Novel diagnostic and therapeutic targets in Marfan syndrome
Radoni, T.

Citation for published version (APA):
Radoni, T. (2012). Novel diagnostic and therapeutic targets in Marfan syndrome

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Total aortic volume measurement as a novel, reliable method to determine progressive global aortic dilatation in Marfan syndrome

Submitted
ABSTRACT

Aim: To assess the feasibility and reproducibility of total aortic volume measurement in 3D MR image data of the aorta in Marfan patients, to compare total aortic volume with aortic diameter measurement and to compare aortic expansion rate between aortic volume and aortic diameters.

Methods: Gadolinium enhanced 3D MRI of the aorta was performed in 62 Marfan patients without previous aortic dissection (mean age 37±13, 32 males (52%), 18 (29%) after prophylactic aortic root replacement). Semi automated 3D analysis software (3Mensio, Bilthoven, the Netherlands) was used to measure total aortic volume. Intra- and inter-observer variability was determined in 10 patients. Aortic diameters of all patients were measured at five levels. After three years the protocol was repeated and aortic expansion rates as measured by volume were compared with those measured by diameter.

Results: Mean aortic volume of 62 Marfan patients at baseline was 233 ml (SD=65 ml). Intra-observer difference was 4.63 ml (ICC= 0.996; SD=4.83). Inter-observer difference was 0.06 ml (ICC=0.979; SD=11.96). A significant correlation was found between aortic volume and age (R=0.6, p<0.005, increase of 1.53 ± 0.27 ml/m²/year). Mean aortic volume increased from 259± 62.5 ml to 282 ±74.7 ml (Cohen’s d 0.3) in 15 patients and mean aortic diameter increased from 24.93 ± 2.76 mm to 25.34 ± 2.91 mm (Cohen’s d 0.1) in 15 patients. The sensitivity of aortic expansion was significantly higher using aortic volume as compared to aortic diameters (effect size 0.3 and 0.1 respectively, p<0.005).

Conclusions: Total aortic volume measurement is a highly reproducible novel method facilitating improved surveillance of global aortic expansion rate in patients with Marfan syndrome. Follow up by the use of aortic volume is more sensitive than follow up by the use of aortic diameter.

Keywords: Marfan syndrome, MRI, aortic volume
INTRODUCTION

Marfan syndrome is an autosomal dominant systemic connective-tissue disorder caused by a mutation in the fibrillin-1 gene (FBN1) with an incidence of approximately 2-3 per 10000 individuals (1). FBN-1 encodes for the extracellular matrix protein fibrillin-1, which has structural and regulatory functions in the extracellular matrix (2). Development of aortic aneurysms during adolescence and early adulthood, with subsequent risk of aortic dissection and sudden death, is the leading cause of morbidity and mortality in patients with Marfan syndrome (1). Therefore, surveillance of aortic dimensions is of utmost importance in daily clinical practice for well-timed surgical intervention (3-5). The total aorta can be visualized by three dimensional (3D) imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT). Generally, aortic expansion rate is evaluated by repeated measurements of the diameter at different levels of the aorta. However, gradual total aortic expansion might be missed by measuring mere aortic diameters during follow-up (5). Post processing of 3D MRI and CT images of the aorta facilitates total aortic volume measurement, which might improve detection of gradual aortic expansion in patients with Marfan syndrome and related disorders. Accordingly, the aim of this study was to determine feasibility and reproducibility of total aortic volume measurements in Marfan patients by 3D MRI and to compare total aortic expansion rate as determined by total aortic volume measurements with expansion rate as determined by measurements of aortic diameters on the same 3D data sets.

METHODS

Patients

Total aortic volume and aortic diameters were measured in 62 patients with Marfan syndrome on MRI. All patients were participants of the COMPARE study, which studies the effect of losartan on the aortic expansion rate in patients with Marfan syndrome (6). The inclusion criteria were diagnosis of Marfan syndrome according to the Ghent criteria (7) and an age of 18 years or older. Exclusion criteria were: current pregnancy, angiotensin converting enzyme inhibitor or angiotensin receptor blocker usage,
previous elective replacement of more than one part of the aorta, and previous aortic dissection. The MRI was repeated after three years in 15 patients without dissection or aortic operation after the first MRI. The study was approved by the AMC medical ethics committee, and all subjects gave written informed consent. The study was conducted in accordance with the declaration of Helsinki.

