Biomechanical rupture risk assessment of abdominal aortic aneurysms based on a novel probabilistic rupture risk index

Stanislav Polzer¹ and T. Christian Gasser²

¹Institute of Solid Mechanics, Mechatronics and Biomechanics, Brno University of Technology, Brno, Czech Republic
²KTH Solid Mechanics, School of Engineering Sciences, KTH Royal Institute of Technology, Stockholm, Sweden

A rupture risk assessment is critical to the clinical treatment of abdominal aortic aneurysm (AAA) patients. The biomechanical AAA rupture risk assessment quantitatively integrates many known AAA rupture risk factors but the variability of risk predictions due to model input uncertainties remains a challenging limitation. This study derives a probabilistic rupture risk index (PRRI). Specifically, the uncertainties in AAA wall thickness and wall strength were considered, and wall stress was predicted with a state-of-the-art deterministic biomechanical model. The discriminative power of PRRI was tested in a diameter-matched cohort of ruptured (n = 7) and intact (n = 7) AAAs and compared to alternative risk assessment methods. Computed PRRI at 1.5 mean arterial pressure was significantly (p = 0.041) higher in ruptured AAAs (20.21 (s.d. 14.15%)) than in intact AAAs (3.71 (s.d. 5.77%)). PRRI showed a high sensitivity and specificity (discriminative power of 0.837) to discriminate between ruptured and intact AAA cases. The underlying statistical representation of stochastic data of wall thickness, wall strength and peak wall stress had only negligible effects on PRRI computations. Uncertainties in AAA wall stress predictions, the wide range of reported wall strength and the stochastic nature of failure motivate a probabilistic rupture risk assessment. Advanced AAA biomechanical modelling paired with a probabilistic rupture index definition as known from engineering risk assessment seems to be superior to a purely deterministic approach.

1. Background

An abdominal aortic aneurysm (AAA) is a local dilatation of the aorta which can eventually rupture and is frequently seen in the elderly population. AAA ruptures have a total mortality rate of between 75 and 90%, and death from ruptured AAAs ranks among the 10 leading causes of death for men above the age of 65 [1]. Decisions on clinical interventions are based on the likelihood of AAA rupture, such that an accurate rupture risk assessment serves as the key to reduce aneurysm-related mortality without substantially increasing the rate of AAA repair, i.e. progressive clinical interventions.

According to the current clinical practice, AAA rupture risk is assessed by the aneurysm’s largest transverse diameter and its change over time, such that AAA repair is generally indicated if the largest diameter exceeds 55 mm or grows faster than 10 mm per year [2,3]. This somewhat crude rupture risk assessment is, however, the subject of increasing discussion, since some AAAs with a diameter of less than 55 mm rupture, whereas many aneurysms larger than 55 mm never rupture [4,5]. In addition to the aneurysm’s diameter and growth rate, many other clinical risk factors including AAA shape, female gender, family susceptibility, high mean arterial pressure (MAP), smoking and fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET), a thick intraluminal thrombus (ILT) layer, fast increase in ILT volume, have been reported in the literature (see among others [6–9]).

Specifically, biomechanical AAA analysis [10,11] (usually based on finite-element (FE) modelling) allows a more holistic rupture risk assessment and
quantitatively integrates many risk factors. Consequently, biomechanical indices like peak wall stress (PWS; see [12] and references therein) and the peak wall rupture index (PWRI; [13–16]) have been regularly shown to be higher in ruptured/symptomatic AAAs than in intact/non-symptomatic AAAs. In recent years, the continuous development of biomechanical AAA rupture risk assessment includes improved modelling assumptions (by considering the zero-pressure configuration [17–20]), the homogeneous stress hypothesis [21], wall calcifications [22,23], wall anisotropy [17,24], poro-elastic tissue descriptions [25,26], fluid–structure interaction [27–29] and highly automatized three-dimensional model generation [30]. In addition, simulation results have been validated with respect to phantom experiments [31], operator variability [32], histological signs of wall degeneration [33] and biological activity [6,34]. Despite this encouraging progress, the variability of biomechanical predictions due to uncertainty of input information remains a challenging limitation. Specifically, for clinical application of the biomechanical AAA rupture risk assessment, key input information like the local wall thickness and the local biomechanical properties of aneurysm tissue remains unknown. Owing to this lack of input information, homogeneous mean population properties are used, and the extent to which this simplification influences the clinical value of the diagnostic prediction remains to be explored.

