Influence of aortitis on late outcomes after repair of ascending aortic aneurysms

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ABSTRACT

Objective: To determine outcomes of repair of ascending aortic aneurysms in patients with histopathologic diagnoses of aortitis.

Methods: We reviewed histopathologic findings and outcomes of elective repair of ascending aortic aneurysms between January 1, 1955, and December 31, 2012. Noninfectious aortitis was identified in 186 patients, and we compared outcomes for these patients with outcomes for others operated on at the same time with diagnoses of medial degeneration (n = 317) or atherosclerosis (n = 232).

Results: Early mortality (<30 days postoperatively) for patients with aortitis was 2%, and overall 10-year survival was 45%, compared with 66% for patients with medial degeneration, and 45% for patients with atherosclerosis ($P < .001$ vs medial degeneration). In addition to histopathologic diagnosis, overall mortality was influenced by older age at operation (hazard ratio [HR]: 1.060; 95% confidence interval [CI], 1.046-1.077; $P < .001$), chronic obstructive pulmonary disease (HR: 1.560; 95% CI: 1.136-2.136; $P = .006$); concomitant coronary artery bypass grafting (HR: 1.980; 95% CI: 1.520-2.600; $P < .001$); and use of circulatory arrest (HR: 1.500; 95% CI: 1.148-1.960; $P = .003$). Risk of aortic reoperation at 10 years was 21% for aortitis patients, compared with 11% for those with medial degeneration, and 19% for patients with atherosclerosis ($P = .028$).

Conclusions: Patients with repaired ascending aneurysms secondary to noninfectious aortitis have low early mortality, but late risks of death and aortic reoperation are increased, compared with these outcomes for patients with aneurysms that result from medial degeneration. (J Thorac Cardiovasc Surg 2015;150:589-94)

Overall survival differed significantly between groups.

Central Message

Patients with aneurysms and aortitis have greater risk for reoperation (21%) than do those with medial degeneration (11%) or atherosclerosis (19%).

Perspective

This study describes outcomes of patients who were found to have aortitis at the time of excision of ascending aortic aneurysms. Compared with patients who have medial degeneration or atherosclerosis, patients with aortitis have an increased risk of aortic reoperation. Precise pathologic diagnosis of ascending aortic aneurysms may be helpful in stratifying prognosis and treatment.

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Inflammation of the aortic wall is an important cause of aortic aneurysms, and noninfectious aortitis is being identified with increasing frequency in patients undergoing elective replacement of the ascending aorta.¹ Of the patients who are found to have aortitis, 96% have no associated systemic illness.² In surgical series, the prevalence of noninfectious aortitis among patients with aortic aneurysms ranges from 4.4% to 8.4%, yet few data are available to guide surgical and postoperative management.^{1,2}

Previous studies of surgical treatment of patients with aortic aneurysms secondary to aortitis have focused on the extent of aortic involvement and surgical methods, including the need for aortic valve replacement.³ However, no large studies have been done of late outcomes of ascending aneurysm repair in patients who have aortitis, compared with patients who have medial degeneration or atherosclerosis. The purpose of this study was to determine whether the outcome of repair of ascending aortic aneurysms, in patients who have noninfectious aortitis, differs from the outcome of operation in patients with aneurysms caused by atherosclerosis or medial degeneration.

METHODS

Cohort Selection

After obtaining approval from the Mayo Clinic Institutional Review Board, we reviewed all patients aged >18 years who underwent surgical replacement of the ascending aorta between January 1, 1955, and December 31, 2012, at Mayo Clinic in Rochester, Minn. Patients were

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Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio

excluded if they did not give permission for research or did not have available pathology reports. Patients were additionally excluded if they had aneurysms secondary to aortic dissection, heritable connective tissue disease (eg, Marfan syndrome or Ehlers-Danlos syndrome), infectious aortitis, or congenital heart disease, including bicuspid aortic valve. Patients with Takayasu arteritis were excluded because they are generally younger and have characteristic clinical presentations and associated obstructive aortic disease (Figure 1).

