Chapter 10
Acute Coronary Syndrome vs. Stable Angina Pectoris: Angioscopic Point of View

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Abstract Coronary artery disease (CAD) has two broad categories of clinical syndromes such as acute coronary syndrome (ACS) and stable angina pectoris (SAP). ACS is well recognized to be a significant contributor to both morbidity and mortality in worldwide, and it is pivotal to understand the mechanisms of ACS in order to predict the occurrence of ACS using a combination of novel imaging modalities and noninvasive biomarkers. Currently, several imaging modalities are investigated to detect vulnerable plaques. In particular, coronary angioscopy can evaluate the luminal surface by direct visualization and plays an important role to elucidate morphological interaction between the plaque and thrombus. In this review, we will focus on the differences in angioscopic findings of plaque morphology, such as plaque color and presence of thrombus in patients with ACS and those with SAP.

Keywords Acute coronary syndrome • Stable angina pectoris • Vulnerable plaque • Plaque rupture • Erosion • Plaque color • Thrombus

10.1 Introduction

The prognosis of patients with stable angina pectoris (SAP) is generally good with an incidence of death or nonfatal myocardial infarction (MI) not exceeding 2 % per year [1]. On the other hand, patients with an acute coronary syndrome (ACS) without ST elevation have much worse prognosis with a 10–15 % incidence of death or nonfatal MI within 1 year after admission [2]. Despite a similar anatomical background, there are different pathophysiologic mechanisms between ACS and SAP. ACS is a clinical syndrome characterized by acute change of ischemic symptom. Plaque disruption, platelet activation, and flow-limiting thrombus formation are recognized as key events in the pathogenesis of ACS [3]. In contrast, such changes do not occur in SAP patients. Because angiography can only provide

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a two-dimensional silhouette of the lumen, it is not suitable to identify plaque vulnerability. Therefore, the challenge for the future is to identify vulnerable plaques prone to disrupt before thrombotic complications occur. There are several imaging techniques that could detect local plaque vulnerability leading to an ACS [4]. Of these, only coronary angioscopy can provide detailed information of the luminal surface of a plaque, such as color, thrombus, or disruption. In the present review, we will focus on the angioscopic characteristics of ACS and SAP.

10.2 Characteristics of the Current Intravascular Imaging Modalities

Intravascular imaging devices can show detailed plaque composition that cannot be detected by angiography, and these findings are thought to play an important role in order to predict future cardiac events such as ACS. Each imaging device has its own advantages and disadvantages (Table 10.1) [4, 5].

Several studies have demonstrated differences in plaque components between ACS and SAP patients using different intravascular imaging devices. When comparing ACS and SAP using intravascular ultrasound imaging (IVUS), patients with ACS have more frequently positive remodeling and noncalcified attenuated plaque in the culprit lesion than in those with SAP [6, 7]. According to optical coherence tomography (OCT) findings, thrombi and plaque disruption and thin-cap fibroatheroma are frequently found within the culprit lesions of ACS patients [8]. In addition to these findings, several studies evaluated surface morphology between lesions in ACS and SAP patients using angioscopy.

Table 10.1 Advantages and disadvantages of the different intravascular imaging devices

Devices	Advantages	Disadvantages
Angioscopy	Good surface visualization (color, thrombus)	Effect of blood noise
	High resolution (10–50 μm)	Unable to visualize the entire circumference
	Forward viewing	Unable to observe deep tissue
		Difficult to quantify
IVUS	Quantification of plaque, wall thickness, and lumen size	Unable to distinguish thrombi from plaque components
	Tissue characterization	Low resolution (80–120 μm)
	Remodeling assessment	
OCT	High resolution (10–20 μm)	Effect of blood noise
	Small-diameter catheters	Limited depth of penetration (1.5–2 mm)
	Fast data acquisition	
	Can detect endothelization, thin cap, and lipid pool	

The angioscopy system is classified into an occlusion balloon type (monorail on guidewire system) or a non-occlusion one (bare fiber system). Angioscopic examination using balloon occlusion type (FULLVIEW NEO, FiberTech Co., Chiba, Japan) is performed while coronary blood flow was interrupted by inflating the balloon, and blood is cleared away by the injection of 5–10 ml of lactated Ringer's or 3 % dextran solution. On the other hand, the non-balloon occlusion type (FiberTech Co.) is designed for pullback visualization without balloon occlusion, while flushing with 3 % dextran solution through a flushing catheter.

