Table 3: Mean preoperative and postoperative regional cerebral blood flow values, as detected with SPECT after administration of acetazolamide

Artery	Preoperative flow (ml/100 g/min)	Postoperative flow (ml/100 g/min)	*P*-value
Rt ACA	46.7 ± 9.5	51.8 ± 10.2	0.09
Lf ACA	46.7 ± 9.4	51.7 ± 9.8	0.09
Rt MCA	48.5 ± 9.4	53.3 ± 10.2	0.09
Lf MCA	47.5 ± 9.1	51.9 ± 9.5	0.10
Rt PCA	50.3 ± 8.9	55.5 ± 9.9	0.08
Lf PCA	50.4 ± 8.9	54.7 ± 9.5	0.12

Rt: right; ACA: anterior cerebral artery territory; Lf: left; MCA: middle cerebral artery territory; PCA: posterior cerebral artery territory.

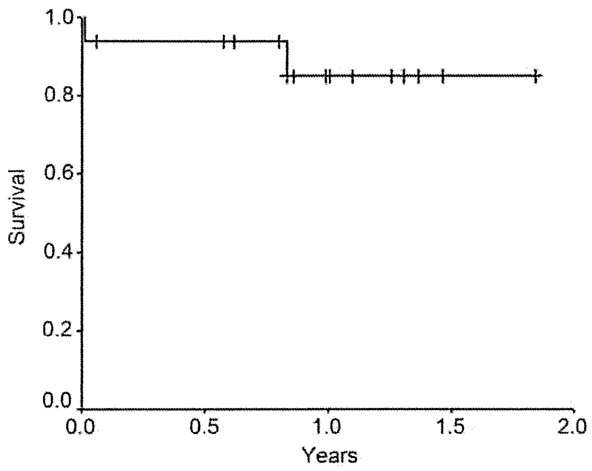

Figure 5: Two-year actuarial survival rate in the series. One patient died during initial hospitalization and another died 10 months postoperatively from chronic obstructive pulmonary disease.

observed. In our series, the mean preoperative values for the CCAs, ICAs and VAs were 454, 223 and 77 ml/min, respectively, and the calculated total cerebral blood flow was 601 ml/min. The postoperative values were 444, 230 and 84 ml/min, respectively, for the CCAs, ICAs and VAs and 629 ml/min for the calculated total cerebral blood flow. Thus, all the mean postoperative values in our study were consistent with the preoperative values, as well as with the values reported by Schöning *et al.*, although we did observe that blood flow volumes in the right CCA and right ICA were significantly greater than those in the left CCA and left ICA after the hybrid procedure. Because the diameter of the left CCA and left ICA is smaller than that of the prosthetic grafts we used (8 mm), the grafts could not increase flow in the vessel. However, the greater flow volume on the right side compensated for the lower volume on the left.

Preoperatively, the mean values for regional cerebral blood flow volume (without administration of acetazolamide) in the territories of the right and left ACA, MCA and PCA in our patients ranged from 37 to 41 ml/100 g/min. These values were slightly lower than the mean value of 45.4 ml/100 g/min observed by Ishii *et al.* [4] in healthy volunteers (mean age 63.5 years). Perhaps our patients had a lower regional flow volume because of their age. Our patient population was relatively old because the hybrid procedure was used primarily in those at high risk of complications from conventional surgery. Postoperative values for regional cerebral blood flow in our study were very similar to preoperative values.

SPECT studies using acetazolamide to assess regional cerebral perfusion showed that our patients had good cerebral vasoreactivity, even after distal hybrid repair. Remarkably, cerebral blood flow hyporeactivity to acetazolamide was not observed in any territory, either preoperatively or postoperatively. These findings indicate that both the right and left hemispheres of the brain had sufficient perfusion reserve both before and after aortic arch repair.