Preoperative and postoperative clinical data were obtained from the patients' electronic health records and a cardiovascular surgical database. Additional follow-up data were obtained from patient and physician correspondence, and from questionnaires sent to patients 1, 3, 5, 10, 15, and 20 years after their operation.

Histopathologic Evaluation

Patients who met study criteria were divided into 3 groups, according to the cause of their ascending aortic aneurysm as assessed via a histologic examination of the surgical specimen, conducted by a cardiovascular pathologist. The resected ascending aortic wall was fixed in 10% neutral buffered formalin, embedded in paraffin, cut at a thickness of 4 μ m, and stained with hematoxylin-eosin and Verhoeff-van Gieson. Typically, 6 to 8 transverse sections were evaluated per patient.

Presence of aortitis was defined as medial inflammation, with associated medial damage. The character of the inflammatory infiltrate was noted as well—specifically, whether giant cells were present. Presence of medial degeneration was defined as fragmentation of elastic lamella, with associated mucopolysaccharide deposition. Presence of atherosclerosis was defined as intimal collections of foamy histiocytes and cholesterol, with or without associated inflammation and associated subjacent secondary medial change. The presence of any aortitis prompted classification as such. Those without aortitis were dichotomized into diagnosis categories of medial degeneration or atherosclerosis, depending on which process was most evident.

Statistical Analysis

Categorical data were summarized as frequency and percentage of samples; continuous data were summarized as mean $\pm$ SD. Categorical data for the groups were compared, using χ^2 analysis or the Fisher exact test; continuous data were compared using standard ANOVA or Kruskal-Wallis ANOVA, as appropriate. The Kaplan-Meier product-limit method was used to draw survival curves and calculate 5-year and 10-year survival, and estimates for freedom from reoperation.

Cox regression models were used to find the univariate and multivariate predictors of overall mortality and time to aortic operation. The multivariate models included variables that were significant on univariate analysis ($P < .05$), with model selection using the stepwise method (backward and forward methods resulted in the same model). All statistical tests were 2-sided.

RESULTS

Between 1955 and 2012, a total of 3177 patients underwent ascending aorta replacement. Of these patients, 735 met criteria for the study and were divided into 3 groups according to aortic pathology (Figure 2). Inflammatory, noninfectious aortitis was identified in 186 patients; medial degeneration was present in 317 patients; and atherosclerosis was the pathologic finding in 232 patients.

Demographics

Among patients with noninfectious, inflammatory aortitis, the mean age was 71 ± 11 years, and 35% of the patients (66 of 186) were men. These demographic data differed ($P < .001$) from data for patients who had medial degeneration (mean age: 64 ± 14 years; 69% men [219 of 317], $P < .001$) and for patients with atherosclerosis (mean age: 66 ± 11 years; 61% men [141 of 232], $P < .001$). Other vascular conditions, such as occlusive peripheral vascular disease ($P < .001$), coronary artery disease ($P = .003$), and stroke ($P = .010$), were significantly less prevalent in patients with medial degeneration, compared with patients who had noninfectious aortitis or atherosclerosis (Table 1). Among the 186 patients with noninfectious aortitis, giant cells were identified in 138 patients (74%), and lymphoplasmacytic infiltrates without giant cells were observed in 48 patients (26%).

Among patients who had preoperative echocardiography ($n = 348$), the mean diameter of the midascending aorta was 57.3 mm in the group with noninfectious aortitis, 51.5 mm in the medial degeneration group ($P < .001$), and 52.7 mm in the atherosclerosis group ($P < .001$). Moderate-to-severe aortic valve regurgitation was diagnosed preoperatively in 56% (103 of 183) of patients with aortitis, 63% (190 of 300) of patients with medial degeneration, and 47% (92 of 195) of patients with atherosclerosis ($P < .001$ for all 3 groups; $P < .010$ for comparison of the medial degeneration group with the atherosclerosis group).

