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.1 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.2 The mortality rate of ruptured abdominal aortic aneurysm (AAA) is approximately 90%.3-5 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.6-8 In-hospital mortality of ruptured AAA was reported to range from 53% to 66% in England and the USA.9

The indications for endovascular repair (EVAR) are rapidly increasing,10 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.11 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.9

Even if patients are admitted to the emergency department, ruptured aortic dissection is also difficult to promptly diagnose.12 Only 15–43% of patients are initially diagnosed correctly.13-15 Approximately 1–2% of patients per hour die after onset.16 Combining pre-hospital with in-hospital mortality rates indicates that 93% of deaths from aortic dissection occur
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 $\geq 3.0$ 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. Fibrous cap, lipid pool, and thrombus have been detected inside AAA on MRI.

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 $\geq 3.0$ 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. Fibrous cap, lipid pool, and thrombus have been detected inside AAA on MRI.
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 angioscopy provides 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.

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).

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
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. 50

With non-obstructive angioscopy, vascular surgeons can view the surface of the aeurysm 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, there has been no systematic early detection is required. While pathologists can thoroughly evaluate a formalin-fixed aorta, there has been no systematic early detection and prevention of thromboemboli and atheroemboli (also called cholesterol embolization syndrome). 52 Both types of emboli may differ in composition and clinical manifestations. Thromboemboli, which are 20–45-fold more common than atheroemboli, 58, 59 are reported to be fragmented pieces of thrombi from the surface of an ulcerated plaque. 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. 58–64 No imaging modality has demonstrated rupture of aortic vulnerable plaque and ruptured plaque in vivo. A preliminary angioscopic 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. 55, 66 Embolization from the abdominal aorta may cause lower extremity ischemia. 62 CT may underestimate the atheromatous plaque burden in the aorta compared with 2-D TEE. 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. 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. 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

---

**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 dilation is only the reflection of aortic injury. A new risk stratification for rupture or dissection might be possible if angioscopic findings can predict aortic events such as aortic death, aortic rupture, or dissection. A prospective registration trial concerning the relationship between angioscopic 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. 54 Novel approaches to intimal repair by drug, 55 stenting, and regenerative therapies 56, 57 in the prevention stage might be more effective under guidance with non-obstructive angioscopy.

Second, non-obstructive angioscopy could aid in early detection and prevention of thromboemboli and atheroemboli (also called cholesterol embolization syndrome). 52 Both types of emboli may differ in composition and clinical manifestations. Thromboemboli, which are 20–45-fold more common than atheroemboli, 58, 59 are reported to be fragmented pieces of thrombi from the surface of an ulcerated plaque. 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. 58–64 No imaging modality has demonstrated rupture of aortic vulnerable plaque and ruptured plaque in vivo. A preliminary angioscopic 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. 55, 66 Embolization from the abdominal aorta may cause lower extremity ischemia. 62 CT may underestimate the atheromatous plaque burden in the aorta compared with 2-D TEE. 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. 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. 69–71

---

**Figure 5.** Number of aortic vulnerable plaques from ascending aorta to iliac artery determined on non-obstructive angioscopy in 75 consecutive patients who had or were suspected to have coronary artery disease and no previous detection of aortic aneurysm.
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.
Angioscopy for Aortic Vulnerable Plaque

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. Cardiothoracic 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.
K.K. is the president of Inter-tec Medicals and the person who developed non-obstructive angiography. S.K. is a technical consultant for Nemoto Kyorin-do.