The limitations of our study include the small number of patients, its retrospective nature, and the lack of long-term follow-up. So far, none of our patients have had a late complication from their repair. However, data on the long-term safety of the procedure and the durability of the patency of the implanted bypass grafts and endovascular devices are not yet available, although extra-anatomic bypass grafting using an ePTFE prosthesis in carotid and subclavian reconstruction has previously been found to provide excellent patency rates [9, 10]. Moreover, use of the hybrid procedure in young, active patients requires specific investigation. We conclude, however, that our study provides good preliminary evidence that efficient regional cerebral blood flow and vasoreactivity are preserved in patients who undergo hybrid distal hemiarch repair for aortic arch disease.

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Risk Model of Cardiovascular Surgery in 845 Marfan Patients Using the Japan Adult Cardiovascular Surgery Database

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SUMMARY

The aim of this study was to evaluate the short-term operative results of patients with Marfan syndrome who underwent thoracic or abdominal aortic surgery in a 4-year period in Japan. Data were collected from the Japan Cardiovascular Surgery Database (JCVSD). We retrospectively analyzed the data of 845 patients with Marfan syndrome who underwent cardiovascular surgery between January 2008 and January 2011. Logistic regression was used to generate risk models. The early mortality rate was 4.4% (37/845). Odds ratios (OR), 95% confidence intervals (CI), and *P* values for structures and processes in the mortality prediction model were as follows: renal insufficiency (OR, 11.37; CI, 3.72-34.66; $P < 0.001$); respiratory disorder (OR, 11.12; CI, 3.20-38.67; $P < 0.001$); aortic dissection (OR, 13.02; CI, 2.80-60.60; $P = 0.001$); pseudoaneurysm (OR, 11.23; CI, 1.38-91.66; $P = 0.024$); thoracoabdominal aneurysm (OR, 2.67; CI, 1.22-5.84; $P = 0.014$); and aortic rupure (OR, 4.23; CI, 1.26-14.23; $P = 0.002$). The mortality prediction model had a C-index of 0.82 and a Hosmer–Lemeshow *P* value of 0.56. In conclusion, this study demonstrated that renal insufficiency and respiratory disorder had great impact on the operative mortality of Marfan patients undergoing cardiovascular surgery. Because patients with aortic dissection or aortic rupture showed high operative mortality, close follow-up to avoid emergency operation is mandatory to improve the operative results. Achieving good results from surgery of the thoracoabdominal aorta was quite challenging, also in Marfan patients. (Int Heart J 2013; 54: 401-404)

Key words: JACVSD

Marfan syndrome (MFS) is the most common multisystem disorder of connective tissue that affects 1 in 5000 individuals.[1)] It is inherited as an autosomal dominant trait and displays a variety of clinical manifestations in the ocular, musculoskeletal, and cardiovascular systems. Aortic root aneurysm and subsequent aortic dissection are the leading cause of morbidity and mortality in MFS patients. Aortic aneurysm in MFS is typically pear-shaped and involves progressive dilatation of the sinus of Valsalva. Early diagnosis and advances in surgical treatment, in particular the Bentall procedure and more recently the valve-sparing procedure, have significantly improved life expectancy in MFS.[2)] There has been no report of any nationwide study in Japan, presumably because the number of operations on MFS patients at each institute is limited. In the present study, risk analysis was performed for MFS patients who had undergone cardiovascular surgery between January 2008 and January 2011, using the Japan Adult Cardiovascular Surgery Database (JACVSD).

METHODS

Study population: The JACVSD was initiated in 2000 to estimate surgical outcomes after cardiovascular procedures in many centers throughout Japan. The JACVSD adult cardiovascular division currently captures clinical information from nearly half of all Japanese hospitals (235 hospitals) performing cardiovascular surgery. The data collection form has a total of 255 variables (definitions are available online at http://www.jacvsd.umin.jp), and these are almost identical to those in the STS National Database (definitions are available online at http://sts.org). The JACVSD has developed software for the Web-based data collection system through which the data manager of each participating hospital submits their data electronically to the central office. Although participation in the JACVSD is voluntary, data completeness is a high priority. Accuracy of the submitted data is maintained by a data audit that is achieved by monthly visits by administrative office members to the participating hospital to check data against clinical records. Data validity is further confirmed by an independent comparison of the volume of cardiac surgery at a particular

