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Pathological Characterization of Yellow and White Plaques Under Angioscopy

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Abstract. Recently it has been reported that the lipid core area and the fibrous cap thickness cannot be deduced from the stenotic ratio. However, there is no comparative study between yellow and white plaques. This study assessed the precise characterization of yellow and white plaques using angioscopy. We observed 198 segments of coronary from autopsy artery using angioscopy, then 46 yellow plaque lesions and 61 white plaque lesions of atheroma were excised and prepared for pathological examination. The stenotic ratio, the plaque area (PA), the lipid core size as a percentage of total vessel area (%C), and the minimum fibrous cap thickness (FCt) were measured and compared between yellow and white plaque groups. In this study, the stenotic ratio and the PA were significantly larger in the white plaque group ($p < .001$). The FCt was significantly thinner in the yellow plaque group (58 ± 18 μm vs. 648 ± 356 μm $p < .0001$). There was no correlation between the stenotic ratio and the %C in the whole cases ($r = .22$). Although it was the same in the white plaque group ($r = .13$), significant correlation between them was shown in the yellow plaque group ($r = .64$). No significant correlation was observed between the stenotic ratio and the FCt in each plaque group. We concluded that a yellow plaque with moderate stenosis could be diagnosed as a vulnerable plaque by the combination of coronary angiography and angioscopy.

Introduction

It has already been reported that plaques with rich liquid components and thin fibrous caps are easy to break [4,10,25], and the formation of thrombus following the rupture of this plaque was one of the causes of acute coronary syndrome [3–4,6,10,25]. However the character of each coronary lesion was different in each patient and even in one patient [2,13,15,16], and it is difficult to distinguish a lesion that will rupture easily from others. Recently, Mann et al [18] reported that there was no significant correlation between the stenotic ratio and the main factors deciding the vulnerability of plaques, such as the fibrous cap thickness and the core size, and that it was difficult to deduce the vulnerability of plaques from coronary angiography.

Recently it has been reported that angioscopy is very useful for the precise observations of intravascular lumen [5,20–22,24]. But there was no comparative study concerning the precise characterization of yellow and white plaques using angioscopy. In this report, we have performed pathological study of both yellow and white plaques and compared our results, in which plaques were divided into two groups, yellow and white plaques, with those of previous report [18].

Methods

We observed 198 segments of coronary artery from 34 cases of autopsy using angioscopy. The model of angioscopy we used was a product by Mitsubishi Electronics. The resolution of this model was 3000 pixels, and the catheter had an outer diameter of 1.55 mm and was 1.2 m long; the distal end (10 cm) was tapered to reduce the outer diameter to 1.1 mm [20]. The angioscopic system consisted of a CCD color camera, a xenon lamp light source, a cathode ray tube display, a video documentation system and an image processor. The color quality of the presentation was automatically controlled, but the intensity was manually controlled. This equipment was a modified version of the commercially available FCA-8000 (Fukuda Denshi Co., Ltd. Tokyo, Japan) [20].

The vessels were placed vertically in a beaker filled up with saline solution and examined. The examination was done by two examiners who were given no information about clinical and pathological findings of each sample. Plaques were classified as either yellow or white by their angioscopic appearance. Yellow plaque was defined as a plaque with solid yellow color that could be clearly distinguished from other intima. Lesions were classified as "yellow" when yellow plaque was observed; all other stenotic lesions were classified as white plaque. When observes disagreed on lesion classification, the lesion was excluded from this study. Intraobserver agreement was measured by having an observer repeat the assessment of each of 20 images (presented in random order) one week later, while interobserver agreement was measured by comparing the assessment of 20 images by two different observers; agreement was 95% in both cases.

