Long-term implications of emergency versus elective proximal aortic surgery in patients with Marfan syndrome in the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Consortium Registry

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Objective: Patients with Marfan syndrome with aortic root aneurysms undergo elective aortic root replacement to avoid the life-threatening outcomes of aortic dissection and emergency repair. The long-term implications of failed aortic surveillance leading to acute dissection and emergency repair are poorly defined. We compared the long-term clinical courses of patients with Marfan syndrome who survive emergency versus elective proximal aortic surgery.

Methods: The Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Registry is a National Institutes of Health–funded multicenter database and biorepository that enrolls patients with genetically triggered thoracic aortic aneurysms. Of the 635 patients with Marfan syndrome enrolled as of March 2011, 194 had undergone proximal aortic replacement. Patients were grouped according to emergency (n = 47) or elective (n = 147) status at the time of surgery.

Results: Patients in the emergency group were more likely to have incomplete proximal aortic resection; 83% of emergency procedures included aortic root replacement, compared with 95% of elective procedures. At long-term follow-up (mean, >6 years), the emergency group had a higher incidence of chronic dissection of the distal aorta and significantly larger diameters in distal aortic segments than elective patients. Patients in the emergency group had undergone more operations (1.31 vs 1.11 procedures/patient; $P = .01$) and had lower activity scores on a health-related quality of life survey.

Conclusions: For patients with Marfan syndrome, failed aortic surveillance and consequent emergency dissection repair have important long-term implications with regard to the status of the distal aorta, need for multiple procedures, and quality of life. These findings emphasize the importance of aortic surveillance and timely elective aortic root aneurysm repair for patients with Marfan syndrome. (*J Thorac Cardiovasc Surg* 2012;143:282-6)

Marfan syndrome is an autosomal dominant inherited disorder caused by mutations in the gene that encodes fibrillin-1. The syndrome is characterized by systemic connective tissue manifestations involving the ocular, skeletal, and

cardiovascular systems, among others. Cardiovascular complications, especially aortic root dissection and rupture, are the most common causes of death; their peak incidence is in the third and fourth decades of life.¹⁻⁴ The life expectancy of patients with Marfan syndrome has dramatically improved since aortic root replacement with a composite prosthetic valve conduit was first reported in 1967.^{5,6} Composite valve graft procedures and valve-sparing aortic root replacement procedures are now routinely performed under elective conditions with low morbidity and mortality.⁷⁻¹² Patients with Marfan syndrome typically undergo aortic surveillance with serial imaging of the aortic root and are offered elective aortic root replacement when their aortic root diameter reaches an appropriate size to avoid life-threatening aortic dissection and the high morbidity associated with emergency aortic surgery.

Although the immediate risk of aortic dissection and emergency repair for this patient population has been extensively studied, the long-term implications of failed aortic

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Abbreviation and Acronym

GenTAC = Genetically Triggered Thoracic
Aortic Aneurysms and
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surveillance and emergency dissection repair are poorly defined.¹³⁻²⁰ The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)^{21,22} has established a biospecimen repository and bioinformatics infrastructure to enable research to determine the best practices for optimal clinical management of genetically triggered thoracic aortic aneurysms and related complications. We used the GenTAC Registry to compare the long-term clinical course of patients with Marfan syndrome who survive emergency versus elective proximal aortic surgery.

MATERIALS AND METHODS**Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Registry**

The GenTAC Registry contains longitudinal observational data on patients with conditions related to genetically induced thoracic aortic aneurysms.^{21,22} The Registry also has a biospecimen repository and bioinformatics infrastructure created to support research to determine the optimal clinical management of genetically triggered thoracic aortic aneurysms and related complications. The National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases are co-sponsors of GenTAC.

Patients included in this study were recruited from 5 regional clinical centers that treat patients from a wide geographic catchment area within the United States: Johns Hopkins University, Oregon Health & Science University, University of Pennsylvania, University of Texas Health Science Center at Houston/Baylor College of Medicine, and Weill Cornell Medical College. Research Triangle Institute International serves as the data coordinating center responsible for data management, coordination of training, logistics, and statistical design and analysis.

The targeted enrollment of patients includes adults and children who fall into 1 or more of 12 diagnosis categories, including Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, Turner syndrome, bicuspid aortic valve with ascending aortic aneurysm, and familial thoracic aortic aneurysm and dissection. Available clinical data, imaging results, and blood and tissue samples from each patient are processed and stored by GenTAC to provide a resource that combines clinical and biological data from a large and diverse population of patients with inherited thoracic aortic aneurysm disorders.

Patients

From the 635 patients with Marfan syndrome who were enrolled in GenTAC as of March 2011, we selected those who had undergone proximal aortic replacement procedures. Our analyses focused on procedure information, imaging findings, and quality of life, which was measured with the Activity Score of the Short Form-36 Health Survey²³ and the Karnofsky Performance Status Score.²⁴

Analysis

We used SAS software (SAS Institute, Inc, Cary, NC) to extract data from the secure enterprise network database to create reports and summary

tables and to perform ad hoc statistical analyses. To examine between-group differences in continuous outcomes, we used *t* tests when tests of normality confirmed that the outcomes data were normally distributed. Wilcoxon rank-sum tests were used when continuous outcome data did not follow a normal distribution. To examine between-group differences in categorical outcomes, we used chi-square tests unless the sample sizes were small, in which case Fisher exact tests were performed. For data security purposes, all analyses were performed and all data were stored in a password-protected remote workspace.

