Early Detection of Vulnerable Atherosclerotic Plaque for Risk Reduction of Acute Aortic Rupture and Thromboemboli and Atheroemboli Using Non-Obstructive Angioscopy

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The mortality rate due to rupture of aortic dissection and aortic aneurysm is approximately 90%. Acute aortic rupture can be fatal prior to hospitalization and has proven difficult to diagnose correctly or predict. The in-hospital mortality rate of ruptured aortic aneurysm ranges from 53 to 66%. Emergency surgical and endovascular treatments are the only options for ruptured aortic dissection and aortic aneurysm. No method of systematic early detection or inspection of vessel injury is available at the prevention stage. Regardless of the improvement in many imaging modalities, aortic diameter has remained a major criterion for recommending surgery in diagnosed patients. Previous reports have suggested a relationship between vulnerable plaque and atherosclerotic aortic aneurysm. Non-obstructive angioscopy is a new method for evaluating intimal injury over the whole aorta. It has been used to identify many advanced atherosclerotic plaques that were missed on traditional imaging modalities before aneurysm formation. Non-obstructive angioscopy has shown that atherosclerosis of the aorta begins before that of the coronary artery, which had been noted on autopsy “in vivo”. Strong or repetitive aortic injuries might cause sudden aortic disruption. Aortic atheroma is also a risk factor of stroke and perivascular embolism. Detecting aortic vulnerable atherosclerotic plaque on non-obstructive angioscopy may not only clarify the pathogenesis of acute aortic rupture and “aortogenic” thromboemboli and atheroemboli but also play a role in the pre-emptive medicine.

Key Words: Aneurysm; Angioscopy; Aorta; Dissection; Vulnerable plaque

Still Silent But Virulent: High Mortality of Ruptured Aortic Aneurysm and Dissection

Disruption of the aortic wall causes aneurysm and dissection, which can be rapidly fatal if they rupture. In general, aneurysms remain silent until rupture. Death from a ruptured aneurysm and dissection prior to hospitalization might be erroneously attributed to another cause unless an autopsy is performed. The Hisayama study, in which approximately 80% of deceased subjects enrolled in the study underwent autopsy, showed that the prevalence of aortic aneurysm and dissection among sudden unexpected deaths has increased threefold over 30 years in Japan. The mortality rate of ruptured abdominal aortic aneurysm (AAA) is approximately 90%. Of the approximately 75% of patients with ruptured AAA who reach an emergency department alive, 40% die immediately, 1% per hour dying thereafter, and between 5% and 20% dying during or shortly after surgery. In-hospital mortality of ruptured AAA was reported to range from 53% to 66% in England and the USA. The indications for endovascular repair (EVAR) are rapidly increasing, but the superiority of EVAR is controversial. The EVAR trial 2 showed no benefit from stent grafting compared with no therapy for AAA. The DREAM trial compared EVAR with traditional surgical therapy. The midterm follow-up in the DREAM trial found that at 2 years, the survival curves cross, and, from that point on, stent-treated patients had poorer survival than surgically treated patients with AAA. Even if patients are admitted to the emergency department, ruptured aortic dissection is also difficult to promptly diagnose. Only 15–43% of patients are initially diagnosed correctly. Approximately 1–2% of patients per hour die after onset. Combining pre-hospital with in-hospital mortality rates indicates that 93% of deaths from aortic dissection occur...
Limitation of Size-Based Indication for Treatment

The indication of aortic aneurysm for surgery or EVAR is determined based on dimensions and growth rates of the aneurysm. The incidence of rupture increased with the dimensions and growth rate of aneurysms. There is a hinge point for rupture according to size: these hinge points are thought to be 6 cm in the ascending aorta and 7 cm in the descending aorta.

There is a limitation, however, to the size-based determination of indications for treatment. Computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography are used for the measurement for the aorta, and estimating its true size is difficult.

There is no consensus on whether the aortic wall should be included or excluded in the aortic diameter, leading to a difference of several millimeters in the calculated measurements.

Initially detected aneurysms smaller than indicated for surgery must be periodically monitored until they grow to the critical size or exhibit a growth rate >0.5 cm/year. Among patients screened for AAA, 5.1% had AAA ≥3.0 cm in size: 83% of the aneurysms were 3.0–4.4 cm, 13% were 4.5–5.5 cm, and 4.1% were >5.5 cm.

