Outcomes of Early-Onset Acute Type A Aortic Dissection — Influence of Etiologic Factors —

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Background: Outcomes of early-onset acute type A aortic dissection (ATAAD) associated with Marfan syndrome (MFS) are known, but not with other etiologies.

Methods and Results: ATAAD patients from 2 centers (n=1,001) were divided into 2 groups: age ≤45 years (n=93) and age >45 years (n=908). Although in-hospital death and 10-year survival were similar (12% vs. 7% and 62.6% vs. 67.3%), the 10-year aortic event-free survival differed (50.0% vs. 80.2%; $P<0.01$). ATAAD patients from 3 centers (n=132), all aged ≤45 years, were divided into 5 groups: lone hypertension (HTN, n=71), MFS (n=23), non-syndromic familial thoracic aortic aneurysm and dissection (NS-FTAAD, n=16), bicuspid aortic valve (BAV, n=11), and no known etiologic factor (n=11). The incidence of severe aortic insufficiency varied between groups (HTN: 11%, MFS: 39%, NS-FTAAD: 38%, BAV: 55%, no known factor: 46%; $P<0.01$), whereas in-hospital death did not (14%, 22%, 0%, 0%, and 9%; $P=0.061$). The 10-year survival was 52.2%, 64.7%, 83.6%, 100%, and 90.9%, respectively, and 10-year aortic event-free survival was 55.6%, 36.3%, 77.5%, 90.0%, and 30.0%. Median descending aorta growth (mm/year) was 1.1 (0.1–3.4), 2.3 (0.3–5.3), 1.9 (1.3–2.7), 0.9 (–0.1–2.0), and 1.0 (–0.2–2.9) ($P=0.15$), respectively.

Conclusions: Late aortic events are common in young ATAAD patients. Known etiologic factors, though not BAV, negatively influence late outcomes in these patients.

Key Words: Aortic dissection; Early onset; Hypertension; Marfan syndrome; Non-syndromic familial thoracic aortic aneurysm and dissection

Acute aortic dissection (AAD) typically occurs in older hypertensive persons, with average age at disease onset falling within the 6th decade of life.^{1–3} AAD in relatively young persons is rare. Of the patients with AAD enrolled in the International Registry of Aortic Dissection (IRAD), for example, only 7% (68/951) were 40 years of age or younger.⁴ Hereditary syndromic connective tissue disorders, of which Marfan syndrome (MFS) and Loeys-Dietz syndrome are representative, are known to predispose to aortic dilatation and AAD at an early age.^{5–10} Other factors, including a bicuspid aortic valve (BAV),¹⁰ non-syndromic familial thoracic aortic aneurysm and dissection (NS-FTAAD),^{10–12} and hypertension (HTN), are underlying medical conditions that can lead to early-onset AAD. Hereditary predisposition to developing thoracic aortic disease in all age groups has gained attention. Familial clustering has been reported in as many as 20% of cases of

thoracic aortic aneurysm and of AAD not linked to MFS, and patients with a positive family history have been reported to have an increased aortic growth rate.¹¹

In 2011, we conducted a single-center retrospective study in which we assessed the characteristics and outcomes of the early-onset acute type A aortic dissection (ATAAD) using 45 years as the cutoff age.¹³ We found the 5-year survival rate of young patients with MFS (62.5% [n=8]) to be similar to that of young patients without MFS (72.4% [n=21]).¹³ However, the number of young patients has since been on the increase. In the multicenter retrospective study described herein, we first investigated the characteristics of patients aged ≤45 years and the outcomes of ATAAD in comparison with those of older patients. We then assessed the influence of various etiologic factors on the outcomes, including late aortic growth, in ATAAD patients aged ≤45 years.

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Table 1. Characteristics of ATAAD Patients Aged ≤45 Years and >45 Years

	Age ≤45 years (n=93)	Age >45 years (n=908)	P value
Age (years)	39.1±5.4	66.6±10.2	<0.01
Male sex	85 (91)	437 (48)	<0.01
MFS	15 (16)	10 (1)	<0.01
BAV	6 (6)	10 (1)	<0.01
Current smoking	49 (53)	273 (30)	<0.01
Obesity (BMI >30 kg/m ²)	17 (18)	53 (6)	<0.01
Hypertension	61 (68)	651 (72)	0.43
Diabetes	4 (4)	58 (6)	0.57
COPD	0 (0)	26 (3)	0.19
History of CVD	1 (1)	81 (9)	0.015
Chronic renal failure on dialysis	1 (1)	18 (2)	0.083
Preoperative status			
Syncope	9 (10)	146 (16)	0.1
Shock (systolic BP <80 mmHg)	7 (8)	228 (25)	<0.01
Profound shock requiring CPR	3 (3)	45 (5)	0.63
Severe aortic insufficiency	20 (22)	122 (14)	0.034
Cardiac tamponade	8 (9)	101 (11)	<0.01
Organ ischemia			
Brain	2 (2)	96 (11)	0.016
Coronary	6 (7)	72 (8)	0.61
Visceral	4 (4)	32 (4)	0.93
Kidney	12 (13)	75 (8)	0.13
Lower limb	23 (25)	75 (8)	<0.01
Dissection characteristics			
DeBakey class			
Type I	90 (97)	796 (88)	0.014
Type II	3 (3)	112 (12)	0.014
Location of primary entry site*			
Ascending aorta	58 (62)	572 (63)	0.87
Aortic arch	18 (19)	130 (14)	0.19
Descending aorta or unknown	18 (19)	212 (23)	0.38

