Aortic Syndrome (Takayasu’s Arteritis)
A Historical Perspective
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SUMMARY
Aortitis syndrome named in Japan is widely known as Takayasu’s arteritis internationally. Based on the experiences accumulated since the report of eyeground changes by Takayasu, it has become clear that the clinical manifestations of the disease are quite variable, including pulseless disease, atypical coarctation of the aorta, renovascular hypertension, aneurysms, aortic regurgitation and coronary artery disease. Pulmonary artery involvement is not infrequently present. For an exact diagnosis, it must be kept in mind that two or more of these manifestations are combined in most of the patients. The data of several epidemiological studies are presented and some of the recent literature reviewed. (Jpn Heart J 36: 273–281, 1995)

Key words: Pulseless disease Atypical coarctation of the aorta Renovascular hypertension Aneurysm Aortic regurgitation Coronary artery disease

AORTITIS syndrome is a clinical entity named by Hideo Ueda, Editor-in-Chief of the Japanese Heart Journal from 1960 through 1993. It includes a wide variety of signs and symptoms caused by nonspecific arteritis involving the aorta, its major branches, and not infrequently the pulmonary arteries. Although the etiology of this arteritis is still obscure, elucidation of clinical manifestations has progressed during the past several decades, and advances in therapy have resulted in an improved prognosis.

HISTORY OF DESCRIPTION OF CLINICAL MANIFESTATIONS
Takayasu’s retinopathy: Initially, eyeground changes of the disease were described by Dr. Mikito Takayasu, Professor of Ophthalmology, Kanazawa University, Japan. He noted a peculiar arteriovenous anastomosis around the papilla in a 21-year-old woman. His report of this patient at the Annual Meeting of the Japan Ophthalmology Society in 1905 was followed by a comment by Onishi, who mentioned that in a patient with similar funduscopic findings bilat-

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eral radial arterial pulses were not palpable.

Since Takayasu's report is considered to be the first presentation of a patient with aortitis syndrome, the disease is also called Takayasu's arteritis or Takayasu's disease, which is the term more commonly used internationally.

**Pulseless disease:** In 1948, Shimizu and Sano\(^2\) described a morbid condition characterized by pulselessness, peripapillary arteriovenous anastomosis of the retina (Takayasu's retinopathy), and accelerated carotid sinus reflex, and named it pulseless disease. These features were thought to be due to occlusive arteritis of the subclavian and carotid arteries.

The young female arteritis variety of the aortic arch syndrome described by Ross and McKusick\(^3\) in 1953 corresponds to pulseless disease.

**Atypical coarctation of the aorta:** With the progress of cardiovascular surgery, it became evident that in Japan typical coarctation of the aorta of congenital origin was less common than atypical coarctation of the aorta. While the former reveals a localized constriction at the site of the aortic isthmus, the latter usually exhibits widespread and/or multiple stenotic lesions of the aorta and is considered to be caused by inflammatory changes of the aortic walls.

Inada et al\(^4\) reported that 3 of their 6 patients with pulseless disease had atypical coarctation of the aorta confirmed by aortography, and postulated that both conditions were caused by an identical etiology, most likely arteritis. The middle aortic syndrome described by Sen et al\(^5\) corresponds to atypical coarctation of the aorta.

**Renovascular hypertension:** Danaraj and Ong\(^6\) described 2 children with hypertension in whom necropsy revealed a localized arteritis of the abdominal aorta that had resulted in occlusion of the renal artery orifices. From the histological appearance of arteritis, they suggested the possibility that these cases were variants of Takayasu's disease.

Ueda saw a 23-year-old female patient who was hospitalized under a diagnosis of juvenile hypertension and died of cerebral hemorrhage on the day of admission. At autopsy, renal artery stenosis was found in association with widespread arteritis involving the entire aorta. Histologically, the arteritis was identical to that seen in pulseless disease. Stimulated by this case, Ueda analyzed the previously encountered cases of pulseless disease and those of atypical coarctation of the aorta, and confirmed an intimate relationship between the two conditions. This led him to propose a single term "aortitis syndrome" to include pulseless disease and its variants.\(^7\) It was reported by Ueda that arteritis is the most frequent cause of renovascular hypertension in Japan.\(^8\)

**Aneurysm formation:** Originally, narrowing and occlusion of the diseased arteries were considered to be the basic pathological changes in aortitis syndrome, as observed in pulseless disease, atypical coarctation of the aorta and renovascu-
lar hypertension. Afterwards, however, attention was paid to the fact that the disease may also cause arterial dilatation or aneurysm formation. Vinijchaikul et al.\(^9\) noted one or more aneurysms in 7 of 8 autopsy cases of Takayasu’s arteriopathy.

