TABLE I Results for All Measurements with 10 ms QRS Supplements (dQRS) Interpolated to Emphasize Quantified Change to QTa from Baseline QT Durations

Number of Subjects	QRS (ms)	HR (beats/min)	RR (ms)	RR	QT (ms)	QTc (ms)	dQRS (ms)	QTa (ms)	QTac (ms)
40	70	75.4 ± 3.6	782 ± 0.03	0.88 ± 0.01	358 ± 0.01	409 ± 0.01	10	388 ± 0.01	445 ± 0.01
40	80	74.1 ± 2.9	792 ± 0.02	0.88 ± 0.01	373 ± 0.01	425 ± 0.00	10	393 ± 0.00	447 ± 0.00
40	90	75.3 ± 3.3	785 ± 0.03	0.88 ± 0.01	387 ± 0.01	437 ± 0.00	10	397 ± 0.01	449 ± 0.00

Values are expressed as mean ± SD.
dQRS = supplement to QRS; HR = heart rate; QTa = adjusted QT; QTac = corrected adjusted QT; QTc = corrected QT interval.

QRS of 80 ms, and 15 of the 40 subjects with a baseline QRS of 70 ms to which 10 ms was added, QTac remained normal (Table II).

It is not clear to what extent our experimental supplementation of the QRS represents reality, because under abnormal conditions inapparent QRS changes might accompany clinical T-wave changes. (It is possible that an increase in QRS duration could merge with the onset of the T wave, prolonging the entire QT interval.) Yet in patients with new QT changes, measurable new QRS changes are exceptional, since most disease states and most pharmacologic agents affecting QT intervals appear to be restricted to ST-T (JT) changes.[4] What is clear is that increasing QRS time within the normal QRS duration produced abnormal QTc increases (QTac in this experiment) in the majority (86 of 120) of subjects. Thus, compared with longer normal QRS duration, patients with shorter normal QRS duration can have greater QT increases before the QTc becomes abnormally prolonged. This strengthens the case for using the JT interval rather than the QT interval. Our investigational approach to QT has been "in vitro," designed to stimulate conceptual reconsideration of the QT interval because of its considerable clinical, physiologic, and pharmacologic importance. Patients with shorter normal QRS durations appear to have more "slack" in their QT intervals than those with longer QRS time before an abnormally increased QT becomes apparent. Thus, the QRS duration is a potential confounding factor when comparing patients for physiologic, pharmacologic, and pathologic QT interval changes, strengthening the case for new standards based on the JT interval.

TABLE II Results of QTac with 10 ms Added

Number of Subjects	QRS	10 ms Added	QTac Abnormal	QTac Normal
40	70	10	25	15
40	80	10	29	11
40	90	10	32	8
120			86	34

QRS duration significantly affects QT measurement, even within the normal range of QRS. Baseline QRS of 100 ms permits less slack than QRS of 70 ms before showing the QT effect of QT-prolonging influences, strengthening the case for substituting JT for QT interval.

Since this work was accepted, Zareba et al (Zareba W, Moss AJ, le Cessie S. Dispersion of ventricular repolarization and sudden cardiac death in ischemic heart disease (abstr). *J Am Coll Cardiol* 1994;23:148A.) demonstrated that JT, but not QT, dispersion is a strong independent predictor of sudden cardiac death.

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Effect of Beta-Adrenergic Blockade on Aortic Root Rate of Dilation in the Marfan Syndrome

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Cardiovascular complications, especially aortic root dilation and rupture, are the major causes of morbidity and mortality in the Marfan syndrome.[1–8] Beta-adrenergic blockade therapy to retard the rate of dilation of the aortic root has been suggested as a method of treatment.[9] The optimal dose of the β-adrenergic blocker and the progression or cessation of aortic root dilation on therapy have not yet been established. We compared 2 therapeutic approaches and their effect on the aortic root rate of enlargement.

