Combined Use of Angioscopy and Intravascular Ultrasonography for Diagnosis and Evaluation of Surgical Repair of Aortic Disease

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Angioscopy (AS) and intravascular ultrasonography (IVUS) enable pathological diagnosis of vascular interior and visualization of vascular wall architecture, respectively, and therefore these techniques in combination may give us much information on vascular disease. But, these techniques in combination have been rarely used for diagnosis and evaluation of surgical repair of large vessels. Systematic review on the combined use of AS and IVUS for vascular disease, except those of the coronary arteries, has rarely been published in the literature, so we have described developmental history of AS, and AS and IVUS images of aortic disease before and after surgical therapy that were obtained mostly in our laboratory. Usually, AS system is composed of a 4.5F fiberscope and 9F balloon guide catheter and IVUS system is composed of a 9F, 12 or 20 MHz, 20 CPS probe. They are introduced into the aorta for diagnosis of aortic aneurysm and evaluation of their surgical repair in patients. Recent important findings are as follows: (1) Entry and re-entry of dissecting aortic aneurysm were easily identified by IVUS and entry was frequently found by AS in yellow plaques. Thrombus formation was found by AS in the aortic arch graft, suggesting the necessity of anticoagulant therapy after repair for prevention of cerebral embolism. (2) Disrupted plaques and thrombi were observed by IVUS in the aneurysm, which were frequently not detectable by computed tomography or aortography, in patients with saccular abdominal aortic aneurysm. Fresh and old thrombus in mixture were frequently observed by AS, suggesting recurrent thrombus formation. Incomplete neo-endothelial coverage of the Y-graft even 6 months after grafting and detached threads at the sutured portion were found by AS but not by IVUS. Pseudoaneurysm at the sutured portion was confirmed by AS and IVUS in combination. AS and IVUS in combination give us much information on structural and pathological changes and evaluation of surgical repair of aortic disease.

Key words: angioscopy, aortic aneurysm, intravascular ultrasonography, surgical repair
Peripheral vascular changes in animals were observed by Sugie and Tanabe, Litvack et al., Uchida et al., and Buckmaster et al., among others.

Human coronary arteries were examined by Spears et al., Uchida et al., Sanborn et al., Hombach et al., Sherman et al., Uchida et al., Nakamura et al., Uchida et al., Hombach et al., among others.

Peripheral arteries in patients were examined by Uchida et al., Drobinski et al., Kollar et al., Trubel et al., among others.

The aorta was examined by Uchida et al., Hill et al., Tokuhiro et al., Tsagakis et al., among others.

Peripheral veins were examined by Hoshino et al., Yamaki et al., Nishibe et al., Konami et al., among others.

The caval veins were examined by Uchida et al., but not by others.

The pulmonary arteries were examined by Shure et al., Uchida et al., and others.

The cardiac chambers and valves were examined by Uchida.

Cellular AS, dye-staining AS and molecular AS were developed and used clinically by Uchida et al., Uchida, Uchida et al., Nakamura et al., Uchida et al., among others.

Angioscopy of aorta and venous system was named as aortoscopy and phleboscopy, respectively.

**Our AS System**

Our AS system comprises a light source, 1.7–4.5F fiberscope, 6–9F guiding balloon catheter, intensified chilled coupled device (ICCD) camera, camera controller, image divider, DVD recorder and television monitor (Fig. 1A).

Usually, a 4.5F fiberscope and 9F balloon guide catheter are used for observation of large diameter vessels. The 4.5F fiberscope (AF 14, Olympus Corporation, Tokyo) contains 3000 glass fibers for image guidance and 300 glass fibers for light guidance. The fiberscope is passed through a 9F balloon guide catheter (Fig. 1B; Clinical Supply Co., Gifu). The balloon is inflated with CO₂. The catheter has a Y connector at the proximal end: one channel for fiberscope insertion and another for saline flushing. A small sized angioscope for coronary use was used for observation of peripheral artery or vein (Fig. 1C). The white balance of the AS is adjusted using white gauze immersed in saline solution as the white color.

