－Reviews－

The Development and Clinical Feasibility of Percutaneous Transluminal Coronary Angioscopy

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Introduction

Coronary angioscopy is a new diagnostic tool that permits non-operative imaging of intravascular structures through the use of a fiber optic system. Coronary angioscopy is playing an ever-expanding role in research and in clinical practice because it provides a precise, full-color, three-dimensional perspective of the interior surface morphology of coronary arteries, whereas ordinary coronary arteriography provides only two-dimensional black and white images. Angioscopy now permits detailed examination of the macromorphology of coronary artery disease that hitherto was unavailable except during autopsy. The ability to discriminate among colors in angioscopy makes it relatively easy to distinguish between a thrombus and a plaque, even if the clot is very small [1-3]. Furthermore, angioscopy can also distinguish between types of plaque（e. g., yellow vs white plaque）and types of thrombus（e. g., red vs white thrombus)[4,5]. The three-dimensional perspective and high resolution of angioscopic images can disclose luminal changes in minute plaque ruptures, ulceration, intimal flap or torn tissue strands not typically appreciated by coronary angiography. Therefore, angioscopy is helpful not only in correlating anatomical and pathological features that cannot be detected in routine coronary arteriography, but also in monitoring coronary interventions such as thrombolytic therapy, percutaneous transluminal coronary angioplasty, atherectomy, laser angioplasty or stenting. **Table 1** shows differences among different diagnostic tools. This paper will explore the development of coronary angioscopy, technical considerations, clinical results, and areas for future research and development.

1. The angioscopic imaging system

The angioscopic system consists of an angioscope, a charge-coupled device（CCD）color camera, a lamp light source, a cathode ray tube (CRT), a video documentation system and an image processor. In addition to video tape, angioscopic images can be stored on individual photographic stills, on cinematographic moving film, or on a combination of the two.

2. Angioscope

The coronary artery is small and tortuous. Therefore, very thin, flexible, high resolution imaging optic fibers are required to obtain a high quality angioscopic image. The utility of a fiber optic bundle depends upon its flexibility, which should be maximal, and the reliability of the transmitted image, which should be minimally distorted. Minimizing the number of fibers maximizes the flexibility, but the fewer the number of fibers the more distorted will be the image. At the other extreme, maximizing the number of fibers minimizes distortion while also minimizing flexibility. A compromise is achieved by using thousands of extremely small diameter fibers to make up the bundle, each fiber corresponding to one pixel of the image. Newer technology employs individual fibers less than 3 μm in diameter, which are free to slide over each other throughout the body of the fiberoptic bundle；the fibers are bound together at each end. This technology offers much greater flexibility as well as miniaturization of the angioscopic probe. For percutaneous transluminal coronary angioscopy, 0.2 to 0.3 mm diameter fiber optic bundles containing 3,000 individual fibers are used. Larger diameter fiberoptic bundles containing up to 10,000 individual fibers can be used for intraoperative coronary angioscopy. A tiny lens is attached to the distal end of

Table 1 Characteristics of diagnostic imaging of coronary arteries

	Angiography	Angioscopy	Ultrasonic study
Color	black/wihite	full color	black/white
Image display	2 dimensional	3 dimensional	2 to 3 dimensional
Degree of resolution	+	+++	++
Quantification	+++	+	+++
Entire picture	+++	−	−
Tissue character			
Vessel surface	+	+++	++
Vessel wall	+	−	+++
Thrombus	+	+++	±
Calcification	++	±	+++
Character of plaque	±	++	++

Table 2 Indication of coronarg angicoscopy

Diagnosis
1. Evaluation of arteriographic findings
   Whether the stenosis site is atherosclerotic or thrombotic
   Whether the stenosis site is complex atheroma or stable atheroma
2. Cause, type of disease
   Variant angina, stable angina, unstable angina, acute myocardial, postinfarction angina, Kawasaki disease
3. Mechanism of progression of atherosclerosis
   Sclerotic change of coronary bypass graft
   Sclerosis of coronary arteries after heart transplant
4. Prediction of prognosis (cardiac event)
5. Monitoring progression and regression of atherosclerosis
6. Mechanism of restenosis following coronary angioplasty