This study included patients from the Johns Hopkins Hospital (JHH) and the University of Tennessee (UT)

TABLE I Demographic and Echocardiographic Findings

	A	A vs B	B	B vs C	C	A vs C
	JHH (n = 80)	p Value	UT (n = 20)	p Value	Control (n = 13)	p Value
Male (%)	56 (70)	NS	13 (65)	NS	7 (54)	NS
Age at therapy start (years)	10.4 ± 3.4	<0.005	14.1 ± 3.4	<0.009	10.2 ± 4.6	NS
Age at last follow-up (years)	15.8 ± 6.5	NS	18.5 ± 4.8	NS	15.7 ± 4.3	NS
Duration of follow-up (years)	5.5 ± 2.7	NS	4.2 ± 2.1	NS	5.7 ± 1.8	NS
Initial height (cm)	151 ± 31	<0.0009	177 ± 18	<0.01	146 ± 37	NS
Final height (cm)	174 ± 22	NS	181 ± 16	NS	149 ± 69	<0.04
Initial weight (kg)	41.2 ± 20.4	<0.0002	61.3 ± 19.6	<0.02	37.8 ± 20.9	NS
Final weight (kg)	58.6 ± 19.9	<0.02	71.3 ± 26.1	NS	61.0 ± 24.4	NS
Initial body surface area (m^2)	1.34 ± 0.48	<0.005	1.70 ± 0.53	<0.02	1.27 ± 0.41	NS
Final body surface area (m^2)	1.72 ± 0.40	<0.05	1.92 ± 0.37	<0.05	1.66 ± 0.33	NS
Initial aortic root diameter (mm)	31.1 ± 7.0	NS	34.0 ± 5.4	NS	31.3 ± 7.4	NS
Final aortic root diameter (mm)	37.0 ± 8.6	NS	35.5 ± 7.4	<0.05	42.4 ± 11.1	<0.05
Aortic root growth rate (mm/year)	1.1 ± 1.1	NS	0.7 ± 1.8	<0.03	2.1 ± 1.6	<0.006
Initial aortic root indexed (mm/m^2)	25.2 ± 7.2	<0.003	19.7 ± 4.1	<0.003	26.5 ± 7.9	NS
Final aortic root indexed (mm/m^2)	22.2 ± 5.1	<0.02	19.0 ± 4.6	<0.002	26.0 ± 6.8	<0.02
Aortic root rate of growth ($mm/year/m^2$)	–0.7 ± 1.0	<0.025	0.0 ± 1.5	NS	0.0 ± 1.2	<0.05
Beta-blocker dose (mg/kg/day)	1.3 ± 0.9	<0.008	1.9 ± 0.6	—	0	—

JHH = Johns Hopkins Hospital; UT = University of Tennessee.

(LeBonheur Children's Medical Center). The Marfan syndrome diagnosis was based on standard criteria.[1] We reviewed the charts of all patients diagnosed as having the Marfan syndrome who were initially evaluated at the JHH between 1978 and 1990 and at UT between 1986 and 1992, and who had been evaluated at least once during 1991 to 1992. Patients who had their first visit after reaching age 21 years were not included. None of the patients participated in the formal randomized, prospective trial of propranolol conducted at JHH.[9] During this period, all patients with the diagnosis of the Marfan syndrome were considered for chronic β-adrenergic blockade. Reasons for not prescribing either propranolol or atenolol included history of bronchospasm requiring treatment more than once per year, treatment for diabetes mellitus, severe ventricular dysfunction, resting bradycardia <50 beats/min, and patient or parental refusal.

According to the JHH treatment protocol, the initial dose of the β-adrenergic blocker was 0.5 to 1.0 mg/kg/day and was increased, in increments of 20 to 40 mg of propranolol or 12.5 to 25 mg of atenolol, until adequate β blockade was achieved on the basis of an exercise challenge. Patients aged >5 years were asked to run up and down 2 flights of stairs. The heart rate was measured at the end of this stressor. A heart rate >110 beats/min immediately after exercising indicated a need for an increase in the dose of the β-adrenergic blocker. During the initial period of therapy, frequent follow-up (every 4 to 6 weeks) was required to determine the optimal dose.

