Aortic regurgitation and aortic valve operation in Takayasu arteritis: A meta-analysis

Takayasu arteritinde aort regürjitasyonu ve aort kapak ameliyatı: Bir meta-analiz

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ABSTRACT

Background: This study aims to describe the clinical features of aortic regurgitation, which can be a major complication of patients with Takayasu arteritis, as well as necessitated aortic valve operations in such patients.

Methods: This meta-analysis was based on the literature retrieval of 41 pertinent articles including 159 Takayasu arteritis patients, published between January 2001 and December 2016. There were 12 male and 55 female patients, while gender of 92 patients was not available.

Results: The aortic regurgitation patient profile of Takayasu arteritis population showed a predominance of female gender, type 2a of Takayasu arteritis, and severe degree of aortic regurgitation. Most of them warranted aortic valve operations, the most common of which were aortic valve replacements or composite graft replacements. Of the concurrent cardiac operations, coronary artery bypass grafting was the most frequent, for which the saphenous vein was a preferred graft choice due to the concern of the Takayasu arteritis-impaired arterial graft patency. Postoperative cardiac complications occurred in 31 patients (20.7%) and reintervention was warranted in 13 (41.9%). Logistic regression analysis revealed that the primary aortic valve operation and concurrent cardiac operation were the predictive risk factors of postoperative complications. The mortality rate of the entire patient population was 21.5%.

Conclusion: Takayasu arteritis may cause aortic regurgitation and the majority of the patients warrant an aortic valve operation. The postoperative comorbidity rate remains high. To avoid postoperative complications and subsequent reinterventions, utilization of reinforcing techniques during aortic valve operations, avoidance of cardiac operations during an active stage of Takayasu arteritis and postoperative steroid therapy are recommended.

Keywords: Aortic regurgitation; aortic valve replacement; Takayasu arteritis.

ÖZ

Amaç: Bu çalışmada Takayasu arteriti olan hastaların majör bir komplikasyonu olabilen aort regürjitasyonunun klinik özellikleri ile beraber bu hastalarda gereken aort kapak ameliyatları tanımlandı.

Çalışma planı: Bu meta-analiz; literatürden erişilen, Ocak 2001 ve Aralık 2016 tarihleri arasında yayınlanan ve 159 Takayasu arteriti hastasını içeren 41 ilgili yazıya dayandırıldı. On iki erkek ve 55 kadın hasta varken 92 hastanın cinsiyet bilgisi yoktu.

Bulgular: Takayasu arteriti popülasyonunun aort regürjitasyonu hastası profili; kadın cinsiyetinin, tip 2a Takayasu arteritinin ve aort regürjitasyonunun şiddetli derecesinin hakim olduğunu gösterdi. Çoğu, en yaygını aort kapak replasmanı veya kompozit greft replasmanı olmak üzere aort kapak ameliyatı gerektirdi. Eşzamanlı kalp ameliyatları içinde en sık olan koroner arter baypas greftleme idi; Takayasu arteriti kaynaklı arteriyel greft patensi endişesi nedeniyle safen ven tercih edilen bir greft seçeneği idi. Ameliyat sonrası kardiyak komplikasyonlar 31 hastada (%20.7) oluştu ve 13'ünde (%41.9) yeniden girişim gerekti. Lojistik regresyon analizi ameliyat sonrası komplikasyonlar için belirleyici risk faktörlerinin primer aort kapak ameliyatı ve eşzamanlı kalp ameliyatı olduğunu ortaya koydu. Tüm hasta popülasyonun mortalite oranı %21.5 idi.

Sonuç: Takayasu arteriti aort regürjitasyonuna neden olabilir ve hastaların çoğunluğunda aort kapak ameliyatı gerekir. Ameliyat sonrası komorbidite oranı yüksektir. Ameliyat sonrası komplikasyonları ve sonraki yeniden girişimleri önlemek için aort kapak ameliyatları sırasında güçlendirici tekniklerden yararlanılması, Takayasu arteritinin aktif bir evresinde kardiyak ameliyatlardan kaçınılması ve ameliyat sonrası steroid tedavisi önerilmektedir.