**References**

1. Krüger T, Conzelmann LO, Bonser RS, Borger MA, Czerny M, Wildhirt S, et al. Acute aortic dissection type A. Br J Surg 2012; 799; 1331–1344.
2. Nagata M, Ninomiya T, Doi Y, Hata J, Ikeda F, Mukai N, et al. Temporal trends in sudden unexpected death in a general population: The Hisayama study. Am Heart J 2013; 165; 932–938.
3. Rutledge R, Oller DW, Meyer AA, Johnson GJ Jr. A statewide population-based time-series analysis of the outcome of ruptured abdominal aortic aneurysm. Ann Surg 1996; 223; 492–505.
4. Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, et al. Multicentre Aneurysm Screening Study Group. The Multi-center Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: A randomized controlled trial. Lancet 2002; 360; 1531–1539.
5. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance: UK small aneurysm trial participants. Ann Surg 1999; 230; 289–296.
6. Anagnostopoulos CE, Prabhakar MJ, Kittle CF. Aortic dissections and dissecting aneurysms. Am J Cardiol 1999; 83; 296–303.
7. Hilpert AE Jr, Johns VJ Jr, Kime SW Jr. Dissecting aneurysm of the aorta: A review of 505 cases. Medicine (Baltimore) 1958; 37; 217–279.
8. Masuda Y, Yamada Z, Morooka N, Watanabe S, Inagaki Y. Prognosis of patients with medically treated aortic dissections. Circulation 1991; 84; II77–II13.
9. Karthiksalangam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniacci JD, Hinchliffe RJ, et al. Mortality from ruptured abdominal aortic aneurysms: Clinical lessons from a comparison of outcomes in England and the USA. Lancet 2014; 383; 963–969.
10. Handa N, Yamashita T, Takahashi T, Onohara T, Okamoto M, Yamamoto T, et al. Impact of introducing endovascular aneurysm repair on treatment strategy for repair of abdominal aortic aneurysm: National Hospital Organization network study in Japan. Circ J 2014; 78; 1104–1111.
11. EVAR Trial Participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): Randomised controlled trial. Lancet 2005; 366; 2187–2192.
12. Hansen MS, Nogareja GD, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. Am J Cardiol 2007; 99; 852–856.
13. Męszáros I, Mórocz J, Szlávi I, Schmidt J, Tornóci L, Nagy L, et al. Epidemiology and clinicopathology of aortic dissection. Chest 2000; 117; 1271–1278.
14. Sullivan PR, Wolfson AB, Leckey RD, Burke JL. Diagnosis of acute thoracic aortic dissection in the emergency department. Am J Emerg Med 2000; 18; 46–50.
15. Sullivan PR, Wolfson AB, Leckey RD, Burke JL. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. Am J Cardiol 2007; 99; 852–856.
16. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): New insights into an old disease. JAMA 2000; 283; 897–903.
17. JCS Joint Working Group. Guidelines for diagnosis and treatment of aortic aneurysm and aortic dissection (JCS 2011): Digest version. Circ J 2013; 77; 789–828.
18. Haverich A, Miller DC, Scott WC, Mitchell RS, Oyer PE, Stinson EB, et al. Acute and chronic aortic dissections: Determinants of long-term outcome for operative survivors. Circulation 1985; 72; II22–II34.
19. Pansini S, Gagliardotto PV, Pompei E, Patisi F, Bardi G, Castenetta E, et al. Early and late risk factors in surgical treatment of acute type A aortic dissection. Ann Thorac Surg 1998; 66; 779–784.
20. Chiappini B, Scheipers M, Tan E, Dell’Amore A, Morshuis W, Duscha B, et al. Early and late outcomes of acute type A aortic dissection: Analysis of risk factors in 487 consecutive patients. Eur J Cardiothorac Surg 2002; 26; 180–186.
21. Lai DT, Robbins RC, Mitchell RS, Moore KA, Oyer PE, Shumway NE, et al. Does profound hypothermic circulatory arrest improve survival in patients with acute type A aortic dissection? Circulation 2002; 106; 1218–1228.
