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Original Article

Analysis of Risk Factors for Aortic Enlargement in Patients with Chronic Type B Aortic Dissection

Ken Nakamura, MD,[1,†] Tetsuro Uchida, MD, PhD,[1] Ri Sho, MD, PhD,[2] Azumi Hamasaki, MD, PhD,[1] Jun Hayashi, MD,[1] and Mitsuaki Sadahiro, MD, PhD[1]

Objectives: Uncomplicated type B aortic dissection is generally treated with medical management including antihypertensive therapy. The purpose of this study is to investigate risk factors associated with the aortic enlargement in medically treated patients.

Methods: Between July 2004 and April 2016, 127 consecutive patients with acute type B aortic dissection were treated in our institution. Of these, 104 patients diagnosed with uncomplicated type B dissection were managed medically as an initial treatment. According to the diameter of the dissected aorta, these patients were retrospectively placed into 2 groups: 1) enlargement group (group E: n=36); and 2) unchanged group (group U: n=68).

Results: There was statistically significant difference regarding the initial diameter of the dissected aorta (group E: 42±7 mm, group U: 36±7 mm) ($p<0.01$). As regards the aneurysm growth rate, a significant difference between both groups was noted (group E: 10±32 mm/half-year, group U −3±19 mm/half-year) ($p<0.05$). In all 104 patients, 42 patients (40.4%) had patent false lumen with the average number of 1.5 intimal tears. Multivariate analysis showed the relationship for aortic enlargement were patent false lumen ($p<0.05$, 95%CI 0.407–0.935) and initial aortic diameter ($p<0.01$, 95%CI 1.076–1.158). Aortic event free survival (1/5/10 years) was 100/86/77% in group E and 92/79/79% in group U, respectively no differences between two groups ($p=0.747$).

Conclusions: The medically managed patients with uncomplicated chronic type B dissection showed excellent survival rate during long-term follow-up. The results of surgical or endovascular treatment in patients underwent initial medical therapy were also satisfactory. The patent false lumen and aortic diameter at the onset may impact on aortic enlargement. Considering our results, the feasibility of elective endovascular repairs in stable dissection remains controversial even in the endovascular era. (This is a translation of Jpn J Vasc Surg 2018; 27: 55–60.)

Keywords: uncomplicated chronic type B aortic dissection, medical treatment, aortic enlargement, TEVAR

Introduction

According to a report by the International Registry of Acute Aortic Dissection (IRAD), >70% patients with chronic type B aortic dissection have aortic enlargement, which is a frequent complication in this group.[1)] Surgery for extensive dissecting aneurysm of the aorta is extremely invasive, and therefore, we believe that analyzing factors that contribute to aneurysmal growth and adopting growth prevention measures will help in improving the prognosis in patients with chronic type B aortic dissection.

Subjects and Methods

The subject sample included 127 patients with chronic type B aortic dissection who underwent initial treatment at Yamagata University Hospital, Yamagata Prefecture from July 2004 to April 2016. Of these, 6 patients with traumatic dissection and 17 patients with acute complications were excluded; thus, 104 patients who underwent ongoing treatment after the acute phase (2 weeks after onset) were included in the study (**Fig. 1**). In all patients, the time of onset of acute type B aortic dissection was clear. According to the initial treatment protocol for the target group, bed rest treatment was commenced immediately after hospital admission and we aimed to achieve systolic blood pressure <120 mmHg at 2 weeks after ad-

[1] *Second Department of Surgery, Yamagata University Faculty of Medicine, Yamagata, Japan*
[2] *Department of Public Health, Yamagata University Faculty of Medicine, Yamagata, Japan*

Received: September 27, 2018; Accepted: September 28, 2018
Corresponding author: Ken Nakamura, MD. Second Department of Surgery, Yamagata University Faculty of Medicine, 2-2-2 Iidanishi, Yamagata 990-9985, Japan
Tel: +81-23-628-5342, Fax: +81-23-628-5345
E-mail: ken.nakamura622@gmail.com
† Present address: Nihonkai General Hospital, Sakata, Yamagata, Japan
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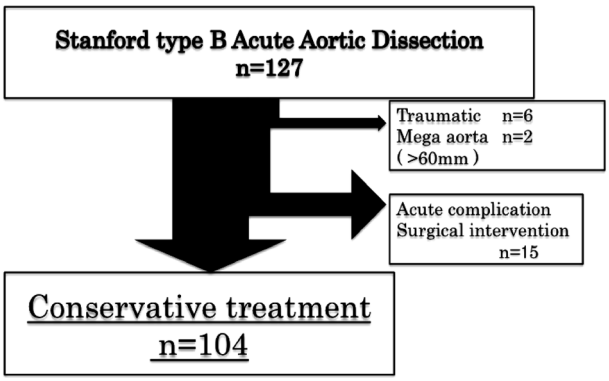

