

Early spontaneous reperfusion after acute myocardial infarction: true association with plaque phenotype or simple clinical observation?

Michael Joner^{1,2*}, MD; Masaru Seguchi¹, MD; Yu Sato³, MD; Renu Virmani³, MD, FACC

1. Deutsches Herzzentrum München, Technical University of Munich, Munich, Germany; 2. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; 3. CVPPath Institute, Gaithersburg, MD, USA

Acute myocardial infarction (AMI), with its subclassification into non-ST-elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI), remains the most frequent cause of death on a global scale. Early reperfusion of the occluded coronary artery is an established groundbreaking treatment reducing mortality and morbidity in patients suffering AMI¹. Extensive knowledge has been gained from seminal autopsy studies to determine the causes of coronary occlusion, which include plaque rupture, erosion, and calcified nodule²; nevertheless, therapeutic options remain limited to early reperfusion utilising coronary stents. Door-to-balloon time is the most critical factor for salvaging myocardium at risk in the setting of coronary thrombosis; however, a non-negligible fraction of patients presents with early spontaneous reperfusion (ESR), a phenomenon confirmed in major trials evaluating patients presenting with AMI³. Against this background, the most effective treatment for patients with ESR has not been established to date. Intravascular imaging using optical coherence tomography (OCT) has revolutionised the understanding of AMI and, for the first

time, may permit differential treatment strategies based on underlying plaque pathology⁴. Whether certain plaque morphologies are associated with presentation as ESR has remained unknown until the publication by Guo et al⁵.

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In the current issue of EuroIntervention, Guo and colleagues describe the findings in 241 patients presenting with STEMI and undergoing OCT imaging, where 45 of 241 (18.7%) patients had ESR defined as Thrombolysis In Myocardial Infarction (TIMI) 3 flow on the initial angiogram. Patients with ESR were overall younger as compared to STEMI patients without spontaneous reperfusion (control group) (53 [43-62.5] vs 58 [49-66] years, $p=0.035$). To overcome important imbalances in patient characteristics, the ESR group was compared to 45 propensity score-matched patients with STEMI and TIMI 0 flow. The authors report that non-ruptured plaques were significantly more frequent in the ESR versus the control group (62.2% vs 35.6%), while plaque ruptures were significantly more frequent in the control group

*Corresponding author: German Heart Centre Munich, Technical University of Munich, Lazarettstraße 36, 80636 Munich, Germany. E-mail: joner@dhm.mhn.de

(37.8% vs 64.4%). Furthermore, the presence of red thrombus was significantly more frequent in the control group (77.8% vs 44.4%). Therefore, it is not surprising that control patients needed stent implantation more emergently as compared to patients with ESR (91.1% vs 68.9%). In addition, OCT data showed larger minimal lumen area in patients presenting with ESR compared to the control group (2.5 ± 1.7 vs 1.8 ± 1.0 mm²).

The main findings of the current study align with key observations from prior research evaluating differences in plaque morphology among patients presenting with AMI. Non-ruptured plaques (i.e., plaque erosions) tend to show less severe vessel narrowing, less plaque burden, and smaller thrombus volume as compared to plaque rupture^{6,7}, which supports the findings that patients with plaque erosion more likely present with non-STE-ACS⁸. Pathologic studies showed that white thrombus is friable and forms at the site of rupture as well as in erosion, while red thrombus is characteristically associated with slow blood flow, which is usually observed in venous thrombosis; however, propagated thrombus is also red and mostly observed in total occlusions⁹ (**Figure 1**). Erosion lesions have less luminal narrowing compared to plaque rupture, and consequently blood flow is often maintained in plaque erosion, which may provoke distal embolisation of non-occlusive

thrombus. This has been documented in landmark pathology studies investigating intramyocardial thrombi in patients with plaque erosion and rupture (71% vs 42%)¹⁰. Thus, one possible mechanism of ESR is the dissolution and distal embolisation of thrombus in the culprit artery.

