Flow displacement and decreased wall shear stress might be associated with the growth rate of an ascending aortic dilatation

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Abstract

OBJECTIVES: Our goal was to evaluate whether four-dimensional (4D) flow magnetic resonance imaging (MRI) can predict the growth rate of dilatation of the ascending aorta (AA) in patients with a tricuspid, normally functioning aortic valve.

METHODS: In this prospective clinical study, aortic 4D flow MRI was performed at the Kuopio University Hospital on 30 patients diagnosed with AA dilatation (maximum diameter >40 mm) between August 2017 and July 2020. The MRI was repeated after a 1-year follow-up, with AA dimensions and 4D flow parameters analysed retrospectively at both time points. The standard error of measurement was used to assess the statistical significance of the growth rate of AA dilatation. Flow displacement (FD) was transformed to a class-scaled parameter using FD > 5% as a threshold.

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RESULTS: Statistically significant growth [median 2.1 mm (1.5–2.2 mm); P = 0.03] was detected in 6 male patients (20%); the AA diameter remained unchanged [0.2 mm (-0.3 to 0.9 mm)] in 24 patients (80%). An increased FD at the baseline was associated with significant growth during the 1-year follow-up in the proximal AA. An association was detected between decreased total wall shear stress and significant aortic growth in the inner curve of the sinotubular junction [529 mPa (449–664 mPa) vs 775 mPa (609–944 mPa); P = 0.03] and the anterior side of the proximal aortic arch [356 mPa (305–367 mPa) vs 493 mPa (390–586 mPa); P < 0.001].

CONCLUSIONS: FD and decreased wall shear stress seem to be associated with significant growth of AA dilatation at the 1-year follow-up. Thus, 4D flow MRI might be useful in assessing risk for AA diameter growth in patients with a tricuspid aortic valve.

Keywords: Ascending aorta • Aortic dilatation • 4D flow MRI • Flow displacement • Wall shear stress

ABBREVIATIONS

| 4D | Four-dimensional |
| AA | Ascending aorta |
| BAV | Bicuspid aortic valve |
| FD | Flow displacement |
| ICC | Intraclass correlation coefficients |
| MRI | Magnetic resonance imaging |
| SEM | Standard error of measurement |
| TAV | Tricuspid aortic valve |
| WSS | Wall shear stress |

INTRODUCTION

Dilatation of the ascending aorta (AA) often develops without any clinically significant symptoms, making it difficult to detect. AA dilatation is usually an incidental finding of chest imaging [1]. In some cases, AA dilatation proceeds as a local aneurysm that may eventually make the AA susceptible to rupture. The incidence of thoracic aortic aneurysms is ~10 cases per 100 000 person-years [2].

In general, common cardiovascular risk factors predispose one to AA dilatation. Furthermore, there are known aetiologies related to AA dilatation, e.g. genetic syndromes such as Marfan, vascular Ehlers-Danlos or Loeys-Dietz [3]. Although AA dilatation can develop in patients with either tricuspid aortic valve (TAV) or bicuspid aortic valve (BAV), the prevalence is much higher in individuals with BAV [4].

The diagnosis of AA dilatation is often made as an incidental finding when imaging the chest area for other purposes [5]. According to the European Society of Cardiology guidelines (2014), AA is classified as dilated when its maximum diameter exceeds 40 mm at any level of the vessel. Because of the asymptomatic progression of AA dilatation, follow-up imaging must be performed regularly. Surgery is indicated when the diameter of the AA exceeds 55 mm in cases without any specific aetiology [6]. In patients with high-risk aetiologies, such as those with genetic syndromes or BAV, the threshold for surgical intervention is lower (~45–50 mm, depending on additional risk factors) [2, 6, 7].

Due to asymptomatic growth, the diagnosis and follow-up of AA dilatation would benefit from new methods. For example, three-dimensional time-resolved phase-contrast magnetic resonance imaging (MRI) [four-dimensional (4D) flow MRI] has proved to have potential in clinical use for assessing altered flow conditions in the aorta [8]. In previous studies, 4D flow parameters, such as flow displacement (FD) and increased wall shear stress (WSS), have been shown to correlate with AA dilatation [9, 10]. However, as far as we are aware, the predictive value of different 4D flow MRI parameters in association with the growth rate of AA dilatation has not been previously studied in patients with TAV, which was the goal of this study.

