Statistical wall shear stress maps of ruptured and unruptured middle cerebral artery aneurysms

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Haemodynamics and morphology play an important role in the genesis, growth and rupture of cerebral aneurysms. The goal of this study was to generate and analyse statistical wall shear stress (WSS) distributions and shapes in middle cerebral artery (MCA) saccular aneurysms. Unsteady flow was simulated in seven ruptured and 15 unruptured MCA aneurysms. In order to compare these results, all geometries must be brought in a uniform coordinate system. For this, aneurysms with corresponding WSS data were transformed into a uniform spherical shape; then, all geometries were uniformly aligned in three-dimensional space. Subsequently, we compared statistical WSS maps and surfaces of ruptured and unruptured aneurysms. No significant \( p > 0.05 \) differences exist between ruptured and unruptured aneurysms regarding radius and mean WSS. In unruptured aneurysms, statistical WSS map relates regions with high (greater than 3 Pa) WSS to the neck region. In ruptured aneurysms, additional areas with high WSS contiguous to regions of low (less than 1 Pa) WSS are found in the dome region. In ruptured aneurysms, we found significantly lower WSS. The averaged aneurysm surface of unruptured aneurysms is round shaped, whereas the averaged surface of ruptured cases is multi-lobular. Our results confirm the hypothesis of low WSS and irregular shape as the essential rupture risk parameters.

Keywords: cerebral aneurysms; cerebral haemodynamics; computational fluid dynamics

1. INTRODUCTION

Blood flow-mediated structural changes of the parent vessel and the aneurysmal wall are associated with initiation, growth and rupture of intracranial aneurysms causing subarachnoid haemorrhage (SAH) [1]. SAH is associated with high mortality (up to 50%) and morbidity (25–50%) [2]. By means of modern non-invasive imaging modalities—three-dimensional rotational angiography (3DRA), computed tomography angiography (CTA) and magnetic resonance imaging (MRI)—more aneurysms without symptoms are detected incidentally. Since the aneurysm treatment options (microsurgical clipping or endovascular coil embolization) are not without risk [3], a treatment decision based on rupture risk analysis allows a trade-off between rupture risk and treatment risk and is expected to improve patient outcome. Current efforts focus on two groups of risk parameters: morphometric and haemodynamic [4–7].

Haemodynamic parameters associated with the rupture risk are wall shear stress (WSS) and its derivatives. Based on a longitudinal study, it was hypothesized that aneurysmal growth occurs at regions exposed to low WSS [4]. By contrast, high WSS and WSS gradients were correlated with aneurysm initiation in an animal aneurysm model [8]. Significantly higher WSS [9,10] and lower WSS [6,11,12] were both associated with ruptured aneurysms. Even more confusingly, Cebral et al. [13] found no correlation at all between WSS and rupture—only the impingement jet size correlated with rupture. Whereas Chien et al. [9] found no correlation for these proposed impingement jet parameters. Jou et al. [14] also found no correlation between maximum and mean WSS and rupture. They found, however, larger areas with low WSS in ruptured aneurysms. In a recently published analysis of 210 cerebral aneurysms, larger maximum WSS and concentrated inflow jets were observed in ruptured aneurysms [5].

Geometric parameters associated with aneurysm rupture are size and shape parameters. Size (aneurysm diameter) is now the only clinically used parameter for
risk evaluation and treatment decision validated by the International Study of Unruptured Intracranial Aneurysms (ISUIA) [15]. The parameter is, however, controversial. ISUIA found a very low risk of rupture for aneurysms of the anterior circulation smaller than 13 mm. A lot of small aneurysms, however, rupture, whereas some giant aneurysms never rupture [16]. In clinical practice, the majority of ruptured aneurysms and unruptured aneurysms needing therapy decisions are of small and medium size (4.0–9.0 mm) [6,7,17]. This stimulated search and development of other geometric risk parameters, which are well described by Dhar et al. [7] and Lauric et al. [18]. The results of studies performing rupture risk analysis based on aneurysm morphometry are similarly confusing as the findings of studies based on haemodynamics. The general agreement is that uneven aneurysms are more prone to rupture [19].

