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Aortic Aneurysms in Takayasu Arteritis

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1. Introduction

Takayasu arteritis is a non-atherosclerotic chronic inflammatory vascular disease of unknown etiology that affects the aorta, proximal parts of its major branches and the pulmonary arteries. The disease may cause stenosis, occlusions and sometimes aneurysm formation in the aorta and/or the affected arteries. As the use of arteriography gradually became a more widespread and the procedure was more generally available, more details of the disease and its manifestation began to be described.
From the historical perspective, Mikito Takayasu is credited with having been the first to describe the disease in 1908, when he presented a case of a 21-year old woman with a peculiar optic fundus abnormality, characterized by arteriovenous anastomosis around the papilla (fig. 1). He made no mention of whether or not radial pulses were absent or diminished. Two other ophthalmologists, Onishi and Kagoshima, also described patients very similar to the one described by Takayasu, adding that their patients had no radial pulses. This is why nowadays, the disease is called Takayasu-Onishi aorto-arteritis. Probably the first description of the disease we now call Takayasu arteritis was actually done by Giovan Battista Morgagni in 1771. Patients with pulseless disease or aortic syndrome were also described by Adams in 1827, Devy in 1839 and William Broadbent in 1875. In 1856, the English surgeon William Savory described pathological and clinical examination findings in a patient who died of pulseless disease and aortic arch syndrome. In this 22-year old woman, autopsy revealed obliteration of left internal carotid artery, together with bilateral subclavian artery occlusion.
Histological descriptions of Takayasu arteritis were reported by Beneke in 1925 and Harbitz in 1926.

2. Epidemiology

Although Takayasu arteritis was first described in the Orient and is undoubtedly more prevalently among patients in India, Africa and South America, the disease has a worldwide distribution, with an increasing incidence in western countries. Retrospective reviews conclude that Takayasu arteritis is more frequent than was previously believed. Although most series collected in the United States include some Asians, these patients are mostly white. The disease affects women in the reproductive age group 5 to 8 times more commonly than men (Lupi-Herrera et al., 1977; Hall et al., 1985; Sato et al., 1998). In India and Japan is responsible for about

5% of all vascular cases. It has a worldwide incidence of 2.6 cases per million inhabitants, but the frequency appears to be increasing, as testified by Mayo Clinic data, in which 22% of patients with diseases of supra-aortic trunks requiring surgery have Takayasu arteritis. In Europe, aortoarteritis has been described in Russia, Scandinavia, France and Italy.

Takayasu arteritis can occur at any age, but it seems more frequent between ages of ten and twenty. However, aorto-arteritis is also present in younger children, who are often misdiagnosed as having rheumatic fever, coartation of the aorta and acute glomerulonephritis. Involvement of the descending thoracic and abdominal aorta occurs more commonly in young adults.

Numerous single case reports and some studies show a strict correlation between pregnancy and Takayasu arteritis.

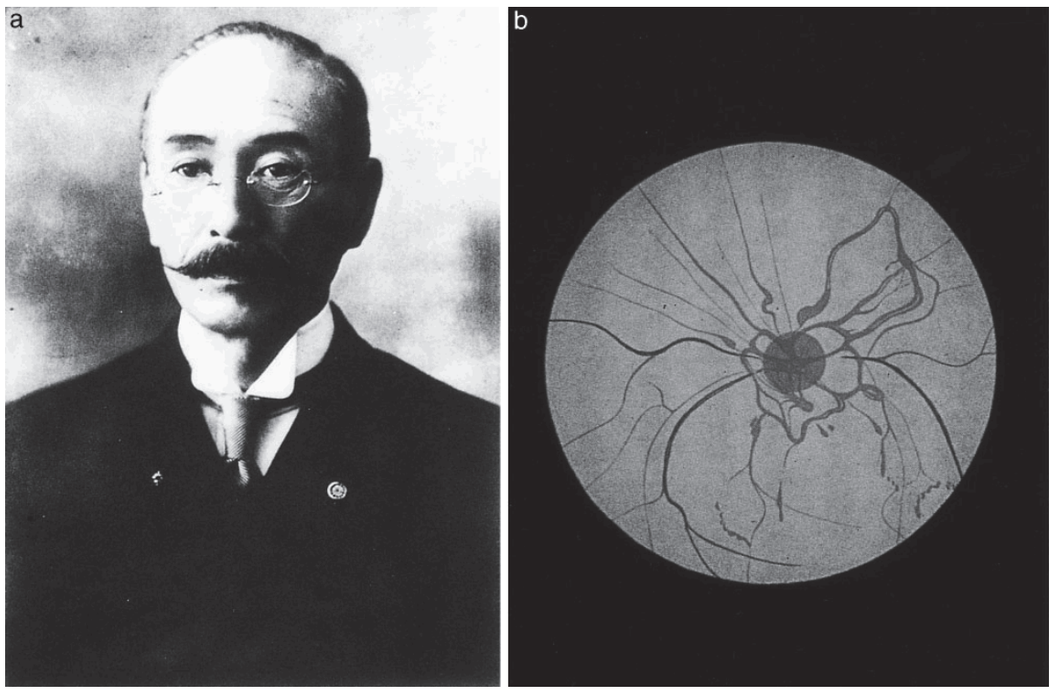


Fig. 1. In 1908, for the first time the Japanese ophthalmologist Mikito Takayasu (a) reported the case of a 21-year old woman with a peculiar optic fundus abnormality, characterised by arteriovenous anastomosis around the papilla (b).

3. Etiology and pathogenesis

Despite the fact that there are no specific immunologic markers of aortoarteritis, autoimmune mechanisms are undoubtedly involved in the pathogenesis. There have been reports of coincidence of Takayasu arteritis and other autoimmune diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, Still's syndrome, ankylosing spondylitis, Reiter's syndrome, inflammatory bowel disease, systemic sclerosis, systemic lupus erythematosus, glomerulonephritis and renal amyloidosis.