MATERIALS AND METHODS

Ethical statement

The present study was approved by the ethical committee of the Northern Savo Hospital district (200/2017, 11/4/2017), and the study followed the Declaration of Helsinki. The patients with AA dilatation scheduled for aortic MRI or computed tomography at the Kuopio University Hospital between July 2017 and July 2020 were recruited to this prospective follow-up study. All patients gave their written informed consent before participating in the study.

Study population

This prospective study included a cohort of 30 patients who were scheduled for aortic MRI angiography due to AA dilatation (diameter >40 mm in any plane of the AA, European Society of Cardiology guidelines 2014) at the Kuopio University Hospital. As baseline, MRI with 4D flow imaging was performed for each patient; the same protocol was repeated after a 1-year follow-up period.

The patient characteristics and risk factors for cardiovascular diseases were collected from their medical records. Hypertension was defined as having medication prescribed for hypertension. Patients who were current smokers or had quit smoking <30 years previously were registered as smokers. Hypercholesterolaemia was defined as the patient having medication for dyslipidaemia. Mosteller’s formula was used to calculate the body surface area [11].

Magnetic resonance imaging

Siemens Magnetom Aera 1.5 T scanner (Erlangen, Germany) was used to conduct the MRI. A true fast imaging with steady state precession with a respiration navigator was utilized in MRI imaging [12]. The 4D flow MRI consensus statement was followed when the imaging parameters were selected for the study [13]. The 4D flow sequence was scanned with free breathing without contrast media and with ECG gating. Artefacts formed as a result of respiration were reduced by averaging. The complete imaging protocol was presented in detail in a previous publication [9].
Data collection and assessment of magnetic resonance images

Measurement of aortic dimensions. Observer 1 (Tarmo Korpela) retrospectively analysed aortic dimensions from MRI angiography images \( (n = 30) \) with the IDS7 (version 17.3.6; Sectra Imtec, Linköping, Sweden) diagnostic workstation. The diameter of the AA was measured in 2 planes: in the sinus of Valsalva and in the middle AA. Diameters were measured according to international recommendations [6]. The measurement of the sinus of Valsalva plane was performed in 3 different directions. In the middle AA plane, 2 measures perpendicular to each other were made (Fig. 1). The measurements of the AA dimensions were repeated by observer 1 after 1 month and also by independent blinded observer 2 (Elina Kariniemi).

Measurement of four-dimensional flow magnetic resonance imaging parameters. The 4D flow parameters were analysed with CAAS MR Solutions software (Pie Medical Imaging, Maastricht, Netherlands, version 5.1). Flow was measured in 10 planes of the thoracic aorta (Fig. 2A). The flow parameters quantified in each plane were peak flow, peak velocity, minimum velocity, time points of flow measurements, forward flow (ml), backward flow (ml), regurgitation fraction (% proportion between backward and forward flow), cardiac output (ml/min), blood volume (ml/cardiac cycle) and FD (% proportion between the centre of the eccentric flow jet and the diameter of the vessel). WSS was divided into circumferential WSS (WSSC) and axial WSS (WSSA) components. Furthermore, total WSS (WSST) was calculated as the geometric sum of WSSA and WSSC. WSS was measured in planes 1 to 5. AA was split into six 60° segments: the starting
point \( (0^\circ) \) was placed in the inner curve and the 60° segments were arranged in a counterclockwise direction (Fig. 2B and C). WSS parameters were registered during peak systole.

**Intra- and interobserver analysis**

For the analysis of intra- and interobserver reproducibility, the 4D flow MRI parameters were measured twice by observer 1 (Tarmo Korpela) and by an independent blinded observer 2 (Elina Kariniemi). Intraclass correlation coefficients (ICC) for the WSS values were calculated by averaging the values of six 60° segments and comparing the means.

**Statistical analyses**

Statistical analyses were performed with IBM SPSS Statistics (version 27, Chicago, IL, USA). Statistical significance was defined as \( P < 0.05 \) and high significance as \( P < 0.001 \). Abnormally distributed parameters are presented as median and interquartile range, normally distributed parameters, as mean ± standard deviation. For abnormally distributed parameters, the Mann-Whitney U-test was used to analyse the statistical significance in the flow parameters between the study groups with and without AA growth. The Wilcoxon signed rank test was utilized to assess the statistical significance in the aortic growth of each patient. The association between dichotomized parameters (FD) and the growth rate of the AA was tested with the \( \chi^2 \) test.

