Changes in Aortic Distensibility and Pulse Wave Velocity Assessed With Magnetic Resonance Imaging Following Beta-Blocker Therapy in the Marfan Syndrome

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It has been shown that β-adrenergic blocking agents may reduce the rate of aortic root dilation and the development of aortic complications in patients with the Marfan syndrome. This may be due to β–blocker-induced changes in aortic stiffness, of which distensibility and pulse wave velocity are in vivo measurable derivatives. We studied changes in distensibility at 4 levels of the aorta and pulse wave velocity along the entire aorta after 2 weeks of β-blocker therapy in 6 Marfan syndrome patients and in 6 healthy volunteers, using magnetic resonance imaging (MRI) combined with brachial artery blood pressure measurements. In both groups, mean blood pressure decreased significantly (Marfan: 86 ± 6 vs 78 ± 5 mm Hg, p <0.05; control: 80 ± 8 vs 73 ± 3 mm Hg, p <0.05) (all data expressed as mean ± 1 SD). At baseline, the Marfan syndrome patients exhibited decreased distensibility at the level of the ascending aorta (2 ± 1 vs 6 ± 2 10^{-3}mm Hg^{-1}, p <0.01) and increased pulse wave velocity (6.2 ± 0.4 vs 3.9 ± 0.4 ms^{-1}, p <0.01) compared with control subjects. Only the Marfan syndrome patients had a significant increase in aortic distensibility at multiple levels and a significant decrease in pulse wave velocity after β-blocker therapy (ascending aorta distensibility: 2 ± 1 vs 4 ± 1 10^{-3}mm Hg^{-1}, p <0.05; abdominal aorta distensibility: 5 ± 2 vs 8 ± 3 10^{-3}mm Hg^{-1}, p <0.05; pulse wave velocity: 6.2 ± 0.4 vs 5.0 ± 1.0 ms^{-1}, p <0.05). Thus, aortic stiffness in Marfan syndrome, together with mean blood pressure, is reduced by β-blocker therapy, and MRI is well suited to detect these changes by measuring distensibility and pulse wave velocity. ©1998 by Excerpta Medica, Inc.

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Aortic stiffness in patients with the Marfan syndrome has been almost exclusively investigated by measuring pulsatility of the aorta.[1–8] The ratio of aortic diameter (or area or volume) and pulse pressure yields a derivative for in vivo measurable stiffness, called distensibility. Previous studies showed significantly decreased distensibility of the ascending aorta in patients with the Marfan syndrome when compared with healthy volunteers. Although β-adrenergic blocking agents have been proven to reduce the rate of aortic dilation and the occurrence of aortic complications in patients with the Marfan syndrome,[9,10] the effects on aortic distensibility are still not completely understood and are the subject of some controversy.[1,5,11] The velocity of the pulse wave through the aorta is another measure for aortic stiffness.[12,13] Pulse wave velocity will be infinite in a complete noncompliant (stiff) tube and decreases with decreasing stiffness. Both distensibility and pulse wave velocity can be investigated by magnetic resonance imaging (MRI).[3,7,12,14] The present study evaluates the capability of MRI in assessing aortic stiffness and in examining the effect of β-blocking agents on aortic stiffness, as determined by distensibility at 4 designated levels along the entire aorta and by pulse wave velocity, in patients with the Marfan syndrome and healthy volunteers.

METHODS

Study subjects and protocol: Six subjects who met the criteria of the diagnosis "the Marfan syndrome" according to the revised Berlin criteria[15] and 6 healthy volunteers were studied. None of the study subjects took β-blocking agents or had undergone surgery. Body surface area was calculated from length and height using the formula of Du Bois and Du Bois.[16] The study population characteristics are listed in Table I. After MRI without medication, all 12 subjects received 200 mg of metoprolol or 100 mg of atenolol daily for a period of at least 2 weeks. Metoprolol and atenolol were equally distributed over the 2 populations. MRI then was repeated.