**Aortic regurgitation:** From accumulated experience, it was noted that development of aortic regurgitation was not unusual in patients with aortitis syndrome. Ueda et al.\(^10\) reported that 9 of 44 patients with aortitis syndrome were diagnosed as having aortic regurgitation based on characteristic auscultatory findings, which were confirmed by phonocardiography in 8 patients. Destruction of the medial elastic fibers of the aortic wall, resulting in dilatation of the ascending aorta, especially the aortic valvular ring, and separation of the commissure, is considered to be the principal cause of aortic regurgitation, though organic changes in valve cusps may also be a contributory factor.

**Coronary artery disease:** It was 1962 when Judge et al.\(^11\) stressed that the lack of involvement of coronary arteries in Takayasu’s arteritis was striking, based on an analysis of 10 reported autopsies, including one they performed. According to a review of the literature by Wakiya et al., coronary artery involvement associated with aortitis syndrome was diagnosed angiographically in only 13 cases (including their own case) until 1977. Thereafter, however, reports of such cases have significantly increased, presumably as the result of widespread use of coronary arteriography and current diagnostic procedures. It may also be attributed to prolonged survival of patients resulting from advances in treatment.

**Variability of clinical pictures:** In most of the patients with aortitis syndrome, two or more different manifestations are seen in variable combination, depending on the distribution and type of the arterial lesions. The possibility of aortitis syndrome should always be considered when symptoms and signs of any patient cannot be explained clearly, especially when the patient is a young woman. An accelerated erythrocyte sedimentation rate of unknown origin is important supporting evidence for the diagnosis of aortitis syndrome.

**Review of Epidemiological Studies**

**Sex distribution:** The first nationwide epidemiological study in Japan was carried out during a period from 1965 to 1966 by the “Committee on Study of Arteritis” (chairman: H. Ueda) sponsored by the Ministry of Education of Japan, and 197 cases of aortitis syndrome were collected. They consisted of 173 females and 24 males, indicating a female to male ratio of 7.2.\(^{13}\) This was followed by the survey conducted from 1973 to 1975 by the “Aortitis Syndrome Research Committee” (chairman: K. Inada) sponsored by the Ministry of Health and Welfare of Japan, where 2,148 cases were registered and the female to male ratio was 8.0.\(^{14}\)
In the subsequent survey conducted from 1982 to 1984 by the “Vascular Lesion of Collagen Disease Research Committee” (chairman: Y. Fukuda) sponsored by the Ministry of Health and Welfare of Japan, the female to male ratio of the 2,606 cases was 9.4.\(^{14}\) Thus, it seems that the female preponderance of the disease became gradually more marked in Japan. The reason for this tendency is not clear.

**Ethnic differences:** There are differences in the female to male ratio in relation to geographic areas and the ethnic origin of patients. It was recently reported to be 6.6 (112:17) in Korea,\(^{15}\) 2.9 (395:135) in China,\(^{16}\) 1.9 (30:16) in Thailand,\(^{17}\) 1.8 (32:18) in Israel,\(^{18}\) and 1.6 (51:32) in India.\(^{19}\) In an earlier report from Singapore,\(^{20}\) which described a series of 48 cases consisting of 38 Chinese, 6 Malays and 4 Indians, the female to male ratio was 2.2 (33:15). Although the disease is only rarely seen in the United States, Hall et al\(^{21}\) reported a study of 32 North American patients, consisting of 23 North American Caucasians, 4 Mexicans, 3 of Oriental descent, one Native American and one of Middle Eastern origin. The female to male ratio of these patients was 4.3 (26:6).

According to the comparative study of Takayasu’s arteritis in 3 Asian countries by Yajima et al.\(^ {22}\) lesions of the aortic arch and/or its branches were found angiographically in 99% of 96 Japanese, 83% of 109 Korean and 68% of 50 Indian patients, while lesions of the abdominal aortic area were found in 34%, 76% and 92%, respectively, indicating differences in the distribution of arterial involvement among the 3 groups. The frequency of aortic regurgitation was significantly higher in Japanese patients (33.3%) than in Korean (6.4%) and Indian patients (4.0%).

It was pointed out by Chugh and Sakhuja\(^ {23}\) that in most Asian countries, Takayasu’s arteritis is the commonest cause of renovascular hypertension, accounting for about two thirds of all patients, whereas many studies on renovascular hypertension from the USA and Europe do not include even a single case of Takayasu’s arteritis.