Aortic Valve

Concomitant aortic valve procedures were performed in 58% (107 of 186) of patients with noninfectious aortitis, 77% (243 of 317) of patients with medial degeneration ($P < .001$), and 59% (137 of 232) of patients with atherosclerosis ($P < .753$). Among patients who underwent concomitant aortic valve operations, aortic valve-sparing procedures were used relatively more often in patients with noninfectious aortitis (40%; 42 of 106) than in patients

FIGURE 1. Patient selection and stratification.

FIGURE 2. Aortic pathology: A, Aortic atherosclerosis is characterized by intimal plaques containing cholesterol clefts and foam cells. The subjacent media show mild, secondary, degenerative changes. B, Medial degeneration is characterized by elastic membrane fragmentation and mucopolysaccharide deposition throughout the media. C, Giant cell aortitis is characterized by medial inflammation with multinucleated giant cells imparting a moth-eaten appearance to the aortic media (*top panels*: hematoxylin-eosin; *bottom panels*: Verhoeff-van Gieson; original magnification $\times 40$ for all).

with medial degeneration (33%; 81 of 243) ($P < .285$) and atherosclerosis (28%; 38 of 137) ($P = .057$).

Among patients with aortitis who underwent aortic valve-sparing operations, 5- and 10-year estimates of risk of aortic valve reoperation were 15% and 22%, respectively, compared with 10% and 10% for patients with aortitis who had aortic valve replacement ($P = .240$). In patients with medial degeneration and patients with atherosclerosis who underwent valve-sparing operations, estimates of cumulative risk of aortic valve reoperation were 5% and 3% (at 5 years), and 11% and 22% (at 10 years), respectively ($P = .072$). Thirty-two patients (17%) in the aortitis group required total root replacement, compared with 108 patients (34%) in the medial degeneration group, and 38 patients (16%) in the atherosclerosis group.

Extent of Aortic Resection

The extent of aortic resection differed in the 3 histopathologically defined groups. Approximately one-half of the patients (48%; 90 of 186) who had aortitis had extensive aortic resection involving the aortic arch (complete or hemiarch), compared with 16% (52 of 317) ($P < .001$) of patients with medial degeneration, and 35% (82 of 232) ($P = .007$) of patients with atherosclerosis. Hemiarch replacements were performed in 59 patients (32%) with aortitis, 44 patients (14%) with medial degeneration, and 53 patients (23%) with atherosclerosis; total arch replacements were performed in 17% (31 of 186), 3% (8 of

317), and 13% (29 of 232) of patients in the 3 groups, respectively.

Aortic Reoperation and Survival

Cumulative risk of aortic reoperation at 5 and 10 years, respectively, was 13% (95% confidence interval [CI]: 7%-19%) and 21% (95% CI: 11%-30%) for patients with aortitis; 6% (95% CI: 3%-10%) and 11% (95% CI: 5%-16%) for patients with medial degeneration; and 9% (95% CI: 5%-14%) and 19% (95% CI: 11%-27%) for patients with atherosclerosis ($P = .025$) (Figure 3). These include aortic reoperations as the second stage of an elephant trunk procedure. Most reoperations were for distal progressive disease, except for 1 patient with aortitis who required total arch replacement after a hemiarch procedure initially. However, when predictors for aortic reoperation were examined in multivariate analysis, the cause of aortic aneurysm was found to not be a significant variable. The predictors of aortic reoperation were peripheral vascular disease (hazard ratio [HR]: 2.290; 95% CI: 1.377-3.802; $P = .001$) and extended aortic arch procedures at the primary operation (HR: 3.510; 95% CI: 2.083-5.930; $P < .001$) (Table 2).