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hospital entered in the JACVSD versus that reported to the Japanese Association for Thoracic Surgery annual survey.[3)]

We examined all MFS patients who had undergone cardiovascular surgery between 1 January 2008 and 31 December 2011. First, those JACVSD records that were obtained without informed consent were excluded from this analysis. Records with missing age (or which were out of range), sex, or 30-day status were also excluded. After this data cleaning, the population for this risk model analysis consisted of 845 patients from 235 participating sites throughout Japan.

Endpoints: The primary outcome measure of the JACVSD was 30-day operative mortality, which was defined exactly the same as the 30-day operative mortality in the Society of Thoracic Surgeons National Database. This includes any patient who died during the index hospitalization, regardless of the length of hospital stay, and any patient who died within 30 days of the operation after being discharged from the hospital. By using the definition from a previous study,[4,5)] major morbidity was defined as any of the following 5 postoperative in-hospital complications: stroke, reoperation for any reason, need for mechanical ventilation for more than 24 hours after surgery, renal failure, or deep sternal wound infection.

Statistical analysis: The statistical model was multiple logistic regression; variables entered in the model were selected from all variables shown in Table I using bivariate tests. The chi-square test analyzed categoric covariates, and the unpaired *t* test or Wilcoxon rank-sum test was used for continuous covariates. A multivariate stepwise logistic regression analysis was then performed for each outcome. Stability of the model was checked every time a variable was eliminated. When all statistically nonsignificant variables had been eliminated from the model, "goodness-of-fit" was evaluated and the area under the receiver operating characteristic (ROC) curve was used to assess how well the model could discriminate between patients who lived and patients who had died. To evaluate model calibration, the Hosmer–Lemeshow test was applied.[6)]

Results

Patient characteristics: Patient characteristics and outcomes of each procedure are shown in Table I. Patient median age was 41.9 ± 13.9 years, and the percentage of male patients was as 59.7%.

Early mortality and morbidity: As shown in Table II, 30-day operative mortality rates and composite rates for mortality or major morbidity were 4.4% and 23.0% respectively.

Model results and performance: Multiple regression analyses for all patients identified 6 preoperative risks affecting operative mortality (Table III). Preoperative comorbid conditions such as high creatinine levels ≧ 3.0 mg/dL or severe chronic lung disease significantly increased the surgical risks. Types of aortic disease such as dissecting aortic aneurysm, pseudoaneurysm, and thoracoabdominal aneurysm, and also mode of surgery such as emergency surgery for rupture of the aneurysm did as well. Model performance was evaluated using the C-index (area under the ROC curve) as a measure of model discrimination and the Hosmer–Lemeshow test as a measure of "goodness-of-fit." The C-index was 0.82 for the mortality model and 0.76 for the composite mortality or morbidity model; the Hosmer–Lemeshow test *P* value was 0.56 for the mortality model and 0.35 for the composite mortality or morbidity model. Details of model performance metrics are shown in Table IV.

Discussion

A clinical diagnosis of MFS is made according to the Ghent nosology when major manifestations are present in 2 organ systems and a third organ system is involved.[7)] The cardinal features of MFS involve the ocular, cardiovascular, and skeletal systems,[1)] but aortic enlargement and dissection, mostly of the ascending aorta, are the primary cause of early death.[8)] In

Table I. Patient Characteristics (*n* = 845)