**Tendency viewed from autopsy records:** In Japan, records of all autopsy cases are registered and published annually. This enabled Nasu\(^ {24}\) to collect 76 autopsy cases of Takayasu’s arteritis registered during a period from 1958 to 1973, and Nagata\(^ {25}\) collected 82 cases registered from 1975 to 1984. Comparison of these 2 series of autopsy cases showed that the peak of age distribution at the time of death moved from the third decade in the former series to the fifth decade in the latter, indicating a prolonged survival of patients. This can probably be attributed to early correct diagnosis and early adequate treatment. It was also noted that the incidence of coronary artery involvement increased from 11% to 45%, renal artery involvement from 24% to 40%, and common iliac artery involvement from 3% to 27%.
Aortic regurgitation: According to epidemiological surveys in Japan, the incidence of aortic regurgitation in aortitis syndrome was 19.0% (236 of 1,386 cases) in the period from 1973 to 1975, and increased to 24.8% (308 of 1,240 cases) in the period from 1982 to 1984, presumably because of prolonged survival of patients. Morooka et al reported that aortic regurgitation associated with aortitis syndrome is significantly more frequent (6 of 11 patients; 55%) in patients older than 40 years of age than in younger patients (2 of 24 patients; 8%).

Review of Recent Literature

Diagnostic criteria: Criteria for the diagnosis of Takayasu’s arteritis were developed by Arend et al from a comparison of 63 patients who had this disease with 744 control patients who had other forms of vasculitis. Six criteria were selected: onset at age of 40 years or younger, claudication of an extremity, decreased brachial artery pulse, difference in systolic blood pressure exceeding 10 mmHg between arms, a bruit over the subclavian arteries or aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. The presence of 3 or more of these 6 criteria demonstrated a sensitivity of 90.5% and a specificity of 97.8%.

Aneurysms: Incidence of aneurysm in Takayasu’s arteritis was analyzed by Matsumura et al in a series of 113 Japanese patients. Although predominant angiographic findings were stenotic or occlusive changes, fusiform or saccular aneurysms were also found in 36 patients (31.9%) in various sites of the aorta and its major branches. Development of aneurysm was most frequent in the ascending aorta (16 patients), followed by the descending thoracic aorta (11), major branches of the aorta (9), abdominal aorta (7) and aortic arch (3). Of 16 patients with aneurysms in the ascending aorta, 7 had aortic regurgitation of a moderate to severe degree. Multiple aneurysms were found in 15 patients. Eight patients had pulmonary arterial aneurysms, all of which were fusiform aneurysms in the main pulmonary artery. The average age was 43.5 ± 12.8 years in the patients with aneurysms and 38.2 ± 15.7 years in those without aneurysms.

Kumar et al analyzed 30 Indian patients with Takayasu’s disease, in whom aneurysms were found by aortography (26 patients), computed tomography (1) or physical examination (3). There were 41 fusiform and 18 saccular aneurysms. In addition, 24 diffuse dilatations were also present. Aneurysms were located most frequently in the descending thoracic aorta (18) and abdominal aorta (18) but less frequently in the ascending aorta (3), aortic arch (2) and branches of the aortic arch (10). Diffuse dilatation was found mostly in the ascending aorta (14). Aortic regurgitation was detected in 14 patients. Multiple
aneurysms were seen in 15 patients. Associated steno-occlusive lesions were found in 23 patients. Event-free survival rate at 5 years in the 30 patients with aneurysms was 82.9% and was similar to that (71.0%) in 70 patients without aneurysms.

**Aortic regurgitation:** Development of aortic regurgitation in aortitis syndrome is usually associated with dilatation of the ascending aorta, and its clinical course is gradually progressive. An unusual case of fatal acute aortic regurgitation due to aortic valve perforation was reported by Satoh et al. In this rare case (15-year-old female), severe inflammation was considered to have extended from the aorta to the aortic valve.

**Coronary artery involvement:** According to the collective review by Amano and Suzuki, 63 patients (including their five) underwent operations for coronary artery disease due to Takayasu's arteritis during a period from 1961 to 1989. Among 92 lesions, involvement of coronary ostia was most frequent (73%) followed by nonostial proximal lesions (18.5%). Of 62 ostial lesions of the left main coronary artery, 42 (67.7%) involved more than 90% stenosis or complete occlusion. Aortic regurgitation was involved in 28 patients (44.4%). CABG was performed in 49 patients and transaortic endarterectomy in 12. Concomitant aortic valve replacement was carried out in 16 patients. Operative mortality was reported in 5 (7.9%) and late death in 3.

Isolated coronary ostial stenosis in a young Japanese woman with Takayasu's arteritis was reported by Noma et al. and 8 additional cases were reviewed.