Details of various types of AS systems have been described elsewhere.

We have developed two intravascular ultrasonography (IVUS) systems; a 5F, 20 MHz, 20 CPS probe for peripheral vessel use and a 9F, 12 or 20 MHz, 20 CPS probe for great vessel use (Fig. 1D).

**AS Procedures**

**Aorta**

Because the aortic diameter is larger than that of the balloon of the guiding catheter, it is impossible to stop aortic flow using the present AS system.

Following aortography and IVUS, the balloon catheter is introduced retrogradely using a guide wire through a femoral artery, and an AS is introduced into the aorta, then the balloon is inflated and gently placed against the aortic luminal surface. Since the balloon protrudes 5 mm ahead of the catheter tip,
the distance between the fiberscope tip and the aortic luminal surface is maintained at almost 5 mm.\textsuperscript{32,35,36} The diameter of the visual field is approximately 1.2 cm in saline. Heparinized saline solution (10 IU/mL) is then infused, usually at a rate of 5–10 mL/s, using a power injector to displace the blood between the luminal surface and the fiberscope. The guiding balloon catheter is pre-shaped for easy placement on the targeted wall segment, usually an “L” or “U” configuration. By slowly pulling back the balloon catheter during the saline infusion, significantly long segments of the aortic luminal surface can be successively visualized. The total amount of saline solution infused should not exceed 500 mL to avoid acute heart failure due to volume overload.

**Measurement of lesion sizes**

Measurement of lesion sizes is beyond the scope of the present AS system because it uses a fish-eye lens. Nevertheless, lesion sizes can be roughly assessed using the diameter of a guide wire tip placed on or adjacent to a lesion.

**Combined Use of AS and IVUS**

**IVUS system**

In our laboratories, AS is preceded by IVUS because the latter enables successive observation of the entire vascular wall whereas AS is limited to spot observation.

The arterial and venous systems are usually examined by AS in combination with IVUS. For a femoral arterial examination, an IVUS probe is introduced antegradely into the superficial femoral artery, in which atherosclerotic lesions often occur, guided by a 0.014 inch guide wire. The guide wire is advanced first, and then the probe advanced to the target lesion. The vascular wall is then imaged successively by slowly pulling back the probe.

Following aortography, an IVUS probe for large vessel use is advanced through a femoral artery into the left ventricle, using a 0.035 inch guide wire. Use of a radiofocus guide wire (Terumo Company, Tokyo) is recommended because it is very steerable. Slowly pulling back the probe, pineapple-like images from the left ventricle down to the iliac artery can be obtained successively within 5 min.

Angioscopy or intravascular ultrasonography images are simultaneously displayed with fluoroscopic images on a television monitor for confirmation of the location of the area under examination (Fig. 1A). The details of the procedures are described elsewhere.\textsuperscript{22,36}

**AS and IVUS Images of Aortic Disease**

**Aorta without aneurysm**

Atherosclerotic lesions of the aorta are observed in the majority of adult patients, whether symptomatic or asymptomatic. Atherosclerotic aortic plaques are classified as regular and complex, as for coronary and peripheral arteries.\textsuperscript{22,47} Figure 2 shows representative examples of atherosclerotic aortic changes frequently observed in adult patients. Fatty streaks (Fig. 2B-1) are observed in the majority of patients. Complex plaques (polypoid or disrupted plaques; Fig. 2C-1, D-1) are often seen using AS in patients without obvious changes on aortography. Atherosclerotic changes observed by AS are infrequent in the ascending aorta, increase in frequency in the suprarenal abdominal aorta, and are even more common in the infrarenal aorta. Disrupted plaques were often covered with fresh or organized thrombi, suggesting thrombus is recurrently formed on the disrupted plaques (Fig. 2D-1). The patients with coronary artery disease have more advanced atherosclerotic changes in the abdominal aorta than those without (Fig. 3).\textsuperscript{22} Aono observed similar tendency.\textsuperscript{26}
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Fig. 2  Aortic lesions in patients without aneurysm observed using IVUS and AS–IVUS images of aorta from A to D correspond to the AS images from A-1 to D-1, respectively. (A and A-1) The intima was thin (<3 mm in thickness) by IVUS (A) and milky white using AS (A-1), indicating normal aorta. (B and B-1) The intima was thick (>3 mm) using IVUS and yellow using AS, indicating fatty streak. (C and C-1) The polypoid plaque using IVUS (arrow) was a yellow polypoid plaque using AS. This plaque belonged to the complex plaque group. (D and D-1) A plaque with irregular configuration by IVUS (arrow) was a disrupted plaque using AS (arrow), indicating a complex plaque. Cited from Uchida22 with permission. IVUS: intravascular ultrasonography