Our hypothesis is that these controversial findings are due to the absence of a link between haemodynamic parameters and geometric locations. Aneurysm rupture, however, is a locally occurring event. Pathological studies revealed that most cerebral aneurysm ruptures (84% of 396) occur in the dome region (upper third part of the aneurysm height) [20,21]. Only 2 per cent of ruptures take place in the neck region (lower third part). The purpose of this work is to establish and to include analysis of statistical WSS distributions of ruptured and unruptured aneurysms groups fixed in three-dimensional space into the rupture risk analysis. A point-to-point comparison of WSS distributions in different aneurysms is challenging owing to the high variability of aneurysm shapes (round, multi-lobular, elliptic and dumbbell) [22]. In order to circumvent this problem, we developed a tool transforming aneurysmal sacs with calculated WSS into a uniform shape. This is done after a uniform alignment of the aneurysms in the three-dimensional space, which is a part of the proposed method. Thereby, the statistical analysis of WSS distributions and the generation of statistical aneurysm shapes in 22 middle cerebral artery (MCA) aneurysms and separately for seven ruptured and 15 unruptured aneurysms became possible. The study was performed with aneurysms of the same location (MCA) as aneurysm site is a known rupture risk parameter [15,17]. To the best of our knowledge, our study shows for the first time statistical WSS maps of ruptured and unruptured aneurysms.

2. MATERIAL AND METHODS

During a period of 3 years (2008–2010), 3DRA data were collected from all patients with cerebral aneurysms (more than 90 cases) without vasospasms at the Helios Hospital Berlin-Buch, Department of Neurosurgery. The total database can be seen at http://www.charite.de/biofluidmechanik/downloads/Datenbank.pdf. Cases with vasospasms were not considered because vasospasms may significantly affect the intra-aneurysmal flow [23]. 3DRA acquires images of aneurysms with high contrast (signal-to-noise relation) and compared with CTA and MRI with higher space resolution. The geometric data for our study were acquired by means of the digital subtraction AXIOM Artis C-arm system with a rotational acquisition time of 5 s with 126 frames (190° or 1.5° per frame, 1024 × 1024 pixel matrix) with a post-processing using LEONARDO InSpace 3D (Siemens, Forchheim, Germany). Preliminary reconstruction of a volume of interest selected by a neurosurgeon generates a stack of 440 image slices with 512 × 512 pixels in-plane resolution resulting in an isovoxel size around 0.25 mm [3]. Thereafter, we performed the voxel labelling using simple thresholding with subvoxel accuracy combined with a region-growing technique [24], which implies an intensive manual interaction. The label field was then converted into a triangulated surface using a Marching Cubes [25] algorithm, which (surface) is smoothed using the Laplacian algorithm. The smoothing procedure is necessary to remove surface mesh artefacts (staircase effect) [3]. The reconstructions were performed using the software ZIBAmira (Zuse Institute Berlin, Germany). The final three-dimensional isosurfaces (figure 1a) were approved by the experienced clinician (neurosurgeon) that is considered to be the gold standard of a segmentation procedure [26].

Altogether 22 saccular MCA aneurysms acquired during the collection period with 3DRA images of
The aneurysm sac geometry is then automatically transformed into a uniform spherical shape (figure 1b) as a component of the ZIBAmira software. First, the aneurysm sac is manually cut off the parent vessel at the aneurysm neck. The cut-off procedure is done freehand, but nevertheless operator-independent for the uniform aneurysm neck. All MCA aneurysms are considered to be bifurcation aneurysms. A tool to transform individual aneurysms into a uniform spherical shape (figure 1b) was developed as a component of the ZIBAmira software. First, the aneurysm sac is manually cut off the parent vessel at the aneurysm neck. The cut-off procedure is done freehand, but nevertheless operator-independent for the uniform aneurysm neck. Four operators including one clinician independently performed the cut-off procedure on five aneurysms with a mean radius of 3.35 mm calculated for five aneurysms including one clinician. The projection for any point is defined as the accumulated change of area over the aneurysm surface. The overall distortion $d$ is defined as $d = \sum_{i=0}^{n} A(t_{\text{sphere}})$. To calculate the radius of the desired sphere, the volume of the aneurysm has to be determined. For that, the open neck area of the aneurysmal sac is closed by projecting each vertex of the edge to the neck plane and triangulating the hole. This closed aneurysm sac is then filled with tetrahedra in order to compute the exact volume and with it the necessary radius $r$ of the sphere. The sphere is fixed in the three-dimensional space by keeping the neck plane and the neck mass centre the same as for original sac. Then, the vertices of the sheared aneurysmal sac together with their WSS data are radially projected onto the uniform sphere keeping the aneurysm volume constant. The projection for any point $p$ is $p' = r \times ((p - c) / |p - c|)$ (figures 1b and 2a). Theoretically, with non-convex aneurysm surfaces, this might lead to overlapping spherical shapes causing degenerated cells. However, the radial projection worked without any artefacts for the aneurysms investigated in this study. Table 1 summarizes rupture state, patient age and sex, aneurysm radius, mean (time- and area-averaged) WSS and with it the necessary radius $r$ of the sphere. The sphere is fixed in the three-dimensional space by keeping the neck plane and the neck mass centre the same as for original sac. Then, the vertices of the sheared aneurysmal sac together with their WSS data are radially projected onto the uniform sphere keeping the aneurysm volume constant. The projection for any point $p$ is $p' = r \times ((p - c) / |p - c|)$ (figures 1b and 2a). Theoretically, with non-convex aneurysm surfaces, this might lead to overlapping spherical shapes causing degenerated cells. However, the radial projection worked without any artefacts for the aneurysms investigated in this study.

