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Family History of Severe Cardiovascular Disease in Marfan Syndrome Is Associated With Increased Aortic Diameter and Decreased Survival

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Objectives. **We attempted to determine whether a family history of severe cardiovascular disease in patients with the Marfan syndrome is associated with increased aortic dilation or decreased survival, or both.**

Background. **The prognostic importance of a family history of severe cardiovascular disease in patients with the Marfan syndrome has been incompletely examined. We hypothesized that such a family history would correlate with increased aortic dilation and would be associated with decreased survival.**

Methods. **One hundred eight affected patients and 48 unaffected family members from 33 multigenerational families with the Marfan syndrome underwent echocardiographic measurement of the aortic root, arch and mid-abdominal aorta. Date of birth and age at death ascertained from family pedigrees were used to perform life table analysis and estimate survival.**

Results. **Aortic root and arch diameters were significantly greater in patients with a family history of severe cardiovascular disease than in patients without such a family history. Of subjects in the highest quartile for aortic size, >80% had such a family history in contrast to <10% of those in the lowest quartile (chi-square 57.37, $p < 0.00001$). Mean age at death and cumulative probability of survival were significantly lower in patients with such a family history.**

Conclusions. **Among patients with the Marfan syndrome, aortic dilation is greater and life expectancy shorter in those with a family history of severe cardiovascular manifestations. These data suggest that such a family history is an important risk factor for cardiovascular events in patients with the Marfan syndrome.**

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Although the Marfan syndrome is a heritable disorder involving several organ systems (1), the cardiovascular complications of the disease are chiefly responsible for its adverse effect on mortality (2,3). Death from aortic aneurysm or dissection (2,4) is the usual cause of a dramatically shortened life span, although survival into middle age and later has become common in recent years (3,5). Nevertheless, the degree of risk for individual patients with the Marfan syndrome remains difficult to evaluate, because the extent of risk for specific cardiovascular events has not been quantified.

In patients with aortic aneurysms not associated with the Marfan syndrome, the degree of aortic dilation has been well correlated with risk of aortic rupture (6). By contrast, in patients with the Marfan syndrome, risk of aortic rupture or dissection and degree of aortic dilation may not depend solely on the degree of dilation (7). Our clinical experience and that of others (8) suggests that sudden death, aortic dissection and cardiovascular surgery in patients with the Marfan syndrome cluster within certain families, whereas other families with this syndrome exhibit only minor cardiovascular abnormalities, such as mitral valve prolapse, or no cardiac disease at all. The present study was designed to examine 1) whether the extent of aortic dilation is increased in patients with a family history of severe cardiovascular manifestations, and 2) whether aortic diameter and family history together provide prognostic information superior to that of either factor alone.

Methods

Study group. Thirty-three multigenerational families with the Marfan syndrome were prospectively evaluated by an investigator before enrollment; a standard clinical protocol approved by the Investigational Review Board of each hospital was utilized 1) to establish the diagnosis of the Marfan syndrome, and 2) to establish suitability for noninvasive echocardiographic studies. Written informed consent was obtained

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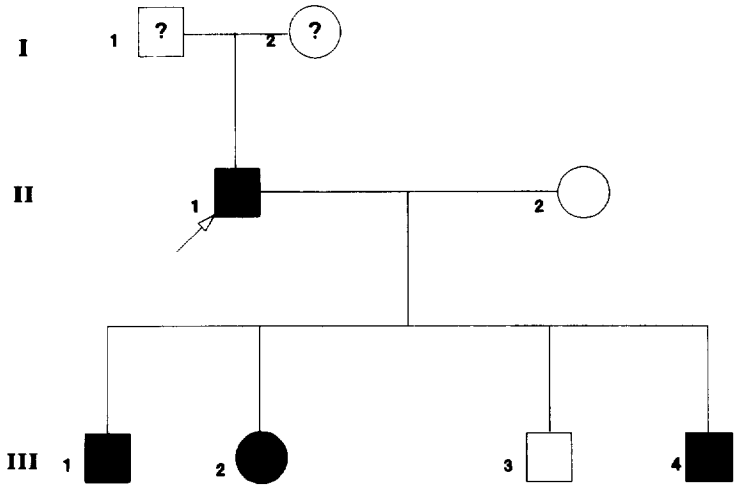


Figure 1. Representative pedigree demonstrating the classification scheme for family history. Subjects II-1, III-1, III-2 and III-4 have the Marfan syndrome (**solid squares** and **circles**). Subject II-1 has had a cardiovascular event (**arrow**) as defined in the text. Subjects III-1, III-2 and III-4 have a positive family history for cardiovascular events, because they have a first-degree relative (Subject II-1) with the relevant history. Subject II-1, however, has a negative family history even though he has had an event, because he has no other known first-degree relative with an event. The status of Subjects I-1 and I-2 are unknown. **Open circles** and **squares** = subjects without the Marfan syndrome; **circles** = female gender; **squares** = male gender.

from all enrolled patients. Initial clinical evaluation included a standardized physical examination, standard anthropomorphic measurements and an ophthalmologic slit lamp examination.