Imaging protocol: Study subjects were placed supine in a 1.5-T MRI scanner (NT15, Philips Medical Systems, Best, The Netherlands). The aorta was imaged in the oblique sagittal plane using a standard

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TABLE I Study Population Characteristics

	Marfan	Control
Men/women	2/4	2/4
Age (yr)	34 ± 7	26 ± 5
BSA (m^2)	2.01 ± 0.16*	1.79 ± 0.16*
Period between scans (yr)	0.5 ± 0.3	0.3 ± 0.3
AA 1 (mm^2/m^2)	385 ± 63*	322 ± 13*
AA 2 (mm^2/m^2)	195 ± 30	190 ± 34
AA 3 (mm^2/m^2)	156 ± 24	148 ± 25
AA 4 (mm^2/m^2)	103 ± 23	112 ± 20

*$p < 0.05$.
AA = aortic area normalized for BSA at the designated levels; BSA = body surface area.

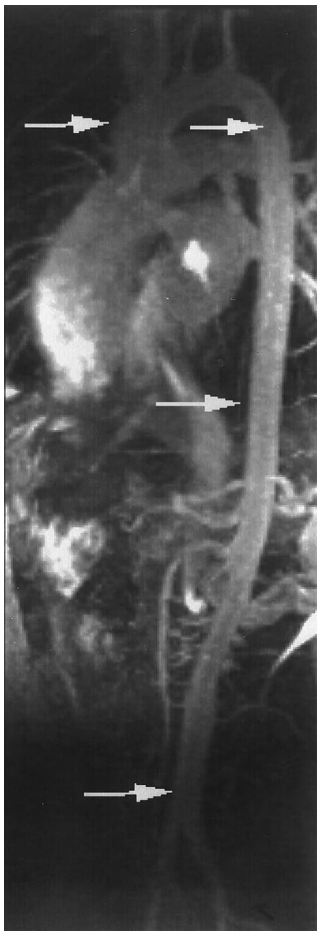

FIGURE 1. Three-dimensional MRI of the aorta. *Arrows* indicate the levels for distensibility measurement. Pulse wave velocity was measured along the entire aorta (from the first *arrow* at the ascending aorta to the *arrow* above the aortic bifurcation).

pulse sequence. A high-resolution gradient-echo pulse sequence with a velocity-encoding gradient (TR = RR interval, TE = 14 ms, matrix size = 256 × 256 mm, field of view = 300 mm, slice thickness = 8 mm, flip angle = 20°) was applied perpendicular to the aorta at 4 levels (Figure 1): at the level of the crossing of the pulmonary artery through the ascending (1) and descending (2) aorta, at the level of the diaphragm (3), and just above the aortic bifurcation (4). This resulted in multiphase image pairs of modulus- and velocity-encoded images with a temporal resolution of approximately 25 ms through the cardiac cycle and a spatial resolution of approximately 1 pixel/mm (Figure 2). All pulse sequences used were triggered on the R wave of the electrocardiogram. Distances between the levels were measured on the console of the MRI scanner by drawing freehand a line through the middle of the aortic lumen in the oblique sagittal images, revealing the long axis of the aorta (Figure 1). During each flow measurement, systolic and diastolic blood pressures were measured using a brachial artery sphygmomanometer cuff.

Image analysis and calculations: A SUN workstation and the FLOW® image analysis software (LKEB, LUMC, Leiden, The Netherlands) were used for image analysis. Aortic contours were drawn manually on the modulus images of all cardiac phases by 2 independent observers and flow (ml/s) through each level was calculated using the velocity values of the corresponding velocity-encoded images (Figure 2). Pulse wave velocity (m/s) was calculated as the ratio of distance between levels and time difference between arrival of the pulse wave at these levels. The pulse wave was considered to "arrive" at a certain level when the mean velocity reached half of its maximum value (Figure 3). A polynomial fit function was applied on the systolic aortic areas to isolate maximal and minimal aortic areas (Figure 4). Distensibility ($mm\ Hg^{-1}$) was calculated by means of the formula:

$$(A_{max} - A_{min})/A_{min} \cdot (P_{max} - P_{min})$$

where A_{max} = maximal (systolic) area (mm^2), A_{min} = minimal (diastolic) area (mm^2), P_{max} = systolic blood pressure (mm Hg), and P_{min} = diastolic blood pressure (mm Hg).

