴ MINOCA is characterized by evidence of myocardial injury (elevated cardiac biomarkers) with no significant atherosclerotic coronary plaque (less than 50% on coronary angiography) or flow-limiting obstructions on coronary angiography.⁵ The pathophysiology of MINOCA is heterogenous, including coronary artery spasm, coronary dissection, unstable coronary plaque, Takotsubo cardiomyopathy, myocarditis, microvascular coronary artery spasm, or embolization.^{6,7} Coronary angiography is able to quantify the coronary stenosis, but unable to identify the plaques at risk, due to the lack of information of the plaque structure or the coronary artery wall. Intravascular imaging, such as optical coherence tomography (OCT) or intravascular ultrasound (IVUS), can visualize the microstructure of the coronary wall and plaque and is able to identify atherosclerotic plaque disruption, plaque erosion, coronary artery dissection, or thrombosis which was not identified during coronarography.⁸ OCT can acquire a high-resolution (10–15 μm) image that allows a better understanding of the pathomechanism of MINOCA patients by a punctual assessment of the coronary wall structure.⁹ Another key diagnostic tool for this patient category is represented by cardiac magnetic resonance (CMR), which is capable to demonstrate the myocardial damage (late gadolinium enhancement, myocardial edema, wall motion abnormalities).²

Spontaneous coronary artery dissection (SCAD) is a rare cause of ACS, which occurs typically in young patients with no cardiovascular risk factors, caused by the disruption of the coronary artery wall, resulting in an intramural hematoma. There are three types of SCAD, and intravas-

cular imaging is necessary to confirm the diagnosis. Nearly half of all cases remain unexplained.¹⁰

The coronary slow flow phenomenon can be described as a delayed progression of the injected contrast material or delayed distal vessel opacification in the major epicardial coronary vessels.¹¹ Our previous experience in MINOCA patients detected another phenomenon, which is believed to play a key role in the pathophysiology of these patients. In a variable percentage of MINOCA patients, coronary angiography described a delayed washout of the contrast material, and the OCT examination showed a subintimal dissection (SD) at this level.

The aim of this study is to assess the underlying mechanism of the delayed washout phenomenon on coronary angiography and the potential role of subintimal coronary artery dissection in the setting of an acute myocardial infarction.

STUDY HYPOTHESIS

This study aims to demonstrate the correlation between subintimal dissection in patients with MINOCA and delayed washout, as a variety of the “slow flow” phenomenon. Based on the observation that some of these patients present delayed washout of the contrast material in the coronary arteries, we propose to validate the association between delayed washout of the contrast material and the presence of subintimal dissection on OCT examination. The study will also evaluate clinical and paraclinical characteristics, associations that could influence the aspect and outcome of patients with SD, as well as early and late outcomes of these patients.

MATERIAL AND METHODS

Study population

This clinical prospective, descriptive research will enroll patients diagnosed with AMI (STEMI or NSTEMI) with non-obstructive coronary artery disease identified by coronary angiography, followed by OCT imaging of the coronary arteries, who will be admitted to the Emergency Clinical County Hospital of Târgu Mureș, Romania.

Patients with STEMI are defined as having continuous chest pain longer than 30 minutes, positive cardiac biomarkers (high-sensitive troponin, creatine kinase myocardial band), ST-segment elevation on surface ECG >0.1 mV in two or more contiguous leads or new left bundle-branch block. In patients with NSTEMI, the infarction will be defined as the absence of ST-segment elevation on the ECG

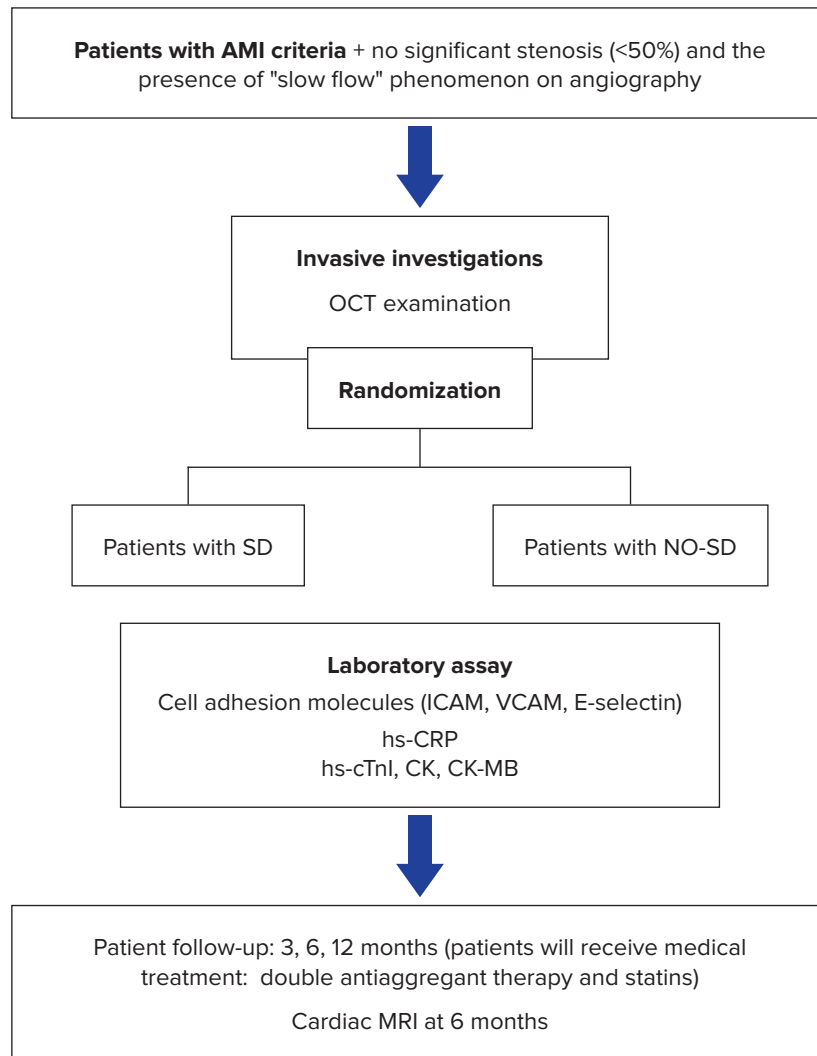


FIGURE 1. Study protocol

with positive cardiac biomarkers and suggestive ischemic symptoms.

