Four-dimensional magnetic resonance imaging-derived ascending aortic flow eccentricity and flow compression are linked to aneurysm morphology †

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Abstract

OBJECTIVES: The impact of specific blood flow patterns within ascending aortic and/or aortic root aneurysms on aortic morphology is unknown. We investigated the interrelation of ascending aortic flow compression/peripheralization and aneurysm morphology with respect to sinotubular junction (STJ) definition.

METHODS: Thirty-one patients (aortic root/ascending aortic aneurysm >45 mm) underwent flow-sensitive 4D magnetic resonance thoracic aortic flow measurement at 3 Tesla (Siemens, Germany) at two different institutions (Freiburg, Germany, and San Francisco, CA, USA). Time–resolved image data post-processing and visualization of mid-systolic, mid-ascending aortic flow were performed using local vector fields. The Flow Compression Index (FCI) was calculated individually as a fraction of the area of high-velocity mid-systolic flow over the complete cross-sectional ascending aortic area. According to aortic aneurysm morphology, patients were grouped as (i) small root, eccentric ascending aortic aneurysm (STJ definition) and (ii) enlarged aortic root, non-eccentric ascending aortic aneurysm with diffuse root and tubular enlargement.

RESULTS: The mean FCI over all patients was 0.47 ± 0.5 (0.37–0.99). High levels of flow compression/peripheralization (FCI <0.6) were linked to eccentric aneurysm morphology (Group A, n = 11), while low levels or absence of aortic flow compression/peripheralization (FCI >0.8) occurred more often in Group B (n = 20). The FCI was 0.48 ± 0.05 in Group A and 0.78 ± 0.14 in Group B (P < 0.001). Distribution of bicuspid aortic valve (P = 0.6) and type of valve dysfunction (P = 0.22 for aortic stenosis) was not found to be different between groups.

CONCLUSIONS: Irrespective of aortic valve morphology and function, ascending aortic blood flow patterns are linked to distinct patterns of ascending aortic aneurysm morphology. Implementation of quantitative local blood flow analyses might help to improve aneurysm risk stratification in the future.

Keywords: Ascending aortic aneurysm • Wall shear stress • Circumferential wall tension • Blood flow • Phase contrast magnetic resonance imaging • Aortopathy • Bicuspid aortic valve • Aortic stenosis • Aortic regurgitation

INTRODUCTION

The pathophysiological interactions between aortic biomechanical factors [1] including local blood flow patterns in ascending or aortic root aneurysms [2–4] and aneurysm morphology [5, 6] are hardly understood. The nature of the complex interplay between left ventricular function, left ventricular outflow tract anatomy, aortic valve type and function as well as ascending aortic flow patterns and pathological morphology of the ascending aorta need to be better characterized in order to improve risk stratification for patients with borderline-sized proximal thoracic aortic aneurysms [7]. This is especially the case for patients with bicuspid aortic valve (BAV), which is associated with an incompletely understood aortopathy and an increased risk of aortic dissection at relatively small aortic diameters. The objective of this study was to investigate the interrelation between the local ascending aortic blood flow patterns and aneurysm morphology in patients suffering from aortic root and/or ascending aortic aneurysms with different types of valve morphology, including all types of BAV and...
valve function. Our basic hypothesis was that two different often found morphological types of aneurysms, ‘sinotubular junction definition’ and diffuse root and tubular enlargement, differ with respect to mid-systolic ascending aortic flow compression.

PATIENTS AND METHODS

Patients

Patients \(n=31\) suffering from isolated ascending aortic aneurysm \((n=11, 35\%)\) and/or aortic root aneurysm \((n=20, 65\%)\) who were treated either at the Heart Center Freiburg University \((n=25, 2012–2014)\) or the University of California in San Francisco \((n=6,\) including earlier treatment from 2000 to 2014) were included in the study. All individuals signed their informed consent and the respective ethics committees (University of Freiburg, Freiburg, Germany, as well as University of California in San Francisco) approved this prospectively designed study. The mean patient age was 53 ± 17 years \((range\ 19–68\ years)\) and the mean ascending aortic size was 55 ± 11 mm. For detailed patient characteristics, see Table 1/Fig. 1. Ten patients \((32\%)\) presented with a BAV including all types of root and cusp configurations \([8]\) \((1\ type\ 0, 1\ type\ 1\ R/N\ and\ 8\ type\ 1\ R/L)\), while the rest had a tricuspid aortic valve. Aortic regurgitation \((AR)\) was the leading clinical problem in 13 patients \((42\%)\), while \(n=7\) patients \((22\%)\) had a leading \((more\ than\ mild)\) aortic stenosis and in the rest of the patients the aortic valve was functioning normally. AR was of type \(1\) in 9 patients \((29\%)\) and type \(3\ AR\) \([9]\) was present in two patients \((6\%)\). For details of aortic valve type, aortic valve configuration and valve function see also Fig. 1.