Mean blood pressure was calculated as $(2 \cdot P_{min} + P_{max})/3$.

Statistical analysis: The aortic areas, drawn by the 2 observers, were correlated and interobserver variability was calculated using analysis of variance.

Results are expressed as mean ± SD unless otherwise specified. The effects of β blockade within groups were compared with the paired *t* test. Differences between groups were compared with the unpaired *t* test. A p value <0.05 was considered significant.

RESULTS

Reproducibility of measurements: Figure 5 shows reproducibility of all areas measured (n = 3,257) in this study. A clear linear correlation between the results of 2 observers was found ($R^2 = 0.98$, $p < 0.001$). Interobserver variability was 5%.

Blood pressure and heart rate during MRI examination: No significant changes in mean blood pressure, pulse pressure, or heart rate occurred during the imaging protocol. Mean systolic and diastolic values were used per study subject.

Differences between and within groups: Differences in distensibility and pulse wave velocity between and within groups are shown in Table II. Significant dif-

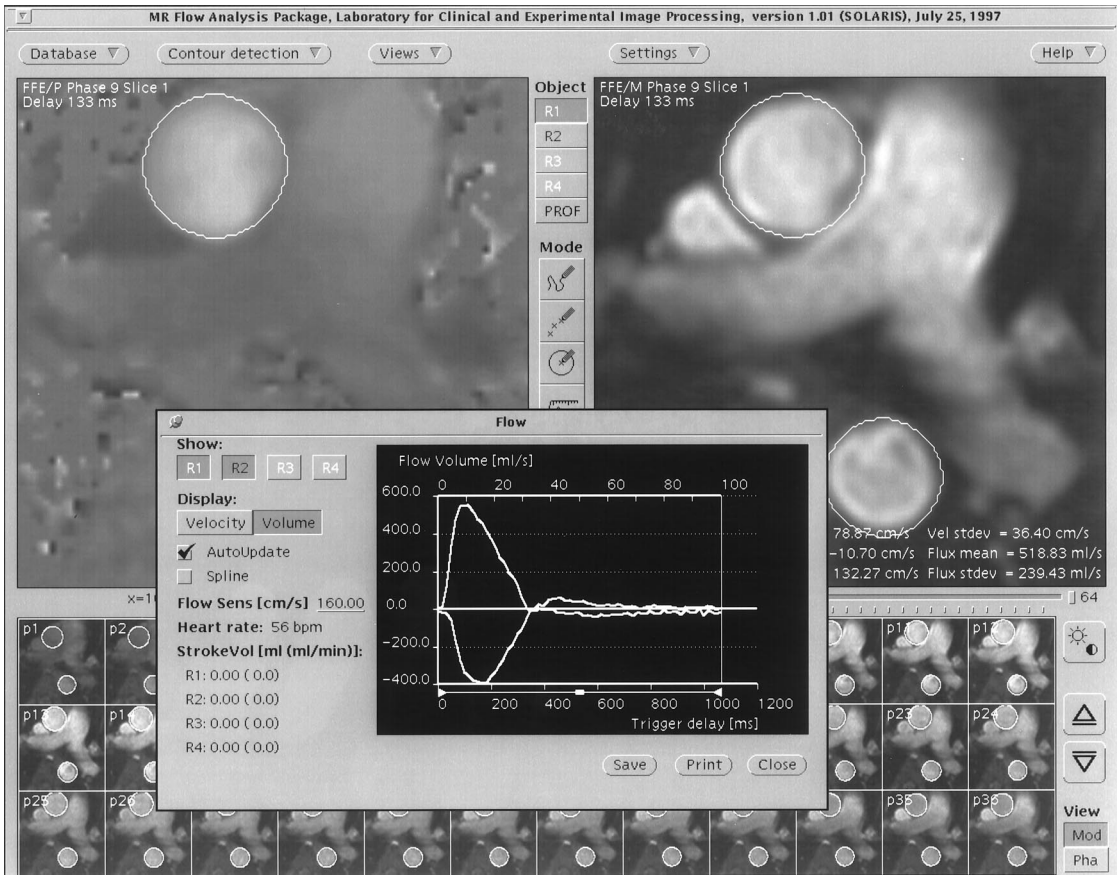