10.3 Angioscopic Findings

10.3.1 Characteristics of Plaque Morphology

From a pathological point of view, atherosclerotic plaques can be classified into two components. These include an atheromatous and a fibrous plaque, which are generally consistent with vulnerable and stable plaques, respectively [9]. Of course, ACS patients have more plaques with characteristics of vulnerability, leading to plaque disruption and thrombosis [3]. From an angioscopic findings, vulnerable plaques show plaque disruption which is defined as having high-yellow color intensity plaque and a mural thrombus formation. Plaque disruption is further classified into two types of plaque morphology such as plaque rupture and erosion [10, 11].

Angioscopically, plaque rupture is defined as the plaque showing dissection, fissuring, ulceration, or confirmed atheroma contents [11]. Plaque erosion is defined as eroded if it shows only reddening and erosion with no evidence of dissection, cleft, or depressed ulceration [11]. On the other hand, plaques in SAP patients usually have a smooth surface with white or light yellow color and no thrombi [12]. Representative image of plaque rupture, erosion, and stable plaque is shown in Fig. 10.1.

10.3.2 Grading of Plaque Color

Plaque color differs in patients with ACS and SAP. According to the relationship between the color of the plaque and its histopathological features, deep-yellow and yellow-red lesions represent either atheroma (53 %) or degenerated plaque (42 %), whereas pate-yellow or gray-yellow lesions were predominantly with degenerated plaque (64 %) and, to a lesser extent, with fibrous plaque (14 %) or atheroma (14 %) [13]. In SAP patients, both types of lesions, smooth gray-white and yellow lesions, were found to be equally distributed [13]. On the other hand, in ACS patients, the yellow color and plaque rupture were frequently found [13]. A previous

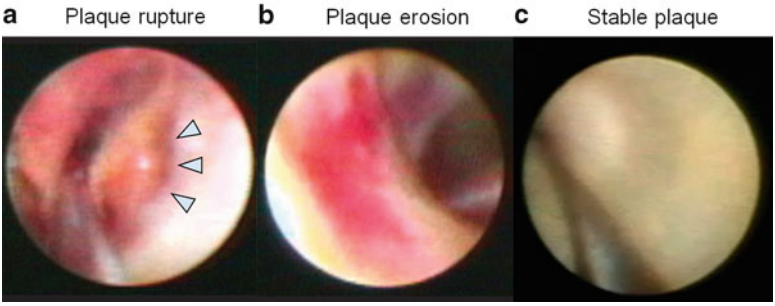

Fig. 10.1 Representative image of plaque morphology by angioscopy. (**a**) Angioscopic image showed a cleft with intensive yellow plaque and a mixed thrombus. (**b**) Angioscopic image showed erosion on a light-yellow plaque with no evidence of dissection. (**c**) Angioscopic image showed a smooth surface of light-yellow plaque without thrombus

angioscopic study reported that the number of yellow plaques in a coronary artery is an independent future risk of cardiovascular events and that patients with multiple yellow plaques per vessel have 2.2-fold higher risk of suffering ACS than patients with no or a single yellow plaque per vessel [14].