Moreover, rheumatoid factor and antinucleal antibodies have been identified. The erythrocyte sedimentation rate (ESR) is elevated during the inflammatory phase. The pathophysiology of Takayasu arteritis is multifactorial. Nevertheless, aorto-arteritis may be

classified as an autoimmune disease, in which cellular immunity is predominant while the role of humoral immunity has still to be fully defined.
The pathologic sequence imcludes stimulation by an antigen of an unknown nature that triggers heat shock protein (HSP)-65 expression in aortic tissue, which induces the expression of MHC class I chain-related gene A (MICA). Gamma-delta T cells and natural killer (NK) cells expressing NKG2D receptors then infiltrate the arterial wall, recognize MICA on vascular smooth muscle cells and trigger a cytotoxic response, provoking an acute inflammation. These inflammatory cells release perforin, a membrane disrupting protein as well as proinflammatory cytokines. These molecules amplify the inflammatory response, recruiting more infiltrating cells and inducing matrix metalloproteinases (MMP) that degrade elastin and collagen in the arterial wall.
Alpha-beta T cells will then start to infiltrate and specifically recognize one or several autoantigens presented by a shared epitope associated with specific MHC on the dendritic cells. The dendritic cells, together with the B cells, could give rise to a humoral immune reaction mainly featuring anti-endothelial cell autoantibodies, that could trigger complement-dipendent cytotoxicity against endothelial cells (Arnaud et al., 2006; Seko et al., 2000).

4. Pathology

Takayasu arteritis is a non-specific inflammatory disease that primarily affects large arteries such as the aorta and its branches. The term includes both occlusive and aneurismal disease. Thickening of the aorta with an intima exhibiting focal and raised plaques is demonstrated in Takayasu arteritis. Stenosis or occlusions of the aortic branches are also frequent. Ecstasias or aneurysms are more frequently found in the distal thoracic and abdominal aorta. Aortic intramural haematoma, dissection with rupture as well as a combination of ascending, arch, descending and abdominal aortic aneurysms are also described (O'Connor et al., 2008; Gupta et al., 2007).
In the absence of pathognomonic clinical findings and laboratory tests, a biopsy could be very helpful but it must be borne in mind that the histopathologic results may depend by the clinical phase of the disease and that a negative histology cannot rule out the possibility of an aorto-arteritis.
Results of laboratory tests, clinical and radiological findings, together with hystopathologic observations, are all pieces of the same puzzle, that need to be fitted together to obtain a correct diagnosis.
Histologically, the "early phase" is characterized by edema, patchy necrosis of the media and elastin and diffuse chronic inflammation with infiltration of the media, adventitia and vasa vasorum by lymphocytes, plasma cells, a variable number of eosinophils, histiocytes and rare giant cells, leading to thickening of the intima and perivascular inflammation determining arterial wall thickening (Fig. 2).
The early patchy destruction of the medial muscolo-elastic lamellae is replaced by progressive fibrosis. Heggtueit et al. (1963) described a band of infarct-like necrosis in several cases. These histopathological findings can be present even in patients receiving immunodepressive drug treatment and even in clinically successful conditions obtained by long-term corticosteroid therapy.
In the "late" or "pulseless phase", transmural sclerosis with a scanty infiltrate or no inflammatory cells is characteristic of aorto-arteritis. The proliferation and adventitia fibrosis

are proportional to the duration and severity of the disease. A secondary thrombosis can occur, with partial or complete occlusion of the arteries.
In the subacute phase and burned-out stage, Takayasu arteritis may escape recognition and be mistaken for arteriosclerosis by a pathologist who is unfamiliar with this systemic arteritis. A disorganization or absence of the elastic lamina of the media, with inadequate supportive fibrous tissue, and focal intimal weakness in this phase, could be responsible for arterial dilatation and aneurysm formation.
Although other causes of aortic aneurysms include extensive degeneration of the media elastic fibres (e.g. Marfan syndrome, Ehlers-Danlos syndrome), the dense adventitial fibrosis and perivasculitis characteristic of Takayasu arteritis will be absent. The lack of atherosclerotic plaques, giant cells, gummas, helps to rule out inflammatory aneurysms, giant cell arteritis and syphilitic aortitis.

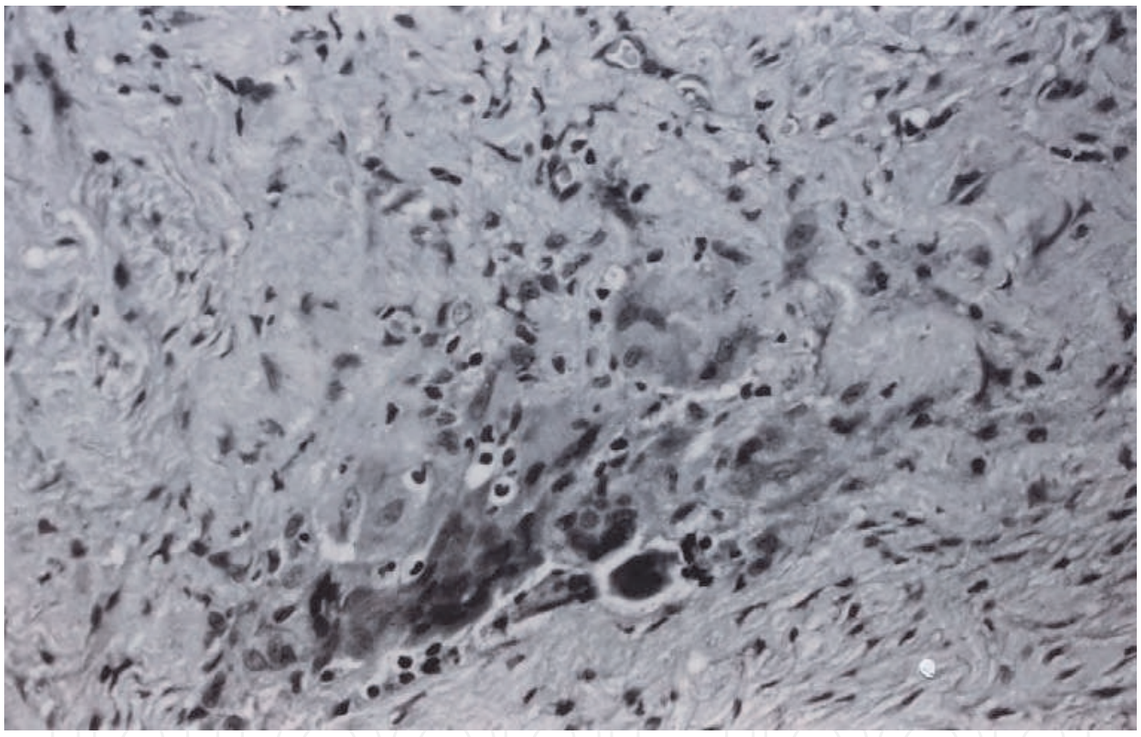


Fig. 2. Histopathologic findings characteristic of Takayasu arteritis: mononuclear inflammatory infiltrate in the media and adventitia with multinucleated giant cells-rich granulomas (hematoxylin-eosin, 100x).