Values are mean ± standard deviation or number (and %) of patients. *Primary entry site includes multiple entry sites in some patients. ATAAD, acute type A aortic dissection; BAV, bicuspid aortic valve; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CVD, cerebrovascular disease; MFS, Marfan syndrome.

Methods

Patients included in the study were identified through a review of aortic databases maintained by 3 institutions: University Heart Center Freiburg/Bad Krozingen (Freiburg, Germany), Jichi Medical University Hospital (Shimotsuke, Japan), and Saitama Medical Center, Jichi Medical University (Saitama, Japan). The databases include patients who began treatment in 1990 (Saitama Medical Center, Jichi Medical University), in 2000 (Jichi Medical University Hospital), and in 2001 (University Heart Center Freiburg/Bad Krozingen). The institutional review board at each of the 3 participating hospitals approved the study, and the requirement for informed consent was waived. Patients were selected for inclusion in the study if ATAAD had been diagnosed on the basis of findings on enhanced computed tomography (CT) or echocardiography, and the aortic dissection was judged to be acute if symptom onset was within 14 days of the patient's hospital admission.

A 2-part study was conducted. In Study A, 1,001 patients who underwent emergency aortic repair for ATAAD at 1

of 2 centers (Jichi Medical University Hospital, 2003–2014, or Saitama Medical Center, Jichi Medical University, 1990–2017) were divided between those aged ≤45 years (n=93; mean age, 39.1 years) and those aged >45 years (n=908; mean age, 66.6 years), and early outcomes (in-hospital mortality and morbidities) and late outcomes (survival and aortic events) were compared between the 2 groups. In Study B, 132 patients, all aged ≤45 years, who underwent emergency aortic repair for ATAAD at 1 of 3 centers (University Heart Center Freiburg, Jichi Medical University Hospital, or Saitama Medical Center, Jichi Medical University) were divided between those with lone HTN (n=71), those with MFS (n=23), those with NS-FTAAD (n=16), those with a BAV (n=11), and those with no known etiologic factor (n=11). Early outcomes (in-hospital mortality and morbidities), late outcomes (survival and aortic events), and thoracic aorta growth rates were compared between these 5 groups.

Lone HTN was defined as a history of medication with a hypertensive drug or known untreated HTN in the absence of a family history of thoracic aortic disease, MFS,

Table 2. Operative Variables and Early Outcomes Among Patients Aged ≤45 Years and >45 Years

	Age ≤45 years (n=93)	Age >45 years (n=908)	P value
Operative variables			
Arterial cannulation site(s)			
Femoral artery	39 (42)	401 (44)	0.68
Axillary artery	45 (48)	340 (37)	0.039
Ascending aorta	2 (2)	6 (0.7)	0.35
Left ventricular apex	16 (17)	185 (20)	0.46
Proximal reconstruction			
Modified Bentall	16 (17)	34 (4)	<0.01
Valve preserving root surgery	2 (2)	1 (0.1)	0.015
Root preserving aortic valve replacement	4 (4)	28 (3)	0.74
Aortic valve resuspension	69 (75)	831 (92)	<0.01
Mechanical valve replacement	20 (21)	40 (4)	<0.01
Biological valve replacement	0 (0)	22 (3)	0.25
Distal extent of aortic resection			
Ascending aorta or HAR	72 (77)	743 (82)	0.29
Aortic arch replacement	16 (17)	141 (16)	0.25
Aortic arch replacement with FET	3 (3)	10 (1)	0.21
Entry resection	73 (79)	683 (75)	0.48
Coronary artery bypass grafting	5 (5)	61 (7)	0.62
Operation time (min)	404 (339–497)	345 (286–430)	<0.01
Cardiopulmonary bypass time (min)	205±72	170±75	<0.01
Early outcomes			
Death within 30 days of surgery	10 (11)	57 (6)	0.10
In-hospital death	11 (12)	67 (7)	0.13
Length of ICU stay (days)	6 (4–11)	6 (4–9)	0.76
Length of hospital stay (days)	27 (20–37)	22 (16–31)	<0.01
Complications			
New-onset stroke	4 (4)	62 (7)	0.47
Cardiac failure requiring ECMO	4 (4)	26 (3)	0.65
Re-exploration for bleeding	5 (5)	40 (4)	0.67
Deep sternal wound infection	0 (0)	11 (1)	0.58