Recently, yellow plaques were further classified according to yellow color intensity: grade 0, white; grade1, light yellow; grade2, yellow; and grade3, intensive yellow (Fig. 10.2) [15]. Several studies reported that yellow color intensity was associated with plaque vulnerability. Uchida et al. reported that ACS events occurred in 3.3 % of white plaque, 7.6 % of non-glistening yellow plaque, and 68.4 % of glistening yellow plaque [16]. Ueda et al. demonstrated that yellow plaques with higher color grade have a higher incidence of thrombus on the plaque (Fig. 10.3) [15]. Furthermore, Kubo et al. revealed that there was a significant negative correlation between yellow color intensity and fibrous cap thickness evaluated by angioscopy and OCT (Fig. 10.4) [17]. Therefore, it is considered that plaque color grade assessed by angioscopy showed a good correlation with plaque stability or instability. Based on these findings, the relationship between plaque color changes and effect of statin therapy was evaluated using angioscopy. The TWINS (evaluaTion With simultaneous angIoscopy and iNtravascular ultraSound) study and TOGETHAR trial demonstrated that reduction of yellow grade detected by angioscopy occurred independently of volumetric plaque change by statin therapy [18, 19].

The major limitation of angioscopic evaluation is that color grading is often different from each observer. Therefore, in order to avoid this problem, Okada and Ishibashi, et al. have attempted a quantitative assessment color analysis using colorimetry apparatus [20, 21].

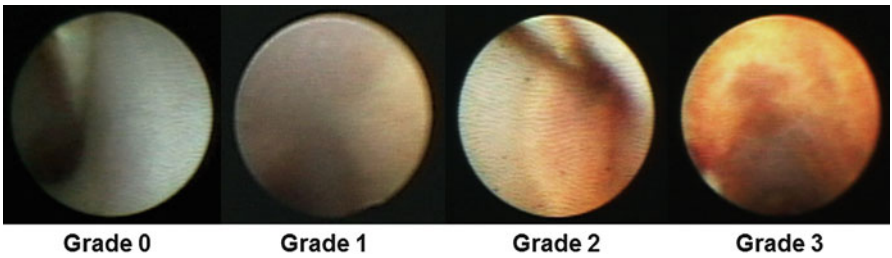

Fig. 10.2 Angioscopic color grading of plaque. Grade 0, *white*; grade 1, *light yellow*; grade 2, *yellow*; grade 3, *intensive yellow*

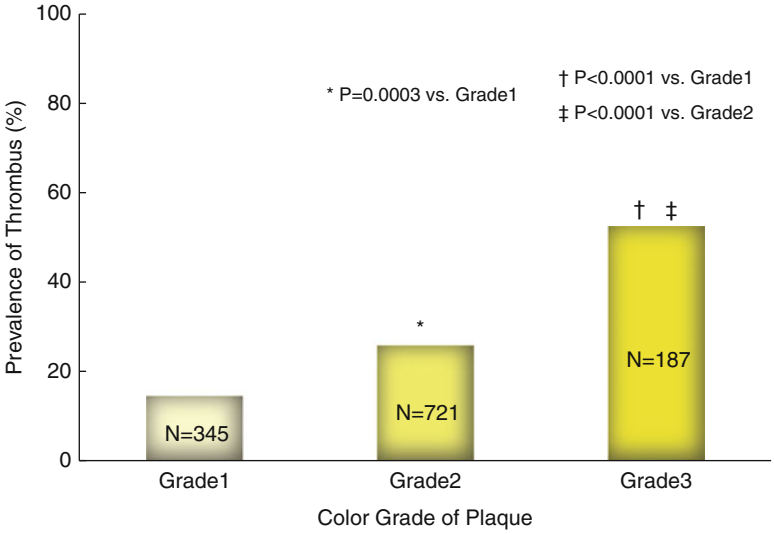

Fig. 10.3 Relation between color grade of plaque and prevalence of thrombus. *Yellow color* intensity of plaque is associated with the prevalence of thrombus. (Reproduced with permission from Ref. Ueda et al. [15])

10.3.3 Characteristics of Thrombus

Angioscopy is superior to other imaging modalities for detecting thrombus. In angioscopic image, thrombus is usually adhering to the intima or protruding into the lumen, which persists even after flushing with lactated Ringer's or dextran solution. Thrombi were further classified by color such as solid red, mixed red, and white mass, although the relationship between thrombus color and clinical outcome is uncertain [22–24]. A white thrombus was defined as a shaggy, irregular, and cotton-wool-like mass in which white area occupies more than two thirds. The majority of red thrombus was solid and globular, and red area occupies more than two thirds.