Fig. 1 Summary flow diagram by patient presentation and treatment.

mission and <130 mmHg thereafter. Contrast-enhanced computed tomography (CT) was performed on the day of and the day after onset, and if there were no findings of exacerbation, water and meal intake, with the patient in the sitting position, was commenced. Once CT was performed at 1 week after onset, standing and walking were commenced. Thereafter, CT was performed each week, and if there were no particular problems, the patient was discharged 3 weeks after the onset. In the event of complications during bed rest treatment, surgical intervention was performed. Observational end points were aortic diameter enlargement and death. Symptoms were evaluated over a longer period by regular CT on an outpatient basis. Aortic diameter enlargement by >40 mm during the observation period or >5 mm during a 6-month period was defined as aortic enlargement. The reason for defining aortic enlargement as >40 mm is based on the ESC guideline 2014[2] which stated that "In healthy adults, aortic diameters do not usually exceed 40 mm" and the fact that at present, in some advanced care institutions, the threshold for preventive therapeutic intervention by thoracic endovascular aortic repair (TEVAR) for subacute type B dissection without complications is defined by an aortic diameter of 40 mm. Furthermore, when selecting the device for therapeutic intervention by TEVAR, conditions, such as in the proximal zone and distance, can increase the difficulty when aortic diameters are >40 mm. Therefore, to compare the group with vascular enlargement exceeding the normal diameter with the normal group, in the present study, aortic diameter enlargement was defined as >40 mm.

Follow-up survey

CT examination was performed every 3 or 6 months after discharge on an outpatient basis at our hospital, and if no aortic diameter enlargement was observed, follow-up observation was performed by CT examination every year. If renal dysfunction was not present, contrast-enhanced CT was performed with 320 slices of 1 mm.

Analysis

In all patients, to evaluate the diameter of the aorta at the site of dissection, we measured the greatest minor axis at the time of the first examination of the largest site on the axial plane. When the diameter at the same site was the largest in the long-term (the latest CT image in the case of a reduction of aortic diameter), we measured the diameter at the site as the long-term aortic diameter. The difference in measurement of these two points divided by the follow-up observation period was defined as the speed of aortic growth. The patients were divided into two groups according to whether the false lumen of the site with the maximum aortic diameter was an obstructive-type thrombus or a patent-type false lumen. If the patent-type lumen had a partial obstructive thrombus, it was defined as a patent-type false lumen. Sites exhibiting rupture of the intimal structure were defined as intimal tears, and we measured the number of intimal tears irrespective of the size of the defect.

Statistical analysis

The incidence and percentage for variables of each classification were recorded using descriptive statistics. For continuous variables, we recorded the sample size, mean, standard deviation, and median, with minimum and maximum values. Survival rates were compared using Kaplan–Meier curves and the log rank test. Univariate analysis was performed using Student's t-test and the Chi-square test, whereas multivariate analysis was performed by Cox regression analysis. Statistical analyses were performed using software SPSS ver. 19 (IBM, New York, NY, USA).

Results

The subjects had a mean age of 69.7±12.2 years, with 66 male subjects (63.5%), a mean body mass index of 23.4±4.6, mean observation period of 31.9±34.6 (range, 1–143) months, and follow-up rate of 89% (**Table 1**). The mean aortic diameter at the initial examination was 37.9±7.7 mm, with a maximum mean diameter during the observation period of 40.8±10.8 mm. The aortic growth speed was 2±10.8 mm at 6 months, with an obstructive-type false lumen in 60 patients (58%). The mean number of intimal tears in patent-type false lumens was 2.1 (**Table 2**). The aortic diameter expanded in 36 patients (35%), occurring within 1 year after onset in>70% of these patients (26 of 36 patients). Growth in the aneurysmal diameter was observed in the long-term, and in some subjects, the longest period of growth in the aneurysmal diameter was observed after 72 months. Surgical intervention was performed for growth in the