The aneurysm sac geometry is then automatically transformed into a spherical shape of identical volume and neck area. A plane passing the neck cross section is computed by minimizing the distances between the aneurysmal neck edge and the plane using the least-squares algorithm (figure 1b). Normally, the neck edge has the shape of a saddle. The aneurysmal sac is then sheared such that the mass centre of the aneurysmal sac located perpendicular to the neck centre of the aneurysmal neck calculated at the neck plane (figure 1b). The shearing reduces the distortion of the surface at the subsequent projection to the spherical shape. The overall distortion reduces the distortion of the surface at the subsequent projection to the spherical shape. The overall distortion $d$ is defined as the accumulated change of area $A$ over the aneurysm surface, i.e. for a surface consisting of $n$ triangular surface cells $t$: $d = \sum_{i=0}^{n} |A(t_{\text{aneurysm}}) - A(t_{\text{sphere}})|$. To calculate the radius of the desired sphere, the volume of the aneurysm has to be determined. For that, the open neck area of the aneurysmal sac is closed by projecting each vertex of the edge to the neck plane and triangulating the hole. This closed aneurysm sac is then filled with tetrahedra in order to compute the exact volume and with it the necessary radius $r$ of the sphere. The sphere is fixed in the three-dimensional space by keeping the neck plane and the neck mass centre the same as for original sac. Then, the vertices of the sheared aneurysmal sac together with their WSS data are radially projected onto the uniform sphere keeping the aneurysm volume constant. The projection for any point $p$ is $p' = r \times ((p - c) / |p - c|)$ (figures 1b and 2a). Theoretically, with non-convex aneurysm surfaces, this might lead to overlapping spherical shapes causing degenerated cells. However, the radial projection worked without any artefacts for the aneurysms investigated in this study. Figure 1c shows exemplary WSS distributions of the original sac and the identical data projected onto the corresponding spherical shape.

The next step is the projection of the WSS data (scalar or vector) of all investigated aneurysms onto one sphere with a uniform surface mesh containing 5000 uniformly distributed vertices. For this purpose, each of these 5000 vertices is identified with that point on every aneurysm sphere, to which the distance is minimal. However, for some aneurysms, their spherical representation is closer to a complete sphere than for

<table>
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<th>Sex</th>
<th>Age (years)</th>
<th>Radius (mm)</th>
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<th>WSS (Pa)</th>
<th>Low WSS (%)</th>
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others. This is due to aneurysms with different aspect ratios (aneurysm height divided by aneurysm neck width), a parameter often used to describe aneurysm sacs [7,16]. As a result, only data from a subset of the aneurysms are available for the neck region of the destination sphere (see §4). If the minimal distance from one vertex of the uniform sphere to a vertex on an aneurysms sphere exceeds a given threshold, this particular aneurysm is ignored for that specific data point (vertex).

