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Acute Coronary Syndrome from Angioscopic Viewpoint

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1. Introduction

Acute coronary syndrome (ACS), i.e. acute myocardial infarction (MI) and unstable angina, is a life threatening disease, and its treatment after onset has greatly improved; however, we are not satisfied with the long-term outcome of the patients with ACS. Furthermore, we cannot adequately prevent the onset of ACS, although we know many risk factors of ACS, e.g. diabetes mellitus, dyslipidemia, hypertension, obesity, and smoking.

As plaque disruption and thrombosis is known as the major cause of ACS, many investigations to identify vulnerable plaques that are prone to disrupt have been performed but failed to identify high-risk lesions of future ACS event. Major reason for this failure may be that disruption of plaques does not always cause ACS and probably very few percentages of disrupted plaques may actually cause ACS. In order to know adequately about the mechanisms for the onset of ACS and to prevent it effectively, we have to clarify those missing factors that are essential for the disrupted plaques to cause ACS.

In this chapter, we would like to elucidate and discuss on the known and unknown mechanisms for the onset of ACS from the angioscopic point of view.

2. Culprit lesions of acute coronary syndrome

The culprit lesions of ACS^{1, 2} have disrupted yellow plaque and thrombus in >90% of cases. The surface of the yellow plaques is irregular and has the adhesion of white or mixed thrombus. The plaque is defined as ruptured^{3, 4} if the protrusion of yellow necrotic core is observed; otherwise, it is defined as eroded (or non-ruptured). Thrombus² directly adhering to the plaque surface is usually white, and it becomes reddish when blood flow is disturbed by massive white thrombus and the fibrin network captures many red blood cells in it, i.e. mixed or red thrombus. In the same way, thrombus becomes yellow when the fibrin network of white thrombus contains protruded necrotic core, i.e. yellow thrombus.

After reperfusion therapy¹ or coronary intervention with balloon or stent, the culprit lesion of ACS gradually loses its thrombogenicity. In the patients with acute MI, 64% of patients still have thrombus at their culprit lesion at one month after reperfusion, while it becomes as low as 5% at 6 months. The prevalence of thrombus at one month is higher in the patients with diabetic patients than in the non-diabetic patients (78% vs. 45%), suggesting that the healing process of disrupted plaque is deteriorated in the diabetic patients.

As >90% of ACS patients have disrupted yellow plaque in their culprit lesions, both ruptured and eroded plaques, which are detected in about 70% and 30% of cases, respectively, by pathologic studies, should be detected as yellow plaques⁵. We have recently revealed⁴ that both ruptured and non-ruptured yellow plaques detected by angioscopy have similar atherosclerotic characteristics including thin-cap fibroatheroma (TCFA) when examined by VH-IVUS (Figure 1).

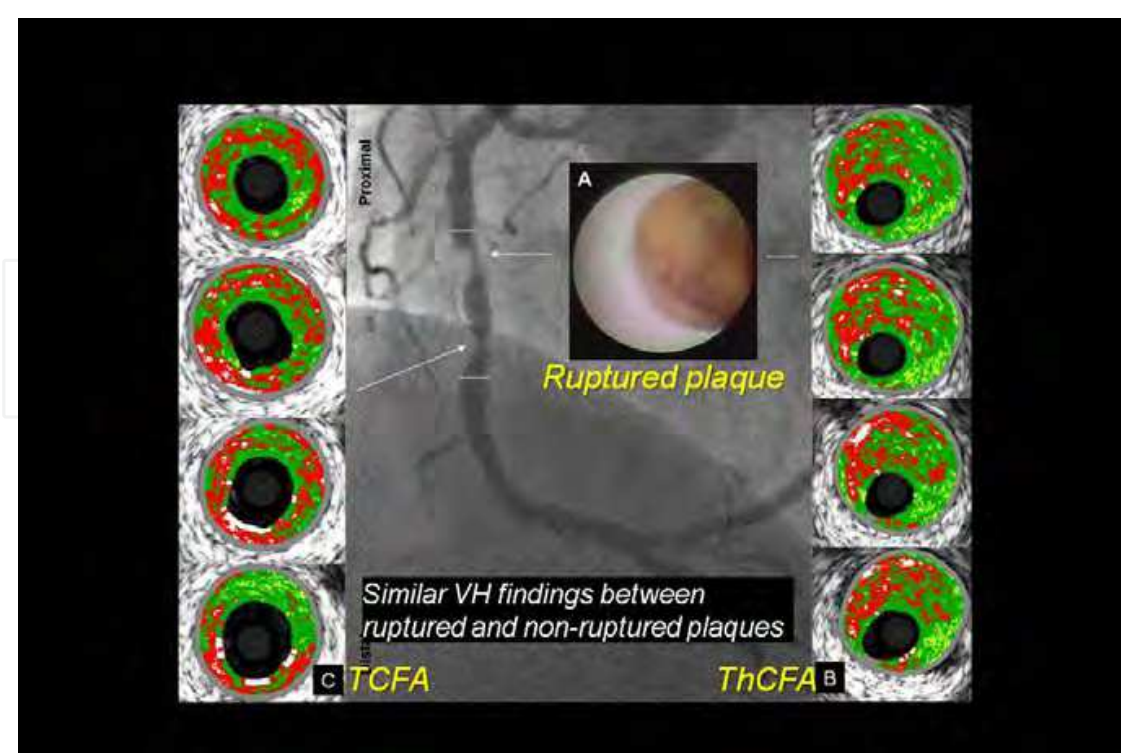
3. Detection of vulnerable plaques by angioscopy