Each lesion diagnosed as yellow or white plaque was marked by a 23G needle and excised. The excised lesions were fixed with 10% of formalin at a pressure of 100 mmHg for 24 hours and 10 paraffin slices with 6 μm

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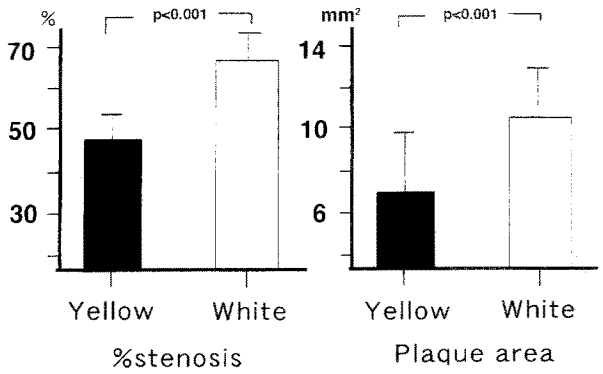

Fig. 1. Comparison of the stenosis (*left panel*) and the plaque area (*right panel*) between yellow plaque group and white plaque group. Both stenosis and plaque area were significantly higher in the white plaque group than in the yellow plaque group. Values represent mean ± SD.

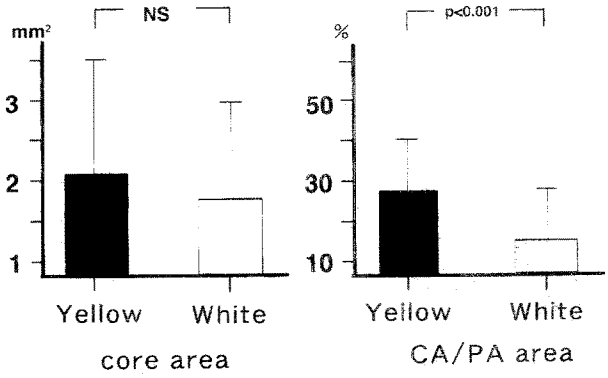

Fig. 2. Comparison of the lipid core area (*left panel*) and the lipid core size relative to overall plaque size (CA/PA) (*right panel*) between yellow plaque group and white plaque group. The lipid core area was not significant between two groups, but the CA/PA was significantly higher in the yellow plaque group than in the white plaque group. Values represent mean ± SD. NS = not significant.

of thickness and with 0.5 mm of interval from every lesion were prepared. Then, they were stained with Hematoxylin-Eosin stain, Masson trichrome stain, elastica van Gieson stain, Sirius red [18] and lipid staining.

The examination process with calibration was recorded by a VHS video tape recorder and the stenotic ratio, the plaque area, the lipid core area and the minimum fibrous cap were measured by Cardio 500 system (Kontron Elektronik, Everett, MA), and the lesion site was measured by a micrometer. Plaque area was calculated by subtracting lumen cross-sectional area from vessel cross-sectional area. Percent area stenosis was equal to plaque cross-sectional area × 100 divided by vessel cross-sectional area. The size of the lipid core area was measured by traced the edge of area not occupied by collagen in the plaque.

The results were shown in the mean ± standard deviation. For the comparison between two groups, Fisher's test and Student's test were used and $P < .05$ was regarded as significant difference. The correlations between the stenotic ratio and the lipid core size as a percentage of total vessel area, and the stenotic ratio and the fibrous cap, were analyzed with the single regression test.

Results

In this study, 46 out of 198 lesions were diagnosed as a yellow plaque, and 61 lesions were actually diagnosed as atheroma out of the lesions diagnosed as a white plaque by both of two examiners. The yellow plaque lesions that were diagnosed by only one examiner (32 lesions), the complex lesions (24 lesions), the lesions with thrombi (4 lesions) and the sites that were diagnosed normal by two examiners (31 segments) were excluded from this study.

Figure 1 shows the stenotic ratio and the plaque area. The stenotic ratio was 48 ± 6% in the yellow plaque group and was 65 ± 7% in the white plaque group, indicating that stenosis was significantly severer in the white plaque group ($P < .001$). The plaque area was 7.3 ± 2.5 mm^2 or 10.7 ± 2.2 mm^2 in the yellow or white plaque group, respectively, showing it was significantly larger in the white plaque group ($P < .001$).