Treatment
1. Selection of the intervention technique (tool)
   Thrombolytic therapy or PTCA
   Stenting or other intervention?
2. Prediction of post-intervention vessel occlusion
3. Determination of the endpoint of the intervention
4. Monitoring intervention
   Addition, modification of therapy
5. Prediction of restenosis following the intervention

the bundle typically allowing a viewing angle of 50-90°. The energy (light signal) output of the fiberoptic bundle is far too small to be viewed directly ; therefore it is transduced to an electrical signal and transmitted to a TV monitor. Light-transmitting fibers are necessary to illuminate the field of view. These are generally composed of multicomponent glass fiber or fused silica and may be set around the image-conducting fibers or may be packed together as a single illumination bundle. The illumination source most commonly employed is a high intensity (300 W) xenon light. Adjustment of the light intensity is a dynamic process and is dependent upon the focal length, the viewing angle of the distal lens, the diameter of the vessel lumen, and the aperture of the video camera lens. Depending on the system used, angioscopic images can then be stored either on videotape, cine film or still photographs. When videotape is utilized, a high resolution 3/4 or 1/2 inch video tape recorder is used for storing the live angioscopic images. If still photography is utilized, ultra high speed daylight type color reversal film (ASA 1600) is used.

3. Angioscopic catheter

To deliver the angioscope percutaneously to a target lesion within the coronary tree accurately and without trauma, we first developed a 1.55 mm a outer diameter, 1.2 m long angioscopic catheter. The distal end (10 cm) is tapered to an outer diameter of 1.10 mm. The catheter is made of polyvinyl chloride or polyethylene and has three or four channels. One channel (0.5 mm in diameter) is designed for irrigation and placement of up to a 0.36 mm (0.014") percutaneous transluminal coronary angioplasty guide wire. One channel is designed for balloon inflation. The remaining channels contain the image and the light guide fibers, respectively. This angioscopic catheter has an inflatable balloon at the tip of the catheter to obtain the blood flow it is intended and to replace it completely by a translucent medium thereby allowing for optimum visibility. Similar systems are now commercially available and utilized by many investigators. In these angioscopic systems, interventional devices such as percutaneous transluminal coronary angioplasty, laser, or atherectomy catheters can be in-

Table 3 Definition and classification of intraluminal findings

	Color	Mobility	Surface and shape	Protrusion to inner lumen
Thrombus	Red	fresh thrombus present	fresh thrombus nappy	intraluminal thrombus present
	Red + white	old thrombus absent	old thrombus sommth luster	mural thrombus absent
	White			
Hemorrhage	Red	absent	Smooth	absent
Intimal dissection (atheroma rupture)	Yellow	part of cross-section may move	irregular	present
	White		thick cross-section	
Intimal flap	Yellow white	present	irregular thin cross-section	present
Ulceration	Yellow white	absent	irregular cave-in	absent
Intimal split	Yellow white	absent	irregular sharp split to outer wall	absent
Stable atheroma	Yellow white	absent	smooth	absent

troduced into the coronary artery over a long guide wire independently.

A monorail coronary angioscope may be more cost effective and simpler to use. Recently, a more sophisticated angioscopic catheter, employing a moveable optic bundle with an outer catheter, has been introduced. The Angioscope (moveable optic bundle) and its guide (outer catheter, 4.8 F) are one unit and both are advanced over-the-guide wire. By inflation of an occlusion cuff on the outer catheter and by moving the optic bundle, coronary lumen may be observed in 5 cm long segments. A conventional angioscope is separated from the inner guiding catheter. An inner guiding catheter, which is advanced to the target lesions by a guide wire, is used as an for angioscopic guide. The angioscope is inserted into the inner guiding catheter. However, this system may need more flushing solution, because there is no occlusion cuff.

4. Indication for coronary angioscopy

Coronary angioscopy may be indicated for all patients with coronary artery disease and those with coronary artery bypass grafts or allografts. Angioscopy is also indicated to investigate the pathogenesis of atherosclerosis in the coronary artery and for monitoring during coronary interventions such as percutaneous transluminal coronary angioplasty or stent. However, there are recognizable limits ; at our institute, angioscopy is not attempted in patients with left main disease, pronounced distal coronary artery disease, or when the affected coronary arteries are too small for insertion of the angioscope [6]. **Table 2** summarizes the currently conceivable applications of coronary angioscopy.