Even if the arteritic process of Takayasu arteritis was originally thought to be confined to the aortic arch and brachiocephalic branches, subsequent clinical and pathological studies resulted in the classification of four topographic types of arterial lesions: type one, originally described by Shimizu and Sano, in which the involvement is limited to the aortic arch and its branches; this affects 8.4% of patients and includes an aneurismal subtype; type two corresponds to the middle aortic syndrome (Kymoto type) with lesions localized in the descending and abdominal aorta and affects 11.2% of cases; type three (Inada type), shares features of types one and two and affects 65.4% of patients. Type four (Lupi-Herrera type) denotes involvement of the pulmonary arteries and is observed in 15% of patients (fig. 3).

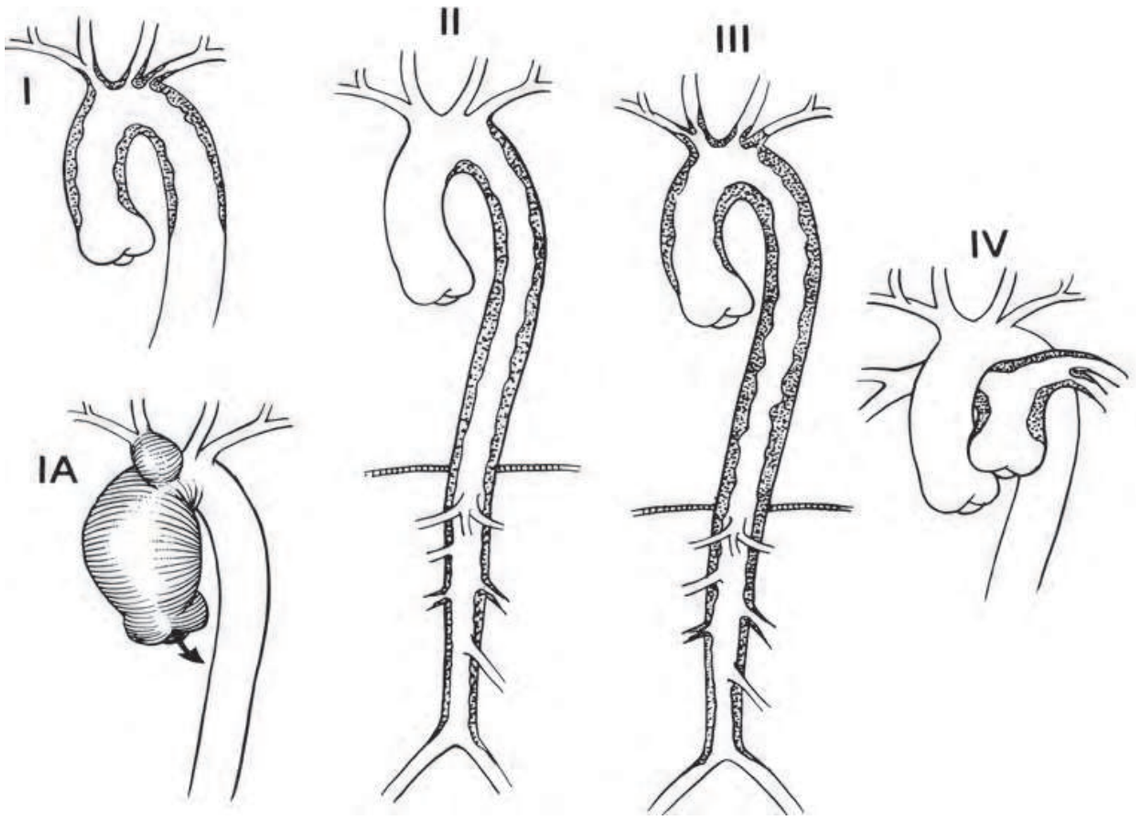


Fig. 3. Topographic classification of Takayasu arteritis (Ueno et al., 1967; Lupi-Herrera et al., 1975).

5. Clinical presentation and natural history

The symptoms of Takayasu arteritis reflect both the systemic inflammatory process and the alterations caused by arteritis. In the early phase of the illness non-specific symptoms are present; they include fatigue, malaise, fever, night sweats, cough, pleurisy with pleural effusion, weight loss, arthralgia, myalgia, skin rush, abdominal pain, vomiting, an elevated erythrocyte sedimentation rate and abnormal plasma protein count (Strachan RW, 1964; Johnston et al., 2002; Nastri et al., 2004).

The incidence of these symptoms is variable. Nakao et al. (1967) reported a history of systemic illness in 53 (63%) of 84 patients, while Lande found systemic symptoms only in 5 (14%) of 35 patients. The age of onset of the aorto-arteritis was between 10-20 years of age in 77% of the cases reported by Lupi-Herrera et al. (1977), between 10 and 29 years of age in 67% of the cases described by Nakao et al. (1967), while the 96 cases reported by Ishikawa (1998) were all under 40 years of age. In all these series, 85 to 90% of the patients were women.

In the pre-pulseless phase, Takayasu arteritis often goes unrecognized, leading to a misdiagnosis. A report by the Mayo Clinic cited a mean delay of 18 months before the true nature of the process is recognized, often not untill the appearance of manifestation of the late phase. These are characterized by arterial stenosis or occlusion after an interval of some months or even years.

The late phase is marked by diminished pulses, vascular bruits, extremitiy claudication, cerebral, ocular or facial ischemia, aortic insufficiency, pulmonary hypertension, cardiomyopathy, angina and myocardial infarction as a result of ostial coronary artery stenosis. Systemic hypertension is frequent in patients with Takayasu arteritis and indicates renal artery stenosis or a baroreceptors disfunction or alterated vascular compliance. Gastroenteric symptoms are extremely rare, because of the rich collateral flow at that level. Ocular symptoms are mainly due to common carotid and/or vertebral artery involvement, and can sometimes depend on systemic hypertension.