Variable	*n*	%
Male sex	507	59.7
Age (years)	41.9 ± 13.9	
Redo	326	38.4
Aortic dissection	487	57.4
Pseudoaneurysm	30	3.5
Rupture	24	2.8
Dilatation	560	66
Aortic root	432	50.9
Ascending aorta	359	42.3
Aortic arch	254	29.9
Descending aorta	165	19.4
Thoracoabdominal	118	13.9
Abdominal aorta	23	2.7
CABG	62	7.3
Mechanical valve	268	31.6
Bioprosthetic valve	48	5.7
Aortic regurgitation ≧ 2	371	43.7
Aortic regurgitation ≧ 3	245	28.9
Emergent operation	169	19.9
NYHA class ≧ 2	244	28.7
LVEF < 50%	18	2.1
Endocarditis	19	2.2
Hypertension	356	41.9
Associated coronary disease	18	2.2
History of myocardial infarction	19	2.2
Smoking	104	12.2
COPD	83	9.8
Diabetes	17	2
Renal insufficiency	24	2.8
Cerebrovascular accident	45	5.3
Aortic valve stenosis	4	0.5
Preoperative congestive heart failure	77	9.1
Prior cardiac operation	50	5.8
Hypercholesterolemia	89	10.5

Table II. Procedural Outcomes (*n* = 845)

	30-day operative mortality (%)	Composite results (%)
All patients	4.4	23
Thoracic aneurysm		
Root	2.1	23.1
Ascending	3.5	31
Arch	5.4	45.1
Descending	8.6	36.4
TAAA	12.4	68.6

Table III. Description of each prediction model (n = 845)

	30-day operative mortality				Composite mortality or major morbidity			
			95%CI				95%CI	
	P	OR	Lower	Upper	*P*	OR	Lower	Upper
Age	—	—	—	—	0.033	1.292	1.02	1.64
Gender	—	—	—	—	0.002	1.829	1.26	2.66
Myocardial infarction	—	—	—	—	0.011	3.566	1.34	9.52
Poor LV function	—	—	—	—	0.032	3.105	1.1	8.76
NYHA ≧ 2	—	—	—	—	0.007	1.688	1.15	2.47
Renal failure	0	11.37	3.727	34.66	—	—	—	—
Respiratory insufficiency	0	11.12	3.195	38.67	—	—	—	—
Reoperation	—	—	—	—	0.001	2.02	1.36	3.01
Rupture	0.02	4.225	1.256	14.22	0	6.975	2.61	18.7
Acute aortic dissection	—	—	—	—	0	2.339	1.53	3.59
Dissecting aortic aneurysm	0.001	13.02	2.796	60.6	—	—	—	—
Pseudoaneurysm	0.024	11.23	1.377	91.66	—	—	—	—
Aortic arch	—	—	—	—	0	2.376	1.61	3.51
Thoracoabdominal aneurysm	0.014	2.668	1.22	5.835	0	3.511	2.12	5.81

Table IV. Performance of each prediction model (n = 845)

	30-day operative mortality	Composite mortality or major morbidity
C-statistic	0.82	0.76
Hosmer-Lemeshow test	0.56	0.35

1968, Bentall reported a technique for the combined treatment of diseases of the aortic valve and the segment of the ascending aorta using a valvulated tube in which the coronary artery ostia were reimplanted.[2] In the years since, this technique has gone through several modifications and has become the procedure of choice for the treatment of aortic valve disease associated with the involvement of the ascending aorta.[9-12] Thus, the life expectancy of patients with MFS has dramatically improved from about 45 years in 1972[8] to 72 years in 1995.[13]

This study demonstrated that the 30-day operative mortality of aortic root surgery including both dissecting and nondissecting aneurysm in MFS patients was 2.1%. The JATS publishes an Annual Report of all Registry data, and the most recent version reported that the 30-day operative mortality of aortic root surgery performed for acute dissecting aneurysm and nondissecting, unrupturred aneurysm was 16.3% and 2.7%, respectively.[1] The better results in our study than the JATS Registry report might be attributed to the younger ages, less atherosclerotic changes of the aortic wall, and less opportunity for accompanying diseases in MFS patients. However, the operative mortality of thoracoabdominal aneurysm in MFS patients was 12.4%, which is not better than the number reported in the JATS Registry report; the 30-day operative mortality of thoracoabdominal procedures for chronic Stanford type B aortic dissection and nondissecting unruptured thoracoabdominal aneurysm was 10.7% and 6.9%, respectively.[1] It is likely that the thoracoabdominal aneurysms in MFS patietns in our study included more extensive types than the JATS Registry report, although classification of thoracoabdominal aneurysms was not clarified in either study.