Because the majority of ACS culprit lesions have disrupted yellow plaques, yellow plaques should be the vulnerable plaques that are prone to disrupt. Yellow plaques are classified into 3 grades⁶ according to its yellow color intensity: grade 1, slight yellow; grade 2, yellow; and grade 3, intensive yellow (Figure 2). We have revealed that yellow plaques of higher yellow color grade have the higher incidence of having thrombus on it, i.e. higher incidence of disruption, suggesting that those plaques are more vulnerable. Furthermore, the yellow plaques of higher yellow color grade have the higher incidence of positive remodeling and the thinner fibrous cap⁷, which supports the idea that those yellow plaques are more vulnerable.

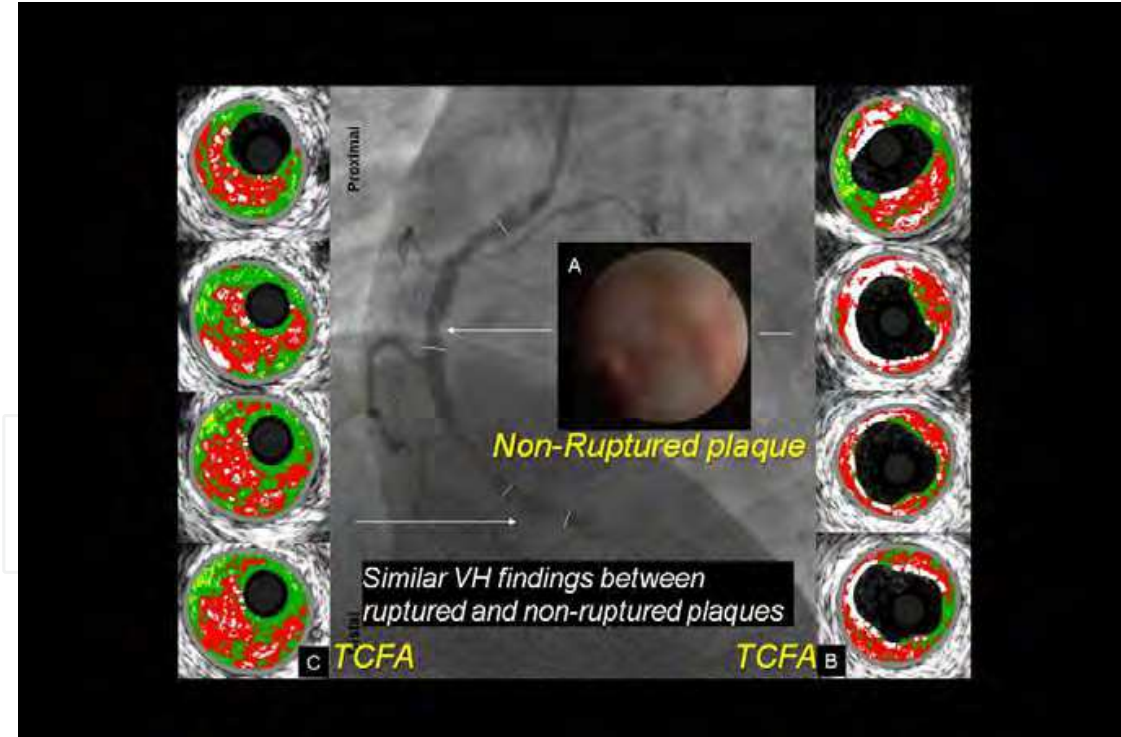
Although we have experienced >5,000 cases of angioscopic examinations and found huge number of yellow plaques, it was quite rare that the plaque caused ACS shortly after the examination. However, the prospective follow-up of the angioscopically examined patients have revealed⁸ that patients with more than 2 yellow plaques per vessel have the higher incidence of ACS event than the patients with 1 or no yellow plaque per vessel during the mean follow-up interval of 4.8 years. Formation of yellow plaques occurs equally in the culprit and non-culprit vessels of MI as it is regarded pan-coronary process of atherosclerosis progression⁹ (Figure 3). Therefore, the patients who have many yellow plaques in their coronary arteries are regarded as vulnerable patients. Judging from the results of this and other angioscopic studies, the probability of each yellow plaque to disrupt and to cause ACS may be estimated⁵ as 25%/year and 0.3-1%/year, respectively.