Anahtar sözcükler: Aort regürjitasyonu; aort kapak replasmanı; Takayasu arteriti.

Takayasu arteritis (TA) is a rare chronic inflammation of the large vessels characterized by granulomatous vasculitis of an unknown etiology.[1] It usually occurs in females at the age of 20-30 years, but TA in patients over the age of 40 has been continuously reported.[2] This disease has a 9:1 female predominance in adults, while the ratio is significantly reduced in pediatric patients.[2] Although TA has a worldwide distribution, the greatest prevalence is seen in Asian countries.[3] The diagnosis of TA can sometimes be difficult, particularly in patients with non-specific symptoms. Thus, a delayed or missed diagnosis until after the occurrence of a major complication is frequent.[4]

Takayasu arteritis usually affects the aorta and its branches, leading to vascular wall thickening, fibrosis, stenosis and thrombus formation.[5] Takayasu arteritis can be divided into six types based on the extent of vascular involvement: type 1 - branches of the aortic arch; type 2a - ascending aorta, aortic arch and its branches; type 2b - type 2a region plus thoracic descending aorta; type 3 - thoracic descending aorta, abdominal aorta, renal arteries, or a combination; type 4 - abdominal aorta, renal arteries, or both; and type 5 - entire aorta and its branches.[6]

Aortic regurgitation (AR) is a major cardiac complication of TA patients with a prevalence of 33%.[7] The prognoses of the patients are often dismal when severe AR is present.[8] However, the management of AR is challenging as lethal complications, such as hemorrhage, pseudoaneurysm formation, valve and suture line detachment and paravalvular leakage, often occur following cardiac operations, probably in the warrant of reinterventions.[9] Active inflammation has been proved to be a predictive risk factor of these lethal complications.[10] Therefore, a cardiac operation in TA patients at an active inflammation stage seems to be risky.[9] AR and aortic valve operation in TA have not been sufficiently elucidated in terms of the clinical features, treatment of choices and prognosis. Therefore, in this study, I aimed to describe the clinical features of AR, which can be a major complication of patients with TA, as well as necessitated aortic valve operations in such patients.

MATERIALS AND METHODS

This meta-analysis, which was conducted at The First Hospital of Putian, Teaching Hospital, Fujian Medical University between January and March 2017, included retrieval of 41 pertinent articles including 159 TA patients from the PubMed, Google and Highwire Press databases for the year range 2001-2016. The study protocol was approved by the The First Hospital of Putian Ethics Committee.

Search terms included "Takayasu arteritis", "Takayasu disease", "aortic regurgitation", "aortic valve insufficiency", "aortic valve replacement", "aortic valve repair", "composite aortic valve replacement", "Bentall operation" and "aortic root replacement". Articles mentioning AR or aortic valve operation with the lack of patients' substantial information were excluded.

Data were carefully extracted for details of the study population, including demographics, clinical features, serum inflammatory biomarkers, vascular involvements (types of TA), aortic valve/aorta pathologies, medical treatment strategies, cardiac surgical procedures, postoperative complications, reinterventions and prognosis, etc.

Statistical analysis

Measurement data were expressed in mean±standard deviation with range and median values and compared by independent sample t-test. Categorical variables were compared by Fisher exact test. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 41 articles[10-50] with 159 patients were included in this study. One article (2.4%) was an original article,[10] two (4.9%) were case series,[26,42] and the remaining 38 articles (92.7%) were case reports. There were 55 (82.1%) females and 12 (17.9%) males with a female predominance of 4.6:1, while gender of 92 patients was not available. Patients were at the age of 39.4±17.1 (range, 0.8-76; median, 39) years (n=69). Eight patients (11.6%) were pediatrics, and 61 (88.4%) were adults (χ^2=81.4, p<0.001). Of the adult patients, 28 (45.9%) were ≤40 years old, while 33 (54.1%) were >40 years old (χ^2=0.8, p=0.365). Age difference was noted between female and male patients (42.4±15.8 vs. 25.1±16.8, p=0.004).