The presence of a systematic error in the intra- and interobserver analyses was tested with a paired samples t-test. Intra- and interobserver reproducibilities were estimated using ICC with a two-way mixed effects model and absolute agreement. The standard error of measurement (SEM) was used to assess the measurement error when comparing aortic dimensions at the baseline and at the 1-year follow-up. The formula for SEM was given by the standard deviation \( \times \sqrt{1 - ICC} \). In the follow-up imaging after 1 year, aortic growth was deemed statistically significant if it exceeded the diameter calculated with the formula [the AA dimension at the 1-year follow-up > \{AA dimension at the baseline + 2 \times SEM\}].

**RESULTS**

**Study population**

The mean age of the patients \( (n = 30) \) was 65.6 ± 8.3 years; 80% were men \( (n = 24) \). The mean body surface area was 2.1 ± 0.2 m², and 87% \( (n = 26) \) of the patients had hypertension. There was no significant difference regarding conventional cardiovascular risk factors (e.g. hypertension, dyslipidaemia, smoking and positive family history) between the patients with or without aortic diameter growth at the 1-year follow-up. All patients had anatomically normal TAV without aortic stenosis. Detailed patient baseline characteristics are presented in Table 1.

**Growth rate of the ascending aortic dilatation**

At baseline, in the entire patient population \( (n = 30) \), the mean AA diameter was 47.9 mm (44.0–49.8 mm) in the sinus of Valsalva plane and 44.0 mm (39.5–47.7 mm) in the middle AA plane. After the 1-year follow-up, the mean diameters were 48.2 mm (44.7–49.9 mm) \( (P = 0.03) \) in the sinus of Valsalva plane and 44.9 mm (39.5–48.4 mm) \( (P = 0.5) \) in the middle AA plane. The growth rate of the sinus of Valsalva was higher in males than in females, in whom no significant growth was detected.

Statistically significant aortic diameter growth was detected in 5 patients in the sinus of Valsalva plane and in 1 patient in the middle AA plane. These patients were combined as a group of 6 patients with AA diameter growth (100% men; mean age 68.5 ± 6.1 years), where the mean growth of the AA diameter was 2.1 mm (1.5–2.2 mm; \( P = 0.03 \)). The AA diameter remained unchanged [0.2 mm (-0.3 to 0.9 mm); \( P = 0.4 \)] in 24 patients (75%...
men, mean age 64.9 ± 8.8 years). The growth of AA diameter is illustrated in Fig. 3.

The detailed growth rates of the patients are presented in Table 2.

**Association of the four-dimensional flow magnetic resonance imaging parameters with aortic growth**

The FD at the baseline associated significantly with the growth rate of AA dilatation in the 1-year follow-up in the proximal AA plane (plane 3). The median FD was 7.5% (6.5–10.5%) in the patients with significant AA growth \( n = 6 \) and 5.0% (3.0–7.5%) in the patients with an unchanged AA diameter \( n = 24; P = 0.038 \). On the basis of these results, FD was transformed into a class-scaled parameter by considering FD ≥5% as a threshold of a risk for subsequent AA diameter growth. When FD was dichotomized, all patients with significant AA growth \( n = 6 \) had FD ≥5% in the proximal part of the AA at the baseline. In other planes, FD did not associate with aortic growth. Illustrative 4D flow images of the displaced flow in the proximal AA are presented in Fig. 4.

The significant growth of AA was associated with decreased total WSS values compared to WSS values in the patients with unchanged AA dimension in the inner curve of the sinotubular junction. In addition, the ratio between WSSC and WSST was higher at the baseline in the patients with significant AA growth in comparison to the patients with an unchanged AA diameter [72.4% (49.6–91.8%) vs 41.0% (30.8–65.1%); \( P = 0.03 \)]. WSS values are presented in Table 3. None of the other 4D flow parameters were associated with aortic growth.

### Table 1: Baseline characteristics of the study population

|                     | Total \( n = 30 \) | AA growth \( n = 6 \) | No AA growth \( n = 24 \) | \( P \)-value |
|---------------------|------------------|------------------|------------------|-------------|
| Age (years)         | 65.6 ± 8.3       | 68.5 ± 6.1       | 64.9 ± 8.8       | 0.4         |
| Gender (male/female)| 24/6             | 6/0              | 18/6             | 0.3         |
| Weight (kg)         | 90.0 ± 17.3      | 89.8 ± 14.9      | 90.1 ± 18.2      | 1.0         |
| Height (cm)         | 176.6 ± 8.2      | 177.8 ± 4.2      | 176.3 ± 9.0      | 0.7         |
| BSA (m²)            | 2.1 ± 0.2        | 2.1 ± 0.2        | 2.1 ± 0.3        | 0.9         |
| Diabetes, n (%)     | 5 (17)           | 1 (17)           | 4 (17)           | 1.0         |
| Hypertension, n (%) | 26 (87)          | 6 (100)          | 20 (83)          | 0.6         |
| Dyslipidaemia, n (%)| 17 (57)          | 4 (67)           | 13 (54)          | 0.7         |
| Positive family history for CVD, n (%) | 9 (30) | 1 (17) | 8 (33) | 0.6 |
| Smoker, n (%)       | 4 (13)           | 0 (0)            | 4 (17)           | 0.6         |

Continuous variables are presented as mean ± SD. Class-scaled variables are presented as frequencies.