Dissecting aneurysm

Dissecting aneurysms often occur without preceding symptoms. There are no reliable methods for predicting this often fatal condition.

Angioscopy and intravascular ultrasonography were performed in patients with chronic dissecting aortic aneurysm in patients with stable condition and just before surgical repair.

Figure 4 shows AS and IVUS images of an aortic dissection (DeBakey I).

Disrupted intimal flaps at the entry, true and pseudolumens are clearly visualized using IVUS. Since AS is a point-to-point observation, whereas IVUS can survey the entire aortic wall, IVUS is superior to AS in the detection of aortic dissection.

We observed that the entry was surrounded by disrupted yellow matter in the majority of patients, except those with Marfan syndrome or annuloaortic ectasia, suggesting that the yellow plaque is the site of initiation of dissection. It remains to be elucidated what type(s) of yellow plaques are the starting points of dissection.

Re-entry

Re-entry of dissecting aneurysm is often observed by IVUS. The re-entry is “tent-like”, “flat- or dome-like configuration. By AS, the surrounding tissue of the orifice of re-entry is white or yellow, suggesting that re-entry is created not only at atherosclerotic but also non-atherosclerotic portions (Fig. 5).

Angioscopy and intravascular ultrasonography are now used in the examination of pathomorphological changes of the ectatic aortic root in patients with annuloaortic ectasia, solitary or associated with Marfan syndrome. AS is now being used to predict aortic dissection in this category of aortic diseases, since our recent finding that fold formation in the ectatic aortic root is a morphological change predictive of dissection, irrespective of the luminal diameter.50

Evaluation of surgical repair of dissecting aneurysm

Figure 6 shows changes in the luminal surface of a graft 6 months after repair in a patient with aortic dissection. The luminal surface of the graft is often covered with mural thrombus.

Saccular aortic aneurysms

Saccular (true) aneurysms can appear in any part of the aorta, but occur most frequently in the infrarenal abdominal aorta.

Figure 7 shows an infrarenal abdominal aorta. Although not detectable using aortography, a large doughnut-like thrombus was detected using IVUS. AS revealed it to be a red thrombus.
Fig. 3  AS and IVUS changes of the aorta in patients with or without coronary artery disease (CAD). (A) Aortic segments observed by AS and IVUS. (B) Number of patients in whom N (no abnormal changes), R (regular plaque), or C (complex plaque) were observed. a–g in panel B correspond to those in panel A, respectively. CAD(−): Patients without CAD. CAD(+): Patients with CAD. Normal segment is frequently seen in the ascending aorta and arch, whereas regular plaques are seen frequently in the descending aorta, and complex plaques are most frequently observed in the abdominal aorta. In addition, regular and disrupted plaques are frequent in patients with CAD. Cited from Uchida and Uchida53 with permission. IVUS: intravascular ultrasonography.