Mean±standard deviation values or median (and interquartile range) or number (and %) of patients are shown. ECMO, extracorporeal membrane oxygenation; FET, frozen elephant trunk; HAR, hemiarch replacement; ICU, intensive care unit.

or BAV. MFS was diagnosed on the basis of the revised Ghent criteria.¹⁴ NS-FTAAD was diagnosed as a thoracic aortic aneurysm and dissection in the absence of a systemic musculoskeletal abnormality, MFS, and -BAV but in the context of a family history of thoracic aortic aneurysm or dissection (i.e., occurrence in a 1st-degree relative). BAV was diagnosed intraoperatively. “No known etiologic factor” was defined as absence of all of the above-named etiologic factors. No patient included in the study had vascular Ehlers-Danlos syndrome,¹⁵ aortitis, or cocaine-induced AAD. Genetic testing was not routinely performed.

Individual follow-up information, including survival or death, the patient’s general health condition, cause of death, and occurrence of an aortic event, was obtained through a review of the patients’ outpatient record or through an interview with the patient’s general practitioner, the patient in question, or a family member. For Study A patients, the mean follow-up period was 5.2±4.7 years, and the follow-up rate was 98.1% (982/1,001). For Study B patients, the mean follow-up period was 5.0±5.1 years, and the follow-up rate was 100% (132/132).

Aortic repair was performed as reported previously.^{8,16–20}

Arterial cannulation was performed at one or more sites for cardiopulmonary bypass (CPB), with the femoral artery, axillary artery, heart apex, or ascending aorta used for arterial inflow.¹⁹ Once CPB was established, systemic cooling to a rectal or bladder temperature of 20–25°C was begun. Proximal repair involved aortic valve resuspension, aortic valve replacement, modified Bentall type aortic root replacement, or valve-sparing aortic root replacement. In patients who presented with aortic root dilatation or an intimal tear at the root level, aortic root surgery was preferentially performed. Distal repair involved ascending aorta replacement, hemiarch replacement, total or partial (1 or 2 branches) arch replacement, or total arch replacement by the frozen elephant trunk technique. The extent of distal aortic resection was determined according to the site of the entry tear, aortic diameter, and the status of the false lumen (FL) in the downstream aorta. Selective antegrade cerebral perfusion was performed in cases of arch replacement.

Segment-specific aortic growth was assessed in patients aged ≤45 years whose dissection extended to the descending thoracic aorta. Patients in whom reoperation of the aortic segment was performed were excluded from further

assessment of aortic growth. The segment-specific growth rate was calculated as previously reported.¹⁶ Briefly, it was determined in patients who had undergone at least 2 postoperative contrast enhanced CT studies that were spaced at least 12 months apart. If more than 2 CT studies were performed after hospital discharge, the most recent image was used in determining the growth rate. The diameter of the descending thoracic aorta was measured at the level of the tracheal bifurcation, and the growth rate was calculated as the difference in diameter between the initial (D1) and final (D2) measurements divided by the time interval (T) between the 2 measurements: growth rate=(D2-D1)/T.¹⁶ Patency of the FL in the descending thoracic aorta was also assessed during the follow-up period; a partially thrombosed FL was included in the patent FL category. A total of 90 hospital survivors were candidates for the aortic growth rate study, and actual CT imaging data were obtained for 75 (83%) of them. The mean CT follow-up period for these patients was 4.9±3.5 years (range, 1.0–18.0 years).

Statistical Analysis

Data are shown as the number (and percentage) of patients, as median values (and interquartile range), or as mean±SD values, as appropriate. Differences in clinical variables between the 2 Study A patient groups were analyzed by chi-square, Fisher's exact, unpaired t-, or Mann-Whitney U-test. Differences in clinical variables between the 5 etiology-based groups (Study B patient groups) were analyzed by chi-square or Fisher's exact test for nominal variables, and one-way analysis of variance was used to compare continuous variables. The Kruskal-Wallis test was used for nonparametric variables. Freedom from time-related events (i.e., death, an aortic event, and reoperation) was estimated by the Kaplan-Meier method and analyzed

by log-rank test. All statistical analyses were performed with SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA), and P<0.05 was considered significant.