Study groups

The enrolled patients will be separated into two groups based on OCT examination, patients with SD and patients with no SD (NO-SD).

Coronary angiography

The coronary angiograms will be performed using the Philips Allura Xper FD20 biplane system. Through radial artery approach, a diagnostic catheter will be introduced into the artery using the Seldinger technique, and by means of a guide wire the catheter will be introduced at the

origin of the coronary artery. The coronary arteries will be visualized by means of fluoroscopy and intracoronary injection of iodine-based contrast material (Iomeron). The obtained angiograms will be analyzed by two experienced interventional cardiologists.

OCT examination

OCT imaging will be acquired using an Abbott imaging system and a Dragon Fly catheter (Abbott), after positioning the catheter. Image acquisition of the region will be performed by automatic pullback from distal to proximal to the selected region. To clear the imaging field from blood flow, continuous injection of contrast or saline will be performed.¹² The obtained images will be stored digitally for further analysis.

All the obtained OCT results will be examined by two experienced investigators. If there will be a significant difference between the two evaluations, a third investigator will be included in the process.

Cardiac MRI

We will perform a cardiac MRI for all enrolled patients 6 months after the hospitalization. CMR will be performed using a 1.5 T Siemens scanner, and images will be acquired during repeated end-expiratory breath holds. All CMR images will be reviewed by two experienced readers. Myocardial edema on the CMR image will be considered as an area of high T2 signal intensity on a segmental basis. Late gadolinium enhancement will be determined for each segment, and only the subendocardial and transmural distribution will be considered as ischemic.

Baseline characteristics

The baseline assessment will include physical examination, family history of CAD, previous MI, postmenopausal status, age, gender, cardiovascular disease, peripheral vascular disease, chronic lung disease, weight, current smoking status, arterial blood pressure, ECG, left ventricular ejection fraction, evaluation of risk factors and comorbidities, serum lipids, creatinine, glomerular filtration rate, creatine kinase, creatine kinase-MB, high-sensitive CRP, high-sensitive cTnI, cell adhesion molecules (ICAM, VCAM, E-selectin), quantitative coronary angiography, in-hospital medication, and in-hospital complications.

The enrolled subjects will receive conservative treatment, without percutaneous coronary angioplasty.

Inclusion and exclusion criteria

All patients will sign an informed consent before enrollment in the study.

Inclusion criteria:

- patients with AMI criteria + no significant stenosis (<50%) on coronary angiography and presenting delayed washout phenomenon.

Exclusion criteria:

- patient's refusal to participate in the study;
- sensitivity to the contrast substance;
- pregnancy.

Statistical analysis

We will perform a descriptive statistical analysis. Continuous and categorical data will be presented as mean $\pm$ SD or median (interquartile range, IQR), and frequencies. Student's t test and the Mann-Whitney U test will be used for the comparison of continuous variables, as appropriate. Fisher's exact test will be performed to find differences in categorical data. The level of significance will be set at $\alpha = 0.05$.

DISCUSSION

There are several possible etiologies that could lead to myocardial infarction in MINOCA patients, most of them not being elucidated so far. In addition, the all-cause mortality of MINOCA patients is high, estimated at 4.7% at one year. At the same time, a group of these patients will remain without an accurate etiologic diagnosis. Therefore, MINOCA patients are less likely to be prescribed medical therapies for a secondary prevention (statins, antithrombotic medication) than patients with evident coronary lesions on coronary angiogram.^{5,13}

Several studies have demonstrated that the majority of myocardial infarction are caused by the rupture of a non-obstructive, non-significant coronary plaque on coronary angiography.¹² OCT examination as a modern invasive investigation can provide a high-resolution longitudinal view and a three-dimensional vessel reconstruction, and can offer detailed information about the vessel wall ultrastructure. Therefore, OCT can characterize plaque ultrastructure and identify the plaques susceptible for rupture.¹²

Because of the lack of information on MINOCA patients with SD in the literature, our study aims to investigate the correlation between subintimal dissection on OCT and the delayed washout phenomenon on coronary angiogram in a group of MINOCA patients. We aim to investigate the clinical evolution of these patients, the effects of dual antiplatelet and plaque stabilization therapy, as well as the assessment of the infarcted area by cardiac MRI.

CONCLUSION

The underlying mechanisms of MINOCA and of the associated delayed washout phenomenon on coronary angiography is still poorly understood. Modern invasive imaging techniques are capable to assess the microstructure of the coronary artery wall and are able to offer the much needed information to elucidate the pathophysiological changes which ultimately cause the acute event. The current study

offers a new, complex – clinical, invasive, and noninvasive imaging, as well as biomarker-based – approach, which might lead to a better understanding and treatment of this pathology.

CONFLICT OF INTEREST

Nothing to declare.

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