This study applied biomechanical modelling and derived a probabilistic AAA rupture risk index which was tested against another available index for predictability. Specifically, the uncertainties in AAA wall thickness (thought to be one of the most relevant input parameters for AAA wall stress predictions) and wall strength were considered. While processing uncertainty in engineering design [35] and risk assessment is well documented [36], to the authors’ knowledge, this concept has not yet been applied to cardiovascular problems.

2. Methods

2.1. Deterministic modelling
2.1.1. Abdominal aortic aneurysm geometry reconstruction from computer tomography-angiography images

Aneurysms were reconstructed from computer tomography-angiography (CT-A) data with the diagnostic system A4clinics Research Edition (VASCOPS GmbH, Graz, Austria). This system applied active contour models to segment the images [30], requiring only minimal user interactions depending on the complexity of the aneurysm and the quality of the image data, and showed clinically acceptable operator variability [32].

2.1.2. Classical abdominal aortic aneurysm biomechanical modelling

After segmentation (see §2.1.1) the aneurysms were analysed with the diagnostic system A4clinics Research Edition (VASCOPS GmbH). The AAA wall and ILT were automatically meshed by hexahedral-dominated elements especially accounting for the reported wall thinning behind the ILT [37]. The FE model was pressurized by the MAP (1/3 systolic pressure + 2/3 diastolic pressure) and used the mixed Q1P0 FE formulation, i.e. tri-linear and constant interpolations for displacements and the hydrostatic pressure, respectively [38]. The model assigned isotropic constitutive descriptions for the aneurysm wall [39] and the ILT, which gradually decreased in stiffness from the luminal to the abluminal sites [40]. In addition, the FE model was fixed at the levels of the renal arteries and the aortic bifurcation, and the CT-A-recorded geometry was regarded as stress-free reference configuration. Further modelling details have been reported elsewhere [13,30].

2.1.3. Advanced biomechanical abdominal aortic aneurysm modelling

After aneurysm segmentation (see §2.1.1), stereolithography files representing the AAA’s geometry (luminal surface, exterior surface and wall–ILT interface) were exported to ICCE CFD 14.5 (Ansys Inc., USA) for FE mesh generation. A typical mesh is presented in figure 1. The aneurysm wall was meshed with tri-linear hexahedral elements (element type SOLID 185, surface element size of 3 mm, four elements across the thickness) while the ILT was meshed with linear tetrahedral elements (element type SOLID 285, element size of 3 mm). The aim of the very fine ILT mesh was to overcome locking phenomena known from linear tetrahedral elements. The wall thickness was spatially constant and three different wall thicknesses were assigned for each AAA model in order to include its influence on the PWS (see §2.3). Mesh generation required significant manual interaction and took between 4 and 8 h for one case. FE meshes were then exported to ANSYS (Ansys Inc.) for FE computation.

2.1.3.1. Constitutive abdominal aortic aneurysm tissue modelling

Owing to the aneurysm-related proteolytic degeneration of structural proteins [41], the AAA wall differs mechanically from the normal aorta. Specifically, the AAA wall is less anisotropic, and, at the same time, the nonlinearity of the stress–strain relation is more pronounced [42]. We previously demonstrated that wall stress computations are not particularly sensitive to constitutive descriptions as long as the wall’s low initial stiffness, followed by its strong stiffening at higher strains, is respected [20]. In order to capture such properties, we applied an incompressible five-order Yeoh strain energy density function [43]

\[ \Psi = \sum_{i=1}^{5} c_i (I_1 - 3)^i, \]  

(2.1)
with $I_1$ denoting the first invariant of the Cauchy–Green deformation tensor. In addition, $c_i$ are stress-like material constants set to $c_1 = 5$ kPa, $c_2 = 0$, $c_3 = 0$, $c_4 = 2200$ kPa and $c_5 = 13,740$ kPa, in order to capture AAA wall mean population properties [20].