Results

Study A: Age ≤45 Years vs. Age >45 Years

Patients' clinical characteristics, comorbidities, preoperative status, and features of the dissection are shown per group in **Table 1**. Patients in the younger group were significantly more likely than those in the older group to be male, obese, have MFS or BAV, and/or be a current smoker (P<0.01 for all). Patients in the younger group were less likely than those in the older group to have DeBakey type II aortic dissection (P=0.014), and as a result, there were significantly fewer incidences of cardiac tamponade and preoperative shock in the younger group (P<0.01 for both). Lower limb ischemia and severe aortic insufficiency were more common in the younger group (P<0.01), but brain ischemia was more common in the older group (P=0.016). Location of the primary entry tear did not differ between the 2 groups.

Operative variables and early outcomes are shown per group in **Table 2**. There was no between-group difference in the arterial cannulation sites, distal extent of aortic resection, or primary entry tear resection rate. Aortic root surgery was performed in more patients in the younger group than in the older group. In contrast, simple aortic valve resuspension was performed in more patients in the older group. Operation time and CPB time were significantly greater in the younger group than in the older group (P<0.01 for both). Total in-hospital mortality was 8% (78/1,001), with in-hospital mortality being 12% (11/93) in the younger group and 7% (67/903) in the older group (P=0.13). Although there was no significant between-group difference in the incidence of postoperative complications,

Table 3. Characteristics of Patients Aged ≤45 Years, per Etiology-Based Group

	HTN (n=71)	MFS (n=23)	NS-FTAAD (n=16)	BAV (n=11)	No known etiologic factor (n=11)	P value
Age (years)	42 (38–43)	31 (25–39)	39 (25–41)	40 (27–42)	39 (34–44)	<0.01
Male sex	63 (89)	20 (87)	14 (88)	10 (91)	11 (100)	0.61
Family history (first degree relative)	0 (0)	15 (65)	16 (100)	0 (0)	0 (0)	<0.01
Obesity (BMI >30 kg/m ²)*	20 (31)	1 (4)	0 (0)	1 (20)	1 (13)	<0.01
Current smoking	32 (45)	5 (22)	8 (50)	3 (27)	5 (46)	0.22
Sleep apnea syndrome	12 (17)	0 (0)	1 (6)	0 (0)	1 (9)	0.032
Hypertension	71 (100)	4 (17)	7 (44)	7 (64)	0 (0)	<0.01
Diabetes	3 (4)	0 (0)	0 (0)	0 (0)	1 (9)	0.37
Chronic renal failure on dialysis	1 (1)	0 (0)	0 (0)	0 (0)	1 (9)	0.48
Preoperative status						
Syncope	7 (10)	1 (4)	0 (0)	1 (9)	1 (9)	0.48
Shock (systolic BP <80 mmHg)	5 (7)	5 (22)	0 (0)	0 (0)	1 (9)	0.067
Severe aortic insufficiency	8 (11)	9 (39)	6 (38)	6 (55)	5 (46)	<0.01
Cardiac tamponade	11 (16)	2 (9)	1 (6)	0 (0)	1 (9)	0.35
Organ ischemia						
Brain	5 (7)	2 (9)	0 (0)	1 (9)	0 (0)	0.42
Coronary	3 (4)	2 (9)	1 (6)	0 (0)	1 (9)	0.72
Visceral	4 (6)	1 (4)	0 (0)	0 (0)	0 (0)	0.47
Kidney	6 (9)	3 (13)	2 (13)	1 (9)	0 (0)	0.61
Limb	17 (24)	3 (13)	6 (38)	0 (0)	1 (9)	0.042
Distal extent of dissection						
Ascending aorta	4 (6)	4 (17)	0 (0)	0 (0)	2 (18)	0.079
Aortic arch or thoracic descending aorta	11 (16)	5 (22)	5 (32)	5 (45)	1 (9)	0.15
Abdominal aorta	15 (21)	5 (22)	5 (31)	0 (0)	4 (36)	0.12
Iliac artery	41 (58)	9 (39)	6 (38)	6 (55)	4 (36)	0.32

Median (and interquartile range) or number (and %) of patients are shown. *BMI was calculated for 91% (120/132) of the patients aged ≤45 years. HTN, lone hypertension; NS-FTAAD, non-syndromic familial thoracic aortic aneurysm and dissection. Other abbreviations are as in Table 1.

the hospital stay was significantly longer for patients in the younger group.

Late outcomes are shown in **Figure 1**. The 10-year survival was similar between the 2 groups at 62.6±7.2% in the younger group and 67.3±2.2% in the older group ($P=0.91$). However, 10-year freedom from aortic events was significantly less common in the younger group than in the older group at 50.0±8.8% vs. 80.2±2.4%, respectively ($P<0.01$). A total of 166 patients died during follow-up, 14 in the younger group and 152 in the older group. Details of late deaths are shown in **Supplementary Table 1**; 57% (8/14) of patients in the younger group died of aortic rupture. This percentage was markedly and significantly higher than that of the older group. Other causes of late death did not differ significantly between the 2 groups.