Figure 2 shows the lipid core area and the ratio of the lipid core area to the plaque area (CA/PA ratio) in both groups. The lipid core area was 2.1 ± 1.9 mm^2 or 1.7 ± 1.2 mm^2 in the yellow or white plaque group, respectively, and showed no significant difference between the two groups. However, the CA/PA ratio was 28.1 ± 11.9% in the yellow plaque group and was 15.8 ± 11.1% in the white plaque group, indicating that the ratio was significantly larger in the yellow plaque group ($P < .001$).

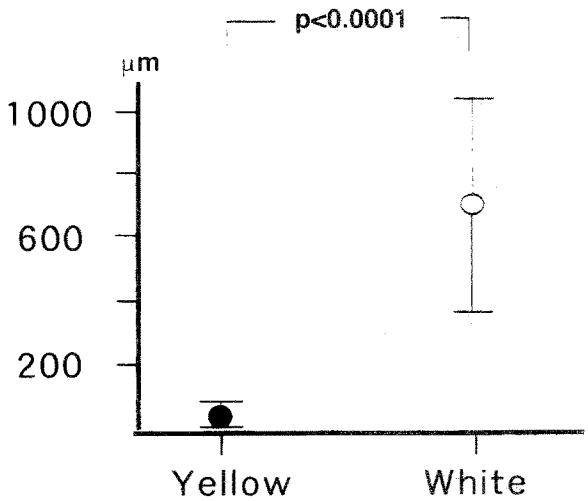

Fig. 3. Comparison of the thickness of the fibrous cap between yellow plaque group and white plaque group. The thickness of the fibrous cap was significantly thinner in the yellow plaque group than in the white plaque group. Values represent mean ± SD.

The thickness of fibrous cap is shown in Figure 3. The thickness was 58 ± 18 μm (35–90 μm) or 648 ± 356 μm (190–1730 μm) in the yellow or white plaque group, respectively, showing that the minimum fibrous cap was significantly smaller in the yellow plaque group ($P < .0001$). The lesions with the fibrous cap thickness ranging from 90–190 μm included some lesions diagnosed as yellow plaque by only one of the two examiners, or diagnosed as neither yellow nor white plaque. This suggested that the fibrous cap thickness of decisively diagnosed as a yellow plaque was less than 90 μm.

Figure 4 shows the correlation between the stenotic ratio and the lipid core size as a percentage of total vessel area (%C) in the whole lesions and in each plaque group. Although there was no correlation between the stenotic ratio and the %C in whole lesions and in white plaque group (in the whole lesions: $r = .22$, $p = .19$; in the white plaque group: $r = .13$, $p = .32$), in the yellow plaque group, the %C increased according to the increase of the stenotic ratio

