Are the high-risk plaques of no-reflow phenomenon equivalent to vulnerable plaques?

Abstract

No-reflow phenomenon during Percutaneous Coronary Intervention (PCI) in Acute Coronary Syndrome (ACS) is associated with some coronary complications such as arrhythmias, heart failure, ventricular remodeling or cardiac death. Therefore, it is very important to predict this phenomenon. The vulnerable plaque, which is almost equivalent to Thin-Cap Fibroatheroma (TCFA), is extrapolated as a predictive factor because the no-reflow phenomenon is caused by the disruption of fibroatheroma (FA). However, these two phenomena have different mechanism of occurrence. In the ACS, it is spontaneous rupture of TCFA. On the other hand, in the no-reflow phenomenon, it is the disruption of fibrous cap by mechanical stimulation such as balloon dilation, subsequent outflow of fragile necrotic core from FA and multiple microvascular obstruction. There are following three major modalities to predict this phenomenon. Intravascular ultrasound can detect whole FA other than calcification but has low resolution to detect fibrous cap. Optical coherence tomography has enough resolution to detect FA but low penetration power to detect whole FA. Cardiac computed tomography angiography can detect whole FA including calcification but has quite low resolution. Therefore, it seems to be necessary to be reconsider whether the theory, that vulnerable plaque is extrapolated as the high-risk plaques of no-reflow phenomenon, is appropriate and which modality is suitable.

Keywords: No-reflow phenomenon ● Cardiac computed tomography angiography ● Very low attenuation plaque ● Intravascular ultrasound ● Attenuated plaque

Abbreviations

ACS: Acute Coronary Syndrome; AP: Attenuated Plaque; CAD: Coronary Artery Disease; CCTA: Coronary Computed Tomography Angiography; FA: Fibroatheroma; IVUS: Intravascular Ultrasound; LAP: Low Attenuation Plaque; MVO: Microvascular Obstruction; NC: Necrotic Core; NIRS: Near-Infrared Spectroscopy; OCT: Optical Coherence Tomography; PCI: Percutaneous Coronary Intervention; TCFA: Thin-Cap fibroatheroma; VH: Virtual Histology; v-LAP: very Low Attenuation Plaque.

Introduction

No-reflow phenomenon during Percutaneous Coronary Intervention (PCI), which is more frequent in Acute Coronary Syndrome (ACS) than stable Coronary Artery Disease (CAD), is associated with some coronary complications [1-4]. No-reflow phenomenon in ACS is pathophysiologically caused by distal atherothrombotic embolism, ischemic injury, reperfusion injury and heightened individual susceptibility of coronary microcirculation to injury [5]. In those, the factor of arteriosclerotic embolism can be predicted and this is consistent with in stable CAD. Although the no-reflow phenomenon is rare in stable CAD lesions and there are few major reports,
it is one of the complications to be noted. It is extremely important to predict this phenomenon because it may sometimes lead to serious complications such as myocardial infarction [1,4]. The vulnerable plaque is extrapolated as a risk factor because the no-reflow phenomenon is caused by the disruption of fibroatheroma (FA), but there seems to be some concerns with this theory. In this review, the risk factors will be reconsidered from the mechanism of occurrence of the no-reflow phenomenon in stable CAD.

**Mechanism of No-reflow Phenomenon and Acute Coronary Syndrome**

The mechanism of arteriosclerotic embolism is that fibrous cap of FA was disrupted by mechanical stimulation such as balloon dilation or stent implantation, and debris of fragile Necrotic Core (NC) flow out to blood flow from FA and cause Multiple Microvascular Obstruction (MVO) [6,7]. This phenomenon is usually transient and reversible, but prolonged ischemia causes myocardial infarction and leading to an unfavorable prognosis. The myocardial damage depends on the degree of MVO, and there are complete no-reflow phenomenon and incomplete no-reflow phenomenon, and the former tends to be more severe MVO and cause myocardial infarction [3,8]. Among FA, Thin-Cap Fibroatheroma (TCFA) is a vulnerable plaque, which is a high-risk plaque that induces thrombus formation by spontaneous rupture of the fibrous cap and causes ACS [9]. Both no-reflow phenomenon and spontaneous ACS are phenomenon that occur with the injury of the fibrous cap and tend to be regarded as equivalent, but there are some big differences here. One is that no-reflow phenomenon is caused by mechanical disruption of fibrous cap by balloon injury, while ACS is caused due to spontaneous rupture of the fibrous cap. Another is that no-reflow phenomenon is mainly caused by MVO due to outflow of the debris of NC, while ACS is mainly caused by thrombus formation and obstruction due to exposure of necrotic core to blood at the site of ruptured plaque [10]. Therefore, no-reflow phenomenon requires the presence of a sufficient amount of fragile and easily flowing out NC, and fibrous cap does not necessarily have to be thin as long as it is mechanically disrupted. On the other hand, ACS requires the presence of thin fibrous cap that causes spontaneous rupture and does not necessarily depend on the quality or burden of atheroma.