The UT treatment protocol included initial evaluation of the patient by a geneticist (JCW) to establish the diagnosis. Cardiac evaluation included a complete history and physical examination, exercise stress test, and 2-dimensional echocardiography including color and continuous-wave Doppler performed on the initial visit. Follow-up visits were at 6 weeks after initiation of therapy and at 6-month intervals thereafter. Maximal exercise stress testing on a cycle ergometer was performed by all patients aged >6 years before the start of therapy and at 12-month intervals thereafter. Atenolol dose, begun at 1 mg/kg/day divided into 2 doses, was increased until maximal exercise heart rate decreased by 30 to 40 beats/min or to about 80% of the baseline maximal heart rate. The goal was to increase the dose to approximately 2 mg/kg/day. The dose was increased until the patient developed clinically unacceptable side effects, reached 2 mg/kg/day, or the exercise heart rate goal described was attained.

The control group was composed of patients at JHH who could not or would not take β-adrenergic blockade therapy and were followed prospectively.

Cross-sectional echocardiography was used to determine the region of the aortic root with the greatest diameter; an M-mode tracing was made of this region and the aortic root diameter measured.[10] Computerized tomography or magnetic resonance imaging were performed when thoracic deformity precluded accurate echocardiographic measurements.

Data are reported as mean ± SD. The chi-square test was performed to evaluate male to female and black to white ratios among the different groups. Mean values of the UT, JHH, and control groups were compared by Student's t test. Analysis of variance was used to evaluate the mean aortic root diameter for age and body surface area. The aortic root versus age formula was derived from polynomial analysis. A p value <0.05 was considered statistically significant.

A total of 113 patients formed the study population, 20 treated patients from UT, 80 treated patients from JHH, and 13 untreated patients from JHH. The black to white ratio was 9 to 11, respectively, for the UT group and 4 to 75, respectively, for the JHH group (p <0.0001). One patient was an Oriental male.

The clinical, demographic, and echocardiographic data at the initial and most recent evaluations (preoperative where pertinent) are summarized in Table I. There was no significant difference in male to female ratio among the 3 groups. The mean age at the initia-

tion of therapy was higher for the UT group than for both of the JHH groups. However, because of a longer follow-up for the JHH groups (although not statistically significant), the difference in age diminished at the last follow-up. Likewise, the size of the patients, as evident from their height, weight, and body surface area measurements, was significantly different between the UT and the JHH groups at the initiation of therapy (Table I). This difference was still significant at the last evaluation.

The dose of the β-adrenergic blocker was significantly higher in the UT group. Propranolol was the initial β-adrenergic therapy in 10 patients of the JHH treated group. Atenolol was subsequently used in 9 of these patients. Only 1 patient was receiving propranolol at the last evaluation. These patients were similar to the other 70 patients who did not receive propranolol in age, height, weight, and aortic root diameter at the initial and final evaluation. The β-blocker dose was significantly larger in the propranolol than in the nonpropranolol groups both at the initiation of therapy and at the last follow-up (initial: 2.0 ± 1.0 vs 0.9 ± 0.8 mg/kg/day, respectively, $p < 0.0005$; final: 2.1 ± 1.3 vs 1.2 ± 0.7 mg/kg/day, respectively, $p < 0.003$).

The mean aortic root diameter was similar among the 3 groups at the initial measurement. At the last evaluation, the mean aortic diameter in the control group was significantly larger than that in either treated group. The aortic root rate of dilation for the control group was 2.1 ± 1.6 mm/year, which was significantly different from the UT (0.7 ± 1.8 mm/year, $p < 0.03$) and JHH (1.1 ± 1.1 mm/year, $p < 0.006$) groups. There was no significant difference in the annual rate of aortic root dilation between the UT and JHH groups. The rate of aortic root dilation for all 3 groups had no significant correlation with the initial aortic root diameter or the initial indexed (mm/body surface area [m^2]) aortic root diameter.