Table 1 Baseline demographic characteristics

Characteristic	Value
Age, y	
Mean±SD	69.7±12.2
Median (range)	71.2 (15–91)
Male, %	63 (66 of 104)
Height, cm	
Mean±SD	160.7±10.4
Median (range)	161 (130–180)
Weight, kg	
Mean±SD	60±14
Median (range)	57.4 (37–97)
BMI, kg/m^2	
Mean±SD	23.4±4.6
Median (range)	22.8 (15.4–33.7)
Marfan syndrome, %	1.9 (2 of 104)
COPD, %	31 (32 of 104)
Follow up period, months	
Mean±SD	31.9±34.6
Median (range)	17 (1–143)

SD: Standard deviation; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease

Table 2 Baseline aortic characteristics

Characteristic	Value
Aortic diameter, mm	
in admission	37.9±7.7
during follow-up (Max diameter)	40.8±10.8
Rate of aortic growth, mm/6months	2.0±10.8
Number of intimal tear	2.1±1.1
Thrombosed false lumen n,%	60, 58

aneurysmal diameter in 17 patients (47%), including replacement of the aneurysmal synthetic graft in 9 patients (53%), TEVAR in 6 patients (35%), and replacement of the aneurysmal synthetic graft combined with TEVAR in 2 patients (12%). All surgeries by TEVAR alone were performed within 1 year after onset; in some patients, replacement of the aneurysmal synthetic graft was performed at a later date (**Fig. 2**).

Upon comparison of the group with aortic enlargement at the site of dissection (group E: 36 patients, 35%) and that without enlargement (group U: 68 patients, 65%), chronic obstructive pulmonary disease was significantly more common among patients in group E [16 (44%) vs. 16 patients (24%), $p=0.039$], the aortic diameter at the initial examination was larger (42±7.1 vs. 36±7.1 mm, $p<0.0001$), and the rate of aortic expansion was greater (10±32 vs. −3±19 mm/6 months, $p=0.028$). After the onset of dissection, the onset of acute-phase delirium tended to be more common in group E [17 (47%) vs. 23 patients (34%), $p=0.078$], and there were no significant

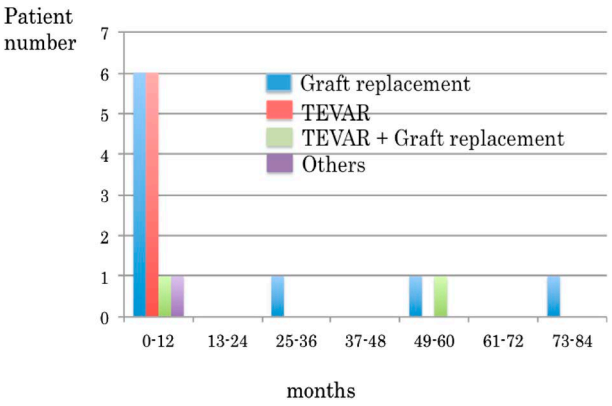

Fig. 2 Surgical intervention of intervals from the onset. Eighteen patients were treated in subacute or chronic phase.

differences between the two groups in usage of artificial respirator and non-invasive positive pressure ventilation. There were no particular differences between the two groups in the types of oral medication continued after discharge. Furthermore, there were no differences between the two groups in the use of oral statins and steroids or in the use of anticoagulant and antithrombotic agents (**Table 3**). Based on the above results, we found that independent risk factors for aortic enlargement were patent-type false lumen (odds ratio 0.617, 95% confidence interval 0.407–0.935, $p=0.023$) and aortic diameter at admission (odds ratio 1.116, 95% confidence interval 1.076–1.158, $p<0.001$) (**Table 4**). In particular, when the aortic diameter cut-off was ≥40 mm, the Kaplan–Meier curve revealed significantly greater aortic diameter enlargement for the group with aortic diameter ≥40 mm at the time of the initial examination ($p<0.0001$) (**Fig. 3**).

Aorta-related death occurred in two patients in group E and two patients in group U, with aorta-related death avoidance rates of 100%/86%/77% in group E and 92%/79%/79% in group U, at 1/5/10 years, respectively, indicating no differences between the groups ($p=0.747$) (**Fig. 4**).