**Prediction of No-reflow Phenomenon and Acute Coronary Syndrome by Intravascular Imaging**

The intravascular imaging is commonly used to evaluate these plaque characters (Table 1). Intravascular ultrasound (IVUS) has good echo penetration, so it is possible to observe the whole plaque, which is suitable for evaluating the quality and quantity of plaque, but the resolution is insufficient for evaluating the thickness of fibrous cap. The presence of Attenuated Plaque (AP) on IVUS is a good predictor of no-reflow phenomenon [11,12]. However, since AP does not always reflect only NC, the positive prediction of no-reflow phenomenon by the presence of AP is not high [13]. Therefore, a special IVUS was devised to improve the diagnostic accuracy of NC. Virtual Histology (VH)-IVUS can detect NC that is difficult to distinguish with gray scale IVUS, and near-infrared spectroscopy (NIRS)-IVUS can quantify the lipid property of plaque. These modalities also have predictive performance of no-reflow phenomenon [14-20], but there are no reports that these are superior to gray-scale IVUS, and further verification is needed in the future. Optical Coherence Tomography (OCT) has a higher resolution than IVUS, can measure the thickness of fibrous cap, and can diagnose TCFA. ACS is caused by spontaneous rupture of thin fibrous cap therefor TCFA is considered as a high-risk plaque of future ACS [21,22]. The thickness of fibrous cap is more important than the quality and quantity of atheroma, so evaluation by OCT is extremely rational in ACS prediction. On the other hand, the pathophysiology of no-reflow phenomenon is mainly the mechanical disruption of fibrous cap by balloons and the subsequent outflow of debris from atheroma, therefore, the incidence depends on the presence and amount of lipid-rich NC, which is likely to be an embolic source. Although there is no comparison data with gray-scale IVUS or other modalities, TCFA is also considered as a good predictor of no-reflow phenomenon [23-25]. It is true that the thinner fibrous cap is more likely to be disrupted by mechanical stimulation, so the no-reflow phenomenon may be more likely to occur in TCFA, but in theory, that factor is not essential. Furthermore, OCT is not necessarily rational for predicting the no-reflow phenomenon because OCT cannot sufficiently evaluate the NC itself, which is the essence of the pathophysiological condition of the no-reflow phenomenon. In fact, there are reports that TCFA is not an independent risk factor of the no-reflow phenomenon because OCT cannot sufficiently evaluate the NC itself, which is the essence of the pathophysiological condition of the no-reflow phenomenon. In addition, Low Attenuation Plaque (LAP), which means less than 30 HU in CCTA, is regarded as a high-risk plaque, suggesting the existence of TCFA, and is considered to be associated with future ACS [28,29]. However, CCTA has a big disadvantage of low resolution, and LAP is an evaluation of atheroma, not fibrous cap. Therefore, it is presumed that the reason why LAP is related to ACS is that the prevalence of TCFA is high in LAP, that is, FA with high lipid component. On the other hand, LAP is also related to the no-reflow phenomenon [30]. This indicates that CCTA can detect
the presence of highly lipid plaque tissue, that is, the presence of NC. In addition, it has been reported that the volume is also associated with the no-reflow phenomenon, which matches the pathophysiological condition that the no-reflow phenomenon occurs when a high volume of fragile tissue flows out to the distal part and is embolized. However, it should be verified again that LAP (<30 HU), which has been shown to be related to ACS, can be generally extrapolated as predictive factor of the no-reflow phenomenon. Our study showed that very low attenuation plaque (v-LAP), which means less than 0 HU in CCTA, is useful for predicting the no-reflow phenomenon in stable CAD [4]. This suggests that it is important that NC has extremely high lipid component regardless of the thickness of fibrous cap (Figure 1).

**Discussion and Conclusion**

In summary, the high-risk plaque of spontaneous ACS is TCFA, and OCT is a suitable modality to detect it, and the high-risk plaque of no-reflow phenomenon is FA with severe lipid component, that is NC, and IVUS and CCTA are suitable. However, although these factors are statistically significant, they do not necessarily have a useful impact as clinical judgment materials. In our study, we succeeded in improving the predictive performance by using the combination of IVUS and CCTA, which are useful for detecting high-risk plaques of no-reflow phenomenon, and obtained a clinically useful impact. In conclusion, the suitable modalities for pathophysiological predicting the no-reflow phenomenon are

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**Figure 1:** 87-year-old male with hypertension, dyslipidemia and diabetes mellitus was performed percutaneous coronary intervention for distal right coronary artery (white line in a,b). Coronary Computed Tomography Angiography (CCTA) cross-section image (dotted red circle of c, d) in target lesion (white line in b) had very low attenuation plaque with minimally -59 HU density. Intravascular ultrasound (IVUS) showed typical 360-degree attenuated plaque (e) in target lesion and Optical Coherence Tomography (OCT) showed lipid rich plaque with thick fibrous cap (90-100 μm). CCTA and IVUS showed high risk sign of no-reflow phenomenon but OCT did not show the TCFA. This patient had no-reflow phenomenon after stent implantation in spite of use of filter wire (g) and coronary flow was recovered after administration of nitroprusside (h).
IVUS and CT, which can evaluate atheroma. As the cutoff value for predicting the no-reflow phenomenon in CCTA, v-LAP (<30 HU), which has a higher lipid property than LAP (<30 HU) generally used as high-risk plaque, is suitable. In addition, there is a limit to the predictive performance with a single modality, and more accurate predictive performance can be obtained by evaluating with multi-modality.

**References**