5. Definition and classification of intraluminal findings (Table 3)

There is no formally established classification system nor definition of angioscopic findings. However, the findings may be arranged into 7 categories according to color, mobility, irregularity of intraluminal surface, shape or protrusion into the inner lumen : (1) thrombus, (2) hemorrhage, (3) dissection, (4) intimal flap, (5) intimal split, (6) ulceration, and (7) stable atheroma (**Table 3**). This classification system, as used in our institute, is based upon generally recognized definitions, as follows.

Thrombus is defined as a red and/or white solid material adhering to the intima or protruding into the inner lumen despite flushing with normal saline.

Hemorrhage is defined as a non-moving flat red color on the inner lumen that persists despite flushing with saline. It is sometimes difficult to differentiate between hemorrhage and a red mural thrombus, especially on a still photograph. In such cases, serial still photos, videotapes or cinematographic techniques that demonstrate movement are needed to discriminate between the two conditions. If shaggy or nappy movement is detected in the red area, a fresh mural thrombus is suggested. Similarly, a white thrombus can be distinguished from the inner wall due to its mobility in serial cine frames. A thrombus that shows no

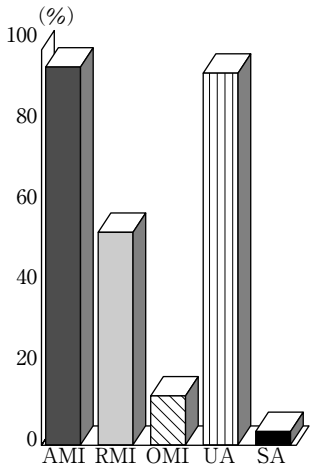

Fig. 1 The frequency of coronary thrombi
Coronary thrombi were found more frequently in patients with acute myocardial infarction (AMI), recent myocardial infarction (RMI), and unstable angina (UA) than in those with old myocardial infarction (OMI) and stable angina (SA).

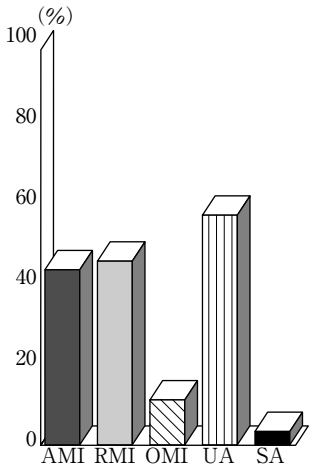

Fig. 2 The frequency of intimal irregularity
Intimal irregularities which indicated plaque rupture were seen more frequently in patients with acute myocardial infarction (AMI), unstable angina (UA), and recent myocardial infarction (RMI) than in those with old myocardial infarction (OMI) and stable angina (SA).

movement and presents with a highly polished surface is considered to be an old thrombus.

Plaque rupture is divided into 4 categories : intimal dissection, intimal flap, intimal split, and ulceration. These classifications were based on morphological appearance and cleft orientation. Intimal flap is defined as a small white disrupted fragment floating in the lumen. Intimal dissection is defined as a large longitudinal dissection plane encroaching on the inner lumen. Intimal split is defined as a sharp cleft in the inner wall. We only use this term after percutaneous transluminal coronary angioplasty. Ulceration is defined as a crater-like lesion suggesting a gap in the intima. Intimal flap and intimal split are usually observed after interventions, e. g., when percutaneous transluminal coronary angioplasty, and intimal dissection and ulceration are observed in acute coronary syndromes, e. g., acute myocardial infarction or unstable angina. Ramee et al.[3] described two types of dissection : thin shaggy white, mobile fronds adhering to the arterial wall and protruding into the lumen, and large thick flaps that appeared to have a longitudinal dissection plane and that encroached on the lumen. In our terminology, the former dissection is called "intimal flap" and the latter dissection is called "intimal dissection".