In contrast to the aneurysm wall, the ILT exhibits a much more linear stress–strain response [40,44], which is nicely captured by the isotropic Ogden-like [45] strain energy density function

$$
\Psi = \sum_{i=1}^{n} c (\lambda_i^p - 1),\tag{2.2}
$$

with $\lambda_i$ and $c_i$ being the $i$th principal stretch and a stress-like material parameter, respectively. Specifically, the ILT is stiffer at the luminal layer ($c = 2.62$ kPa) and gradually softens towards its abluminal site ($c = 1.73$ kPa) [40], which was accounted for in this study. Finally, it should be noted that although ITL tissue is highly porous [46], previous studies have demonstrated that a single-phase model predicts AAA wall stress with sufficient accuracy [25,26].

2.1.3.2. Definition of the finite-element reference configuration

CT-A modality records the aorta at pulsatile blood pressure, and the images provided, of course, do not reflect AAA zero-pressure geometry. The forward FE method requires a (stress-free) reference configuration, and, if residual strains are excluded, the zero-pressure configuration could serve as such a reference configuration. However, for simplicity, FE calculations often use the CT-A-recorded geometry as their reference configuration. Specifically, the PWS for AAA wall models that respected the low initial stiffness of the AAA wall (i.e. like the one introduced by equation (2.1)), differed significantly when either the CT-A-recorded geometry or the (predicted) zero-pressure geometry were used as the FE reference configuration [17,19].

Of the different approaches to estimate AAA zero-pressure configuration from CT-A-recorded geometry [17–20], we used the backward incremental method [18]. Briefly, successive intermediate reference configurations were constructed by subtracting the computed FE-mesh nodal displacements from the previous reference configuration, i.e. until the MAP-loaded model matched the CT-A-recorded geometry. Further details regarding the zero-pressure configuration update algorithm, including its verification, are reported elsewhere [18,20].

2.1.3.3. Residual strains in the load-free configuration

Even a relatively thin wall, paired with a highly nonlinear constitutive model, leads to large stress gradients across the thickness [20]. These stress gradients are not physiological and violate the homogeneous stress hypothesis [47]. Simply put, residual strains in the load-free configuration are a direct consequence of a homogeneous stress state at physiological loading [48], and constitutive descriptions that account for tissue remodelling also predict homogeneous stress across the AAA wall [49]. In order to overcome a non-physiological stress gradient across the wall, the present model employed our recently proposed isotropic growth-based algorithm [21].

2.1.3.4. Boundary conditions and loading protocol

The AAA was fixed at the levels of the renal arteries and the aortic bifurcation and did not otherwise interfere with its surrounding. The blood pressure was gradually increased up to MAP, while, at the same time, the zero-pressure configuration was predicted according to §2.1.3.2, which typically required about 10 iterations. The blood pressure was then kept constant at MAP, and the algorithm to minimize the stress gradient across the wall (see §2.1.3.3) was executed, which required again about 10 iterations. Next the wall stress was computed at 50% elevated blood pressure, i.e. at 1.5 MAP and, for the present work, PWS was defined as the peak of the first principal Cauchy stress all over the aneurysmatic sack. Consequently, potential stress artefacts in the aortic bifurcation and/or at domain boundaries were excluded. Finally, PWS served as the load-related parameter for the suggested probability-based rupture risk criterion as detailed in §2.4.2. Key modelling details are summarized in table 1.

2.2. Statistical analysis

Statistical analysis was performed with Minitab (Minitab Inc.) and the significance level for hypothesis testing was set to a $p$-value of 0.05. Probability distributions were tested with the Anderson–Darling test of non-normality [45]. Data were not drawn from a population with the tested distribution. A two-tailed (non-parametric) Mann–Whitney test was used for difference testing (null hypothesis $H_0$: the median of the two populations do not differ; alternative hypothesis $H_1$: the median of the two populations differ).

2.3. Uncertainty quantification

2.3.1. Abdominal aortic aneurysm wall thickness

The wall thicknesses for the deterministic FE models were spatially constant (see §2.1.3) but statistically distributed according to previous in vitro measurements. Specifically, we used AAA wall thicknesses data published elsewhere [7] and performed the Anderson–Darling goodness-of-fit test (null hypothesis $H_0$: data were drawn from a population with the tested distribution). A two-tailed (non-parametric) Mann–Whitney test was used for difference testing (null hypothesis $H_0$: the median of the two populations do not differ; alternative hypothesis $H_1$: the median of the two populations differ).