The presenting symptoms were available for 32 patients with 63 manifestations. The major manifestations were circulatory (41.3%), followed by constitutional (25.4%), pains (17.5%), neurological (9.5%) and local symptoms (4.8%). Only one patient (1.6%) was asymptomatic.

The patients' symptoms lasted several days to one year before current admission, with a mean of 4.0±4.4 months (range 0.25-12 months; median 2 months) (n=11).[11,12,19-21,23,27,30,40,47,48]

A cardiac murmur was recorded in 17 patients (10.7%), including a diastolic murmur in 11 (74.7%),

a systolic-diastolic murmur in four (23.5%),[13,14,17,36] a to-and-fro murmur in one (5.9%)[21] and an unspecified murmur in one (5.9%) (χ^2=20.9, p<0.001).[16]

The value of C-reactive protein (CRP) was reported in 36 patients: it was normal in 10 (27.8%), and elevated in 26 (72.2%) (χ^2=14.2, p<0.001). In two patients, the CRP values were extremely high as 121 g/L[23] and 2.2 g/dL,[39] and they were excluded from the statistical analysis. The quantitative CRP value was 3.0±5.5 mg/dL (range 0-31 mg/dL; median 1.1 mg/dL) (n=26). The result of erythrocyte sedimentation rate (ESR) was reported in 13 patients: it was normal in two (15.4%), and elevated in 11 (84.6%) (χ^2=12.5, p<0.001). The quantitative ESR value was 68.7±37.7 mm/hour (range 16-131 mm/hour; median 60 mm/hour) (n=11).[12,14,15,20,23,24,28,30-32,47]

The degree of AR was not reported in 118 patients (74.2%).[10,16,18,22,26,35,38,45,50] In the remaining 41 patients (25.8%), one (2.4%) was mild,[29] nine (22.0%) were moderate,[11,12,23,34,37,41,42,49] one (2.4%) was moderate-to-severe[37] and 30 (73.2%) were severe[13-15,17,19-21,24,25,27,28,30-33,36,39,40,42-44,46-48] (χ^2=17.9, p<0.001). Seven patients (4.4%) were associated with mitral regurgitation[23,26,42,47] and one patient (0.6%) was associated with pulmonary valve regurgitation.[14]

By preoperative imaging, the left ventricular dimension was detected in 23 patients (14.5%).[11,13,14,17,24,27,31-34,36,39,40,42] The end diastolic diameter of the left ventricle was normal in four patients (17.4%),[13,42] and left ventricular dilation was found in 19 patients (82.6%)[11,14,17,24,27,31-34,36,39,40,42] (χ^2=19.6, p<0.001). The quantitative value of the end diastolic diameter of the left ventricle was 57.3±9.0 mm (range 44-72 mm; median 60 mm) (n=15). Forty-nine patients (30.8%) had their aortic valve/wall pathologies reported, including aortic valve dilation (57.1%), aortic wall thickening (34.6%) and aortic wall calcification (8.2%). Their ascending aorta dimension was 60.2±12.6 mm (range 45-90 mm; median 56 mm) (n=11). The aortic valve pathologies were cusps thickening (43.8%), poor or non-coapting (18.8%), reduced mobility (12.5%), leaflet fibrosis and retraction (6.3%), cusp detachment and perforation (6.3%), extensive myxomatous deposit (6.3%), and giant cells, elastic lamina destruction and nodular fibrosis (6.3%).

Cases with intra- and postoperative diagnosis of TA were regarded as a delayed diagnosis. The delayed term was 23.4±53.5 months (range 0.5-144 months; median three months) (n=7).[19-21,23,30,32,40] Four patients were misdiagnosed: three as infective endocarditis,[20,21,47] and one as aortic dissection.[48]

In 33 patients (20.8%), the type of TA could be tracked: five (15.2%) were type 1,[28,33,34,37,47] 21 (63.6%) were type 2a,[11-14,17-24,27,29,30,36,38,39,46,48,49] one (3.0%) was type 2b,[31] three (9.1%) were type 3,[32,40,41] two (6.1%) were type 4, and one (3.0%) was type 5.[16] The activity of TA could be traced in 42 patients (26.4%): 37 (88.1%) were active[12,14-16,18-24,26,28,30-32,36,37,39,42,47,48] and five (11.9%) were inactive[11,17,40,46,49] (χ^2=48.8, p<0.001).