6. Clinical implication : Pathogenesis of coronary artery disease

Sherman et al.[2] demonstrated the presence of complex plaques or thrombi, which were not detected by coronary angiography, in the coronary arteries of all patients who underwent bypass surgery for unstable angina. They speculated that the ulceration of plaques may increase the frequency and severity of effort angina, and the subsequent development of partially occlusive thrombi might cause unstable rest angina. On the basis of their study, Forrester et al.[7] proposed that each coronary syndrome has a distinct intimal cause. The thrombus overlying a rupture in the lining of the plaque plays an important role in acute coronary syndromes such as acute myocardial infarction or unstable angina. We and other investigators observed thrombus or plaque rupture or ulceration in patients with acute coronary syndromes (**Fig. 1, Fig. 2**). However, the findings leave some crucial pathophysiological questions unanswered. For example, what type of plaque precedes plaque rupture and formation of a coronary thrombus? In our study, yellow plaque was more common in patients with acute myocardial infarction, recent myocardial infarction and unstable angina than in patients with stable angina and old myocardial infarction (**Fig. 3**). Many sites of plaque ruptures or ulcerations were observed on yellow plaque. Conversely, smooth white plaques were seen in patients with stable angina and old myocardial infarc-

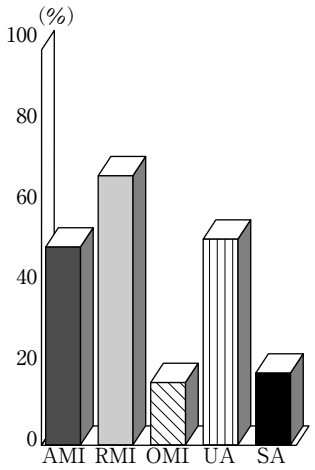

Fig. 3 The frequency of yellow plaque
Yellow plaques were observed more frequently in patients with acute myocardial infarction (AMI), recent myocardial infarction (RMI), and unstable angina (UA) than in those with old myocardial infarction (OMI) and stable angina (SA).

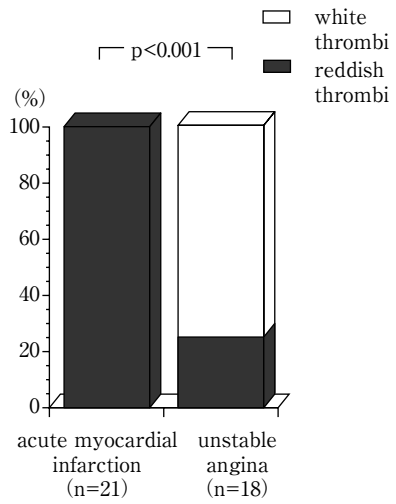

Fig. 4 The comparison of character of thrombi between acute myocardial infarction and unstable angina
Angioscopy revealed reddish thrombi in all patients with acute myocardial infarction. By contrast, white thrombi were observed in most patients with unstable angina.

tion. Nesto et al.[8] confirmed our observation. Yellow plaque is likely to be lipid rich and the fibrous cap is always thin. Routine coronary arteriography usually does not help predict the location of a subsequent myocardial infarction. However, angioscopy may predict the location of a subsequent plaque rupture when yellow plaque is observed.

Allograft coronary artery disease is a major cause of morbidity and mortality in cardiac transplant recipients. Coronary angioscopy was more sensitive than arteriography in detecting coronary artery disease. Intravascular ultrasound is also a sensitive technique for detecting the allograft coronaropathy, but it does not provide information on detailed plaque surface morphology. Angioscopy typically demonstrates two types of coronary surface morphologies, yellow and white plaques. These lesions may represent either two different types or two different stages of allograft coronary diseases in cardiac transplant recipients[9]. Similar yellow and white plaques were also demonstrated by angioscopy in saphenous vein grafts[10]. At present, a study concerning the ability of angioscopy to predict complications during percutaneous transluminal coronary angioplasty, based on differences in plaque surface morphology, is under way.

