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Aortic biomechanics by magnetic resonance: Early markers of aortic disease in Marfan syndrome regardless of aortic dilatation?☆

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ABSTRACT

Background: Previous studies demonstrated the usefulness of MRI in the evaluation of aortic biomechanics in Marfan patients with aortic dilatation. However, these parameters have not been well studied in earlier stages of aortic disease. The present work aimed to study aortic biomechanics: aortic distensibility (AD) and pulse wave velocity (PWV), by MRI in Marfan patients without advanced aortic disease.
Methods: Eighty consecutive Marfan patients were compared with 36 age- and sex-matched controls. MRI images at the level of ascending, descending and abdominal aorta were used to determine AD and PWV.
Results: Marfan patients (27 men; age: 32.0 ± 10.5 years; mean aortic root diameter: 37.2 ± 4.6 mm) had lower AD at all levels (ascending 2.6 ± 2.1 vs. 6.2 ± 3.7 mm $Hg^{-1} \cdot 10^{-3}$, $p < 0.001$; descending 3.1 ± 2.0 vs. 8.3 ± 4.2, $p < 0.001$; and abdominal 4.5 ± 2.2 vs. 14.0 ± 5.2, $p < 0.001$), higher aortic arch PWV (8.1 ± 6.5 vs. 4.3 ± 1.8 m/s, $p < 0.01$) and ascending-to-abdominal PWV (6.1 ± 3.0 vs. 4.7 ± 1.5 m/s, $p < 0.01$) compared with controls. Thirty-five Marfan patients had a non-dilated aortic root (mean aortic root diameter: 34.5 ± 3.8 mm). In multivariable analyses, after adjustment for age, pulse pressure and aortic dimensions, AD remained lower and PWV higher in Marfan patients; even Marfan patients with non-dilated aortic root showed impaired aortic biomechanics compared with controls. *Z*-score for ascending AD < −3.5 distinguished Marfan patients from controls with 82.5% sensitivity and 86.1% specificity.
Conclusions: Aortic biomechanics by MRI were abnormal in the entire aorta in Marfan patients. Moreover, Marfan patients without dilated aortic root showed clear impairment of aortic biomechanics, which suggests that they may be used as early markers of aortic involvement in these patients.

1. Introduction

Marfan syndrome is a hereditary connective tissue disorder caused by mutations in the fibrillin-1 gene [1]. This glycoprotein is essential for extracellular matrix synthesis and, as a result of its alteration, fragmentation and disarray of elastin and collagen occur with impairment of aortic elastic properties and dilatation [2].

Marfan syndrome involves multiple organs. However, aortic complications, such as aortic dissection, are the main determinants of survival [3,4]. Although aortic diameter is the main predictor of aortic complications, a high proportion of dissections in the general population still occur at diameters <50 mm [5], when elective aortic surgery is not clearly indicated [6]. Thus, new risk markers for predicting aortic complications are needed in Marfan patients without aortic dilatation. To this end, markers derived from aortic biomechanics have been advocated [7] but remain to be evaluated.

Although previous studies showed impaired aortic distensibility by MRI in Marfan patients [8–10], the series were short, and included

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cases with advanced aortic disease or patients under cardioactive treatment. In addition, pulse wave velocity was not measured in the majority.

The aim of the present study was to assess aortic biomechanics (distensibility and PWV) by MRI in a cohort of Marfan patients without advanced aortic disease regardless of aortic dimension.

2. Methods

2.1. Study sample

From December 2008 to August 2010, 80 consecutive patients were included in the study after being diagnosed of Marfan syndrome by two experts according to revised Marfan criteria [11]. Exclusion criteria were age <16 years, more than mild aortic regurgitation, or previous aortic surgery or dissection. All patients were referred for MR imaging after a minimum of 1 week's withdrawal of any cardioactive treatment. Twenty-seven patients were previously under cardioactive treatment (betablockers in 24, angiotensin II receptor blockers in 2 and angiotensin-converting-enzyme inhibitor in one).

Thirty-six healthy age- and sex-matched volunteers served as controls. Exclusion criteria were known coronary heart disease, valvular disease, heart failure, hypertension (previous hypertension, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg) or atrial fibrillation.