The mean indexed aortic root size at the initiation of therapy was significantly smaller in the UT group (19.7 ± 4.1 mm/m^2) than in the other groups (JHH, 25.2 ± 7.2 mm/m^2; control 26.5 ± 7.9 mm/m^2, $p < 0.003$). The JHH treated group and the control group had similar mean indexed aortic root diameters at the initiation of therapy. The mean indexed aortic root diameter for the JHH treated group at the most recent follow-up was significantly smaller than its value at the initiation of therapy (22.2 ± 5.1 mm/m^2, $p < 0.0001$). In contrast, the indexed diameter did not decrease in either the UT or the control group.

Five patients required an aortic valve–ascending aorta composite graft replacement in the JHH treated group. These patients were similar to the other 75 patients who did not require surgery in age, height, weight, body surface area, and follow-up duration. The initial and final aortic root diameters in the surgically treated group was significantly larger than in the remaining patients in the JHH treated group (initial 42.0 ± 5.2 vs 30.3 ± 6.5 mm, $p < 0.0003$; final 59.2 ± 4.2 vs 35.5 ± 6.5 mm, $p < 0.0001$, respectively). The indexed aortic root diameter tended to be larger in the surgical than in the nonsurgical group at the initiation of therapy but was not significantly different (29.1 ± 5.8 vs 25.0 ± 7.3 mm/m^2, $p > 0.2$, respectively), and became significantly larger in the surgical group before surgery (31.5 ± 2.5 vs 21.5 ± 4.6 mm/m^2, $p < 0.0001$). The dose of β-adrenergic blocking therapy was significantly larger in the surgical group at the initiation of therapy (1.4 vs 1.0 mg/kg/day, $p < 0.05$) and at the last follow-up before surgery (2.5 vs 1.2 mg/kg/day, $p < 0.0001$). When these 5 patients from the JHH group were excluded, the results of any of the analyses were not altered.

Figure 1 displays the relation of aortic root diameter to age of the 100 treated patients. Each patient is represented by several data points. The equation that best fits these data for age (in years) versus aortic root diameter is: aortic root (mm) = $0.0004\ (age)^4 - 0.026\ (age)^3 + 0.501\ (age)^2 - 2.525\ (age) + 28.933$. There was a rapid increase in aortic root diameter during prepubertal and early pubertal years. The maximal rate of increase, as evident from the slope of the curve, occurred during years 6 to 14. There was continued enlargement in the aortic root after 15 years of age; however, it was at a slower rate than during the childhood years.

The aortic root diameter versus body surface area is plotted in Figure 2. The regression equation with 95% prediction intervals, derived from Henry et al,[11] for nor-

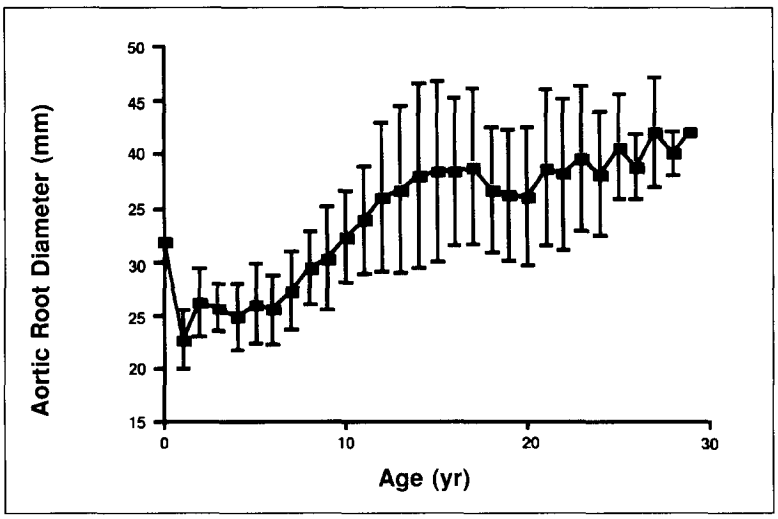

FIGURE 1. The relation between aortic root diameter and age in patients with the Marfan syndrome receiving β-adrenergic blockade therapy. *Boxes* indicate the mean aortic root; *Bars* are 1 SD from the mean.