4. Silent plaque disruption and missing factors for the onset of acute coronary syndrome

Disrupted yellow plaques are sometimes found in the asymptomatic patients or in the non-culprit segments of ACS patients, which are called silent plaque disruptions^{10, 11}. Factors required for the disrupted plaques to cause symptomatic ACS are unknown, which is an important but unsolved issue for clarifying the mechanism of ACS onset. However, thrombogenic potential of blood, thrombogenic potential of necrotic core that would be exposed to blood by plaque rupture, underlying stenosis or stenosis caused by the protrusion of necrotic core at the site of plaque rupture, and/or vasoconstriction may play a role for the onset of ACS after the disruption of vulnerable plaques¹². Investigations to clarify the contributions of these or other factors have not been reported adequately. Although the thrombogenicity of blood, i.e. vulnerable blood, has been regarded one of important factors, reports on this issue are limited. We have recently reported¹³ that originally defined parameter of blood thrombogenicity (blood vulnerability index) is significantly and extremely higher in the patients with acute MI than in the patients with stable coronary heart disease.



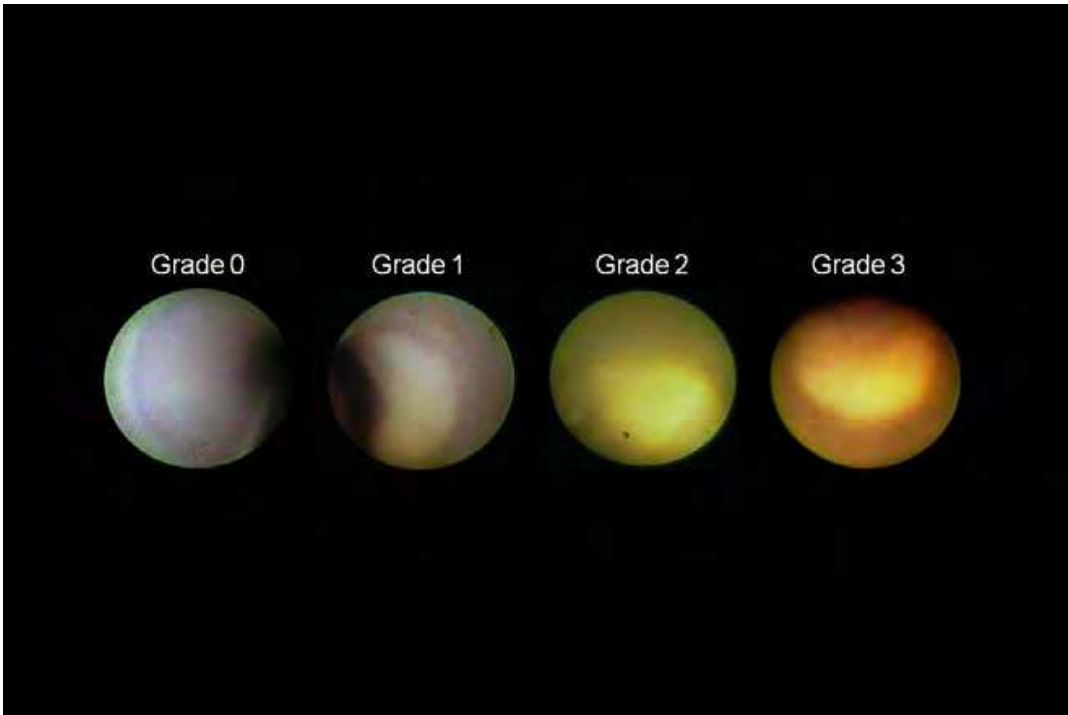
A



B

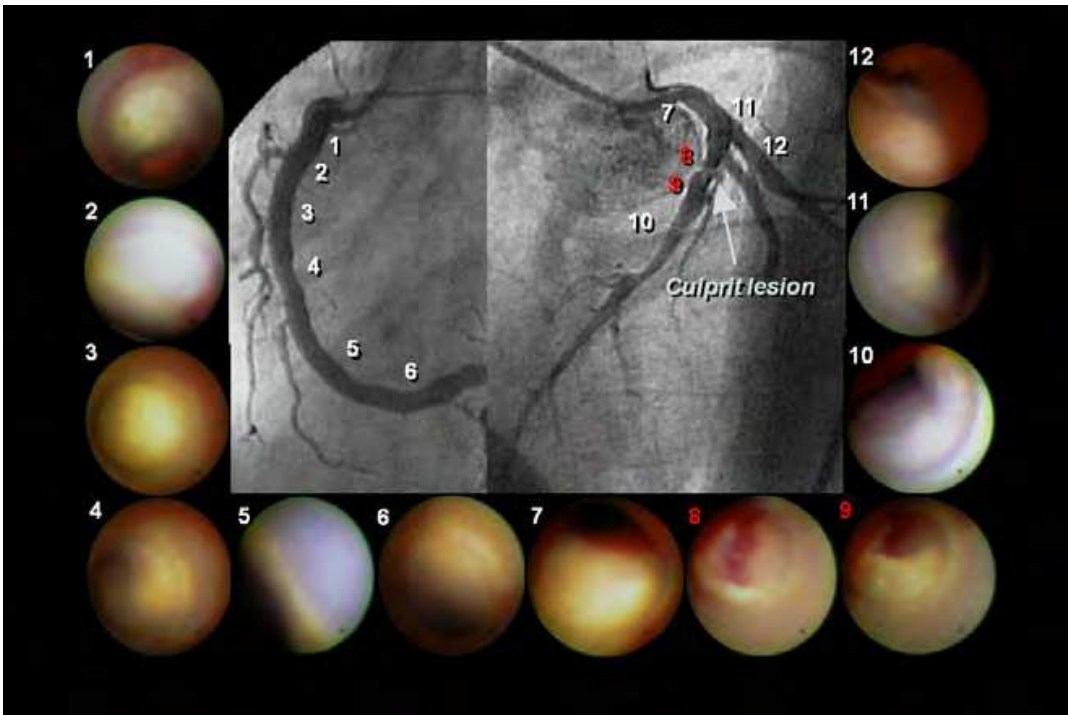
Most of ACS culprit lesions have disrupted yellow plaque, which is classified into ruptured or non-ruptured yellow plaque by angioscopy. Non-rupture would include small rupture and erosion of pathologic classifications. Both of ruptured and non-ruptured yellow plaques have similar atherosclerotic characteristics by VH-IVUS. (From reference #4)

Fig. 1. Culprit lesions of ACS



Yellow plaques are classified into 3 grades according to these standard colors: grade 1, slight yellow; grade 2, yellow; and grade 3, intensive yellow. Grade 0 indicates white color. Yellow plaques of the higher grade are regarded more vulnerable as they have higher frequency of plaque disruption. (From reference #6)

Fig. 2. Classification of yellow plaques according to their color



The yellow plaque at the culprit lesion is disrupted having thrombus on it. There are multiple yellow plaques in the non-culprit segments both in culprit and non-culprit vessels. The formation of yellow plaques is regarded pan-coronary process. (From reference #9)