2.3.2. Abdominal aortic aneurysm wall strength

We have extracted tensile Cauchy strength data from in vitro tensile testing of wall samples published elsewhere [7], and, the same statistical analysis as performed for the wall thickness, revealed that the AAA wall strength may follow one of the following distributions: (i) the lognormal distribution ($p > 0.25$) with $\alpha_Y$ according to equation (2.3) (location $\mu_Y = 7.2607$ and scale $\alpha_Y = 0.38$); (ii) the extreme value distribution ($p > 0.25$) with $\alpha_Y$ according to equation (2.4) (location $\mu_Y = 458.9$) with $\alpha_Y = 0.25$) with $\alpha_Y$ according to equation (2.5) (location $\mu_Y = 7.2698$ and scale $\alpha_Y = 0.21$). The estimated distribution parameters defined a median wall strength of 1.42, 1.43,
1.46 and 1.45 MPa for the lognormal, extreme value, gamma and log-logistic distributions, respectively.

2.3.3. Peak wall stress
Owing to the uncertainty of the input information of the underlying deterministic model (see §2.1.3), the PWS predictions were also uncertain, and, for each case, the PWS followed the individual probability distribution $r_{PWS}$. §2.4.3 details the computation of $r_{PWS}$, and, as demonstrated there, the Anderson–Darling test confirmed that PWS may follow lognormal, gamma and extreme value distributions, respectively.

2.4. Rupture risk criterion definition and computation

2.4.1. Standard deterministic approach
According to the biomechanical AAA rupture risk hypothesis, the wall ruptures if the wall stress exceeds the wall strength. Consequently, the ratio of wall stress and wall strength serves as a dimensionless local risk indicator and its peak, over all the aneurysmatic sack, was used as the rupture risk index. Specifically, we used the PWRI definition provided by A4clinics Research Edition, which relates the local von Mises wall stress to the local wall strength. Here, AAA wall strength was estimated by a scaled version of the model proposed previously [50], and further details are given elsewhere [13,15].

2.4.2. Definition of a probabilistic rupture risk index
Uncertainties from both, PWS predictions and AAA wall strength, were integrated in a novel probabilistic rupture risk index (PRRI). In order to derive such an index we note that the definite integral $\int_0^\infty \rho_Y \, d\rho_Y$ characterizes the probability that the strength of the wall is lower than a deterministic PWS value, see the dashed area in figure 2. The generalization of this result to probabilistically distributed PWS defines the proposed risk index

$$\text{PRRI} = \int_0^\infty \left( \int_0^{PWS} \rho_Y \, d\rho_Y \right) \, d\rho_{PWS}. \quad (2.7)$$

Consequently, $0 \leq \text{PRRI} \leq 1$ quantifies the probability of having low wall strength paired with high PWS, where a simple graphical visualization is unfortunately not possible.

2.4.3. Computation of the probabilistic rupture risk index
In order to compute PRRI according to equation (2.7), both the wall strength distribution $\rho_Y$ and the PWS distribution $\rho_{PWS}$ are

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Table 1. Key biomechanical features used by the standard deterministic and the proposed probabilistic approaches to assess the risk of AAA rupture.

<table>
<thead>
<tr>
<th>method</th>
<th>standard deterministic approach</th>
<th>proposed probabilistic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>constitutive model for the AAA wall</td>
<td>isotropic, hyperelastic derived from uniaxial tensile testing [39] reflecting mean population data</td>
<td>isotropic, hyperelastic derived from planar biaxial tensile testing [42] reflecting mean population data</td>
</tr>
<tr>
<td>FE reference configuration</td>
<td>geometry reconstructed from CT-A images</td>
<td>predicted from CT-A images by the backward incremental method [18]</td>
</tr>
<tr>
<td>constitutive model for the ILT</td>
<td>isotropic, hyperelastic derived from uniaxial tensile tests [40] reflecting mean population data</td>
<td>isotropic, hyperelastic derived from uniaxial tensile tests [40] reflecting mean population data</td>
</tr>
<tr>
<td>wall thickness</td>
<td>considers wall thinning behind a thick ILT layer [37]</td>
<td>spatially constant and lognormal distribution [7]</td>
</tr>
<tr>
<td>residual stress in the FE reference configuration</td>
<td>implicitly accounted by the (about) homogeneous wall stress that is predicted by a single FE across the wall</td>
<td>implicitly accounted through wall stress homogenization at MAP through volumetric tissue growth [13]</td>
</tr>
<tr>
<td>loading for rupture risk estimation</td>
<td>inflation at MAP</td>
<td>inflation at 1.5 MAP</td>
</tr>
<tr>
<td>wall stress measure</td>
<td>von Mises Cauchy stress</td>
<td>first principal Cauchy stress</td>
</tr>
<tr>
<td>wall strength</td>
<td>deterministic and reflecting gender-related mean population data. Spatially variable based on normalized local diameter and ILT layer thickness [50]</td>
<td>spatially constant, lognormal distributed and reflecting mean population data [7]</td>
</tr>
<tr>
<td>rupture risk index definition</td>
<td>according to A4clinics Research Edition</td>
<td>according to eqn (2.7)</td>
</tr>
<tr>
<td>total analysis time for one patient</td>
<td>10–20 min with standard PC hardware</td>
<td>about one week with high-end hardware (6 core 3.4 GHz CPU with 24 GB RAM)</td>
</tr>
</tbody>
</table>