There is a sex difference in rupture risk. Women had the same growth rates but a fourfold increased risk of rupture compared with men. Moreover, dissections can occur at small aortic size.

The growth rate of aneurysm is variable even within an individual. Aneurysms in the descending aorta grow faster than aneurysms in the ascending aorta. Large aneurysms grow more rapidly than small aneurysm.

Some previous reports have suggested that aortic atherosclerotic plaque might cause progression of aneurysm and rupture. Repeated intraplaque hemorrhages play a major role in the evolution of thrombotic occlusive disease, similar to the role of intraluminal thrombus in the progression of AAA toward rupture. Ruptured atherosclerotic plaque may cause spontaneous rupture of the aorta.

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Figure 1. (A) The conventional non-obstructive angioscopy system. Low-molecular-weight dextran is infused from the probing catheter to obtain a visual field. (B) The dual-infusion system for non-obstructive angioscopy. Low-molecular-weight dextran is infused both from the probing catheter and the guiding catheter to obtain a visual field. CCD, charge-coupled device.

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Angioscopy for Aortic Vulnerable Plaque

By the 1980s, coronary angioscopy had been used in patients at the time of peripheral or coronary bypass surgery, in addition to its use in experimental models. After the completion of trials aimed at developing the system, two types of angioscopy became available: non-obstructive angioscopy, which was developed in Japan (Figure 1), and occlusion-type angioscopy, which was developed in the USA. Occlusion-type angioscopy has one key limitation: occlusion by balloon catheter for the removal of blood and to clarify the visual field may cause myocardial ischemia.

The main methodology in the original non-obstructive approach was to visualize the aortic wall in vivo using a flexible balloon catheter for blood aspiration and inflation. This allowed for the visualization of the aortic wall surface with a full-color, 3-D perspective of the vessel surface morphology and reasonably accurate information regarding factors such as coronary plaque rupture, yellow plaque, plaque regression, dissection, thrombus, and intimal stent coverage. By the 1980s, coronary angioscopy had been used in patients at the time of peripheral or coronary bypass surgery, in addition to its use in experimental models. After the completion of trials aimed at developing the system, two types of angioscopy became available: non-obstructive angioscopy, which was developed in Japan (Figure 1), and occlusion-type angioscopy, which was developed in the USA. Occlusion-type angioscopy has one key limitation: occlusion by balloon catheter for the removal of blood and to clarify the visual field may cause myocardial ischemia.

Figure 2. A representative case of abundant aortic plaque. A 49-year-old man with hypertension, hyperlipidemia, and diabetes mellitus was admitted due to atypical chest pain. Coronary angiography of (A) left coronary artery and (B) right coronary artery did not show significant stenosis. (C, D) Location of plaques on non-obstructive angioscopy projected onto a volume-rendered contrast-enhanced computed tomography image for (C) anterior and (D) posterior projection. No ectasia, dissection, or aneurysm was observed in the aorta. (E) Non-obstructive angioscopy of the aorta showed 26 plaques including ruptured plaque with mixed thrombi (panels 18–26), small fissure (panels 5, 11), and white thrombus (panels 15, 18).
artery, pulling back from the ascending aorta to iliac artery, or by left brachial artery, pulling back initially from the ascending aorta to aortic arch, then directing the guiding catheter to the common iliac artery with a guidewire, and finally pulling back from the common iliac artery to aortic arch. A representative case is shown in Figure 2. Twenty-six yellow plaques including 5 ruptured plaques and 3 erosions were identified in an aorta without significant ectasia or dissection. Waves of thrombi on the vulnerable plaque spontaneously ripple, and they are torn and scatter like cotton or dandelion fuzz (Figure 3).

The preliminary data from ascending aorta to iliac artery in 75 consecutive patients who had or were suspected to have coronary artery disease and no previous detection of aortic aneurysm indicate that atherosclerosis of the aorta is more advanced than atherosclerosis of the coronary artery (Figure 4). Surprisingly, plaque rupture or erosion was found in 86.7% of patients, and the number of plaque ruptures and erosions averaged 5.3±5.0 per patient (Figure 5). These findings are

Angioscopy was to obtain a visual field by injecting low-molecular-weight dextran into the space between the 4-Fr probing catheter and the fiber (Figure 1A). Consequently, the blood is diluted, and the field of vision is widened. Non-obstructive angioscopy is relatively safe, because adequate blood flow is maintained throughout the process of image acquisition. Initially this method was used in the coronary artery, and it has since been applied to other larger arteries such as the renal artery and pulmonary artery.