**Magnetic Resonance Imaging**

Aortic volumes and aortic diameters were assessed in all patients by 3D MRI, performed with a 1.5 Tesla MR system (Avanto, Siemens, Erlangen, Germany) using a phased array cardiac receiver coil. All scans were obtained in a single center (AMC, Amsterdam, The Netherlands). To visualize the total aorta, a three-dimensional, T1-weighed, spoiled gradient-echo sequence (FLASH3D) was applied in the oblique sagittal direction after administration of 0.1 mmol/kg intravenous gadolinium (FA 25 degrees, FOV 500 mm, 80 slice/slab, base resolution 384, phase percentage 60-80%, 10% slice oversampling). This resulted in a 3D set of contrast enhanced images encompassing the total aorta with a near isotropic resolution of 1.4x1.3x1.4 mm/voxel.

**Image Processing**

Total aortic volume was determined using 3D vessel analysis software (3mensio vascular, 3mensio medical imaging BV, Bilthoven, the Netherlands) (8). MRI angiographic datasets were loaded in the program (Fig. 1). A centerline was generated by manually placing control points in the center of the aorta, starting at the aortic valve to the aortic bifurcation (Fig. 2). Subsequently, the software constructed a stretched vessel view of the aorta. After manually placing points at both sides of the aortic lumen in four cross-sections (Fig. 3A) the software calculated total aortic volume (Fig. 3B).
Figure 1: *The aorta is represented in the program in three adjustable cross sections and as a whole.*

![Figure 1: The aorta is represented in the program in three adjustable cross sections and as a whole.](image)

Figure 2: *The other centreline points are manually placed and represented in three directions*

![Figure 2: The other centreline points are manually placed and represented in three directions](image)
Aortic diameters were measured at five levels: the aortic root (mean diameter of three sinuses), the ascending and descending thoracic aorta at the level of the pulmonary root, at the level of the diaphragm and just above the bifurcation. Mean diameter was calculated as the average of these 5 measurements. Intra- and inter-observer variability of aortic volume was determined by analyzing 10 datasets twice by one observer (WS) and once by another observer (PW). Intra- and inter observer variability of diameter measurements was determined in 15 patients by the same observers.

**Figure 3:** A - *The aorta is represented in a stretched view in four directions. The border of the aortic lumen is manually indicated at both sides in all four directions* B - *Total aortic volume is indicated by the program*
**Statistical Methods**

Statistical analysis was performed by commercially available software (SPSS, release 17.0 for Windows; SPSS, Chicago, IL). Intra- and inter-observer agreements were determined with the interclass correlation coefficient and processed in a Bland-Altman plot. Correlations were analyzed with Pearson correlation. Effect size was calculated with Cohen’s $d$. P-values smaller than 0.05 were considered to be statistically significant.

**RESULTS**

The mean age in 62 Marfan patients was 37 ± 13 years and 52% was male. Aortic volume measurement took approximately 20 minutes per patient. No evident aortic aneurysms were found. Mean aortic volume was 233 ml (SD=65). Aortic volume was comparable in men and women (121 ± 32 ml/m² vs 112 ± 39 ml/m² respectively, p=0.3). Baseline characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37 ± 13</td>
</tr>
<tr>
<td>Male</td>
<td>32 (52)</td>
</tr>
<tr>
<td>Lenght (cm)</td>
<td>188 ± 11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>Previous aortic root replacement</td>
<td>18 (29)</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>233 ± 65</td>
</tr>
<tr>
<td>Volume normalised for BSA (ml/m²)</td>
<td>116 ±32</td>
</tr>
</tbody>
</table>

There was no significant difference in aortic volume in patients with and without previous aortic root replacement (255 ± 67 ml vs 224 ± 62 ml respectively p= 0.08). Volume corrected for BSA was strongly associated with age (R=0.6, p<0.005, increase of 1.53 ± 0.27 ml/m²/year). Mean aortic diameter corrected for BSA also showed a strong correlation with age (R=0.6, p<0.005, increase of 0.67 ± 0.14 mm/m²/year, Figure 4a and 4b).
Figure 4: Correlation between age, aortic volume (A) and diameter(B)