Fig. 4  Aortic dissection (DeBakey I) observed in a 48-year-old female. Arrow in an aortogram. (A) Segment examined using IVUS and AS. (B) Intimal flap (a), entry (b), true lumen (T) and pseudolumen (P) confirmed using IVUS. (C) Narrowed true lumen in the descending thoracic aorta (T). (D) The entry observed using AS was a yellow plaque. (E) A mural thrombus in the pseudolumen observed using AS, which accidentally entered into the pseudolumen. (F) Intimal flap observed using angioscopy. Blood flow was seen through the pseudolumen. Cited from Uchida22 with permission. IVUS: intravascular ultrasonography
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**Fig. 5** Re-entry of aortic dissection. By IVUS, re-entry is classified into tent-like (A and A-1), flat (B and B-1) and dome-like (C and C-1) configuration. The orifice edge of them is yellow (A-2, B-2, and C-2), indicating the re-entry occurred in the atherosclerotic portions. IVUS: intravascular ultrasonography

**Fig. 6** Six months after open repair of aortic dissection with artificial graft. The same patient as that in Fig. 4. (A) Aortogram after grafting (arrow). (B) IVUS image of the proximal end of the graft located in the ascending aorta (arrow). (C) IVUS image of the graft in the arch. Arrow: bellows of the graft. (C-1) Angioscopic image of the graft which corresponds to C. Red and yellow portions suggest fresh and organized thrombus, respectively (arrow). (C-2) Dye staining angioscopic image after topical administration of Evans blue dye. Blue portions indicate fibrin-rich thrombus (arrow). Cited from Uchida with permission. IVUS: intravascular ultrasonography
IVUS is more sensitive in detecting calcification than AS because the latter can only visualize exposed calcifications. In our series of 12 patients with abdominal aortic aneurysm, thrombus was observed in all, either red, white, or red-and-yellow, indicating thrombi are formed recurrently within aneurysms. Moreover, exposed atheromatous tissue was frequently observed, indicating that plaque disruption was likely induced by distension of the aortic wall (Figs. 8 and 9). Blood turbulence within aneurysms may also play a part in thrombus formation.

Evaluation of open repair of saccular aortic aneurysm
The combination of AS and IVUS is very useful in the evaluation of surgical repair of aortic aneurysms.

Figure 10 shows changes in the Y graft 1 month after open repair. Pseudoaneurysm was found at the sutured segment of the native aortic stump and the graft using both AS and IVUS. Sutures on atheromatous tissues were also found. It is possible that because fragile atheromatous tissues were ligated, the sutures were loosened and endoleakage occurred, leading to pseudoaneurysm formation.

In our study the luminal surface of artificial graft was often covered with thin mural white thrombi 6 months after surgery. Occlusive thrombus of the graft was observed in three patients. Neo-endothelialization of the graft surface was often incomplete at 6 months (Figs. 11 and 12).

Stent grafts are now widely used in the treatment of aortic aneurysms. However, migration of the stent graft and endoleakage occur not infrequently, suggesting the need for precise calibration of the aneurysm neck, and confirmation of the absence of thrombus and fragile atheromatous tissues using AS and IVUS in combination.

New AS Techniques

Dye-staining AS for tissue imaging
In the field of coronary AS, dye-staining AS is widely used for molecular or tissue imaging of the coronary wall and thrombi using biocompatible and low-molecular dyes. This technology is used for discrimination of platelet aggregates and fibrin in the aorta (Fig. 7).

Cellular imaging using intravascular microscopy
We devised an angiomicroscope that magnifies the target up to 350×. Use of this angiomicroscope is limited to straight vessels such as the femoral or iliac artery, not curved or tortuous vessels. Using this angiomicroscope, foam cells in the disrupted plaque can be clearly discerned in patients.

Fig. 7 An infrarenal saccular aneurysm observed in a 72-year-old male. a and b in (A) segments examined using both IVUS and AS. A doughnut-shaped thrombus was observed in the aneurysm body using IVUS (a-1). AS revealed it to be a red thrombus (a-2). A calcified plaque was detected in the distal segment of the aneurysm using IVUS (b-1). The calcified plaque reflected light using AS (b-2). Cited from Uchida with permission. IVUS: intravascular ultrasonography.
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Fig. 8 Changes in the saccular aneurysm on IVUS and AS. A doughnut-like thrombus on IVUS (arrow in A) is a white thrombus on AS (arrow in A-1). A protruded mass on IVUS (arrowhead in B) is an exposed atheroma on AS (arrowhead in B-1). Arrow in B-1 is a red thrombus. A flap on IVUS (arrow in C) is also a flap on AS (arrow in C-1). Calcium on-IVUS (arrow in D) is also a calcium on AS (arrow in D-1). IVUS: intravascular ultrasonography

