Biomechanical changes during abdominal aortic aneurysm growth

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Abstract

The biomechanics-based Abdominal Aortic Aneurysm (AAA) rupture risk assessment has gained considerable scientific and clinical momentum. However, such studies have mainly focused on information at a single time point, and little is known about how AAA properties change over time. Consequently, the present study explored how geometry, wall stress-related and blood flow-related biomechanical properties change during AAA expansion. Four patients with a total of 23 Computed Tomography-Angiography (CT-A) scans at different time points were analyzed. At each time point, patient-specific properties were extracted from (i) the reconstructed geometry, (ii) the computed wall stress at Mean Arterial Pressure (MAP), and (iii) the computed blood flow velocity at standardized in and out flow conditions. Testing correlations between these parameters identified several non-intuitive dependencies. Most interestingly, the Peak Wall Rupture Index (PWRI) and the maximum Wall Shear Stress (WSS) independently predicted AAA volume growth. Similarly, Intraluminal Thrombus (ILT) volume growth depended on both the maximum WSS and the ILT volume itself. In addition, ILT volume, ILT volume growth and maximum ILT layer thickness correlated with PWRI as well as AAA volume growth. Consequently, a large ILT volume as well as fast increase of ILT volume over time may be a risk factor for AAA rupture. However, tailored clinical studies would be required to test this hypothesis and to clarify whether monitoring ILT development has any clinical benefit.

Keywords: Aorta, AAA, Rupture Risk, Blood Flow, Wall Stress, Thrombus, ILT, Wall Shear Stress, Oscillatory Shear Index
Introduction

Degradation of elastin, collagen and apoptosis of Smooth Muscle Cells (SMC) may lead to Abdominal Aortic Aneurysm (AAA) formation in the infrarenal aorta, which in turn may result in aortic rupture. Elective surgical or endovascular AAA repair is offered to prevent such catastrophic events, and repair is indicated as soon as the risk of aortic rupture exceeds the interventional risks. While the risks of intervention are reasonably predictable, assessing AAA rupture risk remains challenging during clinical decision making. Present clinical guidelines recommend AAA repair as soon as the diameter reaches 55mm or grows faster than 10mm/year. However, a considerable portion of AAAs rupture below the size of 55mm (especially in female patients and current smokers), whereas many aneurysms larger than 55mm never rupture. Consequently, a more robust AAA rupture risk assessment would be of great clinical value.

The Biomechanical Rupture Risk Assessment (BRRA) quantitatively integrates many known risk factors for AAA rupture, allowing a more holistic risk assessment. The BRRA has gained considerable momentum, but the derived indices are essentially based on information at a single time point, and currently little is known about how AAA biomechanical parameters change over time.

Almost all clinically relevant AAAs contain an intra-luminal thrombus (ILT) composed of fibrin and blood cells. The role of ILT is still contentious, but it is thought to play an important role in AAA progression. A thin thrombus layer may protect the vessel wall from rupture by acting as a stress buffer, thus decreasing the rupture risk of the aneurysm. Conversely, a thick ILT layer can cause the wall to weaken, for example due to hypoxia. The ILT also provides an ideal environment for proteolytic agents. These chemicals can be conveyed through the porous ILT and diminish wall strength by proteolytic degradation of elastin and collagen. Such a wall weakening mechanism could explain why a thick ILT layer and fast increase in ILT volume have been linked to AAA rupture risk.

The present study aims at investigating how geometry, wall stress-related and blood flow-related biomechanical properties change during AAA expansion. Despite the fact that effects of blood flow on AAA growth have been reported, the interaction between these factors is still poorly understood. Knowledge about the time course of such parameters may lead to a better estimate of AAA rupture risk and improve monitoring protocols of AAA patients.
Methods

Patient cohort

AAA patients from Karolinska University Hospital, Stockholm, Sweden with at least five high resolution Computed Tomography-Angiography (CT-A) scan recordings were included. Most of the CT-A scans were performed for diagnostic purposes and AAA surveillance. Patient characteristics are listed in Table 1, and the blood pressure was averaged over all available measurements to avoid temporal fluctuations. The use of anonymized patient data was approved by the local ethics committee.

Table 1: Patient characteristics and timeline of Computed Tomography-Angiography (CT-A) scans.

| Patient ID | Age at baseline (years) | Gender | Blood pressure (mmHg) | Number of CT-A scans and follow-up times (years from baseline) |
|------------|-------------------------|--------|-----------------------|-------------------------------------------------------------|
| A          | 76                      | Male   | 140/80                | 5 0/0.7/2.2/2.7/3.9                                         |
| B          | 64                      | Female | 207/113               | 5 0/2.0/3.0/4.0/5.9                                         |
| C          | 63                      | Male   | 160/100               | 7 0/0.6/1.5/2.7/4.2/5.3/8.4                                 |
| D          | 73                      | Female | 140/80                | 6 0/0.3/0.6/1.3/3.5/3.7                                     |