Fig. 3. Coronary arteries in acute MI patients

5. Stent thrombosis and atherosclerosis

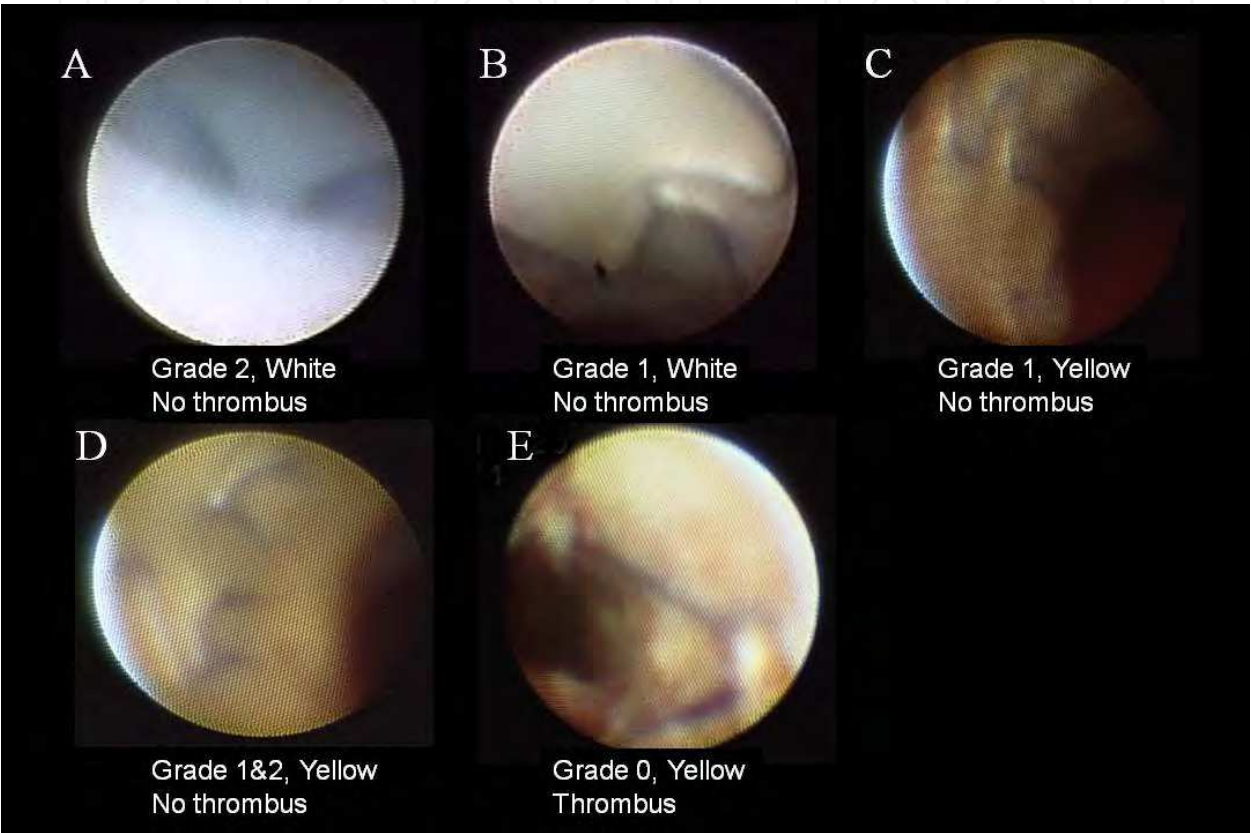
Bare metal stent (BMS) is gradually covered by neointima and the coverage is usually completed by 3-6 months after implantation¹⁴. Neointima at 3-6 months is generally white and its surface is smooth; and stent is not seen buried under neointima. Yellow plaques under stent are also covered and buried under the neointima. Neointima becomes thinner and rather transparent at about 3 years again¹⁵, although its surface is smooth and thrombus is not detected on its surface. Therefore, the implantation of BMS stabilizes the vulnerable plaques by the formation of thick fibrous neointima over the plaques, which is called sealing effect of BMS. It takes about 10 years for the formation of vulnerable plaques in the fibrous healthy neointima over BMS leading to its disruption and onset of ACS. Very late stent thrombosis (VLST) in the BMS is indeed quite rare especially within a few years after implantation.