When low-molecular-weight dextran is dual-infused from the 4-Fr probing catheter along with a 6-Fr guiding catheter (Figure 1B), the visual field can be obtained more clearly than with a single infusion, and the application of non-obstructive angioscopy can be expanded to vessels larger than coronary arteries, including thoracic and abdominal aorta. Angioscopic observation of the aorta is performed continuously while a 6-Fr guiding catheter is slowly pulled back and rotated for vessel-wide screening. The approach can be either by femoral artery, pulling back from the ascending aorta to iliac artery, or by left brachial artery, pulling back initially from the ascending aorta to aortic arch, then directing the guiding catheter to the common iliac artery with a guidewire, and finally pulling back from the common iliac artery to aortic arch. A representative case is shown in Figure 2. Twenty-six yellow plaques including 5 ruptured plaques and 3 erosions were identified in an aorta without significant ectasia or dissection. Waves of thrombi on the vulnerable plaque spontaneously ripple, and they are torn and scatter like cotton or dandelion fuzz (Figure 3).

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consistent with a previous pathological study reporting that the percentage area affected with fatty streaks and raised lesions was greater in the aorta than in the coronary artery.\textsuperscript{50}

With non-obstructive angioscopy, vascular surgeons can view the surface of the aneurysm at the location where operation is required. While pathologists can thoroughly evaluate a formalin-fixed aorta, there has been no systematic early detection or inspection of vessel injury at the prevention stage. Non-obstructive angioscopy can provide intra-arterial live imaging in vivo. Even inside a normal-sized aorta (Figure 6), spontaneous plaque ruptures and intimal injury appear as a swirling storm. For instance, white thrombi (Figure 6C, panels 6,25,29), mixed thrombi (Figure 6C, panels 3,8,10,17), subintimal hematoma (Figure 6C, panels 5,11,22,23,26–28), and small intimal fissures that might cause aortic fragileness were observed (Figure 6C, panels 8,21,23,26–28). Using non-obstructive angioscopy, many types of advanced atherosclerotic plaque were clearly demonstrated that were missed on traditional imaging modalities (Figure 6D).

Intramural hematoma,\textsuperscript{51} penetrating atherosclerotic ulcer,\textsuperscript{52} and ulcer-like projection\textsuperscript{53} detected on CT may represent important signs for increased rupture risk. CT, however, seems to visualize intimal injury less clearly compared with non-obstructive angioscopy (Figure 7). Diagnosis at an earlier stage of aortic injury might play a role in preventing unexpected rupture of aneurysm and dissection. Intramural hemorrhage and aortic aneurysm smaller than is indicated for surgery should not be ignored if observed on non-obstructive angioscopy, because intimal injury does exist.

Two New Paradigm Shifts in Acute Aortic Rupture and Embolism

No existing method allows observation of intimal injury in vivo more precisely than non-obstructive angioscopy. Thus, non-obstructive angioscopy of the aorta may produce two paradigm shifts. The first is that direct evaluation of intimal injury might enable pre-emptive therapies for aortic rupture or dissection. The change in aortic size resulting from atherosclerotic dilatation is only the reflection of aortic injury. A new risk stratification for rupture or dissection might be possible if angiographic findings can predict aortic events such as aortic death, aortic rupture, or dissection. A prospective registration trial concerning the relationship between angiographic findings and prognosis is ongoing. Recently, it was reported that treatment with doxycycline, which inhibits matrix metalloproteinases, suppressed the development of AAA in the experimental elastase-induced rodent model of AAA.\textsuperscript{54} Novel approaches to intimal repair by drug,\textsuperscript{55} stenting, and regenerative therapies\textsuperscript{56} in the prevention stage might be more effective under guidance with non-obstructive angioscopy.