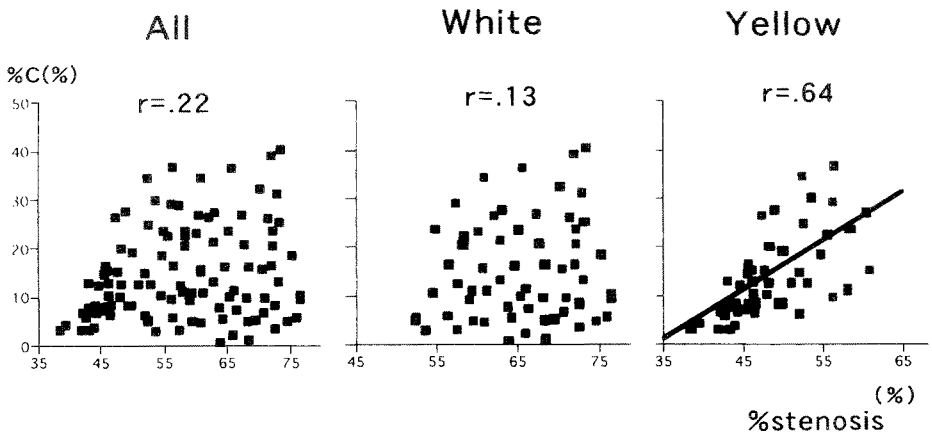

Fig. 4. The lipid core size as a percentage of total vessel area (%C) plotted against percentage of area stenosis (%S). There was no significant correlation in either all plaque (*left panel*) or white plaque (*middle panel*). However, there was significant correlation in yellow plaque (*right panel*). (%C = −34.26 + 0.995 × %S, r = .64, p < .0001).

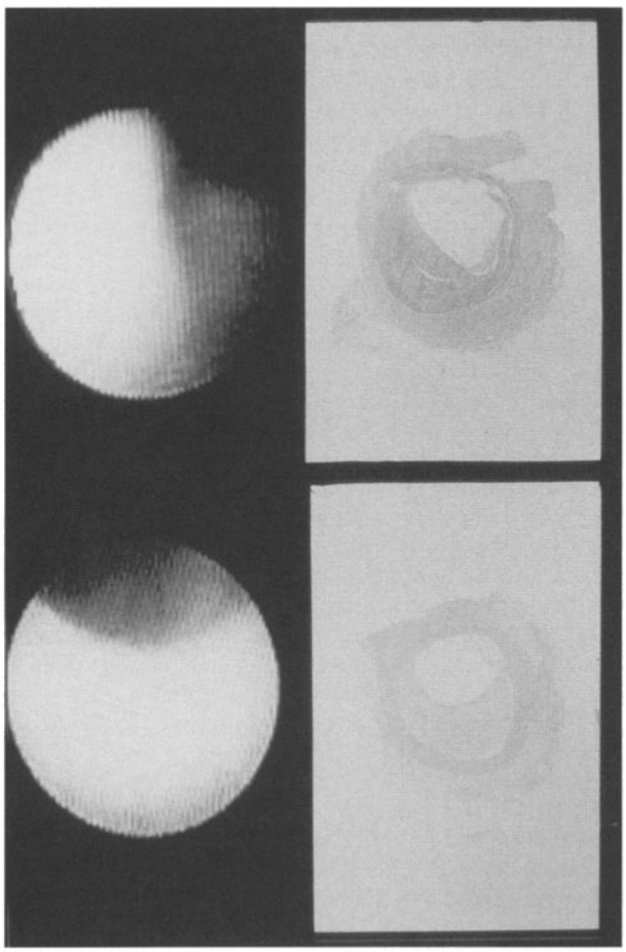

Fig. 5. The white lesions. The stenotic ratio of both white lesions are almost the same, but in the lower right panel, almost no lipid core is observed (*lower right panel,* Hematoxylin-Eosin stain, ×7), whereas in the upper right panel, the lipid core can be observed under the thick fibrous cap (*upper right panel,* Hematoxylin-Eosin stain, ×7). Both upper left panel and lower left panel show angioscopic images and each panel corresponds to right panel.

(%C = −34.26 + 0.995 × the stenotic ratio, r = .64, p < .0001). One suggested reason for these results is that in the white plaque group, the %C (shown in Figure 5) and the fibrous cap thickness (shown in Figure 3) varied widely in comparison with the yellow plaque group, in which the minimum fibrous cap thickness did not vary so widely, and, even in the lesions with stenosis, partial yellow plaque lesion guaranteed the widely spreading lipid core, as shown in Figure 6. This suggested that it was possible to deduce the volume of the lipid core from the stenotic ratio in a lesion diagnosed as yellow plaque by angioscopy.