Angioscopy is clearly more sensitive in detecting thrombus than is intravascular ultrasound or coronary angiography. A number of authors have observed the process of thrombolysis during acute myocardial infarction. As a generality, all authors report that occlusive or intraluminal thrombi were always found in the offending artery. Inoue et al.[11] reported that angioscopy could be used to identify a subset of patients with incomplete clot lysis that may be prone to reocclusion. Sherman et al.[2] and we[1] confirmed that thrombi existed in patients with unstable angina as well as in those with acute myocardial infarction. Coronary angioscopy in our study showed that thrombi observed in unstable angina differed from those observed in acute myocardial infarction. Patients with unstable angina were frequently observed to have white thrombi, but none were seen in patients with acute myocardial infarction. In contrast, reddish thrombi were observed in all patients with acute myocardial infarction but in only a few patients with unstable angina (**Fig. 4**). Differences in color probably reflect differences in the composition of the thrombus, and may be related in part to the different ages of thrombi. The relation between the appearance of coronary luminal changes and clinical symptoms is shown in **Fig. 5**.

7. Coronary interventions

(1) Angioplasty

If percutaneous angioscopy comes to have an important clinical role, it will be in association with coro-

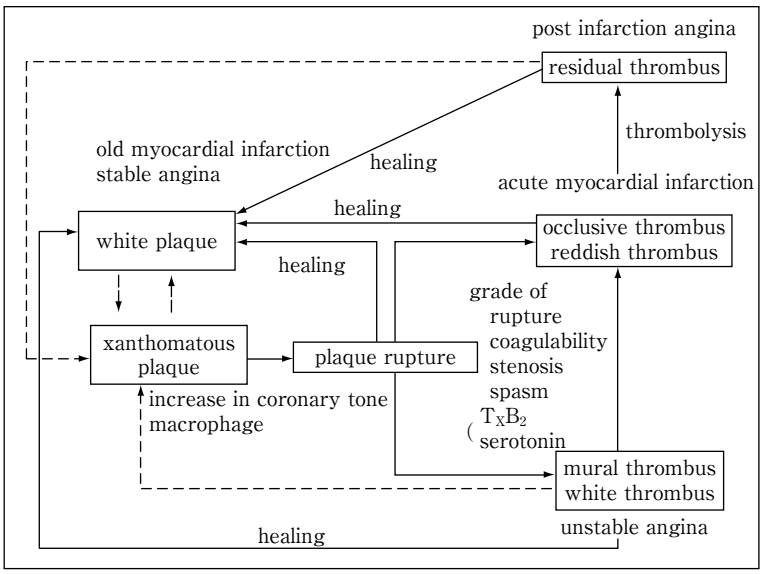

Fig. 5 Line drawing of the relation between appearance of coronary luminal changes and clinical syndromes

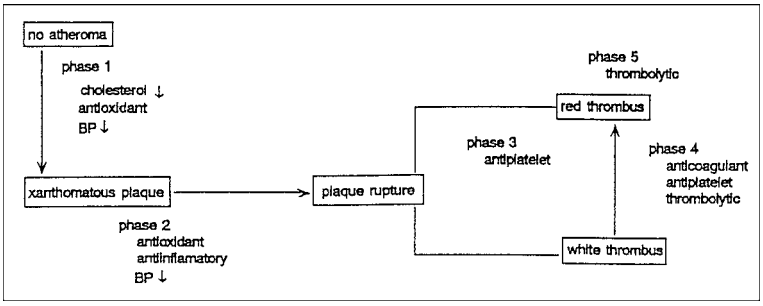

Fig. 6 Chart of therapeutic interventions based on angioscopic findings

nary interventions such as angioplasty, atherectomy or stenting. Angioscopy showed coronary surface damage that was largely undetectable by arteriography. Immediately after the procedure, intimal flap, fissure or disruption were observed in most patients [2, 12, 13]. In our study, the thrombi or fibrin deposits were observed in two thirds of the patients despite the use of anticoagulants and antiplatelet agents before and during procedure[14]. A better understanding of the mechanisms of thrombus formation at the angioplasty sites may provide insights into the pathogenesis of both acute closure and restenosis following angioplasty.