There were two important variables affecting both the 30-day operative mortality rates and the composite results; ruputure for operative indication (OR, 3.67; 95% CI, 2.80 to 4.81 and OR, 3.67; 95% CI, 2.80 to 4.81) and thoracoabdominal aortic aneurysm (OR, 3.67; 95% CI, 2.80 to 4.81 and OR, 3.67; 95% CI, 2.80 to 4.81). Other factors, like preoperative high creatinine levels ≧ 3.0 mg/dL, severe chronic lung disease, dissecting aortic aneurysm, and pseudoaneurysm were also significant risk factors for the 30-day operative mortality in our study.

Aortic root dilatation, with subsequent aortic valve regurgitation, aortic dissection, or rupture, is a common and morbid cardiovascular abnormality in MFS patients.[14] As shown in our study, because the morbidity and mortality rates in MFS patients undergoing elective root surgery is low, and besides, emergency operation for aneurysmal rupure or acute dissection worsens the clinical results, early recognition of the disorder, identification of presymptomatic patients, and subsequent institution of surgical therapy is mandatory to reduce the frequency of catastrophic aortic events.

Symptomatic aneurysms have a much worse prognosis than asymptomatic ones, and should be resected regardless of size. There is an operative mortality of up to 20% for acute ascending aortic dissection in MFS. MFS patients who suffer aortic dissection have a significantly reduced long term survival, reported at 50–70% at 10 years.[15] These facts emphasise the importance of prophylactic aortic surgery before aortic dissection occurs in MFS. Recent guidelines have suggested that prophylactic aortic surgery be performed in adults with MFS when the aortic root diameter exceeds 5 cm.[15] Aortic surgery should also be considered in MFS when the aortic root exceeds 4.5 cm and there is a family history of aortic dissection, when there is rapid aortic growth (> 5–10 mm per year), and when significant aortic insufficiency is present. Aortic diameter should be measured serially by a transthoracic echocardiogram at multiple levels and compared to normal values based on age and body surface area. Unfortunately, there is no information about size criteria for operative indication in the study. Because Japanese people are generally smaller than people in western countries and the size of the vasculature might be accordingly smaller, further investigation is warranted to elucidate the true criteria of aortic size for operative indication in Japanese people.

Our study found that the operative mortality of thoracoabdominal aneurysm in MFS patients was not better than the JATS Registry report in the general population. Although endovascular treatment has been demonstrated to be effective in type B aortic dissection and descending thoracic aneurysms in non-Marfan patients, it may have limited durability in MFS patients, because the aorta is prone to dilate in these connective tissue disorders.[16,17)]

The validity of our study is limited because the odds ratio of several factors for the 30-day operative mortality were quite high (> 10) and suboptimal. These high odds ratios are attributed to the small number of each factor and therefore the figures themselves are not reliable, although these factors surely affect the results significantly. Additional limitation is that we did not divide our data into analyzing and validation data sets because of the relatively small volume of data. It would be possible to perform a validation of our risk model by dividing into the 2 data sets when the volume of data becomes large enough.

In conclusion, we have reported a risk stratification study on cardiovascular surgery that uses a nationwide cardiovascular surgery database. By analyzing 845 patients, the 30-day operative mortality rate was 4.4%. Renal insufficiency and respiratory disorder had great impacts on the operative mortality of MFS patients undergoing cardiovascular surgery. Because patients with aortic dissection or aortic rupture showed high operative mortality, close follow-up to avoid emergency operation is mandatory to improve the operative results in MFS patients. Achieving good results from surgery of the thoracoabdominal aorta was also quite challenging in MFS patients.

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