Diagnosis of the Marfan syndrome was based on the presence of typical musculoskeletal, ocular or cardiovascular features and the presence of a family history for the disease, as defined in the Berlin nosology (9). In the absence of a molecular diagnosis for all patients, the clinical diagnosis represented by the Berlin nosology is the best available criterion. For those patients lacking definitive phenotypic characteristics (aortic dilation by quantitative criteria, aneurysm or aortic dissection, dolichostenomelia or ectopia lentis), the presence of a first-degree relative with a definite diagnosis and a major manifestation from at least one affected organ system were considered adequate to make the diagnosis (9). Diagnosis of the Marfan syndrome was verified by at least two investigators working independently. Full musculoskeletal and cardiovascular data were collected for normal family members and were reviewed by an investigator not affiliated with the subject's center of origin to ensure accuracy of diagnosis and prevent misclassification.

For each subject enrolled in the study, a cardiovascular event was defined as 1) nonischemic cardiovascular death; 2) history of aortic dissection; 3) history of cardiac surgery (defined as aortic repair or replacement, aortic or mitral valve surgery alone or in combination, and excluding coronary artery bypass graft surgery). A positive family history of severe cardiovascular disease was defined as the presence of at least one adult first-degree relative with the Marfan syndrome who had experienced a cardiovascular event. A representative pedigree (Fig. 1) demonstrates that subjects with a first-degree relative who had had an event (Subjects III-1, III-2, III-4) were considered to have a positive family history, but that subjects without a known first-degree relative who had had an event (Subject II-1) were considered to have a negative family history, whether or not they had had an event. Subjects who had a family history defined as positive for their relatives but negative for themselves (i.e., Subject II-1 in Fig. 1) served as the index case and were excluded from the analysis of aortic dimension; we followed this procedure to perform as conservative an analysis as possible and to avoid biasing the results in a positive direction (10).

Echocardiographic analysis. Subjects underwent a full Doppler echocardiographic study that included imaging and measurement of the aortic root, ascending aorta, midabdominal aorta and transverse aorta at the left carotid artery. Procedures previously reported were used for proximal aortic measurement and were adapted for more distal segments (11). First-degree unaffected relatives and unaffected spouses of affected patients served as normal control subjects.

Survival analysis. Date of birth for all affected family members and age of death for all deceased family members were obtained retrospectively. The Cutler-Ederer estimate (12) was used to generate survival curves, and the Gehan (Wilcoxon) (13) procedure was used to test for differences between cumulative probability of survival for patients with a positive or negative family history. The relative risk of dying associated with a positive family history risk was estimated by using Cox regression analysis.

A logistic regression model was constructed to examine which factors, if any, were correlated with cardiovascular events. Cardiovascular events (death, aortic dissection or cardiac surgery), were grouped together as the dependent variable. Independent variables included in the model were age, gender, use of beta-adrengic blocking agents and a positive or negative family history. Variables were entered simultaneously. The regression coefficient, significance and odds ratio are reported for each variable in the model.

Other statistical analyses. All data are expressed as mean value ± SD unless otherwise specified. Continuous variables among groups were compared by Kruskal-Wallis analysis of variance. Because of a difference in body size between groups

Table 1. Characteristics of Study Subjects

Subject Status	Marfan Syndrome: Positive FH (n = 64)	Marfan Syndrome: Negative FH (n = 44)	Normal Subjects (n = 48)	p Value
Age (yr)	28 ± 16	32 ± 18	33 ± 15	0.16
Gender (M/F)	31/33	19/25	19/29	0.10
Body surface area (m^2)	1.66 ± 0.44	1.88 ± 0.38	1.79 ± 0.33	0.01*
Systolic BP (mm Hg)	117 ± 15	121 ± 19	124 ± 18	0.23
Aortic root				
Diameter (cm)	3.7 ± .9	3.4 ± 0.7	3.0 ± 0.5	0.002*
Index (cm/m^2)	2.3 ± .6	1.9 ± 0.4	1.8 ± 0.4	< 0.001*
Observed/expected diameter	1.33 ± 0.23	1.13 ± 0.15	1.02 ± 0.13	< 0.0001*
Aortic arch				
Diameter (cm)	2.1 ± 0.7	1.9 ± 0.8	1.9 ± 0.5	0.34
Index (cm/m^2)	1.3 ± 0.5	1.0 ± 0.4	1.1 ± 0.3	0.03*
Abdominal aortic diameter (cm)	1.6 ± 0.4	1.5 ± 0.5	1.5 ± 0.4	0.81
Index (cm/m^2)	1.0 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	0.11
MVP (%)	39	25	2	< 0.001*