Intra-observer and inter-observer difference were 4.63 ml (ICC= 0.996; SD=4.83, Fig 5A) and 0.06 ml (ICC=0.979; SD=11.96, Fig 5B) respectively. Intra- and inter-observer variability of aortic diameter determined in 15 patients at 5 levels showed comparable results (ICC=0.971 and 0.974, respectively). In three years time, mean aortic volume increased from 259 ± 62.5 ml to 282 ±74.7 ml (Cohen’s d 0.3) in 15 patients and mean aortic diameter increased from 24.93 ± 2.76 mm to 25.34 ± 2.91 mm (Cohen’s d 0.1) in 15 patients (Figure 6). The difference in effect size was significant (p<0.005).
Figure 5: Bland-Altman plot of the inter-observer (A) and intra-observer (B) variability

**A**

Bland-Altman inter-observer variability

-1.96 SD 0 1.96 SD

-20 -10 0 10 20

difference (ml)

mean volume (ml)

**B**

Bland-Altman intra-observer variability

-1.96 SD 0 1.96 SD

-10 -5 0 5 10

difference (ml)

mean volume (ml)

Figure 6: Individual growth curves of aortic volume corrected for BSA and mean diameter in 15 patients
DISCUSSION

Here we demonstrate that total aortic volume assessment by 3D MRA is a highly reproducible and sensitive method facilitating surveillance of global aortic expansion rate in patients with Marfan syndrome. Aortic dissection beyond the aortic root in Marfan patients has always been difficult to predict and may occur at a relatively normal aortic diameter (9). Gradual aortic dilatation may precede aortic complications and may be unnoticed when mere aortic diameters are taken into account.

An increasing number of studies are being performed to evaluate the volume of abdominal aneurysms (5, 10-12). We found similar high reproducibility of volume measurement as these studies. All these studies used CT imaging instead of MRI. In our opinion image acquisition with MRI is favorable in our patient group because of the prevention of radiation exposure.

Furthermore, we show that aortic volume measurement is more sensitive than diameter measurement for surveillance of aortic expansion rate. Volume measurements are physically more logical to use, because smaller changes in aortic size can be detected earlier due to the fact that a change in three dimensions is reflected by a much smaller change in one dimension. This might be important in clinical trials evaluating the effects of medication (i.e. losartan) on aortic expansion rate in patients with connective tissue disease like Marfan syndrome. The use of aortic volume instead of diameters may reduce the follow-up time and effect size needed to observe the differences. This might also be true for other connective tissue disorders like the Loeys Dietz syndrome (LDS)(13). This syndrome is characterized by aneurysms throughout the arterial tree, arterial tortuosity and aortic dissections at even smaller diameters than observed in Marfan syndrome (14).

Although the used software was developed for CTA image analysis, it was successfully applied to volumetric MRI datasets. The main limitation of present study is that, because of the use of MRI datasets, additional manual interaction was required. Manual interaction commonly results in a lower degree of reproducibility; however, even with the manual interaction the method proofed to be highly reproducible. Another limitation is that aortic volume measurement was rather time demanding. Measuring aortic
diameters took approximately 5 minutes per patient while total aortic volume measurement took approximately 20 minutes per patient. This might be a limitation for the introduction in daily patient care of not-complicated MFS patients.

In conclusion, total aortic volume measurement is a highly reproducible novel method facilitating improved surveillance of global aortic expansion rate in patients with Marfan syndrome and possibly other connective tissue diseases affecting the vascular system. Studies evaluating global aortic expansion rate should consider measuring total aortic volume.

ACKNOWLEDGEMENTS

This study is supported by a grant from the Netherlands Heart Foundation (grant no. 2008B115) and the consortium Fighting Aneurysmal Disease (FAD).

Aortic volume measurement software (3mensio Vascular) was provided by 3mensio medical imaging BV, The Netherlands.
REFERENCES