AA: ascending aorta; BSA: body surface area; CVD: cardiovascular disease; SD: standard deviation.

**Figure 3:** A box plot describing the change in aortic diameter after the 1-year follow-up in the entire patient population.

### DISCUSSION

Dilatation of the AA is a common incidental finding during chest imaging. After diagnosis, patients with dilatation that is below operation thresholds require regular imaging follow-up. So far, the mechanisms of AA dilatation remain unclear, and only a few predisposing factors, with the exception of some genetic syndromes, are known [6]. Due to the possibility of asymptomatic growth of the AA, new methods are needed that would allow an early intervention before any serious complications occur. Currently, the only prognostic factor of a suspicion of AA diameter growth is a prior tendency to growth. The goal of our study was to evaluate AA growth and predisposing 4D flow MRI parameters with a 1-year follow-up in patients with AA dilatation and a normal aortic valve. Statistically significant AA growth was detected in 20% of the patients, all of whom were men. The key finding of the present study was that an increased FD and decreased WSS values had an association with the AA growth rate.

The normal annual aortic root growth caused by ageing is ~1 mm in 10 years in healthy individuals [14]. Davies et al. estimated that the annual growth in patients with hypertension who suffer AA aneurysms varied from 0.8 mm to 1.6 mm/year. Furthermore, the AA growth rate was calculated to be dependent on the location of the aneurysm: In the AA it was 0.7 and 1.9 mm/year in the descending aorta [15]. In this study, in the subgroup of patients with progressive AA diameter growth, the median annual aortic growth was found to be 2.1 mm/year in the sinus of Valsalva plane. In our study, due to the small number of patients, significant growth was determined using the SEM method. With this method, every fifth patient displayed significant growth in the AA. It is noteworthy that all of the patients with significant growth rates were men and had hypertension. On the other hand, over 80% of the patients without AA dilatation also had a history of hypertension. Thus, it seems that,
although hypertension is very common in patients with AA growth, it is not the only explanatory factor.

In our study, the strongest parameter predicting AA diameter growth was FD in the proximal AA. The shift of systolic flow from the centreline of the AA has been demonstrated to pose a burden on the aortic wall, especially on the same side experiencing the flow [9]. As far as we are aware, predictive causalities of 4D flow parameters have not been previously examined in patients with normal aortic valve anatomy and without any genetic syndromes. Instead, investigations in patients with BAV and Marfan syndrome have been published [10, 16–18]. Hope et al. [19] have shown that eccentric aortic flow, caused by BAV, leads to a faster growth rate of 1.2 mm/year of the aortic diameter compared to normal laminar flow with a growth rate of 0.3 mm/year.

Furthermore, we discovered that FD was >5% in all patients in whom there was significant aortic growth at the 1-year follow-up, whereas FD was under 5% in all patients not exhibiting aortic growth. As a result, we transformed FD to a class-scaled parameter by using the 5% displacement as a prognostic threshold for subsequent dilatation. Increased FD during follow-up imaging might be a useful parameter in the risk evaluation of the patients with AA dilatation. The reproducibility for the dichotomized FD threshold proved to be moderate. Further studies are needed to assess the relationship and reproducibility between FD and AA diameter growth.

Both increased and decreased WSS values have been reported to be associated with aneurysmal growth of the aortic diameter [9, 10, 20]. Previously, it has been shown that increased stress in the aortic wall evokes an endothelial dysfunction, leading to a thinning of the aortic wall that makes it vulnerable to aortic dilatation. Different pathophysiological mechanisms behind the decreased WSS have been postulated. For example, Jiang et al. [21] demonstrated that, in patients with hypertension, lower WSS values (systolic peak) and increased intima-media thickness of the common carotid artery were related to arterial dilatation as well as to the formation of atherosclerotic plaques and