Another possible mechanism of ESR is coronary artery vasospasm, which is associated with both plaque erosion and transient STEMI^{11,12}. In contrast to lesions with plaque rupture, where necrotic core occupies large proportions of the intima and media, and causes destruction of structural vessel boundaries, both the internal elastic lamina (IEL) and external elastic lamina (EEL) with sandwiched medial wall remain intact and functional in plaque erosion, suggesting that vasospasm resulting from excessive contraction of medial smooth muscle cells is a possible underlying mechanism¹³. Although only one case (2.2%) showed vasospasm in the current study, the acetylcholine/ergonovine provocation test was not performed in this study and, consequently, the involvement of vasospasm cannot be confirmed. Evaluation of myocardial microvascular obstruction (e.g., myocardial blush grade¹⁴, cardiac magnetic resonance imaging, and coronary flow reserve) may be helpful to determine which aetiology, vasospasm or dissolving thrombus (with or without distal embolisation), contributed to ESR.

Although the authors must be congratulated for performing such timely research applying intravascular imaging in the setting of AMI, several limitations must be discussed to help interpret the relevance of the current study with regard to implications in patients presenting with AMI. While OCT imaging is able to capture relevant plaque morphologies, its specificity to identify the underlying plaque pathology in the presence of coronary thrombus is limited. Therefore, the authors should have considered using glycoprotein IIb/IIIa inhibitors for better visualisation. Also, it has been well documented in a number of OCT studies that thrombus aspiration using export catheters may significantly modify plaque morphology, especially in the setting of AMI and coronary thrombosis¹⁵, which raises concerns as to the appropriate classification of these cases. As residual thrombus burden obscures underlying plaque pathology, interpretation of OCT imaging data may be misleading in the setting of AMI. Furthermore, patients with TIMI 1-2 flow were not included in the current analysis, which leaves room for introduction of selection bias. Patients presenting with TIMI 1-2 flow in the setting of STEMI may exhibit significant residual thrombus burden in the presence of ESR causing slow flow because of downstream thrombus embolisation. Consequently, a large number of patients with different underlying plaque pathologies may have been missed in the current trial. As a matter of fact, presentation of patients with either NSTEMI or STEMI may be determined by patient-specific factors such as individual ischaemia burden, pre-conditioning, collateral development, mismatch of demand versus supply, and preclinical anticoagulation, rather than only plaque pathology. While differential treatment options stratified by underlying plaque pathology may indeed be useful in improving patient outcome as exemplified in the EROSION trial¹⁶, re-classification of patients based on the presence or absence of ESR may hold

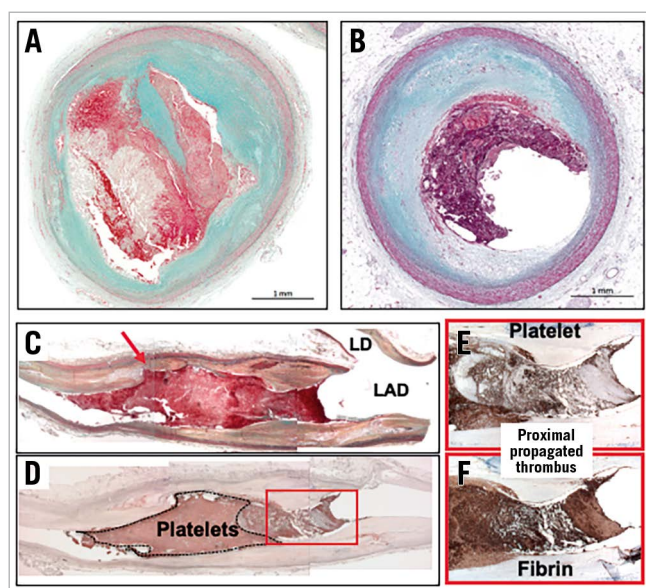


Figure 1. The pathology of plaque rupture and plaque erosion. A) Plaque rupture and (B) erosion histologic sections. Plaque ruptures tend to show more severe luminal stenosis (90% cross-sectional area stenosis), while plaque erosion has less severe narrowing (60% area stenosis). C) Longitudinal section of a left anterior descending artery (LAD) with plaque rupture. The red arrow shows the site of rupture with overlying white thrombus predominantly composed of platelets. Note the proximal thrombus is a propagated red thrombus and shows layered thrombus rich in fibrin and red cells (D-F). A) – C) Movat pentachrome stain, (D) CD61, (F) Fibrin II. Panels C and D are reproduced with permission from Alfonso F and Virmani R⁹.

prognostic value. However, modifying therapeutic options will require additional prospective randomised trials.

Conflict of interest statement

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