Geometrical Analysis

The aorta was semi-automatically segmented between the renal arteries and the aortic bifurcation (A4clinics Research Edition, VASCOPS GmbH, Graz, Austria). Segmented geometries included luminal and exterior AAA surfaces and used a predefined wall thickness that accounted for the reported wall thinning behind the ILT\textsuperscript{22}. The reproducibility of the applied method has been reported previously\textsuperscript{21,2,41}, and a typical AAA segmentation is shown in Figure 1(a). The maximum diameter ($d_{\text{max}}$), the maximum ILT layer thickness ($H_{\text{ILT max}}$), and luminal ($V_{\text{lum}}$), thrombus ($V_{\text{ILT}}$) and total ($V_{\text{tot}}$) volumes were calculated for each aortic geometry (Table 2).
Table 2: Definition of geometrical and biomechanical parameters. Bold face notation denotes vector or tensor quantities, and the region of interest was (manually) specified between the lower level of the renal arteries and the upper level of the aortic bifurcation, respectively.

| Notation | Description | Remark |
|----------|-------------|--------|
| $d_{\text{max}}$ | Maximum outer diameter perpendicular to the luminal centerline | |
| $H_{\text{ILT max}}$ | Maximum thickness of the Intra-Luminal Thrombus (ILT) layer, i.e. maximum distance between wall-ILT interface and the luminal surface | |
| $V_{\text{lum}}, V_{\text{ILT}}, V_{\text{tot}}$ | Volumes of the lumen, ILT and the total vessel. | |
| $P_{\text{WS}}$ | Peak Wall Stress. Highest von Mises stress in the wall all over the AAA | $P_{\text{WS}} = \max[\text{Wall stress}]$ |
| $P_{\text{WR}I}$ | Peak Wall Rupture Index. Highest ratio between the calculated wall stress and the estimated wall strength all over the AAA. | $P_{\text{WR}I} = \max\left[\frac{\text{Wall stress}}{\text{Wall strength}}\right]$ |
| $v_{\text{min}}, v_{\text{max}}, v_{\text{mean}}$ | Minimal, maximal and mean magnitude of the blood flow velocity. The mean blood flow velocity is derived by averaging the magnitude of the blood flow velocity $v$ over the time $T$ of the cardiac cycle, and the volume of the lumen $V_{\text{lum}}$. | $v_{\text{min}} = \min|v|$; $v_{\text{max}} = \max|v|$; $v_{\text{mean}} = \frac{1}{T} \int_0^T \frac{1}{V_{\text{lum}}} \int_0^{V_{\text{lum}}} |v| \, dv \, dt$ |
| $\gamma_{\text{min}}, \gamma_{\text{max}}$ | Minimal and maximal scalar shear rates over the cardiac cycle. These quantities are derived from the spatial velocity gradient $\text{grad} v$, i.e. a quantity that denotes how fast the blood velocity changes in space. | $\gamma_{\text{min}} = \min|\gamma|$; $\gamma_{\text{max}} = \max|\gamma|$ with $\dot{\gamma} = \sqrt{2}I_{\text{sym}} I_{\text{sym}}$ and $I_{\text{sym}} = (\text{grad} v + \text{grad}^T v)/2$ |
| $WSS_{\text{min}}, WSS_{\text{max}}$ | Minimal and maximal magnitude of the Wall Shear Stress (WSS) vector $WSS$ over the cardiac cycle. $WSS$ denotes the mechanical stress induced by blood flow onto blood-tissue (wall or ILT) interface. | $WSS_{\text{min}} = \min||WSS||$; $WSS_{\text{max}} = \max||WSS||$ |
| $OSI$ | Oscillatory Shear Index. OSI is computed from the averaged magnitude of $WSS$ and its magnitude $|WSS|^{37}$. OSI denotes oscillatory behavior of the flow caused by complex flow patterns. Specifically, the extreme cases $OSI = 1$ and $OSI = 0$ denote oscillating and unidirectional flows, respectively. | $OSI = \frac{1}{2} \left( 1 - \frac{AWSSV}{AWSS} \right)$ with $AWSS = \frac{1}{T} \int_0^T |WSS| \, dt$ and $AWSSV = \frac{1}{T} \int_0^T WSS \, dt$ |
Figure 1: Analysis method performed for each patient at each time point. (a) Lateral Computed Tomography-Angiography (CT-A) slice with segmented Abdominal Aortic Aneurysm (AAA). Yellow, blue and green curves denote the luminal surface, exterior surface and wall-thrombus interface, respectively. (b) Rupture risk index plot derived from the structural biomechanics-based analysis at Mean Arterial Pressure (MAP). (c) Wall Shear Stress distribution at t=0.25 s of the cardiac cycle derived from a Computational Fluid Dynamics (CFD) computation. At the inlet and the outlets, the indicated volume flow rate and pressure versus time responses were prescribed.