*Difference significant. Unless otherwise indicated, values are expressed as mean value ± SD. BP = blood pressure; F = female; FH = family history of severe cardiovascular disease; M = male; MVP = mitral valve prolapse.

of patients with the Marfan syndrome, aortic diameters were also compared after normalizing for body surface area and age. Proportions were compared by using contingency tables. Statistical calculations were performed with the use of SPSS software.

Results

Patient characteristics and analysis of aortic dimensions. Of one hundred fifty-six eligible subjects from 33 families (Table 1), 108 patients had the Marfan syndrome; the remaining 48 family members served as control subjects. Members of 18 families were identified as having a family history of severe Marfan cardiovascular disease; 95% of these patients had musculoskeletal manifestations and 48% had ocular manifestations. Family members from the remaining 15 families were free of severe Marfan cardiovascular disease; 96% of these patients had at least one major musculoskeletal manifestation, 52% had ocular manifestations and 59% had at least mild aortic dilation (≥110% of normal).

Patients affected with the Marfan syndrome with a family history of severe cardiovascular disease did not differ significantly from patients without such a family history with respect to mean age, gender distribution or systolic blood pressure, but they had a smaller body surface area (Table 1). Both groups had significantly greater aortic root and aortic arch diameters than those of normal subjects (Table 1). Aortic arch and transverse aortic diameter were also compared after normalizing for body surface area (Table 1); both dimensions were greater in patients with a positive family history. Abdominal aortic diameter was not significantly increased in either of the two groups of patients with the Marfan syndrome.

To further account for differences in age or body surface area, expected (normal) two-dimensional echocardiographic aortic diameters for all subjects were calculated from values established in a population of normal children and adults (11), and aortic size was expressed as the ratio of observed to expected diameter. Patients with a family history of severe cardiovascular disease had a significantly greater observed/expected aortic diameter ratio than that of patients without such a family history or normal subjects (Fig. 2, Table 1). Patients with a negative family history also had a greater observed/expected aortic diameter ratio than that of normal control subjects.

To further examine whether increased aortic root size was correlated with a family history of severe cardiovascular manifestations, we classified the entire study group into quartiles according to aortic size (normalized for age and body surface area as before). Patients with the Marfan syndrome and a family history of severe cardiovascular disease comprised >75% of subjects in the quartile of greatest aortic diameter (Fig. 3) but <10% of subjects in the lowest quartile (chi-square = 57.37, $p < 0.00001$). Patients without a family history of severe cardiovascular disease were equally distributed among the four quartiles (Fig. 3).

A significantly greater proportion of patients with a family history of severe cardiovascular disease were taking beta-adrenergic receptor antagonists (41% of patients with a positive family history in contrast to 21% of patients with a negative family history at the time of initial evaluation, chi-square = 4.83, $p = 0.027$). Distribution of specific beta-blockers and mean dose was similar in these two groups of patients (Table 2).

Survival analysis. To examine the relation between a family history of severe cardiovascular disease and survival, survival curves and mean age at death for patients with and without such a family history were calculated. Date of birth for all affected subjects and age at death for all deceased members