22. Sabik JF, Lytle BW, Blackstone EH, McCarthy PM, Loop FD, Cosgrove DM. Long-term effectiveness of operations for ascending aortic dissections. J Thorac Cardiovasc Surg 2000; 119; 946–962.
23. Tsi TTT, Evangelista A, Nienaber CA, Tripathy U, Sechtem U, Fattori R, et al. Long-term survival in patients presenting with type A acute aortic dissection: Insights from the International Registry of Acute Aortic Dissection (IRAD). Circulation 2006; 114 (1 Suppl); I350–I356.
24. Tsi TTT, Fattori R, Tripathy U, Isselbacher E, Myrmel T, Evangelista A, et al. Long-term survival in patients presenting with type B acute aortic dissection: Insights from the International Registry of Acute Aortic Dissection. Circulation 2006; 114; 2226–2231.
25. Minami T, Imoto K, Uchida K, Yasuda S, Karube N, Suzuki S, et al. Mid-term outcomes of acute type B aortic dissection in Japan single center. Ann Thorac Cardiovasc Surg 2013; 19; 461–467.
26. Elefteriades JA. Natural history of thoracic aortic aneurysms: Indications for surgery, and surgical versus nonsurgical risks. Ann Thorac Surg 2002; 74; S1877–S1880.
27. Brewer DC, Cronenwett JL, Halliwell JW Jr, Johnston KW, Krupski WC, Matsumura JS, et al. Guidelines for the treatment of abdominal aortic aneurysms: Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. J Vasc Surg 2003; 37; 1106–1117.
28. Carty MA, Rizzo JA, Hamilton GL, Mandapati D, Darr U, Kopf GS, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysms? J Thorac Cardiovasc Surg 1997; 113; 476–491.
29. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010; 55; 841–857.
30. Lee ES, Pickett E, Hedayati N, Dawson DL, Pevec WC. Implementation of an aortic screening program in clinical practice: Implications for the Screen For Abdominal Aortic Aneurysm Study. Am J Med 2009; 126; 1055–1056.
31. Michel JB, Delbosc S, Ho-Tin-Noé B, Leseche G, Nicoletti A, Meilhac O, et al. From intraplaque haemorrhages to plaque vulnerability: Biological consequences of intraplaque haemorrhages. J Cardiovasc Med (Hagerstown) 2012; 13; 628–634.
32. Komanapalli CB, Tripathy U, Ravichandran PS, Slater MS. Spontaneous rupture of the thoracic aorta. Eur J Cardiothorac Surg 2006; 29; 616–618.
33. Kramer CM, Cerilli LA, Hagspiel K, DiMaria JM, Epstein FH, Kern JA. Magnetic resonance imaging identifies the fibrous cap in atherosclerotic abdominal aortic aneurysm. Circulation 2004; 109; 1016–1021.
34. van Heeswijk RB, Pellegrin M, Flögel U, Gonzales C, Aubert JF, Mazzolini L, et al. Fluorine MR imaging identifies the fibrous cap in atherosclerotic plaque in vivo. Radiology 2014 December 12, doi:10.1148/ radiol.14141371.
35. Mato G, Izquierdo-García D, Badimon JJ, Fayad ZA, Fuster V. Noninvasive assessment of hypoxia in rabbit advanced atherosclerosis using 18F-fluoromisonidazole positron emission tomographic imaging. Circ Cardiovasc Imaging 2014; 7; 312–320.
36. Kodama K, Asakura M, Ueda Y, Yamaguchi O, Hirayama A. The role of plaque rupture in the development of acute coronary syn- drome evaluated by the coronary angiography. Intern Med 2000; 39; 333–335.
37. Asakura M, Ueda Y, Yamaguchi O, Adachi T, Hirayama A, Hori M, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: An angiographic study. J Am Coll Cardiol 2001; 37; 1284–1288.
38. Hirayama A, Saito U, Ueda Y, Takayama T, Honye Y, Komatsu S, et al. Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. Circ J 2009; 73; 718–725.
39. Komatsu S, Hirayama A, Ueda Y, Okawara Y, Ogasawara N, Kashiwase K, et al. Coronary ruptured plaque mimicking spontane-
Angioscopy for Aortic Vulnerable Plaque