Isolated aneurysms are described in only 2% of the patients reported by Sheikhzadeh series (Sheikhzadeh et al., 2002). An association of stenotic and aneurismal lesions is present in nearly all patients with Takayasu arteritis. This observation, together with the high prevalence of systemic hypertension, has led to speculation that elevated blood pressure is an important contributor to aneurysm formation.

The aneurysmal symptoms include a pulsatile mass, embolism from mural thrombus and rupture leading to hemotorax or death. Rupture of aneurysms is uncommon perhaps because their wall tents to be rather thick (Matsumura et al., 1991). The natural history of Takayasu arteritis has not been well elucidated because of the paucity of reported series and numbers of patients.

Most patients with Takayasu arteritis have a favorable prognosis because the disease progresses slowly and the progress of the disease can be arrested if adequate treatment is provided.

During a follow-up study (ranging from 3 months to 15 years) by Morooka et al. (1972), an aortitis syndrome was observed in 64 patients: 4 died of heart failure, 3 of cerebral haemorrhage, 2 of cerebral infarction, 2 perioperatively, 1 of respiratory failure and 1 by suicide. In the review of experiences and studies of pulseless disease reported by Sano and Saito (1972), 77 patients were followed up from 1 to 21 years: 5 died of heart failure, 3 of cerebral embolism, 2 following corrective surgery, 1 of renal failure and 6 of unspecified cause.

In the series of 197 patients (24 men and 173 women) reported by the Japanese National Committee on the Study of Aortitis, death occurred in 25 (12%) cases. In the series of 54 patients reported by Ishikawa (1978) 8 deaths (15%) occurred during an 18-year follow-up period: 3 patients of stroke, 3 of congestive heart failure, 1 during aortic reconstruction and 1 of steroid withdrawal shock.

As regard non-Japanese patients, of the 107 cases (90 women, aged 4 to 45 years) from Mexico reported by Lupi-Herrera et al. (1977), 16 (15%) died during the 19 year follow up: 10 of heart failure, 3 of renal failure, 1 of cerebral haemorrhage, 1 of a ruptured subclavian aneurysm and 1 of perforation of a gastric ulcer.

Of 88 patients (34 men and 54 women, aged 6 to 48 years) from India reported by Subramanyan et al. (1989), 10 (11.4%) deaths occurred during follow-up (83.6+/-74.4 months): 4 of hearth failure, 2 of stroke, 1 of hemoptysis, 1 of ischemic myocardial arrest and 2 of unknown causes.

In a study on 32 North American patients (6 men and 26 women, aged 15 to 48 years) reported by Hall et al. (1985), 2 died during the 13-year follow-up, 1 of a ruptured aortic aneurysm and 1 of pneumonia.

In a small series of 20 cases (all women, aged 7 to 57 years) reported by Shelhamer et al. (1985), only 1 died during the follow-up period lasting a mean of 4.67 years (range 2 to 113 months).

In a series of 73 patients (61 women) reported by Sato et al. (1998), 5 deaths occurred during mean 5-year follow-up, 2 due to heart failure, 2 due to active disease and sepsis and 1 during abdominal aorta surgery.
The overall survival rate in patients with Takayasu disease after the onset of symptoms is reported to be 83% to 94% at 5 years and 83% at 15 years (Ishikawa & Metani, 1994; Sato et al., 1998; Subramanyan et al., 1989; Hall et al., 1985; Ishikawa, 1981).
Usually, aneurismal dilatation develops in patients over the age of 40, although cases of a descending thoracic aorta aneurysm have been reported in a 23-year-old woman (Chieh et al., 2003) and in a 25-year-old man (Regina et al., 2007). The annual risk of rupture is relatively low, ranging from 1% to 7% (Matsumura et al., 1991; Sunramanyan et al., 1989). In a series of 120 patients (111 women, 9 men), Ishikawa & Maetani (1994) reported 16 deaths related to Takayasu disease during a median follow-up of 13 years (range 1 month to 34 years), 5 of congestive heart failure, 4 of cerebrovasclar incidents, 3 after postoperative complications, 2 of acute myocardial infarction and 2 of other causes.
However, these Authors warned that a progressive disease course as well as complications arising from the disease, including aneurysm formation, have a poor long-term prognosis. Indeed, they reported that the 15-year survival rate for patients with both a progressive disease course and major complications, such as aneurysmal changes, was 43% compared with a survival rate of 96.4% in patients with no complications.
The rate of growth and risk of rupture of Takayasu aneurysms are thought to be lower than those of atherosclerotic aneurysms (Robbs et al., 1994). Sueyoshi and colleagues (2000) followed 17 aneurysms in 14 patients with Takayasu arteritis by CT scans for a mean follow-up period of 52.9 months. Eight of these aneurysms did not increase in size, while six grew slowly (at a mean growth rate of 0.03 cm/year). Only three aneurysms increased rapidly in size and ruptured (the mean growth rate was 1.16 cm/year for these aneurysms). They also showed that calcium deposits in the scarred media and intima seems to limit further enlargement of aortic aneurysms. Aortic wall scars are more severe in patients with Takayasu arteritis than in those with atherosclerosis. Therefore, aneurysms associated with this disease increase in size more slowly than atherosclerotic aortic aneurysms.

5.1 Diagnostic criteria

In 1990, the American College of Rheumatology (Arend WP et al., 1990) defined specific criteria for clinical diagnosis of Takayasu arteritis (Tab. 1).
For the purposes of classification, a patient is deemed to have Takayasu arteritis if at least three of the following six criteria are present: age at disease onset less than or equal to 40 years; claudication of the extremities; a diminished brachial artery pulse; a blood pressure difference between the arms more than 10 mmHg; an audible bruit over the subclavian arteries or abdominal aorta; angiographic abnormalities.
The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

5.2 Laboratory findings

Although there are no specific diagnostic laboratory tests, the non-specific Erythrocytes sedimentation rate (ESR) is elevated in 68 to 83% of the patients tested. C-Reactive-Protein, gamma-globulin, antistreptolysin-O titers are also abnormal. A mild anemia and a mild to moderate leukocytosis may be present. The Mantoux test is positive in a high percentage of

cases. Less than 10% of patients show rheumatoid factor, antinuclear antibodies or LE cells. Albuminuria and hematuria can be found, but are rare.