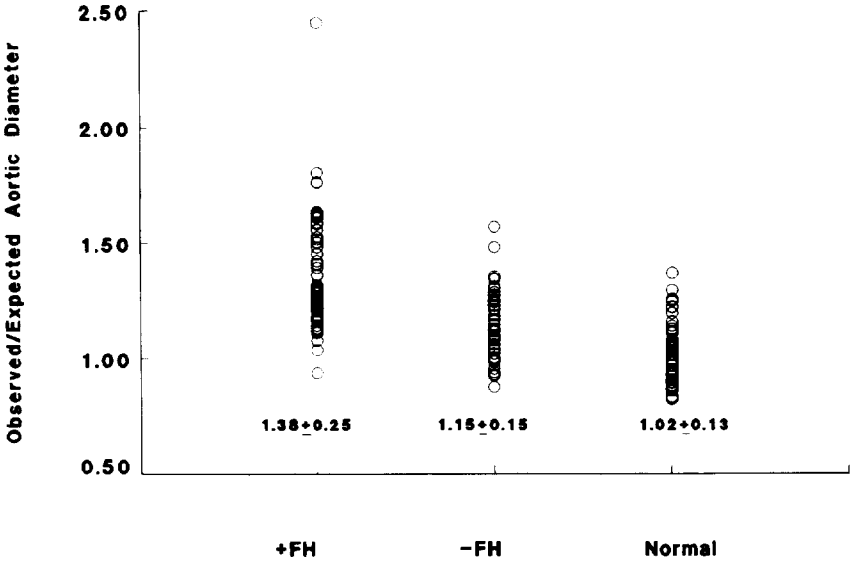
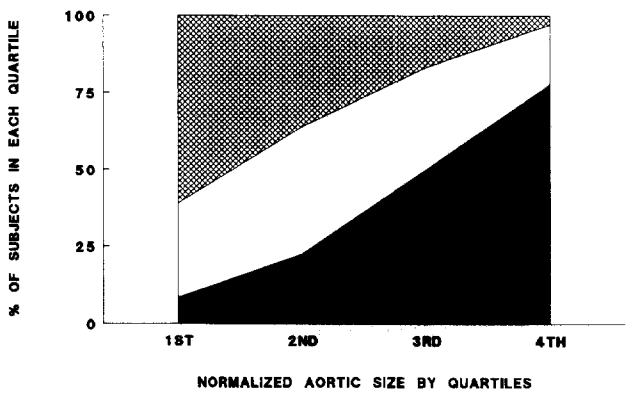


Figure 2. Distribution of aortic root normalized for body surface area among patients with the Marfan syndrome with a positive (+FH) or negative (−FH) family history of severe cardiovascular disease and normal control subjects. The difference between patients with the Marfan syndrome with a positive family history and the other two groups is highly significant.

were available for 221 family members, including members who did not participate in the echocardiographic study. Since 1970, 26 patients have died; 18 of these had a family history of severe cardiovascular manifestations, and 8 did not. Mean age at death was 38 ± 18 years for those with a positive family history in contrast to 65 ± 20 years for those with a negative family history ($p = 0.002$, 95% confidence intervals (CI) for the difference = −43 to −11 years). The age at which 50% of the subjects are projected to have died (median survival, Fig. 4) was estimated at 68 years for patients with the Marfan syndrome with a family history of severe cardiovascular disease and 74 years for those without such a history (Gehan statistic = 9.15, $p = 0.025$). The relative risk of dying before age 65 for patients with a positive family history was 2.6 times the risk for patients with a negative family history ($p = 0.023$, 95% CI 1.40 to 4.83).

Figure 3. Analysis by quartiles of increasing aortic size. The graph demonstrates the proportion of patients with the Marfan syndrome with a positive (**solid area**) or negative (**open area**) family history of cardiovascular manifestations and normal subjects in each quartile. Patients with the Marfan syndrome from severely affected families constitute >75% of the highest quartile and <10% of the lowest quartile. **Crosshatched area** = normal subjects.



A total of 47 patients had a cardiovascular event (cardiovascular death, dissection or surgery); the logistic regression model identified increasing age and a positive family history as significantly associated with events, in that order (Table 3). Beta-blocker use was significantly associated with a *decreased* probability of events.

Discussion

This study demonstrates that both the degree of aortic dilation and the length of the dilated segment are greater in patients with the Marfan syndrome who have a family history of severe cardiovascular disease (Table 1). Affected patients with such a family history also have a shorter life span than that of patients from families with mild cardiovascular disease (Fig. 4). The absence of major clinical cardiovascular complications in multiple generations of those families without a family history of severe cardiovascular manifestations argues strongly against any misclassification of families. Furthermore, the criteria used to define family history were conservative; a first-degree relative with severe cardiovascular disease was required to establish a family history for succeeding members, and index cases were not analyzed to avoid ascertainment bias (10).

Table 2. Distribution of Type and Dose of Beta-Adrenergic Blocking Agents

	Positive FH		Negative FH	
Agent	%	Dose (mg)	%	Dose (mg)
Atenolol	42	54 ± 33	50	65 ± 46
Nadolol	40	44 ± 26	44	39 ± 11
Metoprolol	6	...	0	...
Propranolol	12	...	6	...
Total	100		100	

Data are presented as percent of patient group or mean value ± SD. FH = family history of severe cardiovascular disease; ··· = not known.