Jain et al.[15] performed percutaneous coronary angioscopy in 10 patients following abrupt occlusion occurring immediately after balloon angioplasty. The primary cause of the abrupt occlusion was thrombus in 2 patients and occlusive dissection in 8 patients. Seven of the occlusive dissections were associated with non-occlusive mural thrombi. These findings suggest that angioscopy may allow the selection of the optimum therapy (thrombolysis, long balloon inflations, atherectomy, or stents) in patients with acute occlusion.

(2) Stent

Stent is now widely used for coronary intervention because of its lower restenosis rate compared to percutaneous transluminal coronary angioplasty[16, 17]. However, stenting for acute coronary syndrome was contraindicated as thrombotic reocclusion might occur in a relatively early period following stenting. Recently many reports have shown that coronary stent placement is feasible in these patients and results in excellent short term results. We studied with angioscopy the morphologic characteristics of culprit lesions before and after stent implantation. Before stenting, angioscopically visible occlusive or protrusive thrombi were observed in all patients. After stenting, mural thrombi but not occlusive or protrusive thrombi were

observed in all cases.

These findings demonstrate that coronary stents compress the occlusive or protruding thrombi and cover the ruptured thrombogenic plaques ; consequently, smooth surface and wide vessel lumina are obtained. In contrast to stent implantation, protrusive thrombi were found after percutaneous transluminal coronary angioplasty or thrombolytic therapy in many cases with acute coronary syndromes. These finding disclose that stent implantation as an acute stage intervention in patients with acute coronary syndromes induced more favorable clinical outcomes with fewer adverse cardiac events.

8. Intimal morphology and its therapeutic implications

We demonstrated that there were some differences of composition in plaque or in thrombus[4, 5].These differences are thought to cause the different clinical states of ischemic heart disease. From these studies, intervention to prevent acute coronary syndrome can be considered to follow a sequence of 5 phases (**Fig. 6**) : (phase 1) prevent yellow plaque ; (phase 2) prevent plaque rupture ; (phase 3) inhibit platelet aggregation ; (phase 4) anticoagulation ; (phase 5) lyse thrombus. Let us further consider these phases. Phase 1 : Yellow plaque is likely to have a high concentration of cholesterol and its ester, which is believed to be derived from plasma low-density lipoprotein (LDL)[18]. One mechanism by which the extracellular cholesterol is accumulated could be by way of oxidation of intra-intimal LDL followed by its ingestion by macrophages, which bind modified apoprotein via their scavenger receptors. Therefore, antioxidant agents or drugs, such as vitamin C or vitamin E, may help prevent the formation of yellow plaque. In any event, lowering the serum cholesterol level is very important. Phase 2 : It is reported that erosion of the fibrous cap is caused by both free radical formation and the production of enzymes capable of destroying collagen and elastine. Therefore antioxidants and anti-inflammatory agents may impede atheroma rupture. Phase 3 : Platelet aggregation at the site of plaque rupture is the initial step of thrombosis. Therefore, antiplatelet agents could be used to impede progression of the thrombus to total occlusion and to myocardial infarction. Phase 4 : In our preliminary study of coronary thrombolysis using angioscopy, the efficacy of thrombolytic therapy was less in patients with grayish white thrombi than in those with reddish thrombi. This result is compatible with the report[19] that platelet thrombi are much more resistant to thrombolysis with tissue plasminogen activator than are erythrocyte-rich clots. Phase 5 : Possible mechanisms for high resistance to lysis include the release of plasminogen activator inhibitor, clot retraction and an increase of cross-linking in the clot, which is activated by platelets. In these cases, new anticoagulant (e. g., hirudin, argatroban) and antiplatelet agents may be more effective than thrombolysis[20].

In summary, fiber optic angioscopy has already disclosed important qualitative aspects of intraluminal changes, even though the technique is still relatively unsophisficated. It should also be possible to successfully combine this technique with other advanced therapeutic procedures, such as stent, laser angioplasty, atherectomy or percutaneous transluminal coronary angioplasty. At present we have taken only the first few steps in observing coronary luminal changes in living people. An exciting future is before us.

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(Received, October 23, 1998)
(Accepted for publication, November 20, 1998)