Height and weight were measured and body surface area (BSA) calculated according to the Du Bois formula [12]. The study complies with the declaration of Helsinki and was approved by the local ethics committee and patients or their representatives gave their signed informed consent.

2.2. Image acquisition

In Marfan patients, images were acquired on a 1.5 T scanner (Signa Excite GE, Milwaukee, WI) and in control subjects on a 3.0 T scanner (Trio Tim, Siemens). Images were acquired in both groups using ECG gating and breath-holding.

For acquisition of thoracic aorta images, a phase-contrast sequence with through-plane velocity encoding was applied perpendicularly to the ascending and descending aorta at the level of the pulmonary artery bifurcation. Maximum velocity encoding was 150 cm/s, slice thickness 6 mm, matrix 192 × 192, and temporal resolution <30 ms. A second acquisition with the same parameters was made just below the diaphragm to visualize the proximal abdominal aorta. SSFP cine sequences at the same location of the thoracic and abdominal aorta were acquired (slice thickness 6 mm, matrix 256 × 256, temporal resolution <30 ms) (Fig. 1). In Marfan patients, SSFP cine in the plane of the aortic root was also acquired. The end-diastolic frame was used to measure aortic root diameters.

A sagittal–oblique view of the aortic arch using a bright-blood sequence (slice thickness 6 mm, matrix 256 × 256) was used to visualize aortic length.

Brachial blood pressure was measured in the supine position just after MRI acquisition. Pulse pressure (PP) was calculated as systolic blood pressure minus diastolic blood pressure.

2.3. Aortic dimensions, distensibility and pulse wave velocity (PWV) measurements

Aortic contours were semi-automatically traced through all cardiac cycles using the ARTFUN software (INSERM U678, Paris, France). Manual selection of the center of the aorta and a point close to the vessel wall on a single image were the only user intervention. Tracing of aortic borders through all cine images was then automatically performed (Fig. 2). The validation and accuracy of ARTFUN measurements of aortic dimensions and PWV measurements by MRI have been reported previously [13–15].

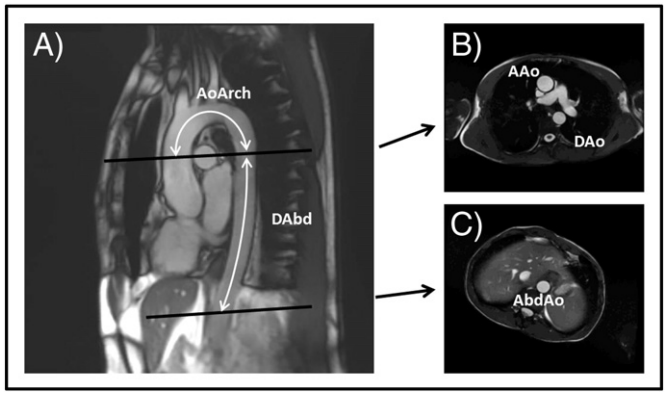

Fig. 1. Aortic views used for the measurement of aortic distensibility and PWV. A: sagittal–oblique long-axis view of the aorta with the levels used for axial planes (black lines) and the segments used for the calculation of PWV (white arrows). AoArch: aortic arch. DAbd: descending-to-abdominal aorta. B: bright-blood axial plane of the thoracic aorta. AAo: ascending aorta. Dao: descending aorta. C: bright-blood axial plane of the abdominal aorta. AbdAo: abdominal aorta.