FIGURE 2. Analysis of contours with the FLOW software package. An axial plane at the level of the *upper arrows* in Figure 1 through the ascending and descending aorta is shown. Contours of the ascending *(upper circle)* and descending *(lower circle)* aorta are drawn on the *right-sided (modulus) image,* encompassing the velocity-encoded area on the *left-sided (phase) image.* Mean velocity and flow can be calculated.

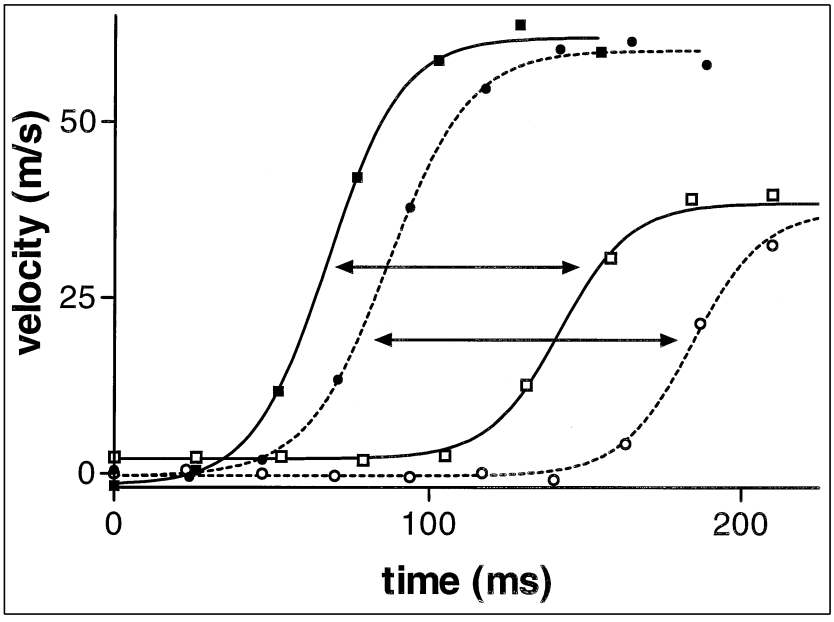

FIGURE 3. Measurement of pulse wave velocity before *(solid line; closed squares:* level 1, *open squares:* level 4) and after *(dotted line; closed circles:* level 1, *open circles:* level 4) β-adrenergic blockade. Clearly, it takes longer for the pulse wave to reach level 4 after β blockade.

ferences in distensibility at the level of the ascending aorta and pulse wave velocity at baseline are shown. Both groups showed a significant decrease in mean blood pressure. The Marfan group showed increased distensibility at levels 1 (ascending aorta) and 4 (abdominal aorta) and decreased pulse wave velocity. Only a significant difference in ascending aorta distensibility remained after β-blocking therapy.

DISCUSSION

In vivo examination of aortic stiffness with MRI: Our study extends the findings of previous studies that MRI enables the in vivo examination of aortic stiffness.[3,7,14] Together with its excellent sensitivity and specificity in visualization of aortic disease, MRI offers the combi-