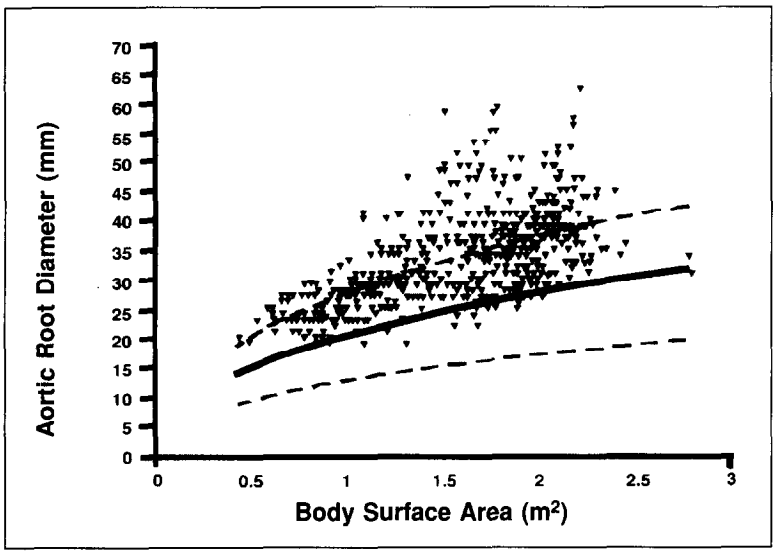

FIGURE 2. Aortic root diameter in the study patients. M-mode echocardiographic aortic root dimension measurements are plotted against the body surface area. *Solid line* and *dashed lines* indicate the mean values and 95% prediction intervals, respectively, for aortic root dimension in normal children according to Henry et al.[11]

mal children that predicts aortic root diameter from age and body surface area is: 24.0 (body surface area$^{1/3}$) + 0.1 (age) – 4.3 ± 18%. The normal values plotted on this graph are derived from each patient's age and body surface area at the time his or her corresponding aortic root diameter was measured. In our study group, the regression equation was: 38.3 (body surface area$^{1/3}$) – 9.6. The mean aortic root diameter in the patients with the Marfan syndrome was at or above the 95th percentile for normal children with the same body surface area and age.

Our data indicate that aortic root dilation occurs throughout life in the patient with the Marfan syndrome. The rate of dilation is accelerated during early childhood and adolescent years. To our knowledge, all published data have compared aortic root to body surface area, not to age, so actual comparison to normative data based on age is difficult. Nonetheless, there is clear evidence that the aorta is dilated in some very young patients with the Marfan syndrome.[12,13] The mean aortic root diameter for our patient population at any given body surface area was at or above the 95th percentile of the confidence interval for aortic root diameter in normal persons. Data herein demonstrate the wide variability in the observed aortic root diameter. Differences in aortic root diameter are but one aspect of the extensive clinical variability in all organ systems affected by the Marfan syndrome. The 5 patients who required aortic surgery had larger aortic root diameters at initial evaluation even though they were similar, on average, to the other patients in their clinical and demographic features. The initial aortic root diameter did not correlate with the rate of dilation in any of the treatment or control groups. Other factors (i.e., other than the absolute size of the root) may be involved in determining the progression of aortic root dilation. Recently, Roman et al[14] suggested that generalized, rather than localized, aortic root dilation was associated with an increased incidence of complications and an accelerated rate of dilation. We did not evaluate this aspect in the current study. The type of β blocker given in our study did not appear to have a significant impact on reduction in aortic root dilation. The larger dose of propranolol compared with atenolol is probably a reflection of the different potency of the 2 drugs.

In conclusion, we evaluated the efficacy of chronic β-adrenergic blockade in 2 different groups of patients with the Marfan syndrome by comparing them with patients who did not receive any therapy. The greatest rate of aortic root dilation was observed in the group that did not receive any therapy. The treatment did not affect somatic growth. Treatment at a younger age blunted the rate of aortic root growth to a greater extent, so that the indexed aortic root size decreased during follow-up. The larger dose may produce a slower rate of aortic root growth when data from a larger number of patients are analyzed. However, treatment did not normalize the aortic root index.