Study B: Age ≤45 Years, Etiology-Based Groups

Clinical characteristics, comorbidities, and the extent of dissection for patients aged ≤45 years grouped by etiology are shown in **Table 3**. Age differed significantly between the 5 etiology-based groups ($P<0.01$). The MFS group was the youngest, followed in order by the NS-FTAAD, no known etiology, BAV, and lone HTN groups. There was a positive family history in 65% (15/23) of patients in the MFS group; 17% (4/23) of patients in the MFS group, 44% (7/16) of patients in the NS-FTAAD group, and 64% (7/11) of patients in the BAV group had been diagnosed with HTN. Of note, severe aortic insufficiency was quite

prevalent at 38–55% in 4 of the 5 groups (excluding the lone HTN group). Obesity (body mass index >30 kg/m²) was significantly more prevalent in the HTN group (31%) than in the other groups. Lower limb ischemia was more prevalent in the HTN group and NS-FTAAD group (at 24% and 38%, respectively) than in the other 3 groups, whereas ischemia of other organs did not differ in prevalence between groups. Dissection extending into the iliac artery occurred in more than 50% of patients in the HTN and BAV groups.

Operative variables and early outcomes for the patients aged ≤45 years and grouped by etiology are shown in **Table 4**. The modified Bentall procedure ($P<0.01$) and valve-sparing aortic root surgery ($P=0.014$) were performed more frequently in the MFS group, BAV group, and no known etiology group than in the other 2 groups. Simple aortic valve resuspension was performed in a significantly high percentage of patients in the lone HTN group (86% [61/71]) and NS-FTAAD group (75% [12/16]) ($P<0.01$, for both). Neither the distal extent of aortic resection nor operation time nor CPB time differed significantly between groups. Total in-hospital mortality was 12% (16/132), with in-hospital mortality being highest in the MFS group at 22% (5/23). There were no in-hospital deaths in the NS-FTAAD group or BAV group. Lengths of intensive care unit and hospital stays and the incidences of postoperative complications did not differ significantly between the 5 etiology-based groups.

Table 4. Operative Variables and Early Outcomes of Patients Aged ≤45 Years, per Etiology-Based Group

	HTN (n=71)	MFS (n=23)	NS-FTAAD (n=16)	BAV (n=11)	No known etiologic factor (n=11)	P value
Operative variables						
Proximal reconstruction						
Modified Bentall procedure	8 (11)	17 (74)	1 (6)	5 (46)	3 (27)	<0.01
Valve preserving root surgery	1 (1)	0 (0)	3 (19)	0 (0)	2 (18)	0.014
Root conservative aortic valve replacement	1 (1)	0 (0)	0 (0)	2 (18)	1 (9)	0.084
Aortic valve resuspension	61 (86)	6 (26)	12 (75)	4 (36)	6 (50)	<0.01
Mechanical valve implantation	8 (11)	17 (74)	1 (6)	7 (64)	4 (36)	<0.01
Distal extent of aortic resection						
Ascending aorta replacement or HAR	54 (76)	21 (91)	13 (81)	9 (82)	9 (82)	0.57
Aortic arch replacement	13 (18)	2 (9)	3 (19)	2 (18)	1 (8)	0.72
Aortic arch replacement+FET	2 (3)	0 (0)	0 (0)	0 (0)	1 (8)	0.45
Coronary artery bypass grafting	3 (4)	0 (0)	1 (6)	1 (9)	0 (0)	0.48
Operation time (min)	384 (329, 480)	475 (385, 695)	379 (363, 428)	397 (352, 462)	360 (315, 425)	0.12
Cardiopulmonary bypass time (min)	187 (142, 237)	224 (177, 256)	207 (158, 222)	202 (161, 234)	158 (139, 197)	0.43
Length of ICU stay (days)	6 (3, 12)	5 (3, 8)	5 (4, 7)	4 (4, 5)	4 (3, 8)	0.24
Length of hospital stay (days)	21 (15, 30)	23 (13, 33)	21 (17, 25)	19 (14, 27)	21 (13, 31)	0.97
Early outcomes						
Death within 30 days of surgery	10 (14)	3 (13)	0 (0)	0 (0)	1 (9)	0.13
In-hospital death	10 (14)	5 (22)	0 (0)	0 (0)	1 (9)	0.061
Complications						
New-onset stroke	8 (11)	0 (0)	1 (6)	0 (0)	0 (0)	0.083
Re-exploration for bleeding	6 (9)	3 (13)	0 (0)	0 (0)	2 (18)	0.17
Ventilation >48 h required	36 (51)	8 (35)	4 (25)	2 (18)	3 (27)	0.078
Renal replacement therapy required	10 (14)	3 (13)	1 (6)	0 (0)	1 (9)	0.44

Number (and %) of patients are shown. Abbreviations are as in Tables 1–3.