Table 1. Sixty alternative cardiac operations other than an aortic valve operation

Alternative cardiac operation	n	%	Reference
Coronary artery bypass grafting	20	33.3	[10,14,19,26-29,31,34,40,48] (AA-left carotid & AA-brachiocephalic trunk bypasses in one patient [28] & pulmonary valve exploration [14] in another)
Total aortic arch replacement	13	21.7	[10,26]
Coronary ostial repair	9	15	[10,36]
Cervical arterial bypass	5	8.3	[10,26]
Mitral valve replacement	4	6.7	[10,23]
Hemiarch replacement	2	3.3	[10,26]
Ascending aorta replacement	1	1.7	[17,30]
Ascending aorta + arch replacement	1	1.7	[46]
Coronary fistula ligation	1	1.7	[33]
Partial arch replacement	1	1.7	[26]
Coronary ostioplasty	1	1.7	[12,39]
Mitral valve repair, aortic root homograft replacement, reimplantation of the left coronary artery	1	1.7	[47]
Multiple extra-anatomical bypasses	1	1.7	[25]

AA: Ascending aorta.

The treatment of choice was recorded in 157 patients: seven (4.5%) were conservatively,[13,16,42,43] and 150 (95.5%) were surgically treated.[10-12,14,15,17-36,38-40,42,44-50] The aortic valve operations that were performed in these patients were: aortic valve repair in three (2%)[12,30,32] (in one of them, aortic valve repair was performed after a three-week steroid treatment),[32] aortic valve replacement in 98 (65.3%),[10,11,14,17,18,20,22-28,31,33-35,38-40,42,44,46,48-50] composite graft replacement in 47 (31.3%),[10,15,19,21,26,29,36,45] valve-sparing root replacement in one (0.7%),[26] and no aortic valve intervention but with other cardiac operation instead in one (0.7%).[47] Alternative cardiac operations were performed in 31 patients (20.7%) (Table 1).

As for coronary/carotid artery bypass in TA patients, more venous grafts were used than the arterial ones: five patients with nine venous bypasses (to the left main coronary artery (n=1),[29] to the left anterior descending coronary artery (n=3),[14,27,34,40] to the right coronary artery (n=2),[34,40] to the obtuse marginal branch (n=1),[34] and to the left vertebral artery (n=1),[34] respectively) versus three patients with three arterial bypasses (previous surgery: hepatic artery to the left anterior descending artery,[43] left internal mammary artery to the left anterior descending coronary artery[48] and left internal mammary artery to the left coronary artery in reintervention[47] in one patient each) (χ²=1.0,

p=0.317 for patient number; and χ²=6.0, p=0.014 for bypass number).

Pathological studies revealed giant cell granulomatous reactions in six patients: in the aortic tissues in four (66.7%),[18,21,23,30] in the aortic and sternal biopsies in one (16.7%),[24] and in the aortic wall and mitral valve in one (16.7%).[20] The pathologies of aortic wall based on postoperative pathological investigations in 14 patients were shown in Table 2.

In the surgical patients, 16 patients (10.7%) received steroid therapy preoperatively,[13,15,26,31,32,34,42,49] and 19 patients (12.7%) received steroid therapy postoperatively.[13,15,26,31,32,34,42,49] Post-treatment ESR and CRP were reported for six[12,14,18,32,47,48] and four patients,[12,14,18,47] respectively. The time interval for these biomarkers to recover to normal was 6.8±6.9 months (range 0.75-18 months; median 4.5 months) (n=6).