Structural analysis

Non-linear Finite Element (FE) models were used to compute the stress in the AAA wall at Mean Arterial Pressure (MAP). Peak Wall Stress (PWS), i.e. the highest von Mises stress in the aneurysm wall, was extracted from each simulation (A4clinics Research Edition, VASCOPS GmbH, Graz, Austria). The FE model used hexahedral-dominated finite elements of Q1P0 formulation to avoid volume locking of incompressible solids. The AAA was fixed at the renal arteries and at the aortic bifurcation, and no contact with surrounding organs was considered. Isotropic constitutive descriptions for the aneurysm wall and the ILT were assigned to each model, with the ILT stiffness gradually decreasing from the luminal to the abluminal sites.

A wall rupture risk index was defined by locally dividing wall stress to an estimate of wall strength. AAA wall strength was assigned inhomogeneously and estimated by a scaled version of a model as proposed previously. Finally, the highest wall risk index, or Peak Wall Rupture Index (PWRRI), was extracted. Figure 1(b) illustrates the typical distribution of the wall rupture risk index, and Table 2 details the investigated structural biomechanical parameters.
Hemodynamical analysis

Rigid wall Computational Fluid Dynamics (CFD) models (ANSYS CFX, ANSYS Inc. US) with reported inflow and outflow conditions\textsuperscript{4,32} were used to predict the blood flow velocity. To this end, the AAA lumen was meshed with tetrahedral finite volume elements (about 2mm in size) and five layers of prism elements (layer thickness ranging from 0.1mm to 0.2mm) to adequately capture the boundary layer flow. Five cardiac cycles were simulated, and the shear-thinning viscous properties of blood were captured by the Carreau-Yasuda model using previously reported parameters\textsuperscript{24,25}. Further details regarding the CFD approach and results verification are given elsewhere\textsuperscript{5}.

Hemodynamics parameters were extracted from the fourth calculated cardiac cycle and inside the aneurysmatic vessel domain (MATLAB, The MathWorks Inc., Natick, Massachusetts, USA). Specifically, the minimal ($v_{\text{min}}$), maximal ($v_{\text{max}}$) and mean ($v_{\text{mean}}$) blood flow velocities, minimal ($\gamma_{\text{min}}$) and maximal ($\gamma_{\text{max}}$) scalar shear rates, minimal ($WSS_{\text{min}}$) and maximal ($WSS_{\text{max}}$) Wall Shear Stresses (WSS), and the Oscillatory Shear Index ($OSI$)\textsuperscript{22,23} were computed. Further methodological details are shown in Table 2. Figure 1 (c) illustrates a typical $WSS$ distribution.

Data Analysis

The rates of change over time of the geometrical, structural and hemodynamical parameters at given time points were also investigated, and were calculated as the arithmetic difference between two consecutive CT-A scans divided by the time between the scans. The rate of change of parameter $X$ was denoted by $\Delta X$.

Pooled data from all patients were statistically analyzed (SPSS, IBM Corp. Released 2013. IBM SPSS Statistics, Armonk, USA). All parameters were tested for normality using the Shapiro-Wilk test (significance level: $p < 0.05$), and Pearson and Spearman’s correlation tests (significance level: $p < 0.05$) were used to investigate simple correlation among normal and non-normal distributed parameters, respectively. Analysis of variance (ANOVA) was used to assess multivariate linear regressions.
Figure 2: Development over time of the wall rupture risk index at Mean Arterial Pressure (MAP) in all four Abdominal Aortic Aneurysm (AAA) patients.
Figure 3: Development over time of the Wall Shear Stress (WSS) at $t=0.25$ s of the cardiac cycle, i.e. at the time of peak blood inflow, in all four Abdominal Aortic Aneurysm (AAA) patients.
Results

A complete analysis of a single case at one time point took about ten hours. Figure 2 and Figure 3 illustrate the development of the wall rupture risk index and WSS over time for all four patients, respectively.

Diameter and biomechanical rupture risk index

$PWRI$ and $d_{\text{max}}$ varied considerably over time (Figure 4). AAA C is rather stable and slightly below the mean $PWRI$ versus diameter curve. At baseline, AAA B has a slightly smaller diameter than AAA C (49mm versus 52mm) but a higher $PWRI$, and within 5.9 years its diameter grows up to 60mm. Interestingly, $PWRI$ increases rapidly at first but slightly decreases later. Case D is rather small at baseline (42mm) and at a $PWRI$ between the cases B and C. After 3.5 years, the diameter in case D reaches 48mm, but subsequently both diameter and $PWRI$ reduce. AAA A is already large at baseline (71mm), and within 2.2 years its diameter grows to 82mm, subsequently shrinking by about 4mm.