Table 5. Medications Administered to Hospital Survivors During the Follow-up Period (Total Survivors and Survivors Grouped on the Basis of Etiologic Factors)

	Total patients (n=116)	HTN (n=61)	MFS (n=18)	NS-FTAAD (n=16)	BAV (n=11)	No known etiologic factor (n=10)	P value
β-blocker	n=90	46 (75)	15 (83)	15 (94)	9 (82)	5 (50)	0.12
Calcium-channel blocker	n=59	36 (59)	5 (28)	8 (50)	5 (46)	5 (50)	0.23
ACEI/ARB	n=56	29 (48)	3 (17)	9 (56)	7 (64)	8 (80)	0.013
Warfarin	n=35	7 (12)	14 (78)	2 (13)	7 (64)	5 (50)	<0.01

Number (and %) of patients are shown. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. Other abbreviations are as in Tables 1,3.

Medications administered during the follow-up period are shown for the total patients and per etiology-based group in **Table 5**. Beta-blocker was the most commonly administered antihypertensive drug, followed by calcium-channel blocker and then angiotensin-receptor blocker/angiotensin-converting enzyme inhibitor. Warfarin was administered in greater percentages of patients in the MFS, BAV, and no known etiology groups than in the other 2 groups, probably because of the relatively high incidences of mechanical aortic valve implantation in these 3 groups. Late survival and aortic event-free survival rates are shown in **Figure 2**. The 10-year survival was as follows: 52.2±10.2% in the lone HTN group, 64.7±11.8% in the MFS group, 83.6±10.8% in the NS-FTAAD group, 100% in the BAV group, and 90.9±8.7% in the no known etiology

group. Late survival was notably decreased in the lone HTN group in comparison with the other 4 groups. The probability of 10-year survival, however, did not differ significantly between the groups. The 10-year freedom from aortic events was as follows: 55.6±10.7% in the lone HTN group, 36.3±15.4% in the MFS group, 77.5±11.6% in the NS-FTAAD group, 90.0±9.5% in the BAV group, and 30.0±24.7% in the no known etiology group. The probability of 10-year freedom from aortic events was lower in the MFS group than in the lone HTN group ($P=0.043$), but was not significantly lower in the other 3 groups.

A total of 17 patients aged ≤45 years died during follow-up and details are shown in **Supplementary Table 2**. Aortic rupture was the leading cause of death among patients aged ≤45 years, with a total of 9 patients dying from aortic

Figure 2. Kaplan-Meier curves for late survival (**A**) and freedom from aortic events (**B**) among ATAAD patients aged ≤ 45 years and grouped on the basis of etiologic factors. ATAAD, acute type A aortic dissection; BAV, bicuspid aortic valve; HTN, lone hypertension; MFS, Marfan syndrome; NS-FTAAD, non-syndromic familial thoracic aortic aneurysm and dissection.

Figure 3. Segment-specific aortic growth (at the level of the tracheal bifurcation) in relation to etiologic factors. The segment-specific aortic growth rate was calculated in patients whose dissection extended into the descending thoracic aorta. P values were obtained by Kruskal-Wallis test. Abbreviations are as in Figure 2.

rupture (lone HTN group, $n=4$; MFS group, $n=3$; FTAAD group, $n=2$). The incidence of deaths during follow-up and their causes did not differ significantly between the 5 etiology-based patient groups.

In examining segment-specific aortic growth rates, we first divided the total 75 patients aged ≤ 45 years into 2 groups according to postoperative patency of the FL of the descending thoracic aorta. Among these patients, the aortic growth rate was significantly increased in those with a

patent FL in comparison with those with a thrombosed FL ($P<0.01$) (**Supplementary Figure A**). When we examined the aortic growth rate in relation to the distal extent of aortic resection, we found the aortic growth rate to be increased, but not significantly, in patients who underwent ascending aorta or hemiarch replacement vs. total or partial aortic arch replacement (**Supplementary Figure B**). When we compared thoracic aorta growth between the 5 etiology-based groups (**Figure 3**), we found the median rate to be

≥ 0.9 mm/year in all 5 groups, and although the differences were not significant, growth was notably fast in the MFS and NS-FTAAD groups.