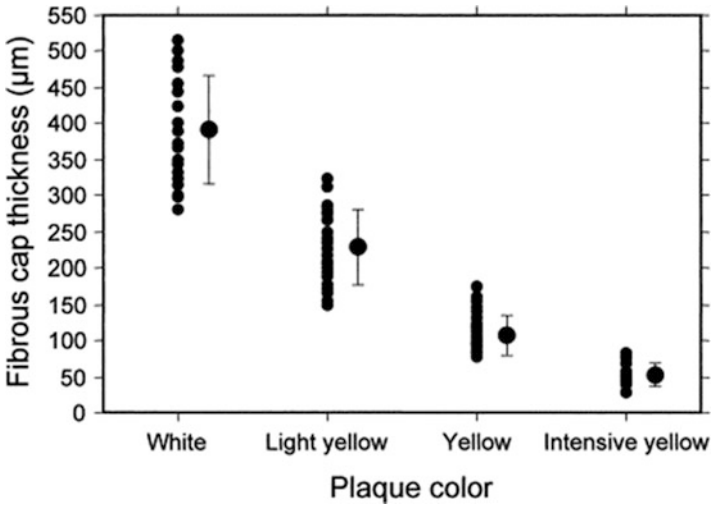

Fig. 10.4 Relation between color grade of plaque and fibrous cap thickness by optical coherence of tomography. There was a significant negative correlation between yellow color intensity and fibrous cap thickness ($P < 0.0001$). (Reproduced with permission from Ref. Kubo et al. [17])

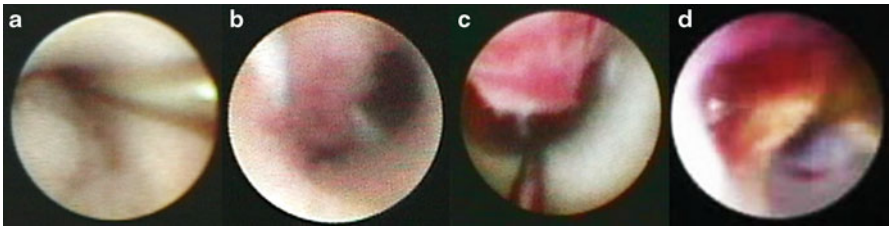

Fig. 10.5 Representative image of thrombus by angioscopy. (**a**) White thrombus, (**b**) mixed thrombus (white > red thrombus), (**c**) mixed thrombus (red > white thrombus), (**d**) red thrombus

Mixed thrombus was defined as white and red in a mosaic pattern (one third to two thirds are red) [25]. Representative images of thrombus are shown in Fig. 10.5.

A previous study reported that plaque rupture and thrombus were present in 17 % of SAP and 68 % of ACS evaluated by angioscopy, respectively [26]. However, the presence of thrombus detected by angioscopy do not necessary lead to the clinical manifestation of an ACS, although the prevalence of thrombus is higher in patients with ACS.

10.4 Summary

The prevalence of cardiovascular disease is growing rapidly, leading to an increasing incidence of ACS. Therefore, it is important to predict individuals at risk of plaque rupture and developing an ACS using novel modalities. Currently, several invasive and noninvasive modalities are under investigation. Coronary angioscopy gives us both plaque characteristics and the presence of thrombus as direct visualized information, which are helpful to assess the effect of preventive treatment and to make a treatment strategy of PCI such as distal protection. However, there are several limitations to perform coronary angioscopy such as the need for an invasive procedure, limited visual field, and induction of myocardial ischemia during the procedure.

Based on clinical findings using invasive imaging modalities such as angioscopy and IVUS, noninvasive screening tests for preventing ACS are developing including MRI detection of plaque inflammation, contrast-enhanced CT for assessment of noncalcified plaques, and positron emission tomography-CT for combined assessment of plaque burden and activity of the inflamed plaques. In the near future, further investigation will develop novel diagnostic procedure for plaque morphology both invasively and noninvasively.

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