The representation of data on the sphere is not favourable for static visualization, because spherical visualization hides the data on the hemisphere not aligned to the viewer. To overcome this drawback, the data represented on the uniform sphere are mapped onto a plane (disc) representation using the azimuthal equidistant projection known from Earth mapping (figure 1c). The centre of the two-dimensional disc corresponds to the dome point of the uniform aneurysm sac. This representation is equidistant for two points on a straight line through the centre point. The area distortion increases with increasing distances from the centre. From the sphere construction, the sphere centre point $c$ and the neck plane normal $n$, defining where ‘up’ is on the sphere, are known. The point that intersects with $n$ coming from $c$ becomes the centre point of the plane. Any point on the surface is described by a vector $p$, relative to $c$ with its length $l$ and an angle $\alpha$ relatively defined to a fixed $0^\circ$ vector corresponding with the 0X vector (figure 2b). The length $l$ is measured on the spheres surface: $l = \|n, p\| \times r$ with $r$ being the sphere radius and the angle given in radian. The angle $\alpha$ is measured between a projection of the vector $p$, to the neck plane and another arbitrary, but fixed vector parallel to that plane.

Owing to the projection of the original sacs onto a sphere, cell sizes have to be changed. These deformations were assessed in order to measure the deviation of the original aneurysmal sacs from the spherical shape. Finally, the average aneurysm surfaces were generated: all aneurysms and their corresponding spherical surfaces were scaled to an identical radius. Then, displacement vectors from each sphere vertex to its original aneurysm counterpart were computed. These displacements are mapped onto a single sphere and averaged for each of the 5000 vertices. Finally, the vertices on that sphere were transformed (normally shifted) according to the averaged displacements, which results in the mean aneurysm surface.

The statistical map generation needs a uniform alignment of all aneurysmal sacs in the three-dimensional space. During the transformation procedure, all aneurysms are automatically located (moved and rotated) in three-dimensional space in order to fulfill the following requirements: the aneurysm neck plane is aligned with the XY-plane (figure 3b) and the centre of coordinates is collocated with the centre of the uniform shape (figure 1b). The Z-axis (blue) is directed towards the dome. Then, the aneurysmal sac is rotated manually around the Z-axis in order to align the X-axis (red) with M2a and M2b, bifurcating branches of the first segment of the MCA. The M2a branch is the vessel topologically next to the anterior cerebral artery (ACA; figure 3b). The direction of the X-axis is selected to be congruent with the axis of M2b. Aneurysms from left and right hemispheres were considered separately. Then, aneurysms of the right hemisphere were mirrored at the interhemispheric plane in order to study all cases together. Medians of WSS values calculated for each vertex of the uniform shape are shown in order to eliminate the impact of outliers owing to the small sample of ruptured cases.

Transient flow was calculated by a fully segregated pressure-based software Fluent 6.3 (ANSYS-Fluent Inc., USA) solving Navier–Stokes equations for incompressible flow. Fluent has been successfully used in biofluid mechanics studies and experimentally validated [28,29]. A surface triangulated mesh with a vessel radius-dependent resolution of 0.15–0.25 mm node distance corresponding to the resolution of the 3DRA acquisition was generated. Then, a high-quality (maximal skewness less than 0.75 and aspect ratio less than 6.0) volume mesh including a boundary mesh layer consisting of three rows of wedges with an increasing depth of wedges by a factor of 1.2 (total depth of 0.3 mm) refining the mesh in the near-wall region was generated. Near-wall mesh refinement warrants the correct calculation of the local WSS. WSS were calculated by partial differentiation of near-wall local velocity fields perpendicular to the corresponding surface elements.
WSS = μ* (∂(velocity)/∂(normal surface)). The mesh procedure was based on results of our mesh independence study. Flow was assumed to be laminar. The non-Newtonian fluid was modelled using the generalized power-law model including haematocrit dependence [30]. All simulations were performed using one waveform obtained from an internal carotid artery (ICA) by means of a phase contrast MRI [31] and one mean flow rate of 222 ml min⁻¹ [32]. The mean flow rate for the ICA was taken from the literature as patient-specific data were not available. ICA was the inlet segment in all investigated cases. The longest possible segments of ICA (figure 1) were reconstructed in order to avoid the dependence of results from the reconstructed domain [33]. This is crucial owing to the complex course of the cavernous ICA generating swirling secondary flow. The flow ratio (Q₁/Q₂) at all bifurcations was split according to Murray’s Law describing a relation between flow rate and vessel diameter (Q ∝ d³ [3]), that is validated for cerebral arteries [34]. Diameters (d) of branching segments were measured in three-dimensional reconstructions using the visual ZIBAmira measuring tools. The arterial walls were assumed to be rigid, and a no-slip condition at the wall was used. The pressure value at the outlet was not imposed. A second-order discretization scheme and a SIMPLEC (semi-implicit method for pressure-linked equations—consistent) model for pressure-flow coupling were used. The convergence limit for relative errors was set at 2 × 10⁻⁵. Unsteady flow simulations were performed through two pulsatile cycles to eliminate the influence of initial transients. Analyses of time-averaged WSS were performed for a second cycle. A small time step of 0.001 s assured a time-step independence of the
solution. Statistical WSS maps of aneurysmal sacs were visualized on the two-dimensional planes (discs; figure 1c) separately for all [22], unruptured [15] and ruptured [7] cases. Furthermore, the dome region corresponding to the upper third part of the uniform aneurysm sphere height was marked. Note that the visualization uses a nonlinear colour map. This is done normally to better visualize small variations. Taking into account the above-mentioned deformation of the cell sizes owing to the mapping procedure, the interpretation of coloured maps should be done with caution. In order to visualize and characterize WSS distributions accurately, we generated WSS histograms. The ranges of WSS values \(0 \leq \text{WSS} \leq \text{WSS}_{\text{max}}\) were divided into 100 classes. For each WSS class, the area corresponding to the respective class was calculated as the percentage of the total wall surface area of the uniform aneurysmal sac (sphere). Note that changes of cell sizes were taken in account during the area calculations and do not affect histograms. As described above, the whole uniform sphere contains 5000 WSS values, whereas the dome region contains about 1700.