Correlation Analysis

Simple correlation analysis. Table 3 summarizes results from the simple correlation analysis, and Figure 5(a-d) illustrates key findings with respect to $d_{\text{max}}$. Interestingly, $d_{\text{max}}$ did not correlate with diameter growth $\Delta d_{\text{max}}$ (Figure 4(a)). Instead $d_{\text{max}}$ correlated with volume growth $\Delta V_{\text{tot}}$, wall shear stress $WSS_{\text{max}}$, and the biomechanical risk index $PWRI$ (Figure 5 (b-d)). Moreover, trivial correlations between the diameter and volumes ($V_{\text{lum}}, V_{\text{tot}}$ and $V_{\text{ILT}}$) were found.

The scalar shear rates $\dot{\gamma}_{\text{min}}$ and $\dot{\gamma}_{\text{mean}}$, and the wall shear stresses $WSS_{\text{max}}$ (Figure 5(e)) and $WSS_{\text{mean}}$ correlated negatively with $V_{\text{ILT}}$. In contrast, the biomechanical risk index $PWRI$ (Figure 5(f)) and the Oscillatory Shear Index $OSI$ showed positive correlations with $V_{\text{ILT}}$. In addition, the mean blood flow velocity $v_{\text{mean}}$ correlated negatively with $V_{\text{ILT}}$.

With respect to growth parameters, it was seen that the maximum ILT thickness $H_{\text{ILT max}}$ correlated with total volume growth $\Delta V_{\text{tot}}$ (Figure 6(c)). In addition, $PWRI$ (Figure 6(b)) and $OSI$ correlated positively, while $\dot{\gamma}_{\text{min}}$ and $WSS_{\text{max}}$ (Figure 6(a)) correlated negatively with $\Delta V_{\text{tot}}$. Finally, simple regression with respect to the ILT growth $\Delta V_{\text{ILT}}$ exhibited correlations with $\dot{\gamma}_{\text{max}}, PWRI$ (Figure 6(d)), $H_{\text{ILT max}}$ (Figure 6(c)) and $\dot{\gamma}_{\text{max}}$ (Table 3).
Figure 4: Development of the maximum diameter diameter $d_{\text{max}}$ and the Peak Wall Rupture Index ($PWRI$) in Abdominal Aortic Aneurysm (AAA) patients A to D. Each time point is labeled with the time in years from baseline. For comparison, the black solid curve denotes $PWRI$ versus $d_{\text{max}}$ property that in average is seen in AAA patients. Dotted curves denote the 5% and 95% confidence intervals, respectively.

Multiple correlation analysis. Multiple linear regression showed that both $WSS_{\text{max}}$ ($p=0.004$) and $PWRI$ ($p=0.001$) are independent predictors of vessel volume growth. Specifically, volume growth increased with low $WSS_{\text{max}}$ and high $PWRI$ following the relation

$$\Delta V_{\text{tot}} = a_0 + a_1 WSS_{\text{max}} + a_2 PWRI$$

with

$$a_0 = -47.2 \text{(CI}_{90\%}) = -89.4/-5.0, \quad a_1 = -0.411 \text{(CI}_{90\%}) = -1.713/0.892 \quad \text{and} \quad a_2 = 124.1 \text{(CI}_{90\%}) = 69.4/178.7,$$

where $\text{CI}_{90\%}$ denotes the 90% confidence interval.

Similarly, high $WSS_{\text{max}}$ ($p=0.023$) and $V_{\text{ILT}}$ ($p<0.001$) independently predicted ILT volume growth according to

$$\Delta V_{\text{ILT}} = b_0 + b_1 WSS_{\text{max}} + b_2 V_{\text{ILT}}$$

with

$$b_0 = -48.38 \text{(CI}_{90\%}) = -75.73/-21.03, \quad b_1 = 2.169 \text{(CI}_{90\%}) = 0.859/3.479 \quad \text{and} \quad b_2 = 0.541 \text{(CI}_{90\%}) = 0.346/0.736,$$

respectively.
Table 3: Correlations of geometrical and biomechanical parameters with (a) the maximum diameter $d_{\text{max}}$, (b) the ILT volume $V_{\text{ILT}}$, (c) the change of AAA volume over time $\Delta V_{\text{tot}}$, and (c) the change of ILT volume over time $\Delta V_{\text{ILT}}$. Results are based on simple correlation analysis.

(a) Correlations with the maximum diameter $d_{\text{max}}$

| Parameter          | Correlation coefficient | $p$-value |
|--------------------|-------------------------|-----------|
| $H_{\text{ILT max}}$ | 0.755                   | <0.001    |
| $V_{\text{lum}} ; V_{\text{tot}} ; V_{\text{ILT}}$ | 0.968; 0.936; 0.822 | <0.001; <0.001; <0.001 |
| $PWS$              | 0.891                   | <0.001    |
| $PWRI$             | 0.672                   | 0.002     |
| $\dot{\gamma}_{\text{min}} ; \dot{\gamma}_{\text{mean}}$ | -0.773; -0.554 | <0.0010.014 |
| $\text{WSS}_{\text{max}} ; \text{WSS}_{\text{mean}}$ | -0.698; -0.459 | 0.001; 0.048 |
| $OSI$              | 0.768                   | <0.001    |
| $v_{\text{min}} ; v_{\text{mean}}$ | -0.695; -0.519 | <0.001; 0.023 |
| $\Delta V_{\text{tot}} ; \Delta V_{\text{ILT}}$ | 0.646; 0.501 | 0.003; 0.029 |