Among all patients, mortality was influenced by associated cardiac disease and the era of operation. Risk of operative death (in the hospital or <30 days postoperatively) was 3% for patients undergoing isolated aortic operations. Operative mortality for ascending aortic replacement with or

TABLE 1. Demographics and operative details

Variable	Aortitis (n = 186)	Medial degeneration (n = 317)	Atherosclerosis (n = 232)	P value
Age (y)	71 ± 11	64 ± 14	66 ± 11	<.001
Gender, male	66 (35)	219 (69)	141 (61)	.001
Smoking history	99 (53)	157 (50)	119 (51)	.590
COPD	36 (19)	29 (9)	40 (17)	.002
Diabetes mellitus	18 (10)	22 (7)	24 (10)	.310
Hypercholesterolemia	109 (59)	149 (47)	106 (46)	.010
Hypertension	136 (73)	214 (68)	137 (59)	.005
PVD	37 (20)	39 (12)	58 (25)	<.001
CAD	81 (44)	99 (31)	96 (41)	.003
Stroke	27 (15)	23 (7)	31 (13)	.010
Arrhythmia	32 (17)	64 (20)	39 (17)	.580
NYHA class				.009
I or II	113 (63)	171 (59)	88 (48)	
III or IV	65 (37)	117 (41)	94 (52)	
Aortic dimensions (mm)				
Annulus diameter	23.5 ± 2.9	24.6 ± 3.8	24.6 ± 2.6	.020
Sinus of Valsalva	40.1 ± 7.3	46.3 ± 8.6	43.4 ± 7.0	<.001
Sinotubular junction	37.0 ± 8.8	41.2 ± 7.7	39.6 ± 8.0	<.001
Midascending aorta	57.3 ± 9.7	51.5 ± 9.8	52.7 ± 9.2	<.001
Arch	35.8 ± 7.4	34.6 ± 6.6	37.7 ± 8.9	.110
Aortic insufficiency, moderate to severe (%)	56	63	47	.010
Aortic stenosis (%)	5	14	20	<.001
EF (%)	58.5 ± 11.3	57.2 ± 10.9	56.5 ± 11.5	.230
Aortic valve procedure				<.001
Replacement	64 (60)	163 (51)	99 (44)	
Sparing	42 (40)	81 (33)	38 (28)	
Arch procedure	90 (48)	52 (16)	82 (35)	<.001
Hemiarch	59 (32)	44 (14)	53 (23)	
Total arch	5 (3)	2 (0.6)	9 (4)	
Total arch and elephant trunk	21 (11)	5 (1.6)	14 (6)	
Total arch and descending	5 (3)	1 (0.3)	6 (3)	
Concomitant MVR	10 (5)	30 (9)	8 (4)	.020
Concomitant CABG	61 (33)	77 (24)	72 (32)	.850
CPB time (min)	132 ± 54	128 ± 58	134 ± 58	.260
Crossclamp time (min)	84 ± 39	92 ± 43	84 ± 38	.090
Circulatory arrest	114 (82)	71 (37)	95 (51)	<.001
Circulatory arrest time (min)	21 ± 11.9	19 ± 8.3	23 ± 13.5	.600
Operative mortality	4 (2)	15 (5)	18 (8)	.020

Continuous data are presented as mean ± SD; categoric data are presented as number of patients (percentage of sample). NYHA class data were available for only 178 patients in the aortitis group, 288 patients in the medial degeneration group, and 182 patients in the atherosclerosis group. For aortic stenosis and EF, echocardiographic data were available for 52% of patients. COPD, Chronic obstructive pulmonary disease; PVD, peripheral vascular disease; CAD, coronary artery disease; NYHA, New York Heart Association; EF, ejection fraction; MVR, mitral valve repair or replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

without concomitant arch replacement, aortic valve replacement, or coronary artery bypass grafting decreased during the study period and was 2% during and after 2010 ($P < .001$) (Figure 4). Overall operative mortality was higher in the atherosclerosis group (8%) than in the noninfectious aortitis group (2%; $P = .008$) and the medial degeneration group (5%; $P = .023$), but this was likely related to the era of operation. Before 1990, atherosclerotic aneurysms (30%) were identified more frequently, compared with aortitis (4%) and medial degeneration (13%).