Groups of root/ascending aortic aneurysm morphology

Routine preoperative thin-slice aortic computed tomography (CT) or magnetic resonance (MR) angiography was used for classification of patients into two different groups according to aortic root and ascending aortic morphology (see Fig. 2). Group A (Fig. 2) was defined as small root with tubular ascending aortic enlargement, also referred to as ‘sinotubular junction definition’ and Group B was defined as diffuse root and tubular enlargement without sinotubular definition.

Four-dimensional phase contrast magnetic resonance imaging

Data assessment. All measurements were performed on 3-Tesla MRI Systems (Trio, Siemens, Germany) at two different institutions \((Heart\ Center\ Freiburg\ University,\ Freiburg,\ Germany,\ and\ University\ of\ California,\ San\ Francisco,\ CA,\ USA)\) between 2010 and 2014. Three-dimensional (3D) anatomical imaging was performed in combination with the acquisition of spatially registered three-directional intraluminal velocity information \((time\-resolved\ 3D,\ 4D)\). Data were acquired using a sagittal oblique 3D volume covering the entire thoracic aorta including the transverse arch and the supra-aortic vessels. ECG gating was used to assess blood-flow information as a function of the cardiac cycle and tissue movement. To reduce artefacts due to respiration, flow-sensitive 4D MRI was combined with navigator gating using a lung-liver interface, which was monitored by executing a navigator pulse at the end of each cardiac cycle. Respiratory control was achieved by gating MR measurements to the respiratory motion.

Table 1: Basic clinical variables, aortic and valvular characteristics of both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=11)</th>
<th>Group B (n=20)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57</td>
<td>50.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>70</td>
<td>45</td>
<td>0.1</td>
</tr>
<tr>
<td>BSA ((m^2))</td>
<td>2 ± 0.15</td>
<td>2 ± 0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Height ((cm))</td>
<td>84.8 ± 10</td>
<td>88.7 ± 14</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>36</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55</td>
<td>55</td>
<td>0.3</td>
</tr>
<tr>
<td>NYHA (1–1.5)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0.5</td>
</tr>
<tr>
<td>BAV (%)</td>
<td>36</td>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>AS (%)</td>
<td>45</td>
<td>20</td>
<td>0.1</td>
</tr>
<tr>
<td>AR (grade)</td>
<td>1.3 ± 1.3</td>
<td>2 ± 1</td>
<td>0.2</td>
</tr>
<tr>
<td>FCI (%)</td>
<td>49 (44–53)</td>
<td>73 (65–89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are given as mean ± standard deviation. Categorical variables are given as fractions of the respective group, medians and interquartile ranges.

BSA: body surface area; LVEF: left ventricular ejection fraction; BAV: bicuspid aortic valve; AS: aortic stenosis; AR: aortic regurgitation; FCI: Flow Compression Index.

Data post-processing and visualization. 4D MR data were preprocessed using fully automated noise filtering and eddy current correction to minimize image noise using an institutional software package. All data were further processed using a commercially available software package (EnSight; CEI, Apex, NC, USA) for interactive 3D data analysis. In every dataset, a mid-ascending emitter plane was created for colour-coded particle trace imaging of local flow patterns. The plane also served as origin for 3D local flow vector fields visualizing the local flow pattern including vortices, helices, peripheralization/compression as well as local flow velocities using colour-coding and represented by the length of the individual vector arrows (Fig. 3).

Quantification of local mid-ascending aortic flow compression

The UTHCSA Image Tool Software \((UTHCSA,\ San\ Antonio,\ TX,\ USA,\ http://compdent.uthscsa.edu/dig/itdesc.html)\) was used to quantify flow compression within the ascending aorta. Ascending aortic flow compression was defined as the constriction of the cross-sectional area constrained by the main systolic jet. For this, the mid-ascending mid-systolic vector field plane was loaded and, using the UTHCSA software, the inner diameter of the luminal surface normalized as 1. The surface area of vectors indicating detectable peak systolic forward flow and representing the main systolic jet was given as a fraction of the complete luminal surface area \((Flow\ Compression\ Index,\ FCI,\ Fig.\ 4)\), with lower numbers indicating higher degrees of local mid-ascending flow compression/peripheralization.