Second, non-obstructive angioscopy could aid in the early detection and prevention of thromboemboli and atheroemboli (also called cholesterol embolization syndrome).\textsuperscript{57} Both types of emboli may differ in composition and clinical manifestations. Thromboemboli, which are 20–45-fold more common than atheroemboli,\textsuperscript{58,59} are reported to be fragmented pieces of thrombi from the surface of an ulcerated plaque.\textsuperscript{60} In addition to causing local mechanical obstruction, these cholesterol crystal emboli also induce an inflammatory reaction that contributes to tissue ischemia and end-organ damage.\textsuperscript{59,61–64} No imaging modality has demonstrated rupture of aortic vulnerable plaque and ruptured plaque in vivo. A preliminary angiographic study demonstrated that thrombi and advanced atherosclerotic plaques were spontaneously ruptured. Complex atheromatous plaques in the aortic arch and descending aorta detected on transesophageal echocardiography (TEE) have been reported to increase the risk of stroke or transient ischemic attack.\textsuperscript{55,66} Embolization from the abdominal aorta may cause lower extremity ischemia.\textsuperscript{62} CT may underestimate the atheromatous plaque burden in the aorta compared with 2-D TEE.\textsuperscript{67} Complex plaque, defined as plaque at least 4 mm thick or having a mobile component detected on TEE, has been considered more likely to cause embolic events.\textsuperscript{68} Detection of thromboemboli and atheroemboli and distinguishing between them might play a role in risk stratification. Moreover, detection of aortic ruptured plaque might predict the risk of thrombotic complication of coronary or the need for aortic catheterization procedures such as intra-aortic balloon pump and transcatheter aortic valve implantation.\textsuperscript{69–71}

Conclusions

Non-obstructive angiography of the aorta is a novel method that may have important implications for the diagnosis and management of vulnerable atherosclerotic plaque. The use of non-obstructive angioscopy, as well as the invasive method, in the diagnosis of aortic disease, the significance of its use in screening, in safety for acute aortic dissection and aneurysm, and in the widening of the field of view should be explored. The significance of “vulnerable plaque” may differ between
Figure 6. Representative case of abundant aortic plaque with coronary artery disease. An asymptomatic 78-year-old man with a history of percutaneous coronary intervention to the middle left circumflex coronary artery, hypertension, and hyperlipidemia. (A,B) Location of plaques on non-obstructive angioscopy projected onto aortography for the (A) thoracic aorta and (B) abdominal aorta. (C) Non-obstructive angioscopy of the aorta showed 32 plaques including ruptured plaque with mixed thrombi (panels 3,8,17,26), small fissure (panels 8,11,13,21,23,27,28), and white thrombus (panels 6,19,29). (D) Comparison of non-obstructive angioscopy, aortography, contrast-enhanced computed tomography, and 10-MHz intravascular ultrasound of the aorta.
coronary artery and aorta. The difference may be clarified on non-obstructive angioscopy. Further research on the applications and clinicopathological correlates of non-obstructive angiographic findings will be valuable in establishing the full potential of the approach for pre-emptive medicine in preventing acute aortic rupture and "aortogenic" thromboemboli and atheroemboli.

Figure 7. A 73-year-old man, who had a history of hypertension and hyperlipidemia, who presented to hospital with severe chest and back pain for 15 min, 2 days previously. Electrocardiogram did not indicate any abnormality. (A) Chest X-ray showed enlargement and protrusion of the left first aortic arch. Cardiotoracic ratio was 48.8%. Coronary angiography did not show any stenosis (data not shown). (B) Volume-rendered, (C) coronal, and (D) sagittal images of thoracic aorta, and (E) coronal image of abdominal aorta from contrast-enhanced computed tomography. Aortic arch aneurysm of 52×47 mm, infrarenal abdominal aortic aneurysm of 40×29 mm, and left common iliac artery aneurysm of 28×25 mm were detected. Arterial wall thickening and intimal protrusion were suspected in the greater curvature of the aortic arch aneurysm. Aortography of the (F) anterior and (G) left 50° oblique projection. Only slight irregularity was demonstrated in the greater curvature of the aortic arch aneurysm. Non-obstructive angioscopy of the aorta (H, panels 1–4) correspond to the same numbers in (D, E), respectively. The inner surface of the aortic arch aneurysm was rough and erosive, probably due to intramural hemorrhage (1). Yellow plaque and mixed thrombi were also detected (2). No flap that could have caused dissection was found. Salmon-pink intramural hemorrhage was detected in the infrarenal abdominal aortic aneurysm (3). A cave-like formation filled with red thrombi was detected in the right common iliac artery aneurysm (4). The patient had not had chest X-ray or CT previously. One speculation is that the patient’s chest and back pain was thought to be related to acute injury including intramural hematoma in the aortic arch. In future, non-obstructive angioscopy might be able to be used to determine whether intimal injury is new or old.
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References
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