Criteria	*Definition*
Age of disease onset ≤ 40 years	Development of symptoms or findings related to Takayasu arteritis at age of ≤ 40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
Blood pressure difference >10 mmHg	Difference of >10 mmHg in sistolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not caused by arteriosclerosis, fibromuscolar dysplasia, or similar causes; changes usually focal or segmental

Table 1. American College of Rheumatology criteria for clinical diagnosis of Takayasu arteritis (1990).

6. Imaging techniques

6.1 Angiography

Angiography is still considered to be the gold standard technique. Thoracic and abdominal aortic angiography must be performed in order to visualize the entire aorta and all its branches (Kissin et al., 2004; Johnston et al., 2002; Nastri et al., 2004). Three basic arteriographic patterns are observed: (1) varying degrees of aortic and/or arterial narrowing; (2) saccular and/or fusiform aneurysm; (3) a combination of both (Fig. 4 a-b).

Angiography can also demonstrate dissections, pulmonary artery involvement and the subclavian steal phenomenon and is useful as a basis for selecting endovascular procedures such as angioplasty and stenting. The disadvantages of angiography include the substantial radiation dose and the frequent need to use a large amount of iodinated contrast medium. Moreover, angiography can evaluate only the intraluminal effects of the pathologies but cannot distinguish between acute and chronic disease.

In case of aneurysms, the dilatation may involve long segments of the aorta or the entire aorta. In some patient a saccular aneurysm is superimposed on diffuse aortic dilatation.

"Skipped" areas of aortic involvement, in which aneurysm and narrowing lesions are alternated with normal segments, are the most characteristic aortographic findings in Takayasu arteritis.

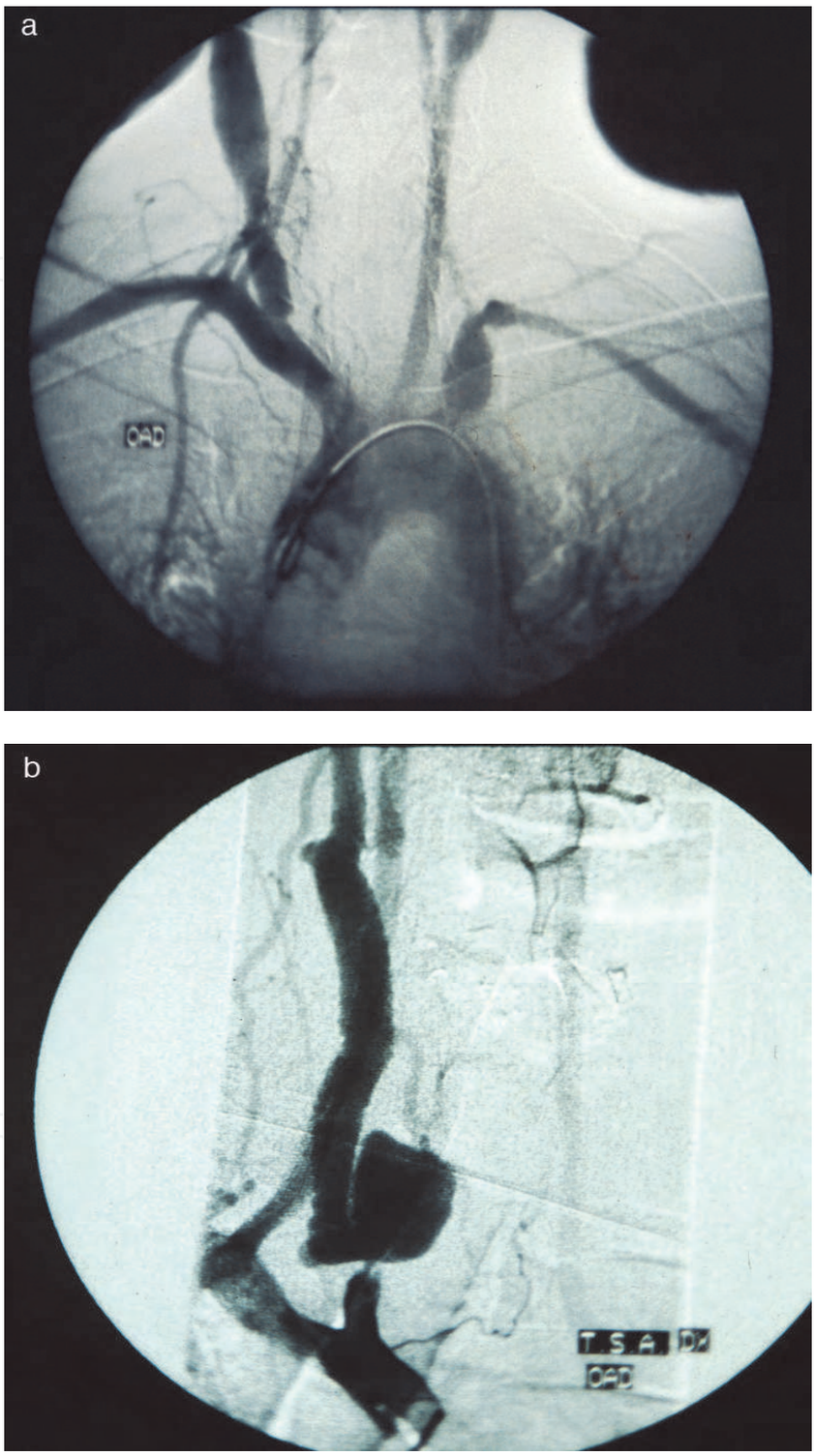


Fig. 4. Angiographic imaging: (a) aneurysmal dilatations of the right common carotid artery and the left intrathoracic sublcavian artery; (b) Pseudoaneurysm after common carotid artery replacement by Dacron graft for Takayasu arteritis aneurysm.