Institutional Review Boards and Consent

Institutional review board approval was obtained for this study at each of the 5 participating GenTAC regional clinical centers. Individual informed consent was obtained from each GenTAC Registry patient.

RESULTS

At the time of the analysis, 635 patients with Marfan syndrome were enrolled in GenTAC. Of these, 194 (31%) had undergone 225 proximal aortic surgical procedures at the time of their enrollment. The patients were divided into 2 groups (Table 1): those whose initial operation was performed on an emergency basis for dissection (*n* = 47) and those whose initial operation was performed electively or urgently for aneurysm or aortic regurgitation (*n* = 147). Patients in both groups were predominantly white, middle-aged, or young adult men. Patients in the emergency group had a significantly higher prevalence of tobacco use (59% vs 32%, *P* = .003). Patients in the elective group were younger than patients in the emergency group at the time of initial surgery (mean age, 34.9 vs 38.0 years), but this difference was not statistically significant (*P* = .2).

There were significant differences between the 2 groups in the types of proximal aortic surgery performed. Aortic root replacement was performed in 95% of initial operations in the elective group, compared with 83% in the emergency group (*P* = .01). The reason for this may be related to the absence of a diagnosis of Marfan syndrome at the time that some patients presented with dissection or to operator unfamiliarity with performing root replacement in an emergency situation. Of the root-replacement procedures performed in the elective group, 58% were composite valve graft procedures and 42% were valve-sparing procedures; in contrast, only 17% of the root-replacement operations performed in the emergency group were valve-sparing procedures (*P* < .0001). Perhaps for this reason, the emergency group underwent more aortic procedures than the elective group (1.31 vs 1.11 aortic procedures per patient, respectively; *P* = .01). In the emergency group, 26.9% of patients had undergone multiple aortic procedures, compared with 9.9% in the elective group (*P* = .003).

We next examined differences in the status of the distal aorta between patients in the emergency and elective groups. For 95 patients (26 emergency, 69 elective), the GenTAC Registry included data from computed tomography or magnetic resonance imaging of the distal aorta

TABLE 1. Demographics

Demographic variable	Group		P value
	Emergency (n = 47)	Elective (n = 147)	
Age at enrollment (y)			.6
<5	0	0	
5–17	1 (2)	5 (3)	
18–39	17 (36)	63 (43)	
40–69	28 (60)	72 (49)	
>69	1 (2)	7 (5)	
White race	44 (94)	138 (94)	.9
Hispanic ethnicity	3 (6)	8 (5)	.7
Male gender	30 (64)	98 (67)	.7
Height (cm)	183.4 ± 11.8 (n = 45)	185.8 ± 12.2 (n = 141)	.3
Weight (kg)	83.0 ± 23.5 (n = 45)	87.1 ± 23.6 (n = 141)	.3
Body surface area (m ²)	2.04 ± 0.31 (n = 45)	2.11 ± 0.32 (n = 138)	.2
History of tobacco use (>100 cigarettes in lifetime)	23 (59) (n = 39)	34 (32) (n = 107)	.003
Age at first operation (y)	38.0 ± 11.1 (n = 41)	34.9 ± 14.2 (n = 130)	.2

Continuous data are presented as mean ± standard deviation, and categoric data are presented as number (%).

performed after each patient's proximal aortic operation (Table 2). The average length of time between first operation and cross-sectional imaging was 6.6 years for the emergency group and 7.2 years for the elective group. Chronic dissection involving any aortic segment distal to the site of repair was significantly more common in the emergency group (73%) than in the elective group (12%; $P < .0001$). Although this relationship was found in each individual segment of the distal aorta examined, the incidence of chronic dissection in the transverse aortic arch in the elective group was particularly low (2%) compared with the incidence of dissection in the descending aortic segments (10%) in that group. These data suggest that the proximal aortic procedures performed in this group were effective at preventing type A aortic dissection, but that these patients have a significant ongoing risk for type B dissection.

The impact of type A aortic dissection on the status of the distal aorta was also noted in differences in aortic diameter (as measured by computed tomography and magnetic resonance imaging) between the 2 groups (Table 3). At long-term follow-up, patients in the emergency group had larger aortic diameters than patients in the elective group in each

aortic segment except the abdominal aorta, where the difference did not reach statistical significance.

In addition to differences in the status of the distal aorta, patients in the emergency and elective groups differed in terms of quality of life as assessed by questionnaires administered at the time of enrollment in GenTAC (Table 4). The average length of time between first operation and quality of life assessment was 4.73 years for the emergency group and 6.34 years for the elective group. Patients in the elective group had higher self-reported Activity Scores on the Short Form-36 Health Survey ($P = .04$) and marginally higher self-reported Karnofsky Performance Status Scores ($P = .06$).