45. Komatsu S, Sato Y, Ueda Y, Achenbach S, Ebihara Y, Hirayama A, et al. Thrombotic occlusion proximal to plaque rupture in acute myocardial infarction: Evaluation by intravascular ultrasound and coronary angiography. *Int J Cardiol* 2007; 123: e12–e14, doi: 10.1016/j.ijcard.2006.11.106.

46. Ueda Y, Nanto S, Komamura K, Kodama K. Neointimal coverage of stents in human coronary arteries observed by angioscopy. *J Am Coll Cardiol* 1994; 23: 341–346.

47. Spears JR, Marais HJ, Serur J, PomerantzFZ, Geyer RP, Sigzener RS, et al. In vivo coronary angioscopy. *J Am Coll Cardiol* 1983; 1: 1311–1314.

48. Litvack F, Grundfest WS, Lee ME, Carroll RM, Foran R, Chaux A, et al. Angioscopic visualization of blood vessel interior in animals and humans. *Clin Cardiol* 1985; 8: 65–70.

49. Nanto S, Ohara T, Mishima M, Hirayama A, Komamura K, Matsamura Y, et al. Coronary angioscopy: A monorail angioscope with movable guide wire. *Am J Card Imaging* 1991; 5: 1–5.

50. Mizuno K, Arai T, Satomura K, Shibuya T, Arakawa K, Okamoto Y, et al. New percutaneous transluminal coronary angioscope. *J Am Coll Cardiol* 1989; 13: 363–368.

51. Emanuelli S, Future challenges to coronary angioplasty: Perspectives on intracoronary imaging and physiology. *J Intern Med* 1995; 238: 111–119.

52. Komatsu S, Ohara T, Takewa M, Takahashi S, Nomamoto T, Kamata T, et al. Nonobstructive angioscopy in patients with atherosclerotic renal artery stenosis. *J Cardiol Cases* 2014; 9: 18–21.

53. Nakanishi N, Nakamura T, Yamano T, Shiraishi H, Matoba S, Matsumura M, et al. Angioscopic observation in chronic thromboembolic pulmonary hypertension before and after ballooon pulmonary angioplasty. *J Cardiovasc Med (Hagerstown)* 2014 August 1, doi:10.2459/CM.0000000000000166.

54. Strong JP, Malcom GT, McManah CA, Tracy RE, Newman WP 3rd, Herderick EE, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: Implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA* 1999; 281: 727–735.

55. Vilacosta I, San Roman JA, Ferreiros J, Aragóncillo P, Méndez R, Castillo JA, et al. Natural history and serial morphologic of aortic intramural hematoma: A novel variant of aortic dissection. *Am Heart J* 1997; 134: 495–507.

56. Stanson AW, Kazmier FJ, Hollier LJ, Edwards WD, Pairolero PC, Sheedy PF, et al. Penetrating atherosclerotic ulcers of the thoracic aorta: Natural history and clinicopathologic correlations. *Ann Vasc Surg* 1986; 1: 15–23.

57. Kaji S, Akasaka T, Katayama M, Yamamura A, Yamabe K, Tamita K, et al. Long-term prognosis of patients with type B aortic intramural hematoma. *Circulation* 2003; 108(Suppl): III07–III11.

58. Petrinec D, Liao S, Holmes DR, Reilly JM, Parks WC, Thompson RW. Doxycycline inhibition of aneurysmal degeneration in an elastase-induced rat model of abdominal aortic aneurysm: Preservation of aortic elastin associated with suppressed production of 92 kDa gelatinase. *J Vasc Surg* 1996; 23: 336–346.

59. Kurowska K, Matsumura JS, Yanamouchi D. Current status of medical treatment for abdominal aortic aneurysm. *Circ J* 2013; 77: 2860–2866.