In the surgical group, postoperative cardiac complications occurred in 31 patients (20.7%),[20-23,32,35,36,38,42,44,47,49,50] and complications occurred twice in one patient at postoperative 18 months and 14 years, respectively.[50] The timing of complication development was at 66.0±70.1 months (range 0.5-204 months; median 36 months) (n=16) postoperatively. Reintervention for complications was warranted in 13 patients (41.9%),[10,21-23,35,36,38,42,44,47] but

Table 2. Pathology of aortic wall based on postoperative pathological investigations in 14 patients

Aortic wall	Pathology	n	%	Reference
Intima (n=8)				
	Fibrous thickening	4	50	[17,21,34,36]
	Thickened with thrombosis	2	25	[45]
	Fibrous thickening with calcification	1	12.5	[46]
	Mild intimal proliferation	1	12.5	[14]
Media (n=10)				
	Elastic lamella disruption	4	10	[21,22,45]
	Elastic lamella disruption + fibrous thickening	2	20	[34,46]
	Collagenous fibrosis	1	10	[17]
	Elastic fiber disarrangement with inflammatory cell infiltration	1	10	[36]
	Granulomatous giant cell aortitis and atherosclerosis	1	10	[18]
	Medial cystic degeneration, elastic fiber fragmentation	1	10	[20]
Adventitia (n=9)				
	Fibrosis + inflammatory cell infiltration	3	33.3	[17,45]
	Inflammatory cell infiltration	2	22.2	[24,34]
	Fibrous thickening	2	22.2	[22,36]
	Inflammatory cell and giant cell infiltration	1	11.1	[21]
	Fibrosis with inflammatory cell and giant cell infiltration	1	11.1	[20]

Table 3. A comparison of prognoses between surgically and conservatively treated patients

Prognosis	Surgical (n=109)		Conservative (n=7)		χ^2	p
	n	%	n	%		
Recovered	42	38.5	2	28.6	0.3	0.599
Improved	1	14.3				
No change	1	14.3				
Complicated	44	40.4	1	14.3	1.9	0.170
Cardiac	31	70.5	1	100	0.4	0.519
Neurological	13	29.5				
Died	23	21.1	2	28.6	0.2	0.641
Early death	6	26.1				
Late death	17	73.9	2	100	0.7	0.407

one patient refused.[22] Besides, 13 patients (11.9%) had postoperative neurological complications.[10,42]

Patients were under a follow-up of 82.3±91.8 months (range 0.5-348 months; median 48 months) (n=51).[10,12-16,18,20-26,30,34-36,38-40,42,44,47,48] Of the 159 patients, prognoses were reported for 116 patients: 44 (37.9%) recovered, one (0.9%) improved, one (0.9%) was unchanged, 45 (38.8%) were complicated and 25 (21.6%) died. A comparison of the prognoses between surgically and conservatively treated patients showed no intergroup difference (Table 3).

Logistic regression analysis revealed that types of aortic operation (p<0.001) and associated cardiac operation (p=0.004) other than TA types (p=0.874), active stage (p=0.281), degree of AR (p=1.000), aorta dilation (p=0.543) and aortic wall thickening (p=0.250) were predictive risk factors of postoperative complications, whereas only postoperative complications (p<0.001) instead of TA types (p=1.000), active stage (p value was undetermined), degree of AR (p=0.122), aorta dilation (p value was undetermined), aortic wall thickening (p=0.992), aortic valve operation (p=1.000) and associated cardiac operation (p=0.994) was a risk factor for reintervention.

DISCUSSION

Takayasu arteritis is a rare, chronic, relapsing large vessel vasculitis, often affecting the aorta and the branches.[51] Chung et al.[52] reported that, of their 85 TA patients, an aneurysmal formation was observed in the aorta or aortic branches in 19 (22.4%), with two (10.5%) having partial thrombosis.[52] The inflammation biomarkers including CRP and ESR implied an ongoing inflammation.[15] A persistent ESR of 120 mm/hour[53] or CRP >0.3 mg/dL[26] indicated an active stage of the disease.[53] Preoperative laboratory showed active inflammation.