DISCUSSION

This study showed that failed aortic surveillance leading to presentation with type A dissection has greater long-term adverse effects than elective aortic root replacement in patients with Marfan syndrome. The implications of emergency type A dissection repair are wide ranging and include higher risk of inadequate aortic root aneurysm resection at the time of initial surgery, less use of aortic valve-sparing procedures, and higher frequency of chronic

TABLE 2. Frequency of distal aortic involvement with chronic dissection

Distal aortic segment with dissection involvement	Group		P value
	Emergency (n = 26)	Elective (n = 69)	
Any segment of the distal aorta	19 (73)	8 (12)	<.0001
Transverse arch	13 (50)	1 (2)	<.0001
Descending thoracic aorta	15 (58)	7 (10)	<.0001
Thoracoabdominal aorta*	15 (58)	7 (10)	<.0001
Abdominal aorta	15 (58)	7 (10)	<.0001

Data are presented as number (%). *Evaluated at the level of the diaphragm.

TABLE 3. Diameters of distal aortic segments

Distal aortic segment	Group					P value
	Emergency		Elective			
	Diameter		Diameter			
	n	(cm)	n	(cm)		
Transverse arch	10	3.96 ± 1.19	26	2.98 ± 0.80	.007	
Descending thoracic aorta	17	4.66 ± 1.42	45	3.02 ± 1.11	<.0001	
Thoracoabdominal aorta*	13	4.16 ± 1.42	17	2.89 ± 1.19	.01	
Abdominal aorta	12	3.88 ± 1.50	26	3.18 ± 1.08	.1	

*Measured at the level of the diaphragm.

TABLE 4. Activity scores on quality of life measures

TABLE 2. Mean heavily scores on quality of life measures					
Measure	Group				P
	Emergency		Elective		
	n	Mean	n	Mean	
Karnofsky performance score	35	82.6 ± 18.7	114	89.0 ± 12.3	.06
Short Form-36 Health Survey activity score	28	12.3 ± 5.4	86	14.7 ± 5.2	.04

dissection and aneurysm formation in the distal aorta. In addition, patients in the emergency group seem to have poorer activity-related quality of life than patients in the elective group in the long term.

As a consequence of these findings, patients in the emergency group are likely to receive more intensive follow-up and care in the future. This study found that the emergency group underwent more aortic procedures than the elective group. Given the higher rate of inadequate aortic root resection and chronic dissection involving the distal aorta in the emergency group, we would expect this difference to grow in the future.²⁰ Quality of life measures may also become more disparate if patients undergoing emergency surgery are more frequently exposed to the morbidity associated with repeated complex aortic repair procedures.

In this study, the term “failed aortic surveillance” was used to refer to failures that occur at many different steps in the diagnosis and management of patients with Marfan syndrome. Unfortunately, the degree of detail currently available through the GenTAC registry does not allow us to determine at which point failure occurred in a given patient. In some instances, failure may have occurred because the patient’s Marfan syndrome was not diagnosed before the patient presented with an acute dissection. Other failures are likely to be due to inadequate or misinterpreted follow-up serial imaging. In addition, a subset of patients with Marfan syndrome present with acute dissection before their aortic root diameter reaches the size (45–50 mm) at which patients are commonly referred for prophylactic, elective aortic root replacement. Each of these types of failure represents an opportunity to improve the monitoring of patients with Marfan syndrome to reduce the frequency of presentation with acute aortic dissection and are the subject of ongoing GenTAC research.

An important weakness of this study is that the analysis was limited to GenTAC participants who were *survivors* of proximal aortic surgery at the time of enrollment. The study therefore underestimates the effects of out-of-hospital death, as well as the higher operative morbidity and mortality associated with acute dissection and emergency repair. In contemporary series, surgical repair of acute type A aortic dissection has been associated with postoperative mortality rates of 15% to 28%.^{13,14,17,25,26} In addition, we did not include perioperative complications of surgery among the outcomes we studied. Another

important limitation of our study is that imaging follow-up was incomplete. This study may underestimate the true incidence of chronic dissection involving the distal aorta in patients undergoing emergency surgery because the Registry relies on patient imaging reports that do not necessarily describe aortic morphology in a systematic fashion. Phase II of the GenTAC Registry, which will include follow-up for each enrolled patient and an imaging core resource, is expected to address these issues to a large degree and to facilitate more detailed studies of event rates and the behavior of the distal aorta in postoperative patients with Marfan syndrome.

CONCLUSIONS

Despite these limitations, this study reveals the wide-ranging, long-term implications of emergency dissection repair in patients with Marfan syndrome with regard to the extent of aortic root resection, status of the distal aorta, and quality of life. Conversely, elective aortic root replacement was found to be effective prophylaxis against the early, life-threatening risks associated with proximal aortic dissection, as well as the late effects of chronic dissection on the distal aorta. These findings emphasize the importance of aortic surveillance and timely elective aortic root aneurysm repair for patients with Marfan syndrome.

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