60. Bashir CA, Rao RR, Ramamurthi A. Perspectives on stem cell-based elastic matrix regenerative therapies for abdominal aortic aneurysms. *Stem Cells Transl Med* 2013; 2: 401–408.

61. Saric M, Kronzon I. Cholesterol embolization syndrome. *Curr Opin Cardiol* 2011; 26: 472–479.

62. Saric M, Kronzon I. Aortic atherosclerosis and embolic events. *Curr Cardiol Rep* 2012; 14: 342–349.

63. Kronzon I, Tunic PA. Aortic atherosclerotic disease and stroke. *Circulation* 2006; 114: 63–75.

64. Tunic PA, Kronzon I. Atheromas of the thoracic aorta: Clinical and therapeutic update. *J Am Coll Cardiol* 2000; 35: 545–554.

65. Flory C. Arterial occlusions produced by emboli from eroded aortic atheromatous plaques. *Am J Pathol* 1945; 21: 549–565.

66. Liew YP, Bartholomew JR. Atheromatous embolization. *Vasc Med* 2005; 10: 309–326.

67. Yutani C, Imakita M, Ishibashi-Ueda H, Hatanaka K, Waki R, Ogawa M, et al. Cerebro-spinal infarction caused by atheromatous emboli. *Acta Pathol Jpn* 1985; 35: 789–801.

68. Masuda J, Yutani C, Ogata J, Kuriyama J, Yamaguchi T. Atheromatous embolism in the brain: A clinicopathologic analysis of 15 autopsy cases. *Neurology* 1994; 44: 1231–1237.

69. Guidoux C, Mazzighi M, Lavallée P, Labrenche J, Meseguer E, Cabrelo J, et al. Aortic arch atheroma in transient ischemic attack patients. *Atherosclerosis* 2013; 231: 124–128.

70. Katsanos AH, Spence JD, Bogiatzi C, Parissis J, Giannopoulos S, Frogoudaki A, et al. Recurrent stroke and patent foramen ovale. A systematic review and meta-analysis. *Stroke* 2014; 45: 3352–3359.

71. Molisie TA, Tunic PA, Kronzon I. Complications of aortic atherosclerosis: Atheroemboli and thromboemboli. *Curr Treat Options Cardiovasc Med* 2007; 9: 137–147.

72. Stern A, Tunic PA, Culliford AT, Lachmann J, Baumann FG, Kanchuger MS, et al. Protruding aortic arch atheromas: Risk of stroke during heart surgery with and without aortic arch endarterectomy. *Am Heart J* 1999; 138: 746–752.

73. Yutani C, Imakita M, Ueda-Ishibashi H, Katsuragi S, Fujita H. Coronary artery embolism with special reference to invasive procedure as the source. *Mod Pathol* 1992; 5: 244–249.

74. Karalis DG, Quinn V, Victor MF, Ross JJ, Polansky M, Spratt KA, et al. Risk of catheter-related emboli in patients with atherosclerotic debris in the thoracic aorta. *Am Heart J* 1996; 131: 1149–1155.

75. Van Mieghem NM, Schipper ME, Faqiri E, van der Boon RS, et al. In vivo coronary angioscopy. *Endovascular Therapy* 2007; 286: 138–147.

76. Matsuo K, Matsuda T, Osumi Y, Nakamura H, Osumi Y, et al. Atherosclerotic plaques in the thoracic aorta: Natural history and clinicopathologic correlations. *Acta Pathol Jpn* 1985; 35: 789–801.

77. Matsuda T, Osumi Y, Nakamura H, Osumi Y, et al. Atherosclerotic plaques in the thoracic aorta: Natural history and clinicopathologic correlations. *Acta Pathol Jpn* 1985; 35: 789–801.

78. Matsuda T, Osumi Y, Nakamura H, Osumi Y, et al. Atherosclerotic plaques in the thoracic aorta: Natural history and clinicopathologic correlations. *Acta Pathol Jpn* 1985; 35: 789–801.