Statistical analysis

Groups A and B were compared using the unpaired \(t\)-test. Numerical variables are given as mean ± standard deviation or median with 95%
confidence interval as appropriate (Fig. 5). The Mann–Whitney rank-sum test was used in case of failed normality testing, which was performed using the Shapiro–Wilk test. For all statistical analyses, the SigmaStat and SigmaPlot 12.0 software package was used (Systat Software GmbH, Erkrath, Germany).

RESULTS

Included patients were either scheduled for surgical treatment of their aortic disease or patients under surveillance for known aortic root and/or aortic valve disease. Seven of the studied patients were treated with a valve-sparing aortic root replacement procedure, 2 with implantation of a composite valved conduit, 1 with isolated aortic valve replacement and 5 patients had some type of either additional or isolated aortic valve repair over the course of the study. In 4 patients, a hemiarch replacement was performed and all patients were treated electively. The rest of the included patients were not operated on after the time of 4D MR scanning. There were n = 11 patients in Group A (eccentric morphology, sinotubular junction definition), while n = 20 patients were defined as Group B (diffuse, including aortic root) regarding aortic
morphology. The distributions of age ($P = 0.41$), valve morphology ($P = 0.33$) and valve function ($P = 0.06$) did not differ significantly between these two groups (see Table 1 for details). Ten patients had a BAV (36 vs 30% in Groups A and B, $P = 0.33$). In 15 patients, no higher grade valvular dysfunction was present. In addition, with regard to aortic valve stenosis ($P = 0.06$) and aortic valve regurgitation ($P = 0.16$), there was no statistically significant difference detectable between Groups A and B but a trend showing more aortic stenosis in Group A and more regurgitation in Group B, as described by others.

There was a strong statistical correlation between the aortic morphology Groups A and B and FCI. The overall mean FCI was $0.47\pm 0.5$ (0.37–0.99). In Group A, the mean FCI was $0.49\pm 0.44$–0.53, while in Group B it was $0.73(0.65–0.89)$. Thus, the FCI seemed to be linked to aortic aneurysm morphology, but no correlation with aortic valve function or specific types of aortic valve configuration was detected. Importantly, sample size was small, rendering statistical analyses possibly underpowered.

No substantial ascending aortic mid-systolic flow compression was detectable in $n = 4$ patients who presented with an FCI $>90\%$. Of these patients, two had AR and the other two normally functioning aortic valves. Flow compression of some degree was found in the majority of 27 patients ($87\%$), with higher grades of flow compression (defined as an FCI $<0.6$) in 12 patients ($78\%$). The patients with higher grades of flow compression with an FCI $<0.6$ had a BAV in 36% of cases ($n = 4$).

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**Figure 2:** Green arrowheads mark the sinotubular junction level. Group A: aortic morphology with a normal-sized aortic root, tubular enlargement on the left (also referred to as ‘sinotubular junction definition’). Group B aortic morphology with diffuse enlargement of the aortic root and the ascending aorta, without definition of the sinotubular junction on the right side.

**Figure 3:** Mid-ascending cross-sectional emitter plane used for visualization of mid-systolic areas of flow using colour-encoded and length-encoded vector fields.

**Figure 4:** Four examples of local mid-ascending velocity-encoded aortic flow vector fields for the two different aortic aneurysm morphology types, respectively, from 8 different patients. Grey lines delineate the respective crosssectional areas of high mid-systolic flow used to express the flow compression index as ‘cross-sectional area of high mid-systolic flow/complete cross-sectional luminal area’. Upper panel: Group A patients with small root, tubular enlargement (see computed tomography image on the upper right). Lower panel: Group B patients with diffuse root and tubular enlargement (see computed tomography image on the lower right).
DISCUSSION

Ascending aortic flow patterns and their local biomechanical sequelae have been the focus of several studies [2-4, 10-17]. Knowledge on the interplay between ascending aortic flow characteristics and the clinical risk profile of a proximal thoracic aortic aneurysm is limited, although several studies reporting flow-sensitive 4D MR-based visualization of flow patterns in ascending aortic or aortic root aneurysms have been reported [3, 4, 10, 15, 16]. In this study, we sought to characterize the relationship between mid-ascending aortic, mid-systolic flow compression and aneurysm morphology in patients with ascending aortic and/or aortic root aneurysm and different valve types and configurations.