The statistical analysis was performed using the statistical package SPSS V. 19. Significance was assumed at \(p \leq 0.05\) for all tests. A Kolmogorov–Smirnov test was performed to assess deviations from a normal distribution. Group differences were assessed by paired \(t\)-Student’s test in the case of normally distributed data. Otherwise, Mann–Whitney \(U\)-test was used in combination with the Levene test proving the equality of variances.

3. RESULTS

The mean WSS of 22 MCA aneurysms (table 1) varied between 0.28 (case A24) and 6.72 Pa (case A75-G) with a median/mean \(\pm\) s.e.m. of 1.95/2.64 \(\pm\) 0.38 Pa. Figure 4 shows statistical WSS maps for all 22 MCA aneurysms and separately for ruptured and unruptured cases.

Analysis of WSS maps for all cases (figure 4a) shows that higher WSS are found in two regions: in the neck area collocated with the M2a branch and in the corresponding half of the dome. Maximal values, however, are found in the neck region.

Mean WSSs in ruptured and unruptured aneurysms (table 1) are not significantly \((p > 0.05)\) different (Mann–Whitney \(U\)-test) with medians/means \(\pm\) s.d.s of 1.85/2.01 \(\pm\) 1.51 Pa versus 1.99/2.94 \(\pm\) 1.85 Pa. In contrast, the normalized areas with WSS below 0.4 Pa approaches significance \((p = 0.06)\) with larger values for ruptured aneurysms (20.8 \(\pm\) 27.2\% vs. 5.77 \(\pm\) 8.48\%, Mann–Whitney \(U\)-test). No significant difference is found between ruptured and unruptured cases for aneurysm radius \(R\) (3.32 \(\pm\) 1.53 mm versus 3.09 \(\pm\) 1.13 mm). A significant inverse correlation with Pearson’s correlation coefficient of 0.48 is seen between normally distributed WSS and radius \(R\) with
WSS = $5.35 \times \exp(-0.3 \times R)$ meaning lower WSS in larger aneurysms.