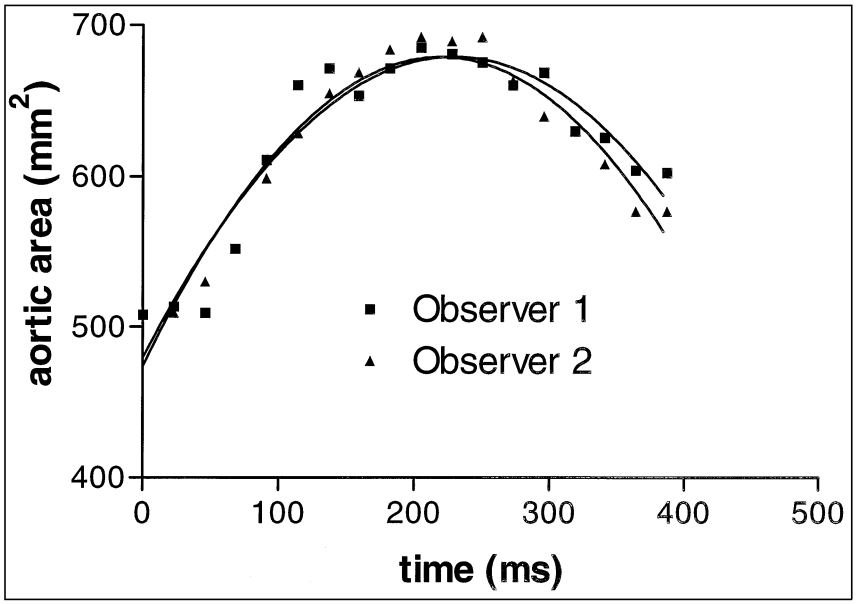

FIGURE 4. A polynominal fit function is applied on the changing aortic area to isolate true maximal and minimal values. Results of the 2 observers are shown.

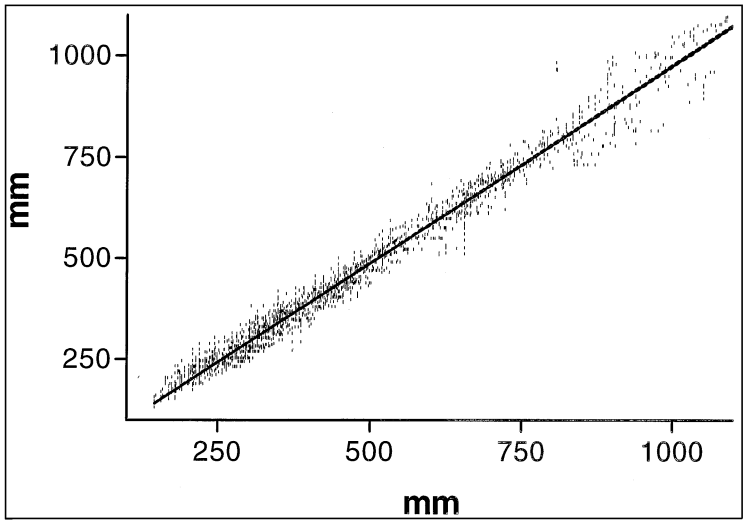

FIGURE 5. Correlation of all measured aortic areas by 2 independent investigators ($R^2 = 0.98$, $p < 0.0001$).

nation of morphologic and functional examination of the entire aorta. With MRI, it is always possible to acquire short-axis images of any part of the aorta, in which aortic area changes can reliably be assessed. Although T1-weighted spin-echo MRI offers the advantage of clear diastolic images,[7] relatively independent of blood flow velocity, a major drawback in distensibility assessment is the need to estimate the time when the maximal systolic area in the artery will be reached, because only 2 images (phases) are generated. With high-resolution gradient-echo MRI, images of all cardiac phases are generated, which facilitates detection of the true maximal area. Moreover, pulse wave velocity can be calculated when a flow-encoding gradient is applied at 2 levels and the distance between these levels is known.[14] However, precautions have to be taken so that a sufficient signal from slow flow during diastole is maintained by choosing a short flip angle (20° to 30°).[17] Because aortic pulse pressure is underestimated when measured with a brachial artery sphygmomanometer cuff,[18] distensibilities could be somewhat lower than reported in the present study. However, almost all other studies used this method because of the advantage of it being a noninvasive procedure.