6.2 Ultrasonography (US)

Assessment of the disease activity in patients with Takayasu arteritis is challenging; the advantage of ultrasonography is that it can measure the wall thickness of the superficial vessels (e.g. carotid intima-medial thickness, a marker of the activity). US provides a higher axial resolution than other cross-sectional modalities (Taylor, 1992). If calcification is absent and there is concentric thickening of the artery, a differential diagnosis of the disease from atherosclerotic changes is easily made.

Color-Doppler visualization of the arterial lumen also allows a better estimation of the hemodynamic changes in both deep seated and fairly visible arteries (Canyigit et al., 2007). The freedom from radiation and contrast media, cost effectiveness and availability are all advantages of this technique. However, it is highly operator-dependent and has limited reproducibility. The examination can be technically difficult in the case of obese patients or when overlying bowel gas obscures the abdominal vasculature.

By using intravascular ultrasound (IVUS), a thickening and altered echogenicity of the media, adventitia and perivascular tissue, even in some portions of the aorta that looked normal at angiography, can be observed (Sharma et al., 1998).

Trans-esophageal-echocardiography has also proven efficacious in evaluating the stage of Takayasu arteritis in patients with aortic aneurysms.

In aorto-arteritis two patterns have been described: (1) intima-media thickening and dense echogenic layers outside the intima-medial thickeness, corresponding to the acute stage, or (2) a single thickened echogenic homogeneous layer corresponding to the scar stage. These results indicate that the ultrasound imaging can accurately determining the phase of Takayasu arteritis.

6.3 Computerized Tomography (CT) angiography

CT angiography has been suggested to be very useful in the evaluation of disease activity of Takayasu arteritis, as it allows evaluation of wall thickness. Moreover, it can provide information about wall enhancement during the active phase of the disease. It is also an excellent method for demonstrating stenosis, dissections, occlusions, calcifications, thrombus formation, concentric wall thickening of the aorta and its branches, pulmonary arteries and coronary arteries and aneurysms. In addition, it allows volumetric data acquisition thanks to high quality two or three-dimensional reconstruction.

CT imaging is quick, but less detailed than conventional angiography in the evaluation of stenotic lesions. Moreover, it carries the disadvantages of exposing the patients to high doses of radiation and iodinated contrast medium.

6.4 Magnetic Resonance Imaging (MRI)

Due to its excellent sensitivity MRI is an established screening modalities for central nervous system vasculitis, although it has limited specificity.

Contrast-enhanced MRI and three-dimensional contrast MR angiography can easily demonstrate stenotic lesions in branches of vessels and detect subtle morphologic and pathologic changes in the arterial wall.

A significant enhancement within and around the aorta is observed on post-contrast MR images in the acute phase of Takayasu arteritis. Enhancement of the vessel walls is also present in the chronic stage, indicating the activity of the disease at the tissue level (Matsunanga et al., 2003; Halefoglu et al., 2005; Nastri et al., 2004).

MRI is very useful in the serial evaluation of patients with aorto-arteritis because it does not involve the use of radiation and iodinated contrast material. Fusiform vascular dilatations, vascular occlusions, mural thrombi and multifocal stenosis have been described at MRI. The major disadvantages of this modality are the longer imaging times, as well as contraindications associated with electronic devices and artifacts from surgical clips.

7. Treatment

7.1 Medical treatment

Anti-inflammatory and immunosuppressive agents are the cornerstone of medical therapy for Takayasu arteritis. Corticosteroids are still used in the active phase of Takayasu arteritis. Disease activity is indicated by the onset or worsening of systemic features (fever and arthralgias with no identified cause), by an elevated erythrocyte sedimentation rate, vascular ischemia or inflammation (claudication, diminished or absent pulses, bruits, asymmetric blood pressure in upper or lower limbs or both, carotidynia).

Several reports have claimed that long term prednisolone therapy contributes to an angiographic improvement (Kulkarni et al., 1974; Ishikawa & Yonekawa, 1987). Some patients, in whom withdrawal from corticosteroids is difficult, may require additional cytotoxic immunosuppressive drugs such as cyclophosphamide or azathioprine. The use of other drugs, such as mycophenolate mofetil and infliximab, has been reported in literature. These agents are usually continued for at least one year after remission and are then tapered until discontinuation. Sometimes, long term low-dose corticosteroid therapy may be required. Osteoporosis preventive measures when patients are started on corticosteroids should be seriously considered.

The management of traditional cardiovascular risk factors such as dyslipidemia, hypertension and lifestyle factors is also important. Thrombosis in the affected vessels with stenotic or occlusive lesions or embolism from aneurysms is usually a complication of the disease. This is the reason why long term aspirin therapy is mandatory to prevent thrombus formation in vessels with endothelial damage. Hypertension related to atypical coartation or stenotic disease of the renal arteries should also be controlled with calcium antagonists, beta-blockers, hypotensive diuretics, cardiac glycoside and coronary vasodilator agents.

7.2 Surgical treatment

Numerous reports have shown that surgery on patients with Takayasu arteritis can safely be performed (Tab. 2). There are very low morbidity and mortality rates except in cases of surgery of an aortic aneurysm, especially of a ruptured aneurysm. There is always a concern about the development of anastomotic aneurysms in arteries that have been used for either inflow or outflow bypasses.

The durability of the reconstructions varies in different reports. However, a high incidence of restenosis or pseudoaneurysm has been described (Robbs et al., 1994). Constant surveillance of patients who have undergone these procedures is necessary. It is not clear whether anastomotic stenoses are due to the recurrence of Takayasu arteritis at the level of the anastomosis or to other reasons (Giordano et al., 1991). Nevertheless, they can be treated with either another surgical procedure or possibly even by percutaneous transluminal angioplasty (PTA).

Less than 20% of adult patients require surgical treatment (Ishikawa & Maetani, 1994). In the pediatric field Kalangos et al. (2006) instead found that 80% of the patients required surgery for stenotic or occlusive lesions; 70% were in the active phase of the arteritis, thus necessitating steroid therapy before and after surgery to prevent disease progression.

As reported by Giordano and coll. (1991) there are general principles that all surgeons should take into account in the evaluation and treatment of these patients. Takayasu arteritis is not the same as atherosclerosis. Patients with atherosclerosis are usually elderly, while patients with Takayasu disease are young. It should not be assumed that because the patient is young, he or she may not suffer significant medical complications.