The statistical WSS maps (figure 4b) show that a larger continuous area of higher WSS values in the dome region is seen only in ruptured aneurysms. Ruptured aneurysms are also associated with larger areas of low WSS (figure 4b,c). WSS maps show geometrically linked differences between ruptured and unruptured aneurysms. A significantly lower WSS is found in ruptured aneurysms ($1.4 \pm 0.76$ Pa versus $2.2 \pm 0.66$ Pa, $p < 0.001$) by a paired (5000 vertices of the uniform shape) Wilcoxon test. The same analysis of WSS maps of the dome region (region inside the black circle) reveals again an overall significantly lower WSS in ruptured aneurysms ($1.89 \pm 0.81$ Pa versus $2.1 \pm 0.49$ Pa, $p < 0.001$). This result seems to be contrary to the WSS maps shown in figure 4b. A large area with high WSS values colour-coded by red is seen in the dome region. This is due to the altered visualization of WSS distributions caused by the colour mapping and changes of the cell sizes described in §2. The quantitatively accurate visualization and characterization of WSS maps are done by WSS histograms. Histograms for the whole surface (figure 4c) show a left shift of the curve towards lower WSS for ruptured aneurysms (shift of the peak from 2.2 Pa towards 1.0 Pa). Histograms for the dome region (figure 4d) reveal a bimodal distribution for ruptured aneurysms with a first peak around 1.0 Pa and a second lower peak around 2.0 Pa. In ruptured aneurysms, both the areas of lower WSS and of higher WSS are larger compared with the histogram of unruptured cases showing only one taller peak around 2.0 Pa.

Figure 5 shows statistical WSS vector fields of 15 unruptured (figure 5a) and seven ruptured (figure 5b) aneurysms. WSS vector fields of ruptured and unruptured aneurysms are similar with a nearly unidirectional flow in the dome region, with the main flow direction along the X-axis. These WSS vector fields are formed by an intra-aneurysmal flow exemplified by two visualized velocity vector fields of one unruptured (figure 5c) and one ruptured (figure 5d) MCA aneurysms: the flow stream of the MCA segment directed towards the interhemispheric plane or an M2a vessel segment (figure 3) enters the aneurysmal sac and forms the aneurysm filling vortex with the vortex core (axis of rotation) aligned with the Y-axis. The ends of the vortex core form critical points (points with zero WSS values). The angle of the stream entering the aneurysmal sac (impingement jet) may vary from case to case, forming a further critical point (impingement area) in the neck or the middle part of the aneurysmal sac (figure 5).

Figure 6a depicts the averaged deformations of cell areas owing to the transformation procedure of original sacs into the uniform shape. Deformation maps were also quantified using histograms (figure 6b). Unruptured aneurysms show significantly smaller absolute changes of cell areas ($1.11 \pm 0.15$ versus $1.29 \pm 0.29$, $p < 0.01$, Mann–Whitney U-test), meaning a significantly larger deviation of ruptured aneurysm from a uniform spherical shape. This is also seen in averaged surfaces of ruptured and unruptured cases (figure 6c).

4. DISCUSSION

A systematic review summarizes 24 risk factors associated with aneurysmal rupture [35], among them site and size of the aneurysm. Wall stress $\sigma$ often described [7] by a simple Laplace law ($\sigma \sim p \times R/s$, with the intra-aneurysmal blood pressure $p$, curvature radius $R$ and wall thickness $s$) is, however, the ultimate parameter defining the rupture of a vessel wall. The rupture location is a function of wall curvature, thickness, properties (elasticity) of the vessel wall and of the surrounding tissue [36]. Wall properties and thickness of vessels and aneurysms are still eluding modern imaging techniques. Nevertheless, aneurysm shape determines intra-aneurysmal flow defining the WSS distribution. WSS and its derivatives in turn determine structural changes [37] and hence properties and thickness of the aneurysmal wall defining the wall stress and thereby the rupture site and risk.

Consequently, many attempts were undertaken to correlate haemodynamic parameters with rupture risk [5,8–14,38]. Our results reconcile seemingly inconsistent findings in the literature: the correlation of rupture risk with low WSS or larger areas with low WSS [11,12,14] and, controversially, with larger mean
or maximal WSS \[10,38\]. Analysis of areas with low WSS is highly interesting since aneurysm walls are exposed to significantly lower mean WSS compared with the parent vessel walls \[6,11,22\]. It was shown that the dome region is exposed to much slower flow \[22\]. Moreover, nearly stagnant flow was detected in the dome of dumb-bell-shaped and in daughter aneurysms \[22\]. In clinical practice, the dome is regarded as the rupture site \[20–22\]. The exact threshold defining the range of low (non-physiological) WSS in the case of cerebral aneurysms is not yet exactly defined. In a first approximation, we use a threshold value of 0.4 Pa to define pathological low WSS. Such a threshold is regarded as responsible for endothelial cell dysfunction causing arterial wall remodelling \[39\]. The third group of parameters based on the analysis of intra-aneurysmal flow structure—larger impingement jet size or highly concentrated inflow jet \[5,13\]—can also be linked to our finding of areas with higher WSS at the dome \(figure\ 4b\). As we found by statistical analysis that aneurysmal sacs of ruptured aneurysms are exposed to the lower area- and time-averaged WSS. This holds true also for the dome region in spite of the existence of a large uniform area with high WSS values \(red\) coloured area in \(figure\ 4b\). Nevertheless, this finding should be considered with caution since the exact rupture sites are unknown and may correlate with areas of high WSS or with areas of low WSS \(blue\) coloured area in \(figure\ 4b\) in the dome of ruptured cases. However, in contrast to the pattern in unruptured aneurysms, the statistical WSS map of ruptured aneurysms reveals only one quarter of the dome area exposed to the higher WSS \(figure\ 4b\). Function and survival of endothelial cells as well as molecular composition of