Overall survival at 5 years was 72% (95% CI: 64%-79%) for patients with aortitis; 84% (95% CI: 80%-

89%) for patients with medial degeneration; and 74% (95% CI: 68%-81%) for patients with atherosclerosis; survival at 10 years was 45% (95% CI: 36%-57%); 66% (95% CI: 59%-73%); and 45% (95% CI: 37%-54%) ($P < .001$), respectively (Figure 5). In multivariate analysis, predictors of overall mortality included older age at operation (HR: 1.060; 95% CI: 1.046-1.077; $P < .001$); chronic obstructive pulmonary disease (HR: 1.560; 95% CI: 1.136-2.136; $P = .006$); concomitant coronary artery bypass grafting (HR: 1.980; 95% CI: 1.520-2.600; $P < .001$); and more extensive aortic resection, as reflected by the use of circulatory arrest during repair (HR: 1.500;

FIGURE 3. Risk of aortic reoperation: Cumulative risk of aortic reoperation at 5 years was 13% for patients with aortitis; 6% for patients with medial degeneration; and 9% for patients with atherosclerosis; for the respective groups, the 10-year cumulative risk of aortic reoperation was 21% (95% CI: 11%-30%); 11% (95% CI: 5%-16%); and 19% (95% CI: 11%-27%) ($P = .025$).

95% CI: 1.148-1.960; $P = .003$). After 1990, overall survival was improved with operation (HR: 0.620; 95% CI: 0.444-0.863; $P < .001$). In pairwise comparison in the multivariate analysis, patients with medial degeneration (HR: 0.720; 95% CI: 0.523-0.984; $P = .040$) had a lower risk of death than patients with aortitis, but outcomes with aortitis versus atherosclerosis were not significantly different (HR: 0.960; 95% CI: 0.705-1.313; $P = .809$) (Table 3).

DISCUSSION

The diagnosis of aortitis may be suspected preoperatively in patients with systemic inflammatory disorders or documented arteritis (eg, temporal arteritis). But, as found in this study and other surgical series, the diagnosis of aortitis in patients with ascending aortic aneurysms is usually made by pathologic examination of the aortic specimen, and patients frequently have few or no symptoms or signs of rheumatologic disorders preoperatively (2). Important clinical features of patients with noninfectious aortitis in our study were older age, high prevalence of female gender, and frequent involvement of the arch portion of the aorta.

In the present study, the diagnosis of aortitis was based on histopathologic evaluations of the resected specimen at operation, and findings in these patients were distinct from other causes, medial degeneration, and atherosclerosis.^{1,4} These findings underscore the importance of

TABLE 2. Multivariate analysis of factors affecting aortic reoperation

Variable	Hazard ratio (95% CI)	P value
Medial degeneration	0.680 (0.360-1.295)	.242
Atherosclerosis	0.850 (0.471-1.526)	.582
Peripheral vascular disease	2.290 (1.377-3.802)	.001
Arch resection	3.510 (2.083-5.930)	<.001

CI, Confidence interval.

FIGURE 4. Operative mortality: Risk of death for repair of ascending aortic aneurysm (within 30 days postoperatively) varied by decade of operation. Mortality was 10% before 1990; 9% between 1990 and 1999; 3% between 2000 and 2009; and 2% during and after 2010. Sample sizes are shown as number of patients (number of events). Error bars indicate 95% CIs.

routine histopathologic assessment of surgically resected aortic specimens: The underlying pathology of aortic disease may guide patient care and screening. The pathologic identification of inflammatory aortitis can lead to the diagnosis of systemic diseases, such as giant cell arteritis, in some patients.^{5,6} Even if patients with inflammatory aortitis do not have an identifiable systemic illness (eg, lupus and giant cell arteritis), they do have an increased risk of peripheral vascular disease.⁷

We found differences in the extent of aortic resection and operative methods among patients in the 3 distinct pathology groups. Almost half of the patients with noninfectious aortitis underwent hemiarch or total arch replacement at the first surgical intervention. The need for these extensive procedures reflects more-extensive involvement of the aorta beyond the ascending portion and is consistent with our previous clinical studies.^{3,8}

Fewer patients with noninfectious aortitis required aortic valve procedures (aortic valve replacement and aortic valve-sparing operations) at the primary operation, compared with patients with medial degeneration or atherosclerosis. Among patients with aortitis who underwent aortic valve procedures, 40% had an aortic valve-sparing operation. Other reports have suggested that valve-sparing operations can be performed frequently in patients with aneurysms secondary to aortitis.