Table 2: The growth rate of the ascending aortic diameter

| Pituitary region (mm) | P-value | Pituitary region (mm) | P-value |
|-----------------------|---------|-----------------------|---------|
| Overall study population |         | Statistically significant growth (n = 6) |         |
| All (n = 30) | 47.9 (44.0–49.8) | 48.2 (44.7–49.9) | 0.03 | 44.0 (39.5–47.7) | 44.9 (39.5–48.4) | 0.4 |
| Men (n = 24) | 48.1 (46.2–49.8) | 48.7 (46.4–50.6) | 0.01 | 44.0 (39.4–47.9) | 44.9 (39.2–48.7) | 0.3 |
| Women (n = 6) | 43.0 (38.3–47.0) | 43.0 (38.4–46.5) | 0.5 | 45.3 (40.9–48.0) | 44.9 (40.7–48.2) | 0.8 |
| Study groups subdivided according to aortic growth |         | Statistically nonsignificant growth (n = 24) |         |
| All (n = 30) | 47.9 (44.6–49.8) | 47.9 (44.6–49.6) | 0.3 | 43.6 (39.2–47.4) | 43.1 (38.8–47.5) | 1.0 |

Results are presented as median (IQR). Wilcoxon signed rank test was used to calculate the P-values.

IQR: interquartile range.
endothelial dysfunction. In this study, total WSS was lower in 2 planes of the AA at the baseline in the patients who would experience AA growth in comparison to those patients without AA growth. The decreased total WSS was associated with AA diameter growth in most of the segments in all 5 planes, being most evident in the inner curve of the sinotubular junction and in the anterior side of the proximal aortic arch. A similar association between decreased total WSS and AA dilatation was demonstrated earlier in patients with TAV [9]. Thus, in the thoracic aorta, a decreased WSS may be an early marker of subsequent AA growth.

Limitations

The main limitations of this study were the small study cohort (30 patients) and the relatively short follow-up time. However, we believe that this is the first study to explore the predicative value of 4D flow MRI parameters in patients with a normal aortic valve. The systematic error in 2 planes of the WSS measurements might have been caused by a lack of routine in using the diagnostic software. However, no similar systematic error was encountered in the assessment of the aortic dimensions, where reproducibility was shown to be strong in both intra- and interobserver measurements. In our study, the reproducibility of the averaged FD values was weak, but with dichotomized FD values, the reproducibility was moderate. Our result of moderate reproducibility for dichotomous FD suggests that it could be a feasible parameter for use in the evaluation of the risk for aortic growth.

CONCLUSION

To conclude, aortic FD and decreased total WSS might be associated with aortic growth in patients with AA dilatation and a tricuspid, normally functioning aortic valve. Thus, 4D flow MRI parameters may be a feasible way to identify those patients with aortic diameter growth who are at a greater risk of experiencing aortic growth. In the future, these parameters may help to stratify follow-up imaging protocols. However, further studies with more patients are warranted.

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Conflict of interest: none declared.

Data Availability Statement

All relevant data are within the manuscript and its supporting information files.

Table 3: Wall shear stress values at the baseline in planes 1–5

| Plane | Segment | Group (n = 6) | Non-group (n = 24) | p-value | WSS% (mean) (SD) |
|-------|---------|--------------|--------------------|---------|------------------|
| Plane 1 | 10 | 0.98 (1.20–2.73) | 5.85 (3.95–7.68) | 0.003 | 39.4 (33.3–59.0) |
| Plane 2 | 10 | 0.98 (1.20–2.73) | 5.85 (3.95–7.68) | 0.003 | 39.4 (33.3–59.0) |
| Plane 3 | 10 | 0.98 (1.20–2.73) | 5.85 (3.95–7.68) | 0.003 | 39.4 (33.3–59.0) |
| Plane 4 | 10 | 0.98 (1.20–2.73) | 5.85 (3.95–7.68) | 0.003 | 39.4 (33.3–59.0) |
| Plane 5 | 10 | 0.98 (1.20–2.73) | 5.85 (3.95–7.68) | 0.003 | 39.4 (33.3–59.0) |
Author contributions

Tarmo Korpela: Data curation; Formal analysis; Investigation; Visualization; Writing—original draft. S. Petteri Kauhanen: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Software; Supervision; Writing—review & editing. Elina Kariniemi: Investigation; Writing—review & editing. Petri Saari: Conceptualization; Methodology; Project administration; Writing—review & editing. Timo Liimatainen: Conceptualization; Methodology; Software; Writing—review & editing. Pekka Jaakkola: Conceptualization; Writing—review & editing. Marja Hedman: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Validation; Writing—review & editing.

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