On the other hand, neointima formation over drug-eluting stent (DES) is generally very poor^{16, 17}; and stent is usually seen through very thin neointima or partly uncovered in the majority of cases (Figure 4). The incidence of thrombus at the stented lesion is significantly higher in the 1st generation DES (Cypher and Taxus DES) than in BMS. Furthermore, the stented lesions become yellow after Cypher DES implantation^{17, 18}, suggesting that DES promotes progression of atherosclerosis (Figure 5). However, Endeavor DES is known to have larger late loss but have as good neointima formation as observed in BMS; and thrombus is rarely detected in this DES. Although the angioscopic findings on the newer DES has not been fully clarified, Xience V and Nobori DES appear to have as thin neointima as 1st generation DES but have lower incidence of thrombus than 1st generation DES.

The mechanisms for the onset of VLST have not been fully clarified; however, uncovered stent strut, uncovered disrupted plaque, new disruption of uncovered yellow plaque, and new disruption of newly formed yellow plaque may be the probable thrombogenic sources¹⁹ that can cause VLST. After BMS and Endeavor DES implantation, thick and white fibrous neointima completely covers stent and plaques; and the incidence of VLST is known to be very low. However, as the neointima over Xience V and Nobori DES is thin and may not reduce the risk of new yellow plaque disruption, we should be careful about the incidence of VLST after the implantation of these stents. From the angioscopic point of view, Endeavor DES would be the safest DES among the DES examined by angioscopy. BMS that has not developed restenosis would be the best condition that should be achieved by newly developed DES in the future, i.e. complete coverage by rather thick white smooth neointima.

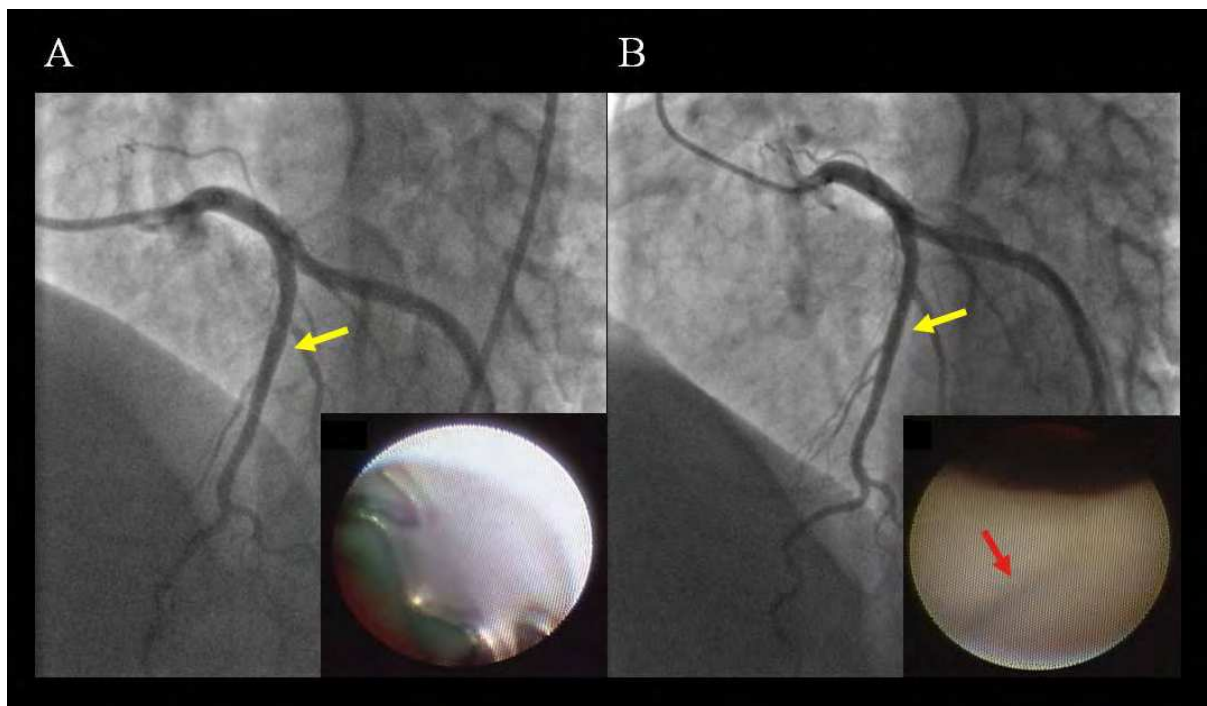
6. Regression of vulnerable plaques by statin treatment

Statin treatment is known to reduce both plaque volume evaluated by IVUS and yellow color evaluated by angioscopy^{20, 21}. However, it has not been clarified which of plaque volume and plaque color is more directly associated with the risk of plaque disruption or the risk of ACS. According to the results of TWINS study²⁰, yellow color of plaques regressed significantly from baseline to 28 weeks but did not change thereafter until 80 weeks under atorvastatin treatment; on the other hand, plaque volume decreased gradually but significantly from baseline to 28 weeks and to 80 weeks. Early effect of statin treatment to reduce the risk of ACS might be reflected by the early regression of yellow color.