Discussion

AAD can develop in young patients against a background of various medical conditions. Early-onset AAD (patient age, ≤ 40 years) occurs in a high number of patients without MFS, with the percentage ranging from 50% to 61%.^{5,21} The clinical characteristics of MFS patients who have suffered AAD and the treatment outcomes in these patients are fairly well understood,^{6,9,21} whereas those of young non-MFS patients who have suffered AAD have been investigated but not as extensively.^{4,22} For example, in previous studies, young non-MFS patients were not subgrouped for an understanding of etiology-related-outcomes. We classified young patients with ATAAD into 5 different etiology-based groups and then compared their clinical characteristics and early and late outcomes. We found first of all that young patients (i.e., ≤ 45 years of age) with ATAAD were more likely than older patients to suffer a late aortic event. The leading etiologic factor in our young patients was lone HTN, and late survival of these patients with lone HTN was worse than that of patients with other etiologic factors. The 10-year aortic event-free rate in this group was moderate in comparison with that in other groups; patients with MFS were the ones most likely to have an aortic event during the follow-up period. Growth of the descending thoracic aorta was shown to be relatively fast for patients with MFS or NS-FTAAD.

Analysis of the IRAD database revealed a high incidence of aortic root dilatation and prior aortic surgery among young patients with ATAAD.⁴ A decreased prevalence of HTN among young patients (<40 years of age) in comparison with older patients (≥ 40 years of age) (34% [23/66] vs. 72% [699/883]), $P<0.001$) was also found.⁴ In contrast, we found the prevalence of HTN to be similar between young and older patients, and the leading underlying condition predisposing to AAD in the young patients was lone HTN. One possible explanation for the discrepancy regarding the prevalence of HTN is the difference between studies in the cutoff age used to define young patients. In the IRAD study, the young patients were aged <40 years. We found a marked and significant difference in age between patients in our 5 etiology-based groups. The median age of patients in our lone HTN group was 42 years, whereas that of patients in our MFS group was 31 years. The age cutoff of 45 years in our study was based on the results of our preceding study.¹³ The risk of HTN increases with age, so it is reasonable to conclude that the difference in prevalence of HTN arose from the difference in the age composition of the study groups.

Treatment outcomes of ATAAD are influenced by preoperative conditions, including hemodynamic status and organ ischemia. Similarly, advanced age can increase the surgical risk in patients with ATAAD.²³ Better outcomes are expected for young patients vs. older patients. Nevertheless, poor outcomes of early-onset AAD have been reported.^{4,22} Januzzi et al reported 22% (15/68) in-hospital mortality among young patients (<40 years of age; ATAAD, $n=46$ and acute type B aortic dissection, $n=22$), and this was not significantly lower than the 24% (216/883) among older patients.⁴ Piccardo et al reported 24% (16/66) in-hospital mortality among non-MFS ATAAD patients

aged ≤ 50 years.²² Among our patients, in-hospital mortality of those aged ≤ 45 years was 12% and not significantly lower than the 7% in-hospital mortality of those who were older. CPB time and operation time were both longer in our young patients, and this might have increased the already high operative risk associated with ATAAD. The increased incidence of aortic root surgery might be related to the longer operation time in the younger group. In addition, patients in the younger group were less likely to have DeBakey type 2 dissection. More distally extended dissection might have induced organ ischemia and coagulopathy in the younger patients.

Interestingly, of the 5 etiology-based groups, our lone HTN group had the worst late survival. One of the major characteristics of the HTN group was greater distal extension of the dissection, with dissection extending to the iliac artery in 56% (41/71) of patients in this group. Although early outcomes in the lone HTN group were acceptable, with in-hospital mortality of 14% (10/71), there were 10 deaths during follow-up, including 4 aortic ruptures and 1 sudden death. The incidence of severe aortic insufficiency was decreased (11%), and 86% (61/71) of patients in this group underwent a simple aortic valve resuspension procedure. Therefore, we believe more aggressive arch replacement to be a preferred approach in young patients with lone HTN.

MFS is a hereditary disorder attributed to a fibrillin 1 gene mutation. The incidence of ATAAD surgery is high among patients with MFS, ranging from 16% to 35%.^{7,8,24,25} Excellent early outcomes of aortic repair for ATAAD in MFS patients have been reported, with in-hospital mortality ranging from 3% to 8.2%.^{6,9} Postoperative follow-up and management for chronic aortic enlargement are of paramount importance for patients with MFS. We previously studied the late outcomes and aortic growth following aortic repair for ATAAD in patients with MFS.^{8,9} The 10-year proximal reoperation-free survival of patients who underwent valve-sparing aortic root surgery or Bentall type aortic root replacement was $88\pm 5\%$, whereas that of patients who underwent supracoronary ascending aortic replacement was $20\pm 16\%$.⁹ Thus, we strongly recommend initial aortic root surgery for patients with MFS. The extent of dissection also appears to influence late outcomes in patients with MFS. The 10-year freedom from descending aortic reoperation was seen in $65\pm 8\%$ of our MFS patients with DeBakey type I dissection, a rate that was significantly lower than the $96\pm 4\%$ seen in our MFS patients with DeBakey type II dissection.⁹ Consistent with this finding, growth of the dissected descending aorta after proximal aortic surgery in MFS patients is reported to be faster than the growth of non-dissected segments.⁸ Our MFS patients had the fastest thoracic aorta growth, and this resulted in increases in the aortic events that occurred. Timely distal reoperation is important in MFS patients with DeBakey type I dissection.