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Figure 2. Rupture risk definition for a deterministic PWS that is paired with probabilistic wall strength. Dashed area defines the probability that wall strength is lower than a deterministic PWS value. (Online version in colour.)
gives the circumferential stress in the thin-walled cylinder of power-law function reduces to the classical Laplace law, which selected too close to each other. Consequently, the numerically intensive deterministic AAA model was only executed a few times, while at the same time the response function covered the whole design space, i.e. reasonable values of the wall thicknesses $h$. Owing to reasonable physical constraints ($PWS \to \infty$ for $h \to 0$ and $PWS \to 0$ for $h \to \infty$), we selected the inverse power-law function $PWS(h) = ah^b$ as response function. Here, the power-law parameters $a$ and $b$ were least-square estimated from the discrete PWS points predicted with the deterministic biomechanical AAA model. Note that the coefficient $a$ refers to PWS at the thickness $h = 1$ mm. Moreover, for $a = p \cdot r$ and $b = -1$, the power-law function reduces to the classical Laplace law, which gives the circumferential stress in the thin-walled cylinder of radius $r$ that is inflated at a pressure $p$.

In order to identify a suitable number of discrete PWS points, i.e. number of PWS computations with the deterministic biomechanical AAA model detailed in §2.1.3 at different wall thicknesses, a retrospective error analysis was performed. Specifically, we compared PRRI computations that were based on three to those that were based on only two discrete PWS points. This analysis revealed maximal 11% difference in computed PRRIs, such that we concluded that three PWS points are sufficiently accurate, i.e. provided enough information for a robust identification of the power-law parameters $a$ and $b$, respectively. This analysis also revealed that the executed wall thicknesses should sample the physical range of AAA wall thickness, i.e. they should not be selected too close to each other.

Next, for each case its response function $PWS(h)$ was used for $10^6$ Monte Carlo calculations, i.e. the PWS was repeatedly calculated using sampling points that followed either lognormal equation (2.3) or extreme value equation (2.4) distributions for the wall thicknesses $h$. It is noted that the selected number of Monte Carlo sampling points was high enough to keep associated absolute fluctuations of PRRI values below 0.02. Finally, the obtained sets of PWS values were statistically analysed as detailed in §2.3. Specifically, the nature of the PWS distribution was Anderson–Darling tested, and pdf parameters for lognormal, gamma and extreme value distributions were identified. Consequently, all information that is needed to compute PRRI according to equation (3.7) was available, and this risk index was computed for all possible 24 combinations of pdfs, i.e. representing wall thickness $h$ (two pdfs), PWS (three pdfs) and wall strength $Y$ (four pdfs), respectively.

### 2.5. Probabilistic rupture risk index validation

In order to validate the PRRI, a cohort of ruptured ($n = 7$) and intact ($n = 7$) AAA were retrospectively analysed, see table 2. All patients but one were male, data were collected at Karolinska University Hospital, Solna, Sweden, and the use of anonymized patient data was ethically approved. Individual cases were selected on purpose in order to obtain best possible diameter-matched groups since simple statistical confirmation ($p = 0.95$) is not very relevant due to very low number of cases in our study. For ruptured cases, blood pressure was taken from the last recording prior to rupture, and for non-ruptured cases at the time of CT-A scanning. Ruptured AAAs had higher MAP (although statistical significance was not reached $p = 0.055$).