(b) Correlations with the ILT volume $V_{\text{ILT}}$

| Parameter          | Correlation coefficient | $p$-value |
|--------------------|-------------------------|-----------|
| $H_{\text{ILT max}}$ | 0.964                   | <0.001    |
| $V_{\text{lum}} ; V_{\text{tot}}$ | 0.804; 0.941 | <0.001; <0.001 |
| $PWS$              | 0.640                   | 0.003     |
| $PWRI$             | 0.693                   | 0.001     |
| $\dot{\gamma}_{\text{min}} ; \dot{\gamma}_{\text{mean}}$ | -0.866; -0.580 | <0.001; 0.009 |
| $\text{WSS}_{\text{max}} ; \text{WSS}_{\text{mean}}$ | -0.829; -0.559 | <0.001; 0.013 |
| $OSI$              | 0.518                   | 0.023     |
| $v_{\text{mean}}$  | -0.584                  | 0.009     |
| $\Delta V_{\text{tot}} ; \Delta V_{\text{ILT}}$ | 0.750; 0.605 | <0.001; 0.006 |

(c) Correlations with the change of AAA volume over time $\Delta V_{\text{tot}}$

| Parameter          | Correlation coefficient | $p$-value |
|--------------------|-------------------------|-----------|
| $H_{\text{ILT max}}$ | 0.804                   | <0.001    |
| $V_{\text{lum}} ; V_{\text{tot}} ; V_{\text{ILT}}$ | 0.697; 0.773; 0.750 | 0.001; <0.001; <0.001 |
| $PWS$              | 0.584                   | 0.009     |
| $PWRI$             | 0.799                   | <0.001    |
| $\dot{\gamma}_{\text{min}}$ | -0.615 | 0.005    |
| $\text{WSS}_{\text{max}}$ | -0.577 | 0.010    |
| $OSI$              | 0.475                   | 0.040     |
| $v_{\text{min}}$  | -0.477                  | 0.039     |
| $\Delta V_{\text{ILT}}$ | 0.694 | 0.001     |

(d) Correlations with the change of ILT volume over time $\Delta V_{\text{ILT}}$

| Parameter          | Correlation coefficient | $p$-value |
|--------------------|-------------------------|-----------|
| $H_{\text{ILT max}}$ | 0.627                   | 0.004     |
| $V_{\text{lum}} ; V_{\text{tot}} ; V_{\text{ILT}}$ | 0.625 ; 0.666; 0.605 | 0.004; 0.002; 0.006 |
| $PWS$              | 0.524                   | 0.021     |
| $PWRI$             | 0.696                   | 0.001     |
| $\dot{\gamma}_{\text{max}} ; \dot{\gamma}_{\text{min}}$ | 0.548; -0.471 | 0.015; 0.042 |
| $v_{\text{max}}$  | 0.734                   | <0.001    |
| $\Delta V_{\text{tot}}$ | 0.694 | 0.001     |
Figure 5: Influence of the maximum diameter on (a) the diameter growth $\Delta d_{\text{max}}$, (b) volume growth $\Delta V_{\text{tot}}$, (c) maximum Wall Shear Stress $\text{WSS}_{\text{max}}$ over the cardiac cycle, and (d) Peak Wall Rupture Index (PWRI) at Mean Arterial Pressure (MAP). Influence of the Intra-luminal Thrombus (ILT) volume on (e) $\text{WSS}_{\text{max}}$ over the cardiac cycle, and (f) PWRI at MAP.
Figure 6: Influence of the change of vessel volume $\Delta V_{\text{tot}}$ on (a) the maximum Wall Shear Stress $WSS_{\text{max}}$ over the cardiac cycle, (b) Peak Wall Rupture Index PWRI at Mean Arterial Pressure (MAP). Influence of the Intra-Luminal Thrombus (ILT) volume growth rate $\Delta V_{\text{ILT}}$ on (c) maximum thickness of the ILT layer $H_{\text{ILT, max}}$, and (d) PWRI at MAP.

Discussion

Clinical and experimental observations have indicated that biomechanical conditions influence the progression of aneurysm disease$^{3,11}$. Despite these observations, a fundamental understanding of these interactions is still missing, particularly the role of the ILT in AAA pathology$^{39}$. The ILT is an active biochemical entity$^{39}$ that influences wall strength$^{44,47}$ and AAA progression$^{30}$. Specifically, clinical studies have linked a thick ILT layer$^{22}$ and fast increase in ILT volume$^{38}$ to increased AAA rupture risk. The present biomechanical study supports these observations through a strong positive correlation of the biomechanical risk index $PWRI$ with both ILT volume $V_{\text{ILT}}$ and its change over...
time $\Delta V_{\text{ILT}}$. Consequently, the suitability of monitoring ILT volume, and its change over time, as additional risk indicators should be explored in larger clinical studies.