In a clinical review, Mennander and colleagues³ found that 61% of patients with aortic valve regurgitation and aortitis were able to undergo a valve-sparing procedure; often, aortic valve regurgitation was secondary to dilatation of the sinotubular junction, but information on the long-term durability of valve-sparing procedures in this population is sparse. Data from the present study show that valve-sparing operations are reasonably durable in patients with aortitis (10-year risk of aortic valve reoperation, 21%).

ACD

FIGURE 5. Overall survival differed significantly among the groups. At 5 years, survival was 72% for patients with aortitis, 84% for patients with medial degeneration, and 74% for patients with atherosclerosis; for the respective groups, 10-year survival was 45% (95% CI: 36%-57%); 66% (95% CI: 59%-73%); and 45% (95% CI: 37%-54%) ($P < .001$).

Risk of reoperation on the aorta did seem to differ in patients with aortitis, compared with patients who had other disorders. However, pathologic group was not a risk factor in multivariate analysis. Independent predictors of aortic reoperation were peripheral vascular disease and aortic arch procedures. Our study and others show that patients with aortitis often undergo more-extended aortic arch procedures.^{3,8} This likely reflects more-extensive aortic involvement with the disease and suggests the need for close postoperative surveillance for additional aneurysm formation.

Presence of aortitis does not seem to increase the early risk of ascending aortic aneurysm repair. In this study, operative mortality (in the hospital or <30 days postoperatively) was 2% in the aortitis patients, and this finding is consistent with earlier reports from Mayo Clinic.^{3,8} Overall survival postoperatively was reduced (45% at 10 years) among patients with aortitis, compared with patients who had medial degeneration, but it was similar to that of patients who had aneurysms caused by atherosclerosis. The explanation for poorer survival of aortitis patients is unclear, but it may relate to progression of the underlying inflammatory disease, which can lead to renal dysfunction.⁹ In this study, we do not have information on

TABLE 3. Multivariate analysis of factors affecting overall survival

Variable	Hazard ratio (95% CI)	P value
Medial degeneration	0.720 (0.523-0.984)	.040
Atherosclerosis	0.960 (0.705-1.313)	.809
Age	1.060 (1.046-1.077)	<.001
Surgical year 1990-1999	0.620 (0.444-0.863)	.005
Surgical year 2000-2009	0.360 (0.246-0.525)	<.001
Surgical year 2010 or later	0.120 (0.045-0.303)	<.001
Presence of COPD	1.560 (1.136-2.136)	.006
Combined CABG	1.980 (1.518-2.595)	<.001
Circulatory arrest	1.500 (1.148-1.960)	.003

COPD, Chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; CI, confidence interval.

the effectiveness of treatment with anti-inflammatory medications such as corticosteroids.

Limitations

Although this investigation examined late outcomes of mortality and aortic reoperation, we analyzed only preoperative and operative factors that might be associated with these end points. In this analysis, we did not have information on postoperative treatment, including anti-inflammatory therapy. We had limited preoperative echocardiographic data availability. Because we excluded patients who did not have pathologic analysis, we limited our cohort size and perhaps the generalizability of our data. This study was retrospective, with the usual limitations related to the design, but we did have many patients, and pathologic confirmation for comparison groups.

CONCLUSIONS

Patients undergoing repair of ascending aortic aneurysms secondary to noninfectious inflammatory aortitis have low early (<1 year) mortality but an increased late (>5 year) risk of death and aortic reoperation compared with patients who have ascending aortic aneurysms secondary to medial degeneration. Postoperative medical management and screening measures and their effects on late outcomes must be studied.

Conflict of Interest Statement

Dr Suri reports consulting fees for Sorin and Abbott and grant support from Edwards, Sorin, and St. Jude. All other authors have nothing to disclose with regard to commercial support.

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