Differences in aortic stiffness between Marfan patients and controls: Similar to other studies, we showed significant differences in aortic distensibility at multiple levels in the aorta and pulse wave velocity between patients with the Marfan syndrome and healthy volunteers.[1–8] Distensibility values obtained in the present study correspond reasonably with those of other investigators who studied the same age group of patients with the Marfan syndrome (Table III). The high pulse wave velocities[19,20] found by Hirata et al[2] may be explained by the distance from the carotid artery to femoral artery being measured and not the actual length of the aorta.

Changes in aortic stiffness after beta blockade in Marfan patients: In our study, only in the Marfan group was a decrease in mean blood pressure following β-blocker therapy accompanied by an increase in ascending and descending aortic distensibility and a decrease in pulse wave velocity. Because of the pressure-diameter relation of the great arteries,[21] a decrease in mean blood pressure could result in increased distensibility when aortic area changes occur close to the collagen-determined (exponential) part of the pressure-diameter curve. This phenomenon may

TABLE II Comparison Within and Between Groups Before and After β-Blocker Therapy

	Marfan (n = 6)			Control (n = 6)			Differences Between Groups	
	Before	After	p Value	Before	After	p Value	Before	After
MBP	86 ± 6	78 ± 5	<0.05	80 ± 8	73 ± 3	<0.05	NS	NS
D1	2 ± 1	4 ± 1	<0.05	6 ± 2	6 ± 0	NS	<0.01	<0.01
D2	4 ± 2	6 ± 2	NS	4 ± 1	6 ± 2	NS	NS	NS
D3	5 ± 1	7 ± 3	NS	7 ± 1	6 ± 2	NS	NS	NS
D4	5 ± 2	8 ± 3	<0.05	5 ± 2	6 ± 1	NS	NS	NS
PWV	6.2 ± 0.4	5.0 ± 1.0	<0.05	3.9 ± 0.4	4.5 ± 1.4	NS	<0.01	NS

D = distensibility (mm $Hg^{-1} \cdot 10^{-3}$) at the designated levels; MBP = mean blood pressure (mm Hg); PWV = pulsewave velocity ($m \cdot s^{-1}$).

TABLE III Aortic Stiffness: Comparison Among Different Investigators

Study	Age	ATA	DTA	DAA	PWV	Method
Savolainen et al[3]	11	4	3	NP	NP	GRE MRI
Reed et al[4]	14	8	NP	NP	NP	TTE
Jeremy et al[6]	26	3	NP	NP	6.2	TTE
Hirata et al[2]	26	4	NP	6	11.6	TTE
Franke et al[8]	28	NP	6	NP	NP	TEE
Haouzi et al[1]	32	2	NP	NP	NP	TTE
Groenink et al (present study)	34	2	4	5	6.2	GRE MRI

Age = mean age of the study group (yr); ATA = ascending thoracic aortic distensibility (10^{-3} mm Hg^{-1}); DAA = descending abdominal aortic distensibility (10^{-3} mm Hg^{-1}); DTA = descending thoracic aortic distensibility (10^{-3} mm Hg^{-1}); GRE MRI = gradient-echo MRI; NP = Not performed; PWV = pulsewave velocity (ms^{-1}); TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