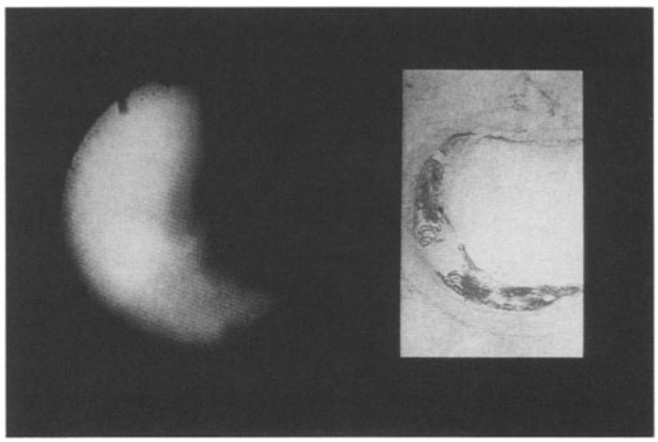

Fig. 6. The yellow plaque. Even in the lesion with partial yellow plaque (*left panel,* in the direction of 9 o'clock of angioscopic image), the lipid-rich area spreads widely according to the stenotic ratio (*right panel,* lipid staining, ×7).

The significant correlation between the stenotic ratio and the minimum fibrous cap was not observed in the whole lesions (r = .38) (Figure 7) and in each plaque group, r = .06 in both yellow and white plaque groups, indicating that it was impossible to deduce the fibrous cap thickness from the stenotic ratio.

Discussion

In this study, we characterized the pathological features of yellow and white plaques observed by angioscopy, and analyzed the possibility to deduce the fibrous cap thickness and the lipid core area, which were the main decisive factors for the vulnerability of plaques, from angiographic findings with the differential diagnosis between yellow and white plaques.

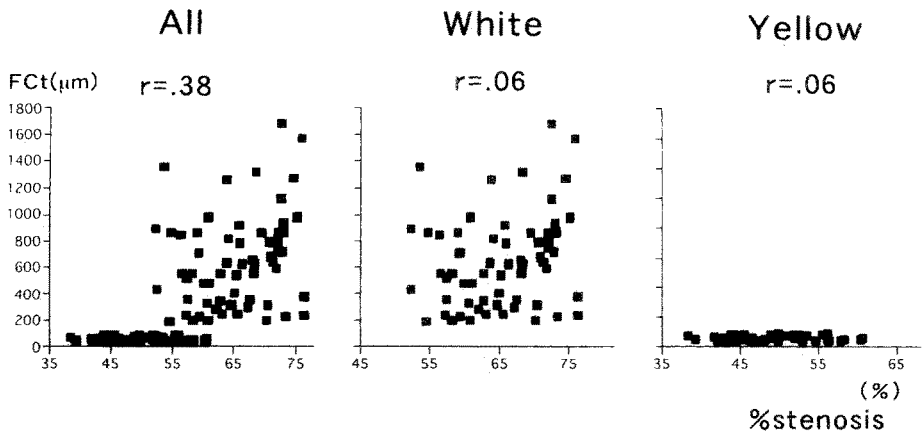

Fig. 7. The fibrous cap thickness plotted against percentage of area stenosis. There is no significant correlation in all three groups [all plaque (*left panel*), white plaque (*middle panel*) or yellow plaque (*right panel*)].