ILT formation requires platelet accumulation, and for platelets to be able to adhere to the vessel, platelets must spend sufficient time in the vicinity of thrombogenic surfaces. Therefore, the adhesion of platelets might be promoted at sites of low $WSS_i$, i.e. an inverse relationship between $WSS$ and aneurysm expansion may exist. Such an inverse relationship is confirmed by our study through the negative correlation of $\Delta V_{\text{tot}}$ with $WSS$. Similar conclusions have been drawn from clinical observations, experimental AAA models$^{11}$, and simulation studies$^{49}$.

The present study found that $PWRI$ and $WSS_{\text{max}}$ independently predicted the growth of total AAA volume $\Delta V_{\text{tot}}$. $PWRI$ is strongly related to the stress in the wall, and our finding is supported by previous experimental studies$^{30}$ showing that the growth of small AAAs is especially sensitive to wall stress. Due to the lack of endothelial cells in AAAs$^{22}$, blood flow properties may only indirectly promote AAA growth through stimulation of the biochemical environment within the ILT. For example, a high $OSI$ could support pumping proteolytic agents through the porous ILT, which in turn could promote AAA growth.

Contrary to intuition, our data showed that the biomechanical risk does not always increase in time. Wall stress is strongly linked to AAA shape parameters like its asymmetry$^{48}$ or, more generally, to the surface curvatures$^{24}$. Consequently, if growth appears to reduce AAA asymmetry, the biomechanical risk for rupture also reduces, i.e. the aneurysm grows into a shape of lower risk for rupture. The fluctuations in $PWRI$ could also be explained by releasing spots of high surface curvatures of the wall through “cracking” of wall calcifications during AAA expansion, for example.

The present study has several limitations. First of all our study was based on a relatively small number of cases due to the requirement of analyzing at least five CT-A scans for each patient. CT-A exposes patients to ionizing radiation and nephrotoxic contrast agents and should not be performed frequently. However, CT-A is practically the only standard image modality providing images accurate enough to build robust computational AAA models. Another limitation is related to the quantification of aneurysm growth. AAA growth is complex, and single parameters like change in maximum diameter or aneurysm volume can only serve as surrogate growth parameters. Therefore, a more rigorous three-dimensional quantification of the changing geometry would have been advantageous.

Numerical models like FE and CFD models introduce numerous modeling assumptions and cannot completely reflect biomechanics of the real aneurysm. In the present study, the constitution of aneurysm tissue and blood was modelled using mean population data. Patient-specific tissue and
blood properties would have likely increased the accuracy of the predictions. As these assumptions were used consistently across all patients they might not influence our conclusions.

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References

1. Adolph R, Vorp DA, Steed DL, Webster MW, Kameneva MV, Watkins SC. 1997. Cellular content and permeability of intraluminal thrombus in abdominal aortic aneurysm. J. Vasc. Surg. 25(5):916-926.
2. Auer M and Gasser TC, Automatic reconstruction and finite element mesh generation of abdominal aortic aneurysms, IEEE Trans. Med. Imag. 29, 1022-1028, 2010.
3. M. Bäck, T. C. Gasser, J-B Michel, and G. Caligiuri. Spotlight Review: Biomechanical factors in the biology of aortic wall and aortic valve diseases. Cardiovascular Research. doi:10.1093/cvr/cvt040, 2013.
4. Biasetti J, Gasser TC, Auer M, Hedin U, and Labruto F. Hemodynamics of the normal aorta compared to fusiform and saccular abdominal aortic aneurysms with emphasis on a potential thrombus formation mechanism. Annals of biomedical engineering, 38(2):380–390, 2010.
5. Biasetti J, Hussain F, Gasser TC. Blood Flow and Coherent Vortices in the Normal and Aneurysmatic Aortas. A Fluid Dynamical Approach to Intra-Luminal Thrombus Formation. J. R. Soc. Interface. doi:10.1098/rsif.2011.0041, 2011.
6. Brown LC, Powell JT. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Ann Surg. 1999;230:289–296; discussion 296–297.
7. Choke E, Cockerill G, Wilson WR, Sayed S, Dawson J, Loftus I, and Thompson MM. A review of biological factors implicated in abdominal aortic aneurysm rupture. European Journal of Vascular and Endovascular Surgery, 30:227–244, 2005.
8. Choksy SA, Wilmink AB, and Quick CR. Ruptured abdominal aortic aneurysm in the huntingdon district: a 10-year experience. Annals of the Royal College of Surgeons of England, 81(1):27, 1999.
9. Darling RC, Messina CR, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms. Circulation. 1977; 56 (II suppl):161-164.
10. Derubertis BG, Trocciola SM, Ryer EJ, Pieracci FM, McKinsey JF, Faries PL, Kent KC. Abdominal aortic aneurysm in women: prevalence, risk factors, and implications for screening. Journal of Vascular Surgery. 2007; 46:630-635.
11. M. M. Dua and R. L. Dalman. Hemodynamic Influences on Abdominal Aortic Aneurysm Disease: Application of Biomechanics to Aneurysm Pathophysiology. Vascul Pharmacol. 53(1-2): 11–21, 2010.