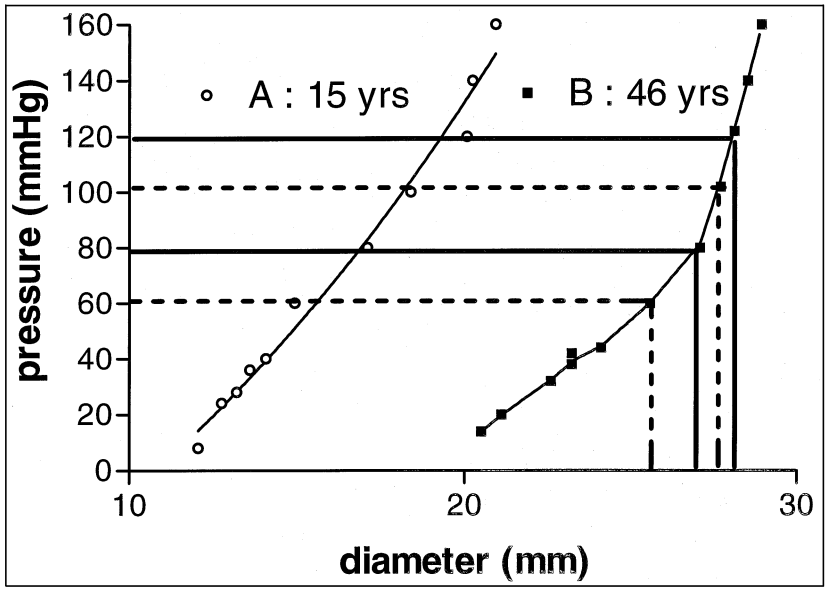

FIGURE 6. Curves of the aortic pressure-diameter relation in a younger subject (A) and an older subject (B) and the influence of lowering of blood pressure on distensibility. *Solid lines* indicate the aortic diameter change at a blood pressure of 120/80 mm Hg. Lowering of the blood pressure to 100/60 mm Hg *(dotted lines)* will result in an increase in diameter change in subject B, because the working area is shifted to the linear part of the curve. This is not the case for subject A, because the pressure-diameter curve is still in the linear part at a pressure of 120/80 mm Hg.

occur in elderly people, as shown by Bader.[22] With increasing age, the great arteries become more dilated and the elastin-determined (linear) part of the pressure-diameter relation shifts to lower pressures. As aortic tunica media changes that occur in the Marfan syndrome do not differ essentially from degenerative alterations,[23,24] it seems reasonable to assume the same causative mechanism. The hypothesis is illustrated in Figure 6. A decrease in mean blood pressure does not influence distensibility when it occurs in the linear part of the curve; this is the case in a normal subject A. Distensibility in subject B, however, is largely determined by the exponential part of the curve; lowering of blood pressure may shift the in vivo working area to the more linear part of the curve, resulting in greater area (or diameter) change (dotted arrow) at a given pressure difference and, so, in higher distensibility.

An undesirable effect of β-blocking agents is increased systemic vascular resistance, which could increase the amplitude of reflected pulse waves[25] and decrease total aortic compliance, as Yin et al[11] demonstrated in Marfan patients with a severely dilated aortic root (5.5 to 8 cm in diameter). Also, Haouzi et al[1] demonstrated a heterogeneous response to metoprolol in ascending aorta distensibility in Marfan patients, depending on ascending aortic diameter. In both studies, however, a significant decrease in aortic stiffness in the Marfan group was achieved by lowering of blood pressure (in the study of Yin et al[11] by adding nitroprusside to propranolol), which seems to underscore the above-mentioned theory. Possibly, the techniques used in the study by Haouzi et al[1] are not sensitive enough to determine distensibility changes in individuals. Variability in echocardiographic (which were not reported) and blood pressure measurements could account for the small distensibil-

ity alterations after β-blocking therapy. In a study by Reed et al,[4] no change in ascending aortic distensibility in children with the Marfan syndrome could be demonstrated before and after β blockade despite a significant decrease in blood pressure. At follow-up, however, patients were 4 years older than at baseline (14.2 vs 18.1 years) and mean distensibility was about twice the value obtained by Savolainen et al,[3] who used gradient-echo MRI to study aortic distensibility in patients with the Marfan syndrome in the same age group (Table III). Although intraobserver variability was reasonable in the study by Savolainen et al,[3] no data on variability on the echocardiographic data from Reed et al[4] were reported. We conclude that β-blocker therapy significantly reduces mean blood pressure and aortic stiffness in patients with the Marfan syndrome but not in healthy controls. Reduction of aortic stiffness could be associated with beneficial effects of β blockers on aortic complications and dilation rate in patients with the Marfan syndrome.

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