With the effort to improve understanding of possible flow-related risk profiles, there is a need to clearly define the respective endpoints. Histological evaluation of local severity or quantity and architectural pattern of matrix degeneration has among others been reported by Girdauskas et al. [18]. Other endpoints studied include aneurysm shape and longitudinal extent of the thoracic aortopathy as, for example, defined by the Stanford group [5, 6].

As classification system of proximal thoracic aortic aneurysms, we chose to use the differentiation between root type and non-root type or 'STJ' definition, referring to the presence of a small root and small sinotubular junction (STJ). Stanford Fazel clusters of BAV aortopathy were not used for classification of aortic root ascending aortic morphology because these have been identified in a cohort consisting of BAV patients only [5, 6]. In addition, the distal aneurysm extent as described by the Stanford Fazel clusters has been found not to be linked to valve type or valve function [5], and so we put the local aneurysm morphology in the focus of the reported study instead of distal extent. In addition, in a recent study by Della Corte et al., the 'root type' aortic aneurysm morphology was also the only morphological differentiation which seemed to be translating into clinical significance [19]. The different parts of the left ventricular outflow tract and aortic root, as well as the tubular ascending aortic stem from different embryological origins can explain the presence of STJ definition in some patients and its absence in others.

Our results imply that local flow patterns as described by flow compression or peripheralization are strongly linked to the aneurysm morphology defined as 'STJ definition'. Valve types including different types of BAVs and valve function including all grades and types of aortic stenosis and AR were evenly distributed between the two groups. However, sample size remains an important limitation and differences might have been undetected as a consequence of small group sizes. AR is probably more frequent among patients with a diffuse type of aortopathy, although not detected by the presented statistical tests. Neither the valve type nor the valve function seemed to be clearly linked to flow compression, although typical S1 R/L flow patterns with intense right-handed helical flow and acute jet angle were found, similarly to those in other reports [12]. It has been shown that cusp fusion type, as summarized by Sievers et al. [8], is a major contributor to local flow patterns and wall shear stress distribution in the setting of a BAV [12]. The vast majority of the cohort studied herein had right-left coronary cusp fusion with associated stenosis (type 1 R/Ls).

Owing to the lack of an intrinsic BAV comparison group, we were not able to compare different BAV types with respect to ascending flow compression or aneurysm morphology. Hope et al. in 2011 reported on 46 patients with BAV and tricuspid valve stratified for normal or eccentric systolic jets. The group found that eccentric systolic flow was linked to higher local levels and also asymmetry of the local shear stress [3]. Another group has reported an association of diffuse-type aortic aneurysm with AR, but several other studies could not demonstrate such an interrelation [5, 20].

Based on the findings of our study, we conclude that there might be other mechanical and morphological determinants of ascending aortic flow patterns than aortic valve morphology and aortic valve function alone. We identified patients with eccentric, compressed and peripheralized flow who did not suffer from aortic stenosis, nor had a bicuspid valve anatomy. At the same time, there were patients who had aortic valve stenosis to a certain degree, but did not show very eccentric or compressed ascending flow patterns. We hypothesize that other biomechanical aspects including aorto-mitral geometry and angle, LV mass geometry and LV mass functional characteristics during systole and maybe other anatomical aspects of the left ventricular outflow tract anatomy below the valve play a role in determination of ascending aortic flow patterns. These seem to be linked to aneurysm morphology, and thus alternative anatomical factors contributing to the characteristics of ascending aortic flow patterns might play an important role in aneurysm development and might also possibly be of significance for clinical risk stratification.

In addition, 4D MR phase contrast-based flow characteristics might play a role in clinical risk stratification of borderline-sized aneurysms in the future, but for this a much more detailed understanding of implications of flow alterations and local ascending aortic biomechanics will be necessary.

LIMITATIONS

Owing to a relatively small sample size, a difference between both groups with regard to valvular and aortic morphological characteristics might have been undetected. However, there seemed to be a homogeneous distribution for all of these variables. We performed a semi-quantitative assessment of mid-systolic mid-ascending flow compression.
CONCLUSIONS

Irrespective of aortic valve morphology and function, specific characteristics of ascending aortic blood flow patterns like flow compression are linked to distinct aortic aneurysm morphology. There might be other determinants of ascending aortic flow patterns than aortic valve morphology and aortic valve function alone. Implementation of local blood flow analyses might help to improve thoracic aortic aneurysm risk stratification in the future.