Discussion

According to the report by IRAD, the 3-year survival rate of patients with acute type B aortic dissection at discharge is 75%–80%.[3] The cause of poor prognosis in the chronic phase is attributed to aorta-related phenomena caused by aortic diameter enlargement, and patients with aortic diameters ≥40 mm are particularly prone to onset of chronic aorta-related phenomena.[4] Similar results were obtained in the present study, and thus, as expected, it is highly likely that patients with aortic diameters ≥40 mm at the time of initial examination will need additional treatment at a later date, and we believe that careful and thorough follow-up observation is necessary.

Table 3 Demographic and clinical characteristics of aortic enlargement in two groups

(a) Univariate correlation of patient characteristics with enlargement of aortic diameter

Characteristic	Enlargement	Unchange	p Value
Age, y			
Mean±SD	70±11	70±13	0.965
Male n,%	24, 67	42, 62	0.920
BMI, kg/m^2			
Mean±SD	23±5	24±5	0.690
COPD n,%	16, 44	16, 25	0.039
Follow-up period, months			
Mean±SD	48±36	31±33	0.015

(b) Initial computed tomography findings

Characteristic	Enlargement	Unchange	p Value
Aortic diameter			
in admission	42±7	36±7	<.0001
during follow-up			
(max diameter)	51±8	36±7	<.0001
Number of intimal tear	2.3	2.0	0.537
Patent false lumen n,%	19, 53	16, 34	0.064

(c) Patient characteristics in intensive care unit

Characteristic	Enlargement	Unchange	p Value
Delirium n,%	17, 55	23, 35	0.078
NPPV required	9, 29	10.15	0.168
Tracheal intubation	3, 10	13, 20	0.256

(d) Medication in discharge our hospital

Medication	Enlargement	Unchange	p Value
Beta blockers n,%	27, 77	49, 74	0.813
Angiotensin converting enzyme inhibitors	5, 14	17, 26	0.215
Angiotensin II receptor blockers	22, 63	44, 67	0.826
Calcium channel blockers	25, 71	54, 82	0.311
α blockers	12, 34	25, 38	0.829
Spironolactone	0, 0	7, 11	0.046
Loop diuretics	4, 11	3, 5	0.232
Thiazide	2, 6	3, 5	0.569
Statins	10, 29	20, 30	0.856
Steroids	3, 8	4, 6	0.311
Anticoagulants	3, 8	2, 3	0.829
Antiplatelets	3, 8	3, 4	0.414

Table 4 Independent factors of aortic enlargement: Cox regression model

Variable	Odds ratio	p	95.0%CI
Patent false lumen	0.617	0.023	0.407–0.935
Aortic diameter (mm) in admission	1.116	<0.001	1.076–1.158

According to the results of the INSTEAD-XL trial, early surgical intervention by TEVAR improves long-term prognosis compared with that with conservative bed rest treatment. However, details of medications and the treatment protocol for conservative bed rest treatment were not specified in detail. In our study, conservative treatment was planned and managed by the Department of Surgery, and even after discharge, the patients consulted the department on an outpatient basis. If the diameter of the aneurysm tended to increase, the timing of therapeutic

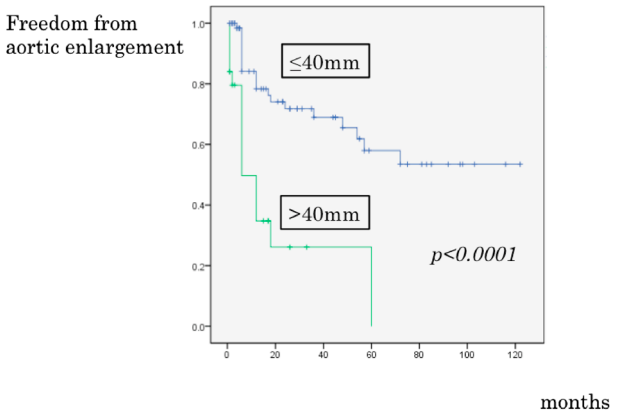

Fig. 3 Kaplan–Meier curve for freedom from aortic enlargement. Cut-off point was determined over 40 mm.