The mean difference of PRRI in the ruptured and the intact cases was tested (Mann–Whitney), and the sensitivity and the specificity of PRRI to predict rupture were analysed.

### 3. Results

#### 3.1. Deterministic wall stress prediction

Typical wall stress results predicted by the advanced deterministic model outlined in §2.1.3 are illustrated in figure 3. For our cases, the applied method (see §2.1.3.2) was able to predict the zero-pressure configuration at a median of maximal difference between CT-A-recorded and MAP-inflated geometry of 0.66 (s.d. 0.82) mm. In addition, considering residual strains (see §2.1.3.3) effectively reduced the stress differences across the wall at MAP-inflation, as it is shown for a single case in figure 3a,b. Specifically, in our cohort the median of maximum and mean stress difference reduced from 1205(s.d. 527) kPa to 172(s.d. 227) kPa and from 95(s.d. 52) kPa to 8(s.d. 8) kPa, respectively. Here, the maximal stress difference occurred usually around the neck and the difference was substantially lower over the aneurysmatic sack. Note that stress predictions in bifurcations were excluded from PRRI computations. Naturally, when raising the inflation from MAP to 1.5 MAP (i.e. the loading level used for PRRI computation), while keeping the residual strains unchanged, the median of maximal and mean stress differences also rose to 328(s.d. 371) kPa and 25(s.d. 10) kPa, respectively, see in figure 3c,d.

### Table 2. Basic characteristics of the cohort of intact and ruptured AAAs used to test the PRRI.

<table>
<thead>
<tr>
<th></th>
<th>intact AAA cases</th>
<th></th>
<th>ruptured AAA cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>max. diameter (mm)</td>
<td>blood pressure (mmHg)</td>
<td>MAP (kPa)</td>
</tr>
<tr>
<td>I1</td>
<td>male</td>
<td>56</td>
<td>134/85</td>
</tr>
<tr>
<td>I2</td>
<td>male</td>
<td>67</td>
<td>125/75</td>
</tr>
<tr>
<td>I3</td>
<td>male</td>
<td>92</td>
<td>135/80</td>
</tr>
<tr>
<td>I4</td>
<td>male</td>
<td>75</td>
<td>140/80</td>
</tr>
<tr>
<td>I5</td>
<td>male</td>
<td>75</td>
<td>130/70</td>
</tr>
<tr>
<td>I6</td>
<td>male</td>
<td>70</td>
<td>140/90</td>
</tr>
<tr>
<td>I7</td>
<td>female</td>
<td>87</td>
<td>120/80</td>
</tr>
<tr>
<td>mean</td>
<td>73</td>
<td>12.9</td>
<td>mean</td>
</tr>
<tr>
<td>s.d.</td>
<td>10.8</td>
<td>0.7</td>
<td>s.d.</td>
</tr>
</tbody>
</table>
3.2. Probabilistic rupture risk index and its validation

Table 3 shows the estimated response function parameters $a$ and $b$. The high coefficients of determination $R^2$ demonstrate that the selected response function (inverse power law) can accurately fit the computed discrete PWS data. Then PRRI was computed according equation (3.7). PRRI values for all 24 pdf combinations are given in the electronic supplementary material, and table 3 presents mean values and absolute variations, respectively. This result showed that the particular combination of pdfs influenced PRRI predictions from 0.12 to 3.01% for the cases at lowest and highest rupture risks, respectively. Note, here '%' should not be understood as relative but absolute variation of PRRI values which are presented in %.

In order to analyse these results further, we limit ourselves to results from lognormal representations of wall thickness, PWS and wall strength. Typical results are presented in figure 4. Mean PRRI, i.e. mean probability of rupture was 5.4 times higher for ruptured than for intact AAAs (20.21(s.d. 14.15)% versus 3.71(s.d. 5.77)%; $p = 0.041$), see also the plots in figure 5a. Given that the median of the PWRI calculated with A4clinics Research Edition was 2.1 times higher in the ruptured group than in the intact group, this difference was not statistically significant ($p = 0.328$), see also the plots in figure 5b. Although not directly comparable, the average probability of rupture in our cohort of 12% was very close to the reported annual probability of rupture in the associated group of the same size, see [51] and references therein.

