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Increased aortic tortuosity indicates a more severe aortic phenotype in adults with Marfan syndrome☆,☆☆

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ABSTRACT

Background: Patients with Marfan syndrome (MFS) have a highly variable occurrence of aortic complications. Aortic tortuosity is often present in MFS and may help to identify patients at risk for aortic complications.
Methods: 3D-visualization of the total aorta by MR imaging was performed in 211 adult MFS patients (28% with prior aortic root replacement) and 20 controls. A method to assess aortic tortuosity (aortic tortuosity index: ATI) was developed and reproducibility was tested. The relation between ATI and age, and body size and aortic dimensions at baseline was investigated. Relations between ATI at baseline and the occurrence of a clinical endpoint (aortic dissection, and/or aortic surgery) and aortic dilatation rate during 3 years of follow-up were investigated.
Results: ATI intra- and interobserver agreements were excellent (ICC: 0.968 and 0.955, respectively). Mean ATI was higher in 28 age-matched MFS patients than in the controls (1.92 ± 0.2 vs. 1.82 ± 0.1, $p = 0.048$). In the total MFS cohort, mean ATI was 1.87 ± 0.20, and correlated with age ($r = 0.281$, $p < 0.001$), aortic root diameter ($r = 0.223$, $p = 0.006$), and aortic volume expansion rate ($r = 0.177$, $p = 0.026$). After 49.3 ± 8.8 months follow-up, 33 patients met the combined clinical endpoint (7 dissections) with a significantly higher ATI at baseline than patients without endpoint (1.98 ± 0.2 vs. 1.86 ± 0.2, $p = 0.002$). Patients with an ATI > 1.95 had a 12.8 times higher probability of meeting the combined endpoint (log rank-test, $p < 0.001$) and a 12.1 times higher probability of developing an aortic dissection (log rank-test, $p = 0.003$) compared to patients with an ATI < 1.95.
Conclusions: Increased ATI is associated with a more severe aortic phenotype in MFS patients.

1. Introduction

Patients with Marfan syndrome (MFS) are at risk for potentially fatal aortic dissections [1,2]. Aortic dissection is generally preceded by aortic dilatation, which is regularly monitored by aortic imaging in clinical practice. At a certain threshold diameter, prophylactic aortic surgery is advised by current clinical guidelines [3,4]. However, identification of MFS patients at high risk for aortic dissection remains difficult and seems to be dependent on prior aortic root surgery, aortic size, aortic distensibility and aortic diameter growth above 0.5 mm/year [5]. Besides gradual expansion of the aortic diameter, the aorta also elongates [6]. Considering the aorta in its anatomically fixed position, aortic elongation may force the vessel to curve and become tortuous [7]. Tortuosity of smaller arteries has already been shown to be a marker for adverse cardiovascular outcomes in patients with connective tissue disorders [8,9]. However, in MFS patients, the aorta rather than the smaller arteries, is generally affected. Therefore, we adapted and applied the tortuosity index of smaller arteries on 3D aortic images, acquired by magnetic resonance imaging (MRI) to establish the aortic tortuosity index (ATI) [8–11]. We subsequently correlated ATI with aortic expansion rate and clinical endpoints in 3–4 years of follow-up.

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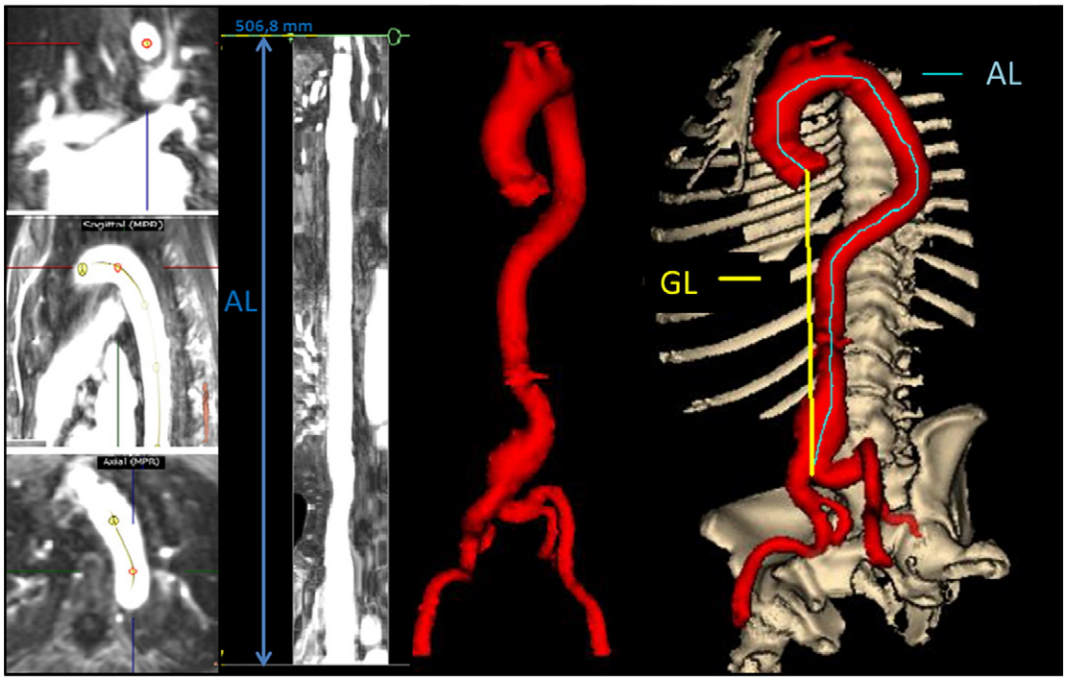