We found that the stenotic ratio and the plaque area were smaller in the yellow plaque group than in the white plaque group (Figure 1). There could be several reasons for that. First, as a yellow plaque tends to rupture before severe stenosis develops, most of the yellow plaque lesions observed in autopsy could be only moderately stenotic lesions. The supporting evidence for this theory is the study reporting the mean stenotic ratio as 48% in the responsible thrombotic lesions for acute myocardial infarction [11], and the time-course study suggesting that most lesions that eventually lead to thrombotic obstruction shows slight irregularity of the vascular lumen in the first angiography [12]. The results, that the fibrous cap was significantly thinner, and the lipid core area increased according to the increase of the stenotic ratio in yellow plaques, suggest the tendency to rupture of a yellow plaque before severe stenosis has developed. Second, there could be a bias in the selection of the sample population out of the autopsy cases. In this study, the ratio of the patients with hematological disease (41%) or cancer (35%) was greater than that of the patients with acute coronary syndrome (24%). Therefore, in such patients with hematological diseases or cancer, long-term malnutrition could possibly exist, which would have an inhibitory effects on the progression of yellow plaque lesions, or rather, cause the retraction of them. Third, white plaque lesions enriched with fibrous factors and smooth muscle cells are stable and tend to develop severe stenosis. This possibility was also reported by the report by Kragel et al., demonstrating that severe stenotic lesions of patients with stable angina pectoris contained rich collagen fibers [15–17]. Fourth, white lesions without apparent protrusions are likely to be misdiagnosed as normal, and those with a stenotic ratio of 50% or less could have escaped from the identification. It was suggested that these reasons caused the significant difference in the stenotic ratio between the yellow and white plaque groups.

Concerning the fibrous cap of plaques, most of its thickness were less than 90 μm in the apparently yellow plaque lesions (Figure 3). The supporting evidence for that is in the report by Miyamoto et al., showing that one of the definitive factors for the plaque color was experimentally proved to be the thickness of the fibrous cap [19]. These results show that the fibrous cap thickness can be deduced to some extent from the plaque color. In order to detect the vulnerable yellow plaques, the observation of their color by angioscopy is more useful than the conventionally used intravascular ultrasound of 30 MHz with limitations of resolution power [5,26]. In this study, there was remarkable difference in the fibrous cap thickness between the yellow and white plaque lesions. This is probably because we excluded the lesions in which the diagnosis between the two examiners were different, and the lesions with slight white changes were diagnosed as normal.

One of the new findings in this study is that in the yellow plaque lesions, the lipid core area increased linearly according to the increase of the stenotic ratio (Figure 4). When the whole lesions were taken into consideration, there was no significant correlation between the stenotic ratio and the lipid core area, as shown in the report by Mann et al. [18]. In this study, however, the population was divided into two groups, the yellow and white plaque groups. It was suggested that in the yellow plaque lesions, the lipid core area increased linearly according to the increase of the stenotic ratio, and the fibrous cap thickness did not vary so widely; however, in the white plaque group, the fibrous core thickness and the lipid core area varied widely, and no correlation was observed. These results suggested that the volume of the lipid core could be to some extent predicted from the combination of the angiographic findings and the color of the plaques observed by angioscopy. But in this study, the stenotic lesions with yellow plaques had no more than moderate stenosis, and it was still unclear whether this correlation was observed in severe stenotic lesion.

Our study suggested that as a yellow plaque had a thin fibrous cap and a relatively large lipid core, even in an insignificant lesion detected by angiography, care should be taken to prevent its rupture. Both myocardial perfusion imaging [7] and intravascular ultrasound [27] can demonstrate regions of coronary artery disease not detectable by conventional angiography, the former by assessment of regional blood flow differences [8–9] and the latter [27] by interrogation of the arterial wall. These approaches can be used to guide angioscopy in its efforts to better define where the plaque is, so that angioscopy can then be used to define the type of plaque present and potential treatment of that plaque. As the yellow plaques were often observed in our patients with the high LDL cholesterol level [14] and a recent report revealed that lipid lowering might stabilize

vulnerable plaques by reduced expression and activity of enzymes that degrade the arterial extracellular matrix and by favoring collagen accumulation in the fibrous cap [1], we concluded that the aggressive lipid lowering by statins was very important for the prevention of cardiac events. Our medical treatment for yellow plaque may be supported by the recent clinical study [23], which described how pravastatin reduced progression of coronary atherosclerosis and ischemic events in patients with coronary artery disease and mild to moderate hyperlipidemia. However, further work is needed to determine the level of cholesterol in patients with yellow plaque lesions in order to prevent cardiac events.

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