Strong correlation has been observed between MAP and PRRI ($r = 0.781$). By contrast, no significant correlation between the maximum diameter and PRRI ($r = 0.308$) was found.

Receiver operator characteristics (ROC) curves for PRRI, PWRI and maximum diameter illustrate the false positive rate (1-specificity) and true positive rate (sensitivity) of these predictors. The areas under the curves, which reflect the discriminative powers of the predictors, were 0.837, 0.673 and 0.531, respectively, for PRRI, PWRI and the maximum diameter. Note that the ROC curve for the maximum diameter was close to the diagonal, such that this predictor did not have any predictive information at all in our cohort. This was expected from the diameter-matching study design (figure 6).

4. Discussion

Despite encouraging results from the biomechanical AAA rupture risk assessment [12–16], the uncertainty of biomechanical predictions due to the uncertainty of input information remains a challenging limitation. Like other failure events, AAA rupture is also complex and a probabilistic risk assessment could have some advantages over a purely deterministic approach.
Figure 4. PWS probability density distributions for typical intact and ruptured AAA cases superimposed on mean population wall strength distribution for intact (a) and ruptured (b) AAA cases. Ruptured cases show higher mode of PWS and/or larger dispersion which results in significantly larger probabilistic rupture risk index. (Online version in colour.)

Table 3. Wall stress data and rupture risk indices for intact and ruptured AAAs. The response function (inverse power-law) parameters $a$ and $b$ are given together with the coefficient of determination $R^2$ to fit deterministic PWS data. Mean PRRI and $\Delta$PRRI refer to results from 24 combinations of pdfs for wall thickness, wall strength and PWS, respectively. Finally, an alternative rupture risk index (PWRI) and the maximal diameter are specified.
We applied a well-established probabilistic method [36] and introduced PRRI, a novel and straightforward probabilistic AAA rupture risk indicator. Most important, PRRI discriminated better between ruptured and intact AAAs than the state-of-the-art deterministic biomechanical method (discriminative power of 0.837 versus 0.673), and reached, although only for our very small cohort, statistical significance ($p = 0.041$ compared to $p = 0.328$ for PWRI from A4clinics Research Edition).

A4clinics Research Edition proportionally adjusts the wall thickness to the patient’s blood pressure, such that the elevated blood pressure in our ruptured group did not directly influence the PWS predictions. Apart from the very small number of patients, this adjustment to the wall thickness may explain why A4clinics Research Edition did not reach a statistical significant discrimination between ruptured and intact cases in our cohort.

Although the consequences of input variability on wall stress and wall strain predictions have been explored [20,39,52,53], to the best of the authors’ knowledge, this work seems to be the first attempt to consider input uncertainties as an integral part of the biomechanical rupture risk of AAA assessment.

AAA biomechanics is complex and wall stress predictions are influenced by modelling assumptions. For this work, we used a biomechanical model, which was as sophisticated as reasonably/practically possible, and regarded AAA wall thickness as the only uncertain input information. Not knowing the individual AAA wall thickness is constantly mentioned as a key limitation of AAA biomechanics simulations, and the wall thickness naturally affects PWS predictions, see among others [54–56]. Specifically, we applied lognormal-distributed and extreme value-distributed wall thicknesses (according to in vitro measurements [7]), which aimed at capturing distinctive effects of this input uncertainty but did not account for the known significant spatial wall thickness variation within
individual cases [57]. Despite the fact that the outlined approach is general, i.e. it allows additional probabilistic input information to be considered, the arising multidimensional probabilistic problem would have severe practical constraints of long computation times. Consequently, the complexity of the biomechanical model should be balanced with respect to the quality of the input information and the sensitivity of the results.

The available discrete data (wall thickness, PWS and wall strength) could be represented by several statistical distributions and the selection of the particular pdf influenced the absolute value of PRRI from 0.12 to 3.01% (see table 3 or electronic supplementary material). PRRI reflects the interference of $p_{PWS}$ and $p_{v}$ such that it is affected by the tails of the particular distributions. Consequently, when selecting pdfs for PRRI computation they should properly capture the extreme values of the sample. However, such extreme sample information (experimental data) might be difficult to collect beforehand. Despite this sensitivity of PRRI, for our cohort pdf selection had negligible influence on PRRI-related ranking of individual cases, and did not affect the discrimination of ruptured from non-ruptured AAA cases. Note that PRRI is not normally distributed and hypothesis testing requests non-parametric statistical tests, which rely on ranking comparison.