12. Fillinger MF, Raghavan ML, Marra SP, Cronenwett J-L, Kennedy FE. In vivo analysis of mechanical wall stress and abdominal aortic aneurysm rupture risk. Journal of Vascular Surgery. 2002; 36:589-597.

13. Fillinger MF, Marra SP, Raghavan ML, Kennedy FE. Prediction of rupture risk in abdominal aortic aneurysm during observation: wall stress versus diameter. J Vasc Surg 2003; 37: 724–732.

14. Gasser TC, Nchimi A, Swedenborg J, Roy J, Sakalihasan N, Böckler D, Hyhlik-Dürr A. A novel strategy to translate the biomechanical rupture risk of abdominal aortic aneurysms to their equivalent diameter risk: Method and retrospective validation. Eur. J. Vasc. Endovasc. Surg. (in press).

15. Gasser TC, Gorgulu G, Folkesson M and Swedenborg J. 2008. Failure properties of intraluminal thrombus in abdominal aortic aneurysm under static and pulsating mechanical loads. J. Vasc. Surg. 48, 179-88. (doi:10.1016/j.jvs.2008.01.036)

16. Gasser TC, Martufi G, Auer M, Folkesson M, Swedenborg J. 2010 Micromechanical characterization of intra-luminal thrombus tissue from abdominal aortic aneurysms. Ann. Biomed. Eng. 38:371-379.

17. Gasser TC, Auer M, Labruto F, Swedenborg J, Roy J. Biomechanical. Rupture risk assessment of abdominal aortic aneurysms: Model complexity versus predictability of finite element simulations. European Journal of Vascular and Endovascular Surgery. 2010; 40:176-185.

18. Greenhalgh RM, Powell JT. "Endovascular repair of abdominal aortic aneurysm". N. Engl. J. Med. 358 (5): 494–501, 2008.

19. Hans SS, Jareunpoon O, Balasubramaniam B, Zelenock GB. Size and location of thrombus in intact and ruptured abdominal aortic aneurysms. Journal of Vascular Surgery. 2005; 41:584-588.

20. He X and Ku DN. Pulsatile flow in the human left coronary artery bifurcation: average conditions. Journal of biomechanical engineering, 118(1):74–82, 1996.

21. Hyhlik-Dürr A, Krieger T, Geisbüsch P, Kotelis D, Able T, Böckler D. Reproducibility of Aortic Diameter, Volume, Peak Wall Stress, and Peak Rupture Risk Index Using Semiautomatic Finite Element Analyses of Infrarenal Aortic Aneurysms. Journal of Endovascular Therapy. 2011, 18:289-298.

22. Kazi M, Thyberg J, Religa P, Roy J, Eriksson P, Hedin U, Swedenborg J. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. Journal of Vascular Surgery. 2003; 38:1283-1292.

23. Ku DN, Giddens DP, Zarins CK, and Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis, Thrombosis, and Vascular Biology, 5(3):293–302, 1985.

24. Lee K, Zhu J, Shum J, et al. Surface Curvature as a Classifier of Abdominal Aortic Aneurysms: A Comparative Analysis. Annals of biomedical engineering. 2013;41(3):562-576. doi:10.1007/s10439-012-0691-4.

25. Leuprecht A and Perktold K. Computer simulation of non-newtonian effects on blood flow in large arteries. Computer methods in biomechanics and biomedical engineering, 4(2):149–163, 2001.
26. Lindquist Liljeqvist M, Hultgren R, Gasser TC, Roy J. Volume growth of abdominal aortic aneurysms correlates with baseline volume and increasing finite element analysis-derived rupture risk. J Vasc Surg. 2016 Apr 19. pii: S0741-5214(16)00078-1. doi: 10.1016/j.jvs.2015.11.051

27. Maier A, Gee MW, Reeps C, Pongratz J, Eckstein HH, Wall WA. A comparison of diameter, wall stress, and rupture potential index for abdominal aortic aneurysm rupture risk prediction. Annals of Biomedical Engineering. 2010; 38:3124-3134.

28. Martufi G and Gasser TC. Review: the role of biomechanical modeling in the rupture risk assessment for abdominal aortic aneurysms. J Biomech Eng, 135(2):021010, Feb 2013.