The reported incidence of AR in TA patients was between 13% and 34%.[7,52,54,55] At echocardiography, aortic valvular regurgitation was found in 14 patients (20.6%).[54] Asymptomatic AR (mild to moderate) was found in 34% and hypertrophy of the left ventricle in 25%, while seven patients (17%) had a stroke or a transient ischemic attack.[55] Lee et al.[56] reported that, among their 26 TA patients with a dilated ascending aorta, 18 patients (69.2%) had AR of more than a mild degree.[56] Aortic regurgitation is an important risk factor for mortality of TA patients.[52] It also decreases survival in young patients of 10-29 years old, and it may reduce the five-year survival to 40%.[57] The development of AR has been considered to be due to the aortic inflammation and subsequent aortic annulus dilation.[58] The thickened aortic root may extend to the mitral-aortic intervalvular fibrosa, leading to mitral regurgitation.[20] An extension of TA into the ventricular septum or mechanical compression of the aneurysm against the conduction system might cause progressive heart block.[22]

Pathological studies revealed that the aortic root in TA patients could be extremely thickened, fibrotic, inflamed, or grossly dilated. The coronary ostia were often involved.[19] Similarly, giant cells, elastic lamina, destruction and nodular fibrosis could be observed in the specimens of the aortic valves.[19]

When the patient was unresponsive to conservative treatment, as disclosed by signs of increased left ventricular end diastolic dimension and decreased ejection fraction, then a surgical operation was warranted.[32] The surgical indication for mild AR was thickened free edges and reduced mobility of the aortic cusps, meanwhile, an aortic valve sparing operation was inappropriate.[29] The coronary ostia obliterated by the thickened and inflamed aortic wall necessitated a bypass grafting procedure.[19] In addition, due to

a poor condition of either the donor or the receipt vessels, a surgical treatment might be declined by the surgeons.[43]

To diminish the postoperative complications and reinterventions, a Teflon or a fresh homologous pericardial strip was proposed to be placed circumferentially on the outside of the suture line for enforcement in tube graft replacement,[21,45] or a buttressed suture around the annulus suture line in valve replacement procedures.[38] The left internal mammary and gastroepiploic arteries might be severely compromised, particularly in the acute phase of TA, and therefore the arterial grafts would not be suitable candidates as a bypass graft.[29] Meanwhile, the saphenous vein grafts were preferred.[43]

Late aortic dilation and valve detachment after aortic valve replacement can be due to the active inflammation.[20] Therefore, postoperative use of methylprednisolone,[19] prednisolone (15 mg/day), azathioprine (50 mg/day) and cyclophosphamide (500 mg/month)[21] are recommended.

As reported by Matsuura et al.,[10] in TA patients with AR receiving aortic valve replacement and those receiving composite graft replacement, the hospital mortality was 4.8% and 7.4%, valve or graft detachment rate was 11.1% and in 3.7%, and late dilation rate was 11.1% and in 3.7%, respectively. The overall 15 year survival rate was 76.1%.

The present study revealed that the TA patients with AR showed a predominance of female gender, type 2a of TA and severe degree of AR. Most of them warranted aortic valve operations, the most common of which were aortic valve replacements or composite graft replacements. Of the current cardiac operations, coronary artery bypass grafting was the most frequent, for which the saphenous vein was a preferred graft choice due to the concern of the TA-impaired arterial graft patency. Postoperative cardiac complications occurred in 31 (20.7%) of surgical patients and reintervention was warranted in 13 (41.9%). The primary aortic valve operation and concurrent cardiac operation were the predictive risk factors of postoperative complications. The mortality rate of the entire patient population was 21.5%.

The main limitation of this article was the missing values of patients from different article sources, which would inevitably affect subsequent statistical analysis. A prospective study with larger patient population is crucial for obtaining more accurate results.

In conclusion, Takayasu arteritis may cause aortic regurgitation and most of such cases warrant a surgical operation. The postoperative comorbidity rate remains high. To avoid postoperative complications and subsequent reinterventions, utilization of reinforcing techniques during the operations, avoidance of cardiac operations during active stage and postoperative steroid therapy are recommended.

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