Funding

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Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr A. Juraszek (Warsaw, Poland): My questions are intended only to add on some details of this well-performed study. Dr Kari, your study results suggest there are factors other than the aortic valve morphology influencing the measured parameters, the flow compression and peripheralization. In which way would you like to investigate the role of left ventricle outflow tract function and morphology? Do you think that performing this kind of measurement in a larger cohort of patients with homogenous distribution of different bicuspid aortic valve forms would show the coincidence between the different bicuspid valve flow patterns and different ascending aorta dilation forms as was observed in some previous studies?

Dr Kari: Regarding your second question, I think that if we would have a much larger patient cohort, and that’s what we’re working on at the moment, we’d probably see some differences with regard to dysfunction, to early valve dysfunction. I do think that valve stenosis will impact on flow compression index or the flow pattern in the ascending aorta, and that might be due to the numbers of included patients that we didn’t find a significant difference. Although, I do think that even in a larger cohort of patients, flow compression would be linked to aneurysm morphology, I think these results wouldn’t really change because it was already very obvious from the data. With respect to your first question, I really think magnetic resonance imaging is the method of choice here, and I thought the first talk was really interesting and fits the second talk perfectly. Another idea would be to actually combine a more engineering kind of approach towards this problem and include modelling, CFD analysis, and people who are not necessarily clinicians and come from two separate directions, the actual measured clinical patient data or magnetic resonance data on the one hand and use it as a proof of concept for results you get from simulations, from computer simulations.

Dr Juraszek: For the MRI, it seems to be generally nice to analyze the flow patterns in the ascending aorta, too. What are, in your opinion, the indications for performing this kind of measurement in patients with smaller aortic dimensions than the individuals included in the study? That means patients with the aorta smaller than 45 mm. Which patient cohort, in your opinion, would benefit from this kind of risk stratification?

Dr Kari: As you said, patients with a mildly dilated root or ascending aortas. And a colleague of mine, Dr Rylski here, he wrote about the fact that many patients do seem to have smaller diameters right before they have a type A dissection. And risk factors for type A dissection in the setting of a normal sized or mildly dilated aorta are hardly understood, I would say. So this is the patient group that it’s all about. Another patient cohort that might benefit from this are patients who have a familial pattern of type A dissections but without a proven or clear diagnosis of connective tissue diseases.

Dr C. Etz (Leipzig, Germany): What Fabian just said is probably one of the most important things that I would like to underscore: the heterogeneity of this disease pattern, the fact that some patients dissect with very small diameters and others with larger diameters. We will always cover those that dissect at the larger diameters when we use the guidelines, but we’ll lose those that dissect in a very small diameter. Probably, this is exactly what we need.

Dr G. Krasopoulou (Oxford, UK): I was intrigued by one of your conclusions, when you said that valve morphology is not a factor that influences as much the aortic flow. I’m unclear because you have small numbers of bicuspid valves, and then you divide them into regurgitation and stenosis. Two completely different
diseases, so I’m not sure how you can come up with that kind of statement. Also, I don’t know if you have any kind of insight on how interventions that we as surgeons do to the valve, especially when we’re performing valve repairs, influence the flow later on? Do we actually manipulate that or not?

Dr Kari: You probably are talking about this point here. This is actually referring to a different study. I’m sorry, I thought I made this clear. This is not actual conclusions from the data we have here. And can you repeat your second question, the changing of morphology through surgery?

Dr Krasopoulus: I am trying to translate your findings into everyday practice. We do get, let’s say, patients that do have a bicuspid valve with a certain degree of ascending aorta dilatation, especially the ones that come with regurgitating valves, and we actually repair them. I don’t know if you or anybody else has looked at how repair affects the progression of their aortopathy.

Dr Kari: Well, ultimately we should be able to do that. The goal should be a multi-model risk model, a risk model for these patients.

Dr C. Etz: Well, if we combine our knowledge with what we learned from Dr Gittenberger-deGroot yesterday in the postgraduate course, she said that all the bicuspid valves that are truly bicuspid and not maybe bicuspid but tricuspid patients have this genetic issue with their aortic ascending aorta. And this is, I think, probably what you described as in the distal extent is probably more depending on the genetic issue why the proximal and the root part is more depending maybe on the flow, which makes flow analysis extremely important. We know from the Leipzig analysis of the type A dissection type that the bicuspid patients tend to dissect or have the entry of the dissection tear further proximally than tricuspid patients—so more in the root. I think this all moves on to become one big picture, so I think it’s very important.