The multi-arterial involvement could mean that the individual has significant renal disease, cardiac disease and other problems that could affect the overall surgical outcome. This is the reason why a complete preoperative evaluation is essential. It is important to maintain a conservative attitude to the management of patients with Takayasu disease.

Surgery should only be resorted to if there is a very significant problem that could affect a patient's prognosis or seriously interfere with the patient's lifestyle. Emergency surgery is not usually necessary since the lesions tend to be chronic, allowing time for collateral circulation to form. It is preferable to avoid surgery during the acute phase of the disease.

PTA has become an effective alternative to surgery for occlusive disease. Initially, there was considerable concern about the long term overall results of this procedure. Dilating a chronic lesion might initially be successful, but long term follow-up might show a restenosis. Restenosis does occur, but since the development of stents, the long term incidence of restenosis seems to be considerably less, although more cases are needed to confirm the effectiveness of this therapy (Takahashi et al., 2002). Therefore it is important, in the initial management of patients who are candidates for operation, to conduct an appropriate pre-surgical work-up to determine the feasibility of PTA.

Surgery always consists in occlusive or stenotic lesion bypassing from proximal to distal vessels, provided that they appear normal on angiography. It must be noted, however, that biopsies of arterial anastomotic sites, even if normal at arteriography, have still shown a 44% incidence of microscopic involvement by Takayasu disease (Kerr et al. 1994).

In case of multiple location of the disease, multistage surgery will need to be selected to reduce the surgical invasiveness. Single-stage surgery is generally preferable, especially for extensive thoracic aortic aneurysms (e.g. aortic arch and descending aorta aneurysm), but because of the excessive invasiveness of this approach, staged surgery must sometimes be performed.

The surgical priority of multiple aneurysms must be decided upon based on the diameter, morphology and propensity for dilatation of the lesion. When staged surgery is selected, rupture of the residual lesion during the interval period is always a concern, so the second stage of surgery must be scheduled as soon as possible after the first. Safi et al. (2001) reported a mortality rate of 5.1% for the first stage and 6.2% for the second stage. The mortality rate during the interval between operations was 3.6%, 75% of these deaths being caused by aneurysm rupture.

Occlusive disease is more prevalent in the United States and Europe, whereas aneurysmal disease is more common in Japan, India, Thailand, Mexico and Africa (Desiron et al., 2000; Matsumura et al., 1991; Kumar et al., 1990). It is not quite clear why there is such a difference.

Study, year	Patient no.	Type of lesions	Treatment	Morbidity	Mortality	Follow-up
Sasaki, 1998	14	Aortic aneurysms (6 type I; 2 type II, 2 type III)	6 graft; 1 aneurysmorraphy; 1 patch angioplasty; 1 Hardy op.; 2 AVR; 3 AVR + wrapping / aneurysmorraphy	4 redo surgery	3 (21.4%) hospital; 5 (35.7%) late	2-252 months
Ando, 2000	87	43 aortic aneurysms (31 type I; 6 type II; 6 type III); 44 aortic regurgitation	38 graft; 5 wrapping; 42 AVR; 2 valved conduit	3 valve detachment; 3 valve failure; 5 subsequent aneurysm op.	5 (5.7%) hospital; 15 (13%) late	1-246 months
Sasaki, 2000	10	Aortic aneurysms (2 type I; 5 type II; 3 type III)	6 graft; 1 patch angioplasty; 1 aneurysmorraphy; 1 Hardy op.; 1 modified Bentall op.	3 redo surgery	1 (10%) hospital; 3 (30%) late	88.8 +/- 46.8 months
Miyata, 2003	106 (155 lesions)	120 occlusive disease; 29 aortic aneurysms	137 graft; 6 patch angioplasty; 4 wrapping; 2 ligation; 2 TEA; 4 other	18 early graft fail 7 late graft fail 31 anastomotic aneurysm	12 (11.3%) hospital; 31 (32.8%) late	8-501.6 months
Kieffer, 2004	33	Aortic aneurysms (27 type II; 6 type III)	32 graft; 1 TEVAR	3 paraplegia; 4 artificial ventilation > 48h; 5 redo surgery	3 (9%) hospital; 2 (6%) late	3-240 months
Fields, 2006	42	39 occlusive disease; 3 aortic aneurysms (1 type I; 2 type II)	Graft	4 early graft thrombosis; 2 minor stroke; 2 cerebral hyperperfusion syndrome; 6 late graft thrombosis	0 hospital; 1 (2.3%) late	1-231.6 months
Lee, 2009	24 (35 lesions)	Occlusive disease	PTA +/- stenting	11 restenosis	0	46.8 months
Yukun, 2010	48 (101 lesions)	Occlusive disease	PTA +/- stenting	8 restenosis	0	3-6 months

AVR: aortic valve replacement; TEA: tromboendoarterectomy; TEVAR: thoracic endovascular aneurysm repair

Table 2. Outcomes following surgical treatment of Taykayasu disease.

Matsumura et al. (Matsumura et al., 1991) described aneurysms in 31.9% of patients with Takayasu arteritis, with a higher frequency in patients over the age of 40, and mostly within the ascending aorta. Aneurysms are a marker of extreme disease activity and are usually found in older patients with a longer history of the disease.

Aneurysm formation is considered one of the major complications related to the prognosis in Takayasu arteritis.

The real incidence of rupture of either the abdominal or thoracic aortic aneurysms is not known, but seems to be low (Matsumura et al., 1991). However, it should be remembered that young patients may have 40 to 50 more years of life expectancy and therefore the risks of aneurysm rupture over that period of time might be quite significant. Repair of abdominal and thoracic aortic aneurysms is indicated if they reach sizes greater than 5 cm.

The new endovascular approach may provide an interesting alternative to patients with thoracic or abdominal aortic aneurysms. Aneurysms also occur in the subclavian, innominate and carotid arteries (Regina et al., 1998). This presents technical problems, since resection and replacement of these arteries can be difficult with a relatively high incidence of stroke. Decision making in these cases must be tailored to the individual, depending upon the extent of involvement and the symptoms and also evaluating the possibility of hybrid intervention with the use of endovascular stent graft (Angiletta et al., 2004).