Various conditions of neointima coverage are observed at 1-year follow-up after DES implantation. A: White and good (grade 2) neointima coverage is observed without thrombus formation. B: Thin (grade 1) neointima coverage is observed without thrombus formation; and the vessel wall under stent is white. C: Thin (grade 1) neointima coverage is observed without thrombus formation; however, the vessel wall under stent is yellow. D: Neointima coverage grade is partly 1 and partly 2. Both of vessel wall under stent and neointima over stent are yellow. Yellow atherosclerotic neointima is often observed after Cypher stent implantation but never after BMS implantation. E: Uncovered stent strut is observed on the yellow disrupted plaque. Thrombus is detected on the yellow plaque and on the stent strut. (From reference #17)

Fig. 4. Angioscopic appearance of DES implanted lesions at follow-up



Cypher stent was implanted on a white vessel wall (A). However, at 1-year follow-up (B), neointima that covered the stent was yellow, suggesting the early formation of atherosclerosis in the neointima. Yellow arrow indicates where the stent was implanted. Red arrow indicates the stent strut. (From reference #17)

Fig. 5. Rapid progression of atherosclerosis in the neointima after DES implantation

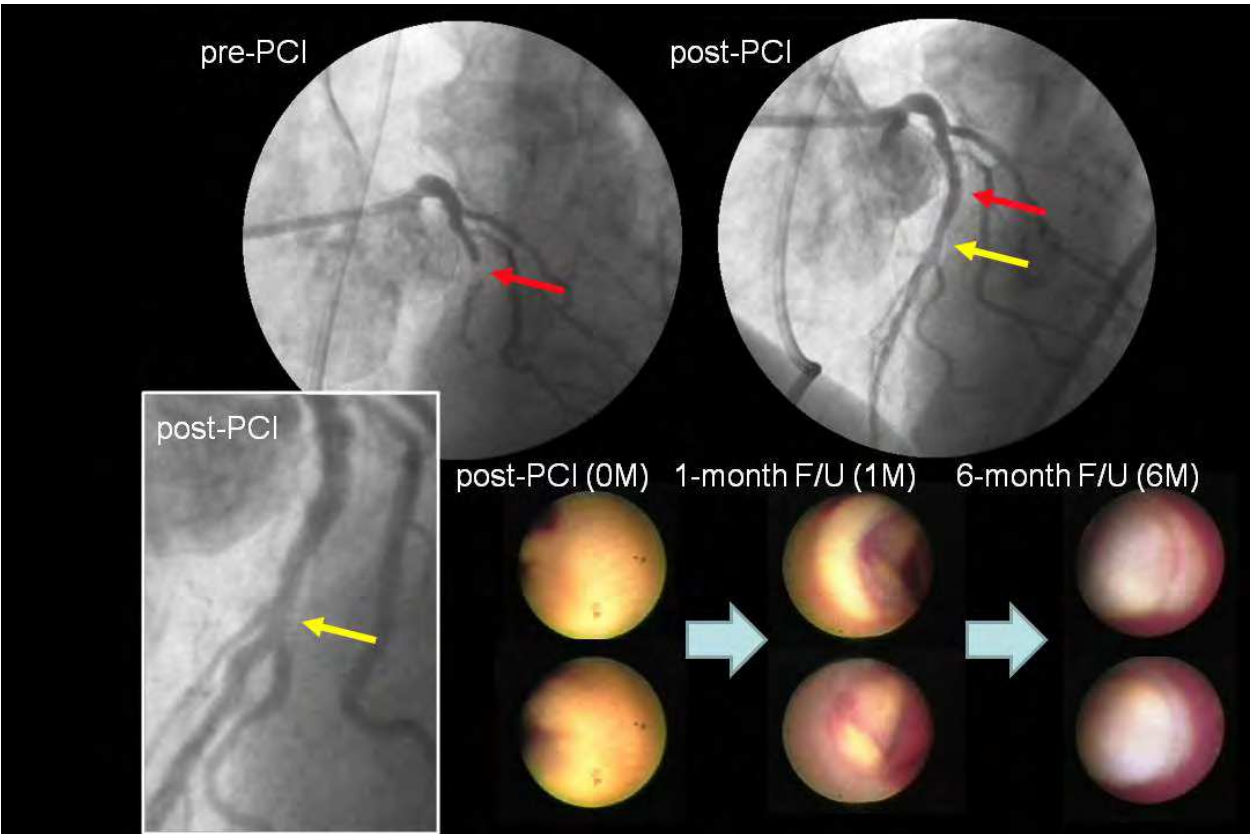
7. Investigation of missing factors and hypothesis on the mechanisms of ACS onset