A high prevalence of BAV is reported among patients with AAD.^{4,26} The prevalence of BAV was significantly increased among our patients aged ≤ 45 years, and BAV was the 4th leading etiologic factor underlying the ATAAD in our young patients. There were no in-hospital deaths among our patients with BAV, and late outcomes were satisfactory. Sherrah et al similarly reported better late outcomes among patients with BAV aged ≤ 60 years than among older patients with NS-FTAAD or MFS.¹⁰ Comparable late outcomes between BAV patients treated by valve

resuspension and those treated by valve replacement have been reported.¹⁷ In cases of ATAAD and underlying BAV in which aortic insufficiency and root dilation are not prominent, BAV resuspension would be a feasible choice.

NS-FTAAD, a familial thoracic aneurysmal disease, is associated with a wide-range of genetic abnormalities, and autosomal dominant inheritance is seen in most of these patients.⁵ The causative genetic defects result in defects in proteins with functionality specific to the aorta, in particular to vascular smooth muscle cells. As a result, abnormalities are usually limited to the cardiovascular system.⁵ The identified genes linked to vascular smooth muscle cell homeostasis include *MYH11*, which encodes smooth muscle-specific myosin isoform;²⁷ *ACTA2*, the smooth muscle-specific isoform of actin (α -smooth muscle actin);²⁸ and *MYLK*, which encodes myosin light chain kinase.²⁹ Sherrah et al reported the outcomes of 760 patients with genetic aortopathy. The patients were aged ≤ 60 years and included 311 with NS-FTAAD, 221 with MFS, and 228 with BAV.¹⁰ In their fairly large-scale study, NS-FTAAD was diagnosed on the basis of pathology-based detection of aortic cystic medial necrosis or a positive family history in the absence of a connective tissue syndrome, HTN, or atherosclerotic disease.¹⁰ Patients with MFS (mean age, 28.1 years) were younger than those with NS-FTAAD (mean age, 41.8 years) and those with BAV (mean age, 38.7 years).¹⁰ Patients with NS-FTAAD are reportedly more likely than others to have aortic dissection, and post-dissection mortality is reportedly comparable between patients with MFS and those with NS-FTAAD.¹⁰ We diagnosed NS-FTAAD in 16 young patients, and the diagnosis was based on a positive family history and absence of physical manifestations of a connective tissue disorder. The AAD occurred at a median of 39 years in patients with NS-FTAAD, and 38% (6/16) showed severe aortic insufficiency. The thoracic aortic growth rate was comparable between the MFS and NS-FTAAD groups. As reported by Sherrah et al,¹⁰ early and late management of NS-FTAAD should be similar to that of MFS.

Study Limitations

Our data should be interpreted in light of our study limitations. The study was conducted retrospectively, and the number of patients in each etiology-based group was relatively small. A larger-scale prospective study is needed to confirm our findings. Second, we did not perform genetic investigation in patients with MFS or NS-FTAAD. Therefore, the gene mutations responsible for the development of ATAAD in these patients were not confirmed. Third, it is possible that some patients in the HTN group had secondary HTN, and it is also possible that genetic abnormalities were missed in this group. Unfortunately, extensive systematic work-ups were not done to assess such etiologic factors in these patients. Fourth, the surgical procedures performed and specific techniques applied in our patients varied, as did the timing of surgical repair. Whether these factors differed between age groups and whether they affected late outcomes is unknown. Fifth, this multicenter study included patients from 3 hospitals in 2 countries: 1 country in Asia and 1 in Europe. It is possible that patients' racial backgrounds influenced their responses to the surgical treatment.

In conclusion, 10-year aortic event-free survival was significantly decreased in our patients aged ≤ 45 years. The most common underlying medical condition was lone

HTN, followed in order by MFS, NS-FTAAD, and BAV. In some cases, there was no obvious etiologic factor. Severe aortic insufficiency was common in 4 of the 5 etiology-based groups (not in the lone HTN group). Early outcomes were acceptable for all 5 groups. However, late survival was particularly decreased in the lone HTN group. Patients with MFS and NS-FTAAD showed relatively fast aortic growth. Our data suggest that disease factors, with the exception of BAV, negatively influence survival and freedom from aortic events in young ATAAD patients.

Disclosures

None.

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Supplementary Files

Please find supplementary file(s);
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