Operative mortality can certainly be affected by whether the problem treated is occlusive or aneurismal disease. Kieffer et al. (2004) reported a satisfactory surgical outcome of descending thoracic and thoracoabdominal aortic aneurysm in 33 patients with Takayasu arteritis operated between 1974 and 2001, despite the extent of the aneurysmal lesions and high frequency of association with visceral and supra-aortic vessel lesions. Robbs et al. (1994), from South Africa, reported an operative mortality of 3% to 4% in their patients with Takayasu arteritis, most of whom had aneurysms. The mortality was related to ruptured aneurysms.

After surgery for Takayasu arteritis, anastomotic false aneurysms (anastomotic detachment) can occur at any time in the long term, although the incidence seems to be low even in the active phase of the disesase. In Western countries, the development of an anastomotic false aneurysm is reportedly rare. To prevent this complication, reinforcement of the sutures with the use of a Teflon felt strip and/or suppression of active or persisting inflammation with corticosteroids, are recommended. In addition, if possible, sites of normal tissue without inflammatory changes should be chosen as anastomotic sites (Miyata et al., 1998).

In surgical repair of aortic aneurysm due to Takayasu arteritis, the outcome has been improved thanks to technical advances. Successful endovascular aneurysmal repair (stent-grafting) for dilated lesions due to aorto-arteritis has been reported (Baril et al., 2006). However, reintervention for a ruptured stent graft and new aneurysm formation after endovascular treatment was also described (Regina et al., 2007) (Fig. 6). The long term efficacy of endovascular aneurysmal repair remains uncertain even for atherosclerotic disease. In inflammatory lesions due to Takayasu arteritis, a positive but cautious approach may be best.

8. Conclusion

Takayasu arteritis can present in wide variety of forms and should be considered in differential diagnosis of a calcified aorta in young women, even in absence of occlusive or stenotic lesions. The presence of a thoracic aortic aneurysm is regarded as a major

complication of this disease. Treatment of aneurysms related to Takayasu arteritis may require a different therapeutic strategy from that generally adopted for atherosclerotic aneurysms, because of the diffuse, progressive and relapsing nature of the disease and, moreover, the patients' greater life expectancy.

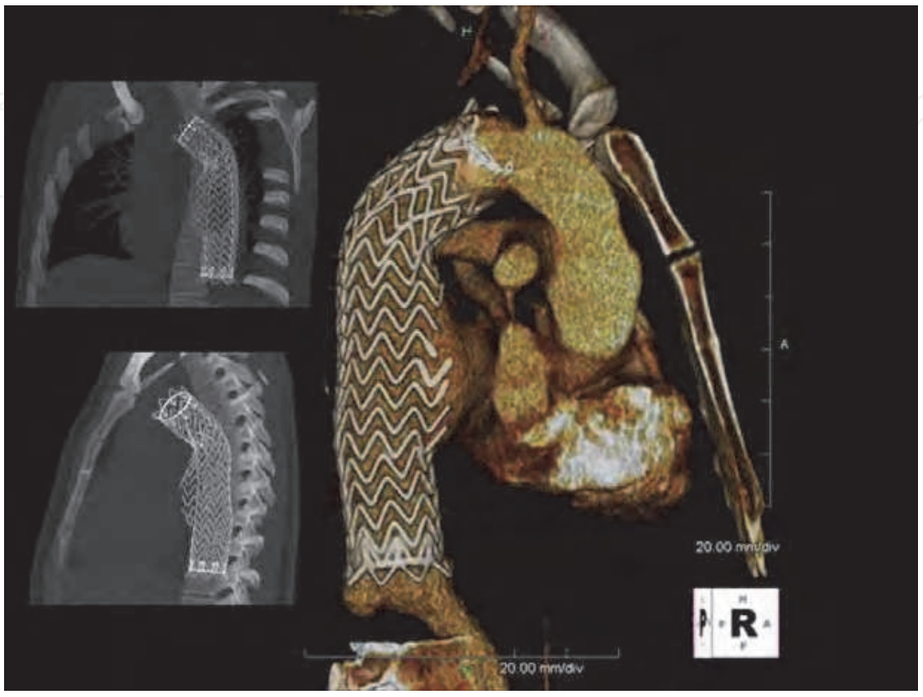


Fig. 6. Thoracic stent-graft bulging rupture after descending aortic aneurysm endovascular repair in a patient with Takayasu arteritis.

Therefore, it is important for physicians to coordinate medical and surgical therapy carefully. An effective control of traditional atherosclerotic risk factors, in addition to achieving suppression of the disease activity, is essential in the management of Takayasu arteritis. Radical surgical treatment of aortic aneurysms is highly recommended if technically feasible.

Long term monitoring of vascular reconstructions in patients with Takayasu arteritis, especially in patients with active disease at the time of initial operation, is mandatory.

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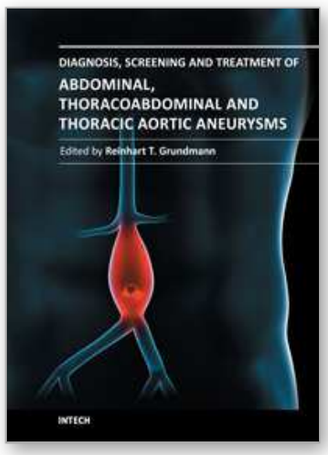
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Diagnosis, Screening and Treatment of Abdominal, Thoracoabdominal and Thoracic Aortic Aneurysms
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This book considers mainly diagnosis, screening, surveillance and treatment of abdominal, thoracoabdominal and thoracic aortic aneurysms. It addresses vascular and cardiothoracic surgeons and interventional radiologists, but also anyone engaged in vascular medicine. The high mortality of ruptured aneurysms certainly favors the recommendation of prophylactic repair of asymptomatic aortic aneurysms (AA) and therewith a generous screening. However, the comorbidities of these patients and their age have to be kept in mind if the efficacy and cost effectiveness of screening and prophylactic surgery should not be overestimated. The treatment recommendations which will be outlined here, have to regard on the one hand the natural course of the disease, the risk of rupture, and the life expectancy of the patient, and on the other hand the morbidity and mortality of the prophylactic surgical intervention. The book describes perioperative mortality after endovascular and open repair of AA, long-term outcome after repair, and the cost-effectiveness of treatment.

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