Fig. 9 Changes in the body of saccular abdominal aneurysm observed on IVUS and AS in 12 patients. Plaques in the aneurysmal body are disrupted and covered with thrombus in the majority patients. P-value < 0.05 disrupted vs not disrupted plaques by angioscopy. AAA: Abdominal aortic aneurysm, IVUS: intravascular ultrasonography

Molecular imaging using fluorescent AS
Molecular imaging of substances comprising atherosclerotic plaques has been intensively studied using a variety of imaging techniques. In vivo molecular imaging of lipoproteins or apolipoproteins such as oxidized low-density and high-density lipoprotein in the coronary artery wall of patients with coronary artery disease. This technique may contribute to the understanding and evaluation of molecular targeted therapies of not only for coronary artery disease but also for aortic disease.

Angioscopy of the aorta by non-obstructive guiding catheter
Recently, observation of the aorta was trialed by angioscopy using non-obstructive guiding catheter without balloon. It...
Fig. 10 A 68-year-old male with an infrarenal saccular aneurysm who underwent open repair with a Y graft. (A) Angiogram of the Y graft. (a and b) Body and right limb of the graft examined using IVUS and AS. A pseudoaneurysm at the sutured site between the native aortic stump and the graft body detected using IVUS (arrow in a-1) and AS (arrows in a-2). Exposed threads were also observed using AS (arrow in a-3). No obstruction was observed in the right limb using IVUS (arrow in b-1), but neointimal coverage of the graft limb was incomplete using AS (arrow in b-2). Cited from Uchida with permission. IVUS: intravascular ultrasonography

Fig. 11 Neo-endothelial coverage of Y-graft 6 months after open repair of saccular abdominal aneurysm. A–D correspond to A-1 to D-1, respectively. Arrows in A–D indicate the portions observed using AS. Arrows in A-1 to D-1: complete neo-endothelial coverage of the graft, incomplete neo-endothelial coverage, a hole in the graft, and hyperplastic neo-endothelium at the sutured portion of graft limb and common iliac artery. Arrowhead in D-1: graft.

remains obscure whether this technique remains for a simple observation of aortic luminal morphology and color but also for cellular or molecular imaging because blood flow is necessary to be stopped at least for 10 s to allow biomarkers to penetrate into the vascular wall and conjugate with the target substance for staining.
**Future Prospects**

The major cause of aortic and peripheral artery diseases is atherosclerosis, as in the case of coronary artery disease. Until now, a number of imaging techniques have been applied to the imaging of the cells such as macrophages, and substances comprising atherosclerotic plaques such as lipids (cholesterol, cholesterol esters and triglyceride), lipoproteins, apolipoproteins, calcium compounds and enzymes, to clarify the molecular mechanisms of atherosclerotic disease, as well as vasculitis such as arteritis and aortitis, the mechanism of which are not well understood.

Although invasive, angioscopy is a high-resolution imaging technique and therefore useful for molecular imaging and for the guidance and evaluation of molecular targeted therapy for vascular disease. Clinical application of fluorescent angioscopy has commenced for molecular imaging of coronary and myocardial disease. This technique is now applied to coronary, peripheral and great vessels in the clinical situation.

**Conclusion**

Recent advances in AS and IVUS technology allow us to examine the vascular interior and wall architecture. These imaging technologies are now used for the diagnosis of vascular diseases, evaluation of surgical and interventional therapies, and guidance of interventions. AS will also be used, as in coronary artery disease, for cellular and molecular imaging to clarify the underlying mechanisms and for molecular targeted therapy of aortic disease.

**Disclosures**

The author has no conflicts of interest to declare.
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