According to the results of PROSPECT trial²², in addition to the presence of TCFA, large plaque burden and narrow minimum lumen area were the risk of future coronary event. Although ACS is known to occur from angiographically mild to moderate stenosis, findings in PROSPECT trial may be consistent with this. Underlying stenosis that can be detected only by IVUS and large plaque burden that may cause abrupt progression of stenosis on rupturing may be important for the onset of ACS. Presence of relatively severe stenosis might be essential for the formation of occlusive thrombus at the disrupted plaque. The larger necrotic core might possibly have the higher thrombogenicity; however, there are very few investigations on the difference of necrotic core thrombogenicity. Vasoconstriction has been speculated to play an important role, although no investigation has ever demonstrated its contribution to the onset of ACS. We have reported¹³ that blood thrombogenicity (blood vulnerability index) is significantly and extremely higher in the patients with acute MI than in the patients with stable coronary heart disease. This high blood thrombogenicity might be either a cause or a result of ACS. However, none of stable coronary heart disease patients including those who had silent plaque disruption had that high blood vulnerability index. Therefore, silent plaque disruption will never result in the extreme increase of blood vulnerability index. Furthermore, ACS patients who were taking dual antiplatelet therapy also had high blood vulnerability index, suggesting that dual antiplatelet therapy was not adequately effective to prevent this increase of blood vulnerability index and thus failed to prevent the onset of ACS.

Process of positive feedback and cyclic flow variation might play an important role for the onset of ACS: i.e. a plaque disruption causes thrombus formation that increases thrombogenicity of blood and more thrombus would be formed; if the occlusive thrombus is formed, it may cause cyclic flow variation depending on the severity of stenosis and the amount of thrombus formed, which may further increase the thrombogenicity of blood; and the thrombus may finally occlude the artery. In this process, the amount of thrombus must be influenced by the thrombogenicity of both blood and exposed necrotic core; and the severity of stenosis would be determined by the underlying stenosis, the stenosis increased by the protrusion of necrotic core on plaque rupturing, and the stenosis caused by vasoconstriction that may be induced by thrombus formation.

It is well known that silent plaque disruption is frequently detected in the patients with ACS²³, suggesting that plaque disruption and/or thrombogenesis is generally promoted in ACS patients (Figure 6). Blood thrombogenicity would be increased in ACS patients as mentioned above. Another idea is that coronary vessels generally have inflammation in ACS patients, i.e. coronary flu syndrome, which might possibly be the initiation mechanism of ACS.

These mechanisms should be examined more intensively by clinical and basic investigations; and blocking some of these steps may be able to prevent the onset of ACS.



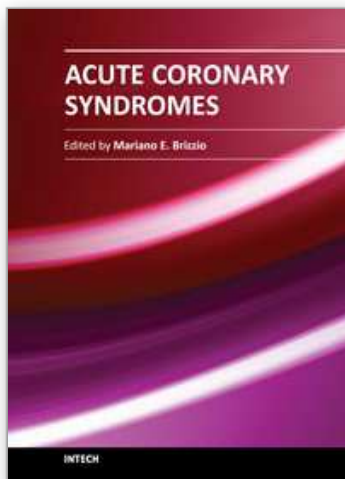
In a patient with acute MI (culprit lesion at red arrow), a silent plaque disruption (at yellow arrow) was detected. The healing process of silently disrupted yellow plaque was observed as the regression of yellow color intensity and the disappearance of thrombus by 6 months. (From reference #23)

Fig. 6. Silent plaque disruption and its healing in the non-culprit segments in acute MI patients

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This book has been written with the intention of providing an up-to-the minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a "daily bases". It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

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