We recommend that patients with the Marfan syndrome should begin β-adrenergic blocker therapy at the earliest age possible and that the dose be adjusted to the largest dose that is clinically tolerated. Our centers differ with respect to the size of the aorta at the time of recommending onset of therapy. The JHH criteria do not include a size cutoff. The UT experience and recommendation is to treat children with aortic size at or above the 95th percentile.

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On-line Quantification of Left Ventricular Volumes and Ejection Fraction by Automated Backscatter Imaging–Assisted Boundary Detection: Comparison with Contrast Cineventriculography

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Two-dimensional echocardiography is a precise and reproducible noninvasive technique for estimating cardiac dimensions and volumes and for quantifying left ventricular (LV) ejection performance. In practice, however, ventricular volumes and function are usually appreciated only qualitatively. This is mainly due to the impracticability of the off-line quantification from videotape recordings, which is time-consuming, observer-dependent, and necessitates meticulous frame-by-frame analysis as well as sophisticated quantification software programs. An echocardiographic automated boundary detection (ABD) system, based on ultrasonic backscatter imaging, has recently been developed and permits on-line and real-time quantification of cardiac chamber dimensions and function.[1] Initially set up only for evaluation of cross-sectional areas, this system now allows quantification of absolute LV volumes and ejection fraction by use of an algorithm that detects the LV long-axis length and orthogonal diameters and uses a modified single-plane Simpson's method for instantaneous volume determination. In the present study, we sought to evaluate the accuracy of this new method of volume determination in comparison with contrast cineventriculography.

Thirty-six consecutive patients (28 men and 8 women, mean age 57 ± 13 years, range 20 to 73) who underwent 2-dimensional echocardiography with ABD within 24 hours of routine cardiac catheterization and angiography served as subjects in the present study. All patients underwent catheterization because of suspected coronary artery disease. Thirty had significant regional and global LV dysfunction. The only selection criterion for inclusion into the study was sufficient echogenicity from the apical 4- and 2-chamber views to allow adequate delineation of the endocardial borders on the conventional 2-dimensional echocardiograms. Forty-four patients were initially screened for inclusion into the study. Eight (18%) were excluded because of inadequate ABD studies.

Echocardiographic views were obtained with a commercially available Hewlett-Packard Sonos 1500 sonographer by use of a 2.5 MHz wide-angle, phased-array transducer with 64 channels. Images were obtained from the apical 4- and 2-chamber views. Once the highest quality possible conventional 2-dimensional echocardiographic images were obtained, the backscatter imaging boundary detection algorithm was activated. The displayed borders are superimposed over the conventional 2-dimensional images and can be turned on and off to evaluate the adequacy of detection on a frame-by-frame basis. In most patients, minor adjustments in time gain and lateral gain compensation settings and transmit gain control were required to obtain optimal tracking and continuity of the endocardial/blood interface on the superimposed conventional 2-dimensional image. A large irregular region of interest was then drawn by the operator through the midmyocardial echoes around the LV cavity to encompass all portions of the end-diastolic and end-systolic cavity borders. LV volumes were calculated from the apical 4- and 2-chamber views with an algorithm that detects the LV long-axis length and orthogonal diameters and uses a modified single-plane Simpson's method for instantaneous volume determination. End-diastolic and end-systolic volumes and ejection fraction from 3 consecutive beats in the 2 views were averaged and compared with those obtained at contrast cineventriculography (performed during cardiac catheterization from the single-plane 30° right anterior oblique projection, by use of a standard Simpson's method, as previously described[2]).

Mean ± 1 SD were calculated. The relation between volumes calculated by the ABD system and those determined at cineventriculography was analyzed by linear regression and residual plot analysis. Student's t *tests for paired data were used to assess differences in volume calculation between the 2 methods.*

LV volumes ranged from 25 to 283 ml by ABD and from 36 to 303 ml by contrast cineventriculography. LV ejection fraction ranged from 19% to 57% by ABD and from 17% to 67% by contrast cineventriculography.

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