29. Martufi G, Auer M, Roy J, Swedenborg J, Sakalihasan N, Panuccio G, Gasser TC. Multidimensional growth measurements of abdominal aortic aneurysms. Journal of Vascular Surgery, ISSN 0741-5214, Vol. 58, no 3, 748-755.

30. G. Martufi, M. Lindquist Liljeqvist, N. Sakalihasan, G. Panuccio, R. Hultgren, J. Roy, T.C. Gasser. Local Diameter, Wall Stress and Thrombus Thickness Influence the Local Growth of Abdominal Aortic Aneurysms. J Endovasc Ther. (accepted for publ.)

31. McGloughlin TM, Doyle BJ. New approaches to abdominal aortic aneurysm rupture risk assessment: engineering insights with clinical gain. Arterioscler Thromb Vasc Biol 2010; 30: 1687–1694.

32. Mills CJ, Gabe IT, Gault JH, Mason DT, Ross J, Braunwald E, and Shillingford JP. Pressure-flow relationships and vascular impedance in man. Cardiovascular Research, 4(4):405–417, 1970.

33. Mower WR, Quiñones WJ, and Gambhir SS. Effect of intraluminal thrombus on abdominal aortic aneurysm wall stress. Journal of vascular surgery, 26(4):602–608, 1997.

34. Nicholls SC, Gardner JB, Meissner MH, Johansen HK. Rupture in small abdominal aortic aneurysms. Journal of Vascular Surgery. 1998; 28:884-888.

35. Raghavan, ML and Vorp, D.A. 2000 Toward a biomechanical tool to evaluate rupture potential of abdominal aortic aneurysm: identification of a finite strain constitutive model and evaluation of its applicability. J. Biomech. 33, 475–482. (doi:10.1016/S0021-9290(99)00201-8).

36. J. C. Simo and R. L. Taylor.Quasi-incompressible finite elasticity in principal stretches. Continuum basis and numerical algorithms. Comput. Meth. Appl. Mech. Eng. 85, 273-310, 1991.

37. Soulis JV, Lampri OP, Fytanidis DK, and Giannoglou GD. Relative residence time and oscillatory shear index of non-newtonian flow models in aorta. In Biomedical Engineering, 2011 10th International Workshop on, pages 1–4. IEEE, 2011.

38. Stenbaek J, Kalin B, Swedenborg J. Growth of thrombus may be a better predictor of rupture than diameter in patients with abdominal aortic aneurysms. European Journal of Vascular and Endovascular Surgery. 2000; 20:466-499.

39. Swedenborg J, Eriksson P. The intraluminal thrombus as a source of proteolytic activity. Ann N Y Acad Sci. 2006 Nov;1085:133-8.

40. The UK Small Aneurysm Trial Participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. Lancet. 1998; 352:1649-1655.
41. Teutelink A, Cancrinus E, van de Heuvel D, Moll F, de Vries JP. Preliminary intraobserver and interobserver variability in wall stress and rupture risk assessment of abdominal aortic aneurysms using a semiautomatic finite element model. J Vasc Surg. 55, 326-330, 2012.

42. Thubrikar MJ. Effect of thrombus on abdominal aortic aneurysm wall dilatation and stress. J Cardiovasc Surg 2003, 44:67–77.

43. Truijers M, Pol JA, SchultzeKool LJ, van Strekenburg SM, Fillinger MF, Blankensteijn JD. Wall stress analysis in small asymptomatic, symptomatic and ruptured abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2007; 33: 401–407.

44. Vande Geest JP, Martino ES, Bohra A, Mackaroun MS, Vorp DA. A biomechanics-based rupture potential index for abdominal aortic aneurysm risk assessment: demonstrative application. Ann N Y Acad Sci 2006; 1085: 11–21.

45. Vande Geest JP, Schmidt DE, Sacks MS, Vorp DA. The effects of anisotropy on the stress analyses of patient-specific abdominal aortic aneurysms. Ann Biomed Eng 2008; 36: 921–932.

46. Venkatasubramaniam AK, Fagan MJ, Mehta T, Mylankal KJ, Ray B, Kuhan G et al. A comparative study of aortic wall stress using finite element analysis for ruptured and non-ruptured abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2004; 28: 168–176.

47. Vorp DA, Lee PC, Wang DHJ, Makaroun MS, Nemoto EM, Ogawa S, and Webster MW. Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening. Journal of Vascular Surgery, 34(2):291–299, 2001.

48. Vorp DA, Raghavan ML, Webster MW. Mechanical wall stress in abdominal aortic aneurysm: influence of diameter and asymmetry. Journal of Vascular Surgery. 1998; 27:632-639.

49. B. A. Zambrano, H. Gharahi, C. Lim, F. A. Jaberi, J. Choi, W. Lee, And S. Baek. Association of Intraluminal Thrombus, Hemodynamic Forces, and Abdominal Aortic Aneurysm Expansion Using Longitudinal CT Images. Annals of Biomedical Engineering, 44, 1502–1514, 2016.