Maximum (systolic) and minimum (diastolic) aortic areas and brachial pulse pressure were used to calculate distensibility of the ascending, descending and abdominal aorta in each subject as follows:

$$\text{Distensibility}\ \left(10^{-3}\text{mm Hg}^{-1}\right) = 1000 \times \frac{\text{Systolic aortic area}\ \left(\text{cm}^2\right) - \text{Diastolic aortic area}\ \left(\text{cm}^2\right)}{\text{Diastolic aortic area}\ (\text{cm}^2) \times \text{Pulse pressure}\ (\text{mm Hg})}$$

Aortic arch, descending-to-abdominal and ascending-to-abdominal aorta pulse wave velocities (PWV) were calculated using the transit time of the flow curves (Fig. 3) and the distance between the two aortic locations of the phase-contrast acquisition. Transit time was calculated by ARTFUN software with the upslope approach, which has been described previously and correlates more with age and aortic stiffness indices than point-to-point approaches such as foot-to-foot and half-maximum methods [15]. The formula used to calculate PWV was:

$$\text{Aortic PWV}(\text{m/s}) = \frac{\text{Distance}\ (\text{mm})}{\text{Transit time}\ (\text{ms})}$$

The distance between aortic levels was measured manually along the center line of the aorta within the bright-blood sequence of the sagittal–oblique aortic image. The first and last markers were placed at the plane used for velocity acquisition.

Since aortic dilatation in Marfan patients more markedly affects the aortic root than the distal ascending aorta [6], we defined aortic dilatation according to aortic root diameters by MRI instead of the ascending aortic area. Marfan patients were divided into two groups based on the presence or absence of aortic root dilatation. The three aortic root diameters (from cusp to commissure) were measured, averaged and indexed by BSA. These normalized values were compared with previously published reference values [16]. Aortic root diameter indexed by BSA >2SD above the expected mean for age and sex was considered to be dilated.

2.4. Statistical analysis

Baseline characteristics are expressed as mean ± SD for continuous variables and percentage for discrete variables. Univariate comparisons of demographic, clinical and imaging variables between groups were performed by Student's *t*-test and the chi-square test as appropriate. Comparisons between controls and Marfan patients with dilated and non-dilated aortic root were made by ANOVA test, and posterior multiple comparisons analysis with Bonferroni correction. Baseline characteristics of Marfan patients were also analyzed stratified by terciles of aortic distensibility and of PWV, with ANOVA and chi-square test as appropriate. Test for linearity was applied when deemed appropriate.

Univariate analyses were performed to assess the relationship between aortic stiffness parameters and demographic and clinical data. Multivariate regression models were later used to evaluate the relationship between aortic stiffness parameters (aortic distensibility at the three aortic levels and PWV) and Marfan syndrome adjusted for other covariates. Each aortic stiffness parameter was introduced in a separate model as the dependent variable and Marfan syndrome as an independent variable. Potential covariates with clinical significance, such as gender, BSA, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), heart rate, hypertension, hypercholesterolemia and smoking were initially included in the model. A stepwise approach was used to select the covariates finally included in the model. Although the distensibility formula contains pulse pressure, we included this covariable in the multivariate analyses to evaluate the relationship between Marfan syndrome and aortic distensibility regardless of the increased pulse pressure observed in these patients. A second model for each aortic stiffness parameter included further adjustment for diastolic aortic area at the level studied. Ascending aorta diastolic area was considered for aortic arch and ascending-to-abdominal PWV and descending aorta diastolic area was considered for descending-to-abdominal PWV. A similar approach was used to compare aortic stiffness between Marfan patients with and without aortic root dilatation, adjusting for significant covariates selected by the stepwise approach.

Since age was defined as a major determinant of aortic distensibility in previous studies [17], simple linear regression with ascending AD as a dependent and age as an independent variable was used in the control group to estimate the mean and standard deviation for ascending aorta distensibility depending on age. These were used to calculate the *Z*-score for ascending AD adjusted for age in Marfan patients with the formula:

$$Z\text{-}score = \frac{AD_{observed} - AD_{estimated}}{SD_{estimated}}$$

where $AD_{observed}$ is the observed value in the Marfan patient; $AD_{estimated}$ is the estimated mean by age and $SD_{estimated}$ is the estimated standard deviation by age.

Receiver operating characteristic (ROC) analysis was used to compare the specificity and sensitivity of the *Z*-score of ascending aorta distensibility adjusted for age to distinguish between Marfan patients and controls.

All reported probability values were 2-sided and a probability value <0.05 was considered statistically significant. Analyses were performed with SPSS® 17.0.0, 2008, SPSS Inc. Chicago, IL, USA.