Fig. 1. View of the image processing software. The seeding points are placed manually central in the coronal, sagittal and axial planes in the contrast enhanced lumen of the aorta (left). Aortic length (AL) is measured in a multiplanar reconstructed stretched view of the aorta. Geometric length (GL) is the Cartesian distance between its 2 endpoints calculated by exported spatial coordinates. Aortic tortuosity index (ATI) is measured by dividing AL (in blue) by GL (in yellow).

We hypothesized that ATI may serve as a marker for severity of aortic disease and may predict aortic expansion rate and clinical outcome, such as elective aortic surgery and aortic dissection.

2. Methods

2.1. Study subjects

Our study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the medical ethics committee of the Academic Medical Centre. All participating subjects gave written informed consent. All patients were participants of the COMPARE study, a randomized trial in which the effect of losartan therapy (100 mg, daily) on the aortic dilatation rate was assessed [12]. At baseline and after three years of follow-up, we examined the patients' medical history and performed MRI of the entire aorta. Clinical events were evaluated until February 2014. *FBN1* mutation analysis was performed in all the patients. When no *FBN1* mutation was found, the following connective tissue genes were subsequently screened: *TGFBR1*, *TGFBR2*, *TGFB2*, *MYH11*, *MYLK1*, *SMAD3*, and *ACTA2*. Because of the possible impact of mutations other than *FBN1* on ATI, we excluded patients with a pathogenic non-*FBN1* mutation for the main analysis. These excluded patients were separately analysed.

2.2. Purpose and outcomes

The primary aim of this study was to investigate the association of ATI with severity of aortic phenotype in MFS patients. Hereto, we 1) investigated applicability and reproducibility of ATI in MFS patients (n = 14) by two investigators, 2) compared ATI of control subjects in whom aortic disease was definitely ruled out (n = 20) with age, sex and length-matched MFS patients (n = 28), 3) correlated ATI with age, aortic root diameter and aortic volume at baseline, and 4) compared ATI between MFS subgroups based on genotypes.

Secondary aims were to assess the predictive value of ATI during follow-up on aortic root dilatation rate, aortic volume expansion rate, the combined clinical endpoint (prophylactic aortic surgery, aortic dissection and death), and separately on aortic dissection. The decision to perform prophylactic aortic surgery was completely at the discretion of the attending cardiologists, based on European and American guidelines [3,4].

2.3. Magnetic resonance imaging

All MRI scans were obtained in two centres (AMC, Amsterdam and LUMC, Leiden, The Netherlands) with a 1.5 T MR system Avanto (Siemens, Erlangen, Germany) or a Philips (Intera, release 11 and 12; Philips Medical Systems, Best, The Netherlands). Contrast-enhanced MRI of the total aorta was performed using standardised protocols, which has been described previously [12,13]. In case of significantly reduced image quality due to metal scoliosis implants, patients were

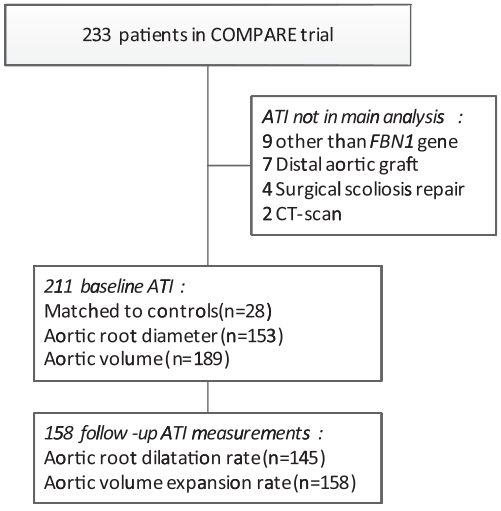

Fig. 2. Flowchart of included patients with Marfan syndrome.