Morooka et al. found coronary artery lesions by coronary angiography in 4 of 19 patients with aortitis syndrome. The lesions were ostial stenosis in 2 patients and atherosclerosis-like main branch stenosis in 2. The latter 2 patients were a 69-year-old female and a 55-year-old female, in whom the duration of the disease was 41 years and 35 years, respectively. Therefore, the possibility was considered that the lesions in the latter 2 patients might have been due to secondary arteriosclerosis superimposed over the skip coronary arteritis.

The possibility of coronary artery disease in aortitis syndrome due to recurrent arteritis or superimposed arteriosclerosis was also pointed out by Hata et al. During long-term observation of their patient, who was diagnosed as having aortitis syndrome at the age of 31 years, 90% stenosis of the left anterior descending coronary artery was found by coronary arteriography at the age of 47 years when the patient complained of chest oppression on exertion. No stenosis of the coronary artery was found when she had the same symptom at age 43.

**Pulmonary artery involvement:** Yamada et al. found pulmonary artery involvement in 21 (70%) of 30 patients with Takayasu's arteritis in whom pulmonary arteriography was performed. Abnormalities were seen most frequently in
the upper lobe pulmonary arterial branches. The frequency of abnormalities in pulmonary arteriograms correlated with the extent of involvement of 7 brachiocephalic vessels (the brachiocephalic, the right and left subclavian, the right and left vertebral, and right and left common carotid arteries).

Sharma et al.\textsuperscript{36} noted pulmonary arterial involvement in 6 (14.3\%) of 42 patients with Takayasu’s arteritis in whom diagnostic pulmonary angiograms were obtained by intravenous digital subtraction angiography. However, the angiographic spectrum of systemic arterial involvement was the same irrespective of the presence or absence of pulmonary arterial involvement.

Usually, pulmonary arterial lesions in aortitis syndrome are clinically asymptomatic, but in occasional cases respiratory events such as chest pain, hemoptysis and pleural effusion may be noted as the initial manifestations of the disease. This was the case in 3 (8.6\%) of 35 patients with aortitis syndrome observed by Kato et al.\textsuperscript{37} A patient with Takayasu’s arteritis who developed severe respiratory failure due to recurrent pulmonary hemorrhage was reported by Koyabu et al.\textsuperscript{38}

**Percutaneous transluminal angioplasty (PTA):** Tyagi et al.\textsuperscript{39} performed PTA in 54 consecutive patients with hypertension and renal artery stenosis caused by Takayasu's arteritis. It was technically successful in 67 (89.3\%) of 75 lesions attempted, and the degree of stenosis decreased from 88.3 ± 4.8\% to 23.5 ± 13.6\% (p < 0.001), resulting in a significant improvement in hypertension (p < 0.001) within 48 hours. Angiographic restudy an average of 14.2 ± 7.8 months after PTA disclosed restenosis at 7 (13.5\%) of 52 lesions and fresh stenosis in one artery. All 8 lesions were successfully dilated. Further improvement in the luminal diameter was observed in 11 lesions (21.2\%). No restenosis was seen at late angiographic restudy in 7 patients an average of 56.1 ± 6.3 months after PTA.

Thirty-three renal artery stenoses in 20 patients were treated with PTA by Sharma et al.\textsuperscript{40} and a technical success was obtained in 28 lesions (85\%) in 17 patients (85\%). Restenosis was found in 6 (21\%) of 28 lesions at follow-up an average of 8 months after treatment.

Rao et al.\textsuperscript{41} analyzed the results of PTA for stenosis of the descending thoracic and/or abdominal aorta in 16 patients with Takayasu's arteritis, who had hypertension or severe bilateral lower limb claudication. Initial technical and clinical success was obtained in all patients. Three patients had symptoms of restenosis during follow-up. Cumulative patency rate calculated by life-table analysis was 67\% at 52 months.

**Effects of adrenocortical steroid therapy:** Ishikawa\textsuperscript{42} evaluated the effects of prednisolone angiographically in patients with Takayasu’s disease who were diagnosed as having active arteritis. Angiographic evidence of improvement in arte-
Racial lesions was noted in 8 of 9 patients treated with prednisolone. In contrast, 3 of 4 patients in whom prednisolone was interrupted or not administered, showed progression of angiographic abnormalities.

**REFERENCES**

3. Ross RS, McKusick VA: Aortic arch syndromes; diminished or absent pulses in arteries arising from arch of aorta. Arch Intern Med 92: 701, 1953
9. Vinjchaikul K: Primary arteritis of the aorta and its main branches (Takayasu's arteriopathy); a clinicopathologic autopsy study of eight cases. Am J Med 43: 15, 1967