Figure 6. \(a\) Cells size deformations averaged for unruptured \(solid\) line and ruptured \(dotted\) line aneurysms. In \(blue\) \(colour\) value 0.5) regions, the cell area was doubled, whereas in \(red\) \(colour\) value 2.0) regions, it was shrunken by a factor of 2. \(b\) Histogram curves of distributions shown in \(a\). \(c\) Averaged aneurysm surfaces of unruptured and ruptured cases. \(Red\) and \(blue\) lines mark cross-section lines of the respective uniform spherical shapes.
vessel walls depend on the WSS and its derivatives like WSS gradients [40]. Thus, it might be speculated that large areas with steep transitions between high and low WSS destabilize the aneurysm wall leading to weak points prone to rupture.

Owing to the generation of statistical WSS maps, individual aneurysms were transformed into the uniform shape. However, different aneurysms have different aneurysm aspect ratios (aneurysm height/neck width). As we noted above (see §2), this means that data for the neck region do not exist from all aneurysms. Figure 7a shows the number of cases used for the statistical mapping of all aneurysms. Note, that for the dome region, all cases were available and could be analysed. This is valid for maps of ruptured and unruptured cases. The dome region is of greater importance, since 84 per cent of rupture sites are located in the upper third of the aneurysmal height [20,21].

Cell size deformations and averaged surfaces (figure 6) showed that ruptured aneurysms deviate more from the spherical shape. The averaged surface of unruptured aneurysms can be described as a round shape, whereas the shape of ruptured aneurysms can be described as multi-lobular. The deformation map of ruptured aneurysms indicates an area in the dome region corresponding to cells of double or more reduced area. Such regions correspond to lobes or blebs in original sacs. This is consistent with the general experience that aneurysms with more irregular shapes have a higher rupture risk [19,22].

The relevance of WSS maps can be tested by visualizing the averaged WSS vector field. In the case of a high variability of intra-aneurysmal flow fields, as it has been noted in the literature [13], the averaged WSS vector field would be of stochastic nature with many critical points with zero WSS and many regions with different flow directions. We consider the relevance of findings based on such a stochastic field as questionable. However, the averaged WSS vector field presented in figure 7b shows unidirectional flow in the dome underlining the relevance of our findings.