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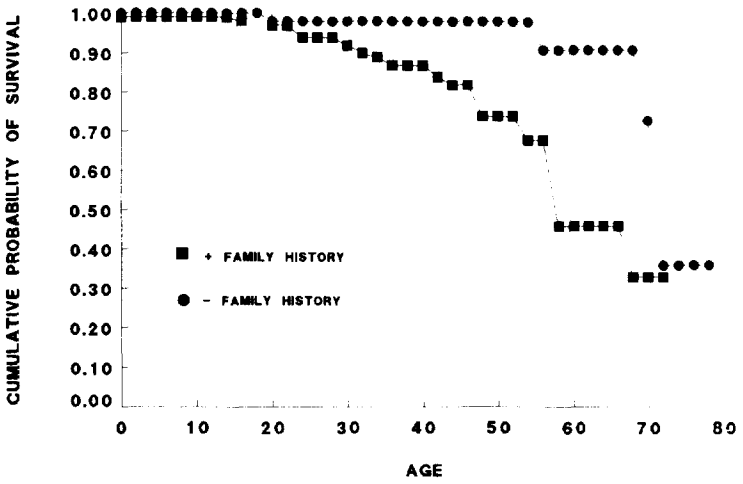

Figure 4. Cumulative probability of survival for patients with the Marfan syndrome from families with a positive (+) or negative (−) family history of severe cardiovascular disease. The median probability of survival is significantly increased in patients with a negative family history. Age is shown in years.

In genetics, dichotomous phenotypic characteristics are ideal variables for segregation analysis; an offspring has either brown eyes or blue eyes, brittle bones or normal bones. In other words, inheritance of traits that follow an "all-or-none" pattern can be delineated with greatest facility and accuracy. For continuous variables, such as the pattern and extent of aortic dilation, segregation analysis is more daunting, because inevitable overlap between groups confounds precision. Furthermore, because aortic dilation in the Marfan syndrome may not occur in childhood, and may not produce morbidity until adolescence or later, younger patients are sometimes difficult to characterize. Nevertheless, several methods of analysis support the hypothesis that families with severe cardiovascular disease are a distinct subgroup that can be identified by the presence of a family history of nonischemic cardiac death, aortic dissection or aortic valvular surgery in combination with severe and diffuse aortic dilation. However, the absence of aortic dimensions obtained before death or cardiac surgery in some patients precluded accurate assessment of aortic diameter as an independent risk factor for cardiovascular events for the entire population of our family history study.

Our finding that the length of the dilated aortic segment was greater in patients with a positive family history agrees with a recently published report (5) that aortic dilation limited to the sinuses of Valsalva in patients with the Marfan syndrome carries a less malignant prognosis than aortic dilation that extends to the aortic arch. Taken together, these two reports suggest that the pathogenesis of aortic disease in patients with this syndrome is related not only to the degree of aortic dilation but also to the length of the affected segment.

Table 3. Logistic Regression Model of Variables Possibly Associated With Cardiovascular Events in Patients With the Marfan Syndrome

Variable	r	p Value	Odds Ratio	95% CI
Family history of severe cardiovascular disease	0.12	0.030*	1.53	1.03–2.27
Beta-blocker use	−0.12	0.026*	0.66	0.43–0.95
Age	0.21	0.001*	1.03	1.03–1.08
Gender	0.0	0.31	0.73	0.49–1.08

*Significant difference. CI = confidence interval; r = regression coefficient.

The molecular basis underlying the Marfan syndrome is an abnormality in the structure of elastin-associated microfibrils, which are distributed in sites affected by the disease. Fibrillin, a 350-kilodalton glycoprotein that is a major structural component of elastin-associated microfibrils, is decreased or abnormal in patients with this syndrome (14). The nucleotide sequence of the *FBN1* gene, which has been localized to the long arm of chromosome 15 (15,16), is composed of multiple cysteine-rich epidermal growth factorlike repeats. Several mutations have been identified within the *FBN1* gene in patients with the Marfan syndrome (17–19). Further research is needed to determine whether specific mutations or types of mutations within the *FBN1* gene correlate with severity of cardiovascular disease.

At present, management of cardiovascular disease in patients with the Marfan syndrome consists primarily of therapy with beta-adrenergic receptor antagonists (20,21), regular echocardiographic follow-up to detect and quantify progression of aortic dilation, and prophylactic aorta and valve replacement when the short-term risk of dissection or severity of aortic regurgitation are sufficient to justify the risk of operation. Identification of those patients at highest risk for aortic disease could facilitate clinical management, allowing for appropriate intervention to prevent or delay significant aortic dilation. Such intervention might have an especially favorable impact on prognosis in patients with the Marfan syndrome most at risk for severe cardiovascular manifestations of the syndrome.

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