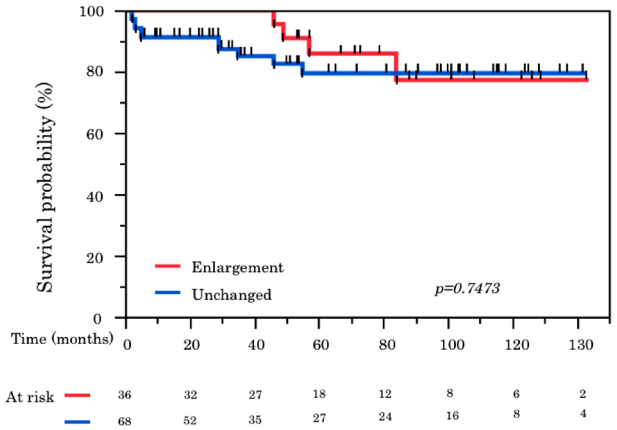

Fig. 4 Kaplan–Meier curve for freedom from aortic related death of 104 patients with enlargement of aortic diameter group and unchanged group in chronic type B aortic dissection.

intervention was planned at the discretion of the surgeon.

Following the onset of Stanford type B acute aortic dissection, it is generally accepted to first provide conservative bed rest treatment. Based on various studies,[7,8] we commenced treatment aimed at achieving a systolic blood pressure of 100–120 mmHg. In the acute phase, we primarily use nicardipine hydrochloride and nitroglycerine, which have an immediate hypotensive effect, and once the patient could consume liquids, combined oral agents were administered. Oral agents in the chronic phase aim at preventing aorta-related adverse events,[9,10] for which the use of beta-blockers prioritized, followed by the selection of an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist.[11] Blood pressure management in the chronic phase aims to maintain the systolic pressure at <130 mmHg.[12] In the present study, we did not obtain results indicating that the type of oral agent administered is an independent risk factor associated with aneurysmal diameter enlargement. In general, two or three types of oral agents were used, and therefore, we believe that it is difficult to draw conclusions from the present study model. Furthermore, few subjects used oral statins and steroids or anticoagulants and antithrombotic agents, which we believe made it difficult to determine a statistically significant effect of medication use.

It has been reported that in the long-term prognosis of patients with chronic type B dissection who are receiving internal medicine, the 5-year survival rate is 64%–79% for all-death avoidance for patent-type false lumens and 74%–97% for that for obstructive-type false lumens. Thus, we can say that our treatment results were generally good.[13–15] In patients with obstructive-type false lumen acute aortic dissection, risk factors for aortic diameter enlargement include the appearance of acute-phase ulcer-like projections,[16] aortic diameter ≥40 mm, and false lumen diameter ≥10 mm.[17] Based on the present study, we also believe that enlarged aortic diameter at the time of initial examination is a predictor of long-term aneurysm formation and supports early surgical intervention; however, the long-term survival rate is good when conservative treatment is provided to patients with acute type B dissection without complications. Therefore, the indication for treatment should be determined with care.

Conservative first-line treatment for patients with chronic type B aortic dissection in the age of TEVAR results in satisfactory therapeutic outcomes. We believe that regular follow-up observation by the surgeon is an effective means for avoiding missing the optimal timing for treatment intervention in the chronic phase. Moreover, with further analysis of prognostic factors, more proactive surgical intervention may become the standard treatment for asymptomatic patients with type B aortic dissection.

Limitations

In the present study, independent risk factors were found by multivariate analysis; however, the preoperative patient background did not include risk factors such as smoking habits and hypertension as variables.

Conclusion

The long-term prognosis of patients with type B dissection who receive conservative treatment during the acute phase was satisfactory. For patent-type false lumen, in patients with aortic diameter at the site of dissection >40 mm at the initial examination, it is highly likely that the diameter of the aneurysm will increase in the long-term. Half of the patients who exhibited growth in the aortic diameter required surgery, and therefore, it is important to conduct further analysis of factors that contribute to the growth in the aortic diameter.

Disclosure Statement

All authors have no conflicts of interest to declare.

Additional Notes

This study was reported at the 45th Annual Meeting of the Japanese Society for Vascular Surgery, April 2017, Hiroshima.

Informed consent for study participation was obtained from all study subjects.

Additional Remarks

This original article was primarily published in the Japanese Journal of Vascular Surgery Vol. 27 (2018) No. 1; however, numerical data errors were detected after the publication. The erratum was published in Vol. 27 (2018) No. 5 of the same journal. This translation reflects these corrections.

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