The goal of our study was to develop a method allowing visualization and analysis of averaged 2.5-dimensional fields of saccular aneurysms (distributions on non-plane surfaces), e.g. WSS values. A group of MCA aneurysms served as model population to test the performance and utility of the method. The method consists of three consecutive steps: uniform alignment of aneurysmal sacs in the three-dimensional space, calculation of the uniform (sphere) aligned sac with the centre located at the coordinate centre and projection of fields (e.g. WSS) onto the surface of the uniform shape. In foreground, the method was primarily developed in order to facilitate the retrospective analysis of rupture risk by incorporating locally bounded parameters (e.g. WSS or WSS space gradient) associated with aneurysm rupture. In an individual patient with an incidentally discovered, not yet ruptured aneurysm of small to medium size, it is difficult to decide if that individual aneurysm is prone to rupture. Therefore, a retrospectively validated method of rupture risk analysis is expected to facilitate therapy decisions. The advantage lies in the correlation of geometry data with haemodynamic parameters, e.g. the WSS—the ‘link’ to the elusive wall properties. The utility of such a rupture risk analysis in clinical practice can only be proven after a validation in a prospective clinical trial. In spite of the encouraging results of the presented study with MCA aneurysms, the advantage expected from the proposed method should be verified first in two further groups of cerebral aneurysms: ICA and anterior communicating artery (AComA) aneurysms. ICA, AComA and MCA aneurysms represent the majority (greater than 80%) of cerebral aneurysms in our clinical practice as well as in the aneurysm populations of other studies [6,15]. Beside the generation and visualization of statistical WSS maps in a generalized manner (figure 6) as done in our study, the method allows a point-to-point comparison of different patient-specific 2.5-dimensional fields. The alignment of aneurysmal sacs allows the generation of statistical shapes. In this study, we used a simple technique generating statistical shapes (figure 6c) of ruptured and unruptured aneurysms by averaging of local radii. Further statistical shape models may be generated as reviewed by Heimann & Meinerz [41]. Finally, a comparison of original and uniform sacs allows a development of new parameters.
to characterize aneurysm unevenness, which is associated with the rupture risk [7,16,18]. In this study, we analysed changes in cell size owing to projection (figure 6a). Further parameters as a Hausdorff distance [42] measured between surfaces of original and uniform shapes are under evaluation.

(a) Study limitations

With 22 cases, the number of investigated MCA aneurysms is limited. This is, however, a relatively large number for a CFD study of cerebral aneurysms of one vessel site. We know of only two other CFD studies in cerebral aneurysms of a defined location with study populations similar to our study: 20 MCA [11] and 26 AComA aneurysms [38]. Other studies contain significantly lower numbers of investigated cases (e.g. eight ICA-opthalmic artery aneurysms [27]).

Patient-specific CFD calculation of WSS has some methodological limitations owing to information that is missing in clinical practice, (e.g. volume flow in the ICA). The acquisition technique with a segmentation and reconstruction procedure generating geometries has the greatest impact on simulation results in haemodynamic studies. We used a relatively simple segmentation technique. Some better segmentation techniques are available [18,26]. There is, however, a direct correlation between the quality of vessel segmentation and the resolution of the acquisition method [18]. Since we used high-resolution image data obtained from 3DRA with a mean isovoxel size of 0.25 mm [3], the development of a complex segmentation technique was not necessary. Geers et al. [43] compared haemodynamic parameters in aneurysm reconstructions based on 3DRA or CTA images of the same patients. They concluded that although relative large differences were found for quantitative haemodynamic parameters, the main flow characteristics were reproduced in the geometries obtained by both imaging techniques. The quantitative differences were produced by different flow rates at the aneurysm site owing to missing small (less than 1 mm diameter) branches in the CTA reconstructions. Our CFD model uses patient-specific vessel and aneurysm anatomy, pulsatile flow, and a non-Newtonian blood model with the patient-specific haematocrit. The inflow rate and waveform were based on literature data. Phase contrast MRI measurements found a relatively low difference of about 5 per cent between measured and literature data [44]. Flow rates of branches were calculated following Murray’s Law or geometric information instead of the real, but unknown resistance of the peripheral vascular bed. Waveforms were found to be very important for time-varying parameters, as oscillating shear stress index (OSI) or standard deviation of the WSS [44]. Consequently, we analysed only time-averaged WSS, known to be independent from the limitations and assumptions of our study, as it was shown in other investigations [10,13,29,45]. Finally, rigid vessel walls were assumed. Wall displacements measured in vivo are relatively small (0.2–0.3 mm) [46]. Simulations with compliant walls using fluid–structure interaction found a negligible impact of compliant walls on the calculation of the time-averaged WSS [47].

5. CONCLUSION

For the first time, statistical WSS maps and averaged surfaces in ruptured and unruptured aneurysms were visualized. Especially, the significant differences in the dome region (lower overall WSS in ruptured cases with larger areas with steep WSS transition), known to be associated with aneurysm rupture, show that the new analysis technique has predictive power that should be examined more closely in future studies. The differences in WSS distributions in ruptured and unruptured aneurysms visualized in a statistical manner help to better understand rupture risk parameters and can explain controversial findings in the literature. Rupture risk analysis is significantly improved owing to the statistical map linking WSS data to corresponding aneurysmal surface locations and owing to the separate consideration of the dome region. Next, we plan to perform similar analysis on other vessel sites (ICA and AComA) of the cerebral circulation.

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