The response curve (inverse power law) represented an accurate surrogate model (see the high $R^2$ in table 3) except for the cases R2 and I5. Interestingly, for these cases not only the value but also the spatial location of PWS changed when different wall thicknesses were executed by the deterministic AAA model. It is also noted that the mean value of the inverse power-law parameter $b$ was very close to $-1$, i.e. in average PWS is closely predicted by the classical Laplace law. However, individually the $b$ value varies considerably, i.e. Laplace law should not be used to predict individual PWS.

The newly introduced PRRI has a clear physical meaning. It refers to the probability at which the wall strength is lower than the PWS at 1.5 MAP, and as such, the rupture probability of the constructed model of AAA at this loading condition. In addition, unlike deterministic risk indicators, our PRRI is also critically dependent on the prescribed blood pressure. Specifically, PRRI depends highly nonlinearly on blood pressure, and when rising from MAP to 1.5 MAP, PRRI increased between 2.5 times (for the case with the highest PRRI) and 150 times (for the case with the lowest PRRI) times in the cases studied. Consequently, more detailed information about the course of the blood pressure in daily life would directly improve the calculations. Also, blood-pressure measurements at rest, i.e. as taken at clinical examinations, underestimate blood vessels’ loading during daily activities, such that the associated PWS values are also very conservative for a rupture risk assessment. Finally, like most of the reported vascular tissue failure models, our approach cannot consider any dynamic effects like tissue fatigue [40] or remodelling [49,58–60]. Consequently, the potential risk from fast local AAA growth [61] is not considered by PRRI either.

AAA rupture is a local event that, as with high wall stress, is triggered by a (locally) weak wall. Direct or indirect evidence for global wall weakening factors (female gender, family susceptibility, angiotensin II receptor antagonist, etc.) and local wall weakening factors (FDG uptake on PET, thick ILT layer, high relative diameter expansion, calcifications, etc.) have been reported, see among others [6–9]. The local weakening factors in particular led us to expect a highly heterogeneous wall strength, which was also indicated by heterogeneous histology of the AAA wall [33]. Our PRRI was computed with a probabilistic, homogeneous wall strength (estimated from in vitro uniaxial tensile test data [7] although biaxial failure data would have reflected the in vivo failure condition more accurately [62] and neither local nor global wall weakening phenomena were considered. However, it would easily be possible to integrate local or global wall weakening factors (female gender, family susceptibility, etc.), which in turn could further refine the AAA rupture risk assessment. The extent to which this additional information would improve the predictability of the PRRI remains to be explored, especially since wall strength and wall thickness are inversely correlated [7,63–65], i.e. local variations of wall thickness and wall strength partly compensate for each other [56].

We did not follow the majority of AAA rupture risk studies and used the first principal stress instead of the von Mises equivalent stress for our PWS definition. Mechanical resistance against rupture of the AAA wall is mainly provided by collagen fibres, such that the principal stress, i.e. the stress in the direction of the majority of collagen fibres [66] could be a more appropriate PWS definition. However, there is a lack of any experimental evidence to prioritize any of the mentioned stress values.

Our probabilistic framework assumed that PWS and wall strength were independent variables, but the reported local correlation between wall stress and patho-histological findings [33] as well as biological activity [6,34] indicate rather the opposite. However, to date no quantitative relationship between PWS and wall strength is available, and once derived, the applied probabilistic framework could easily be extended towards dependent variables [36]. Finally, despite the fact that the reported sensitivity and specificity of the proposed PRRI is very promising, it should be verified in a much larger cohort. However, the very time-demanding computation of the PRRI is currently the most severe barrier against such large-scale validation.

5. Conclusion

Uncertainties in AAA wall stress predictions, the wide range of reported wall strengths and the stochastic nature of failure motivate a probabilistic rupture risk assessment. Accounting for homogeneous but probabilistic distributions of wall thickness and wall strength, and disregarding all other uncertainties, could significantly improve biomechanical AAA rupture risk assessments. Specifically, the sensitivity and the specificity of the rupture risk index, PRRI, were superior to the state-of-the-art biomechanical risk assessment method.

Authors’ contributions. S.P. proposed the concept of the study, performed FE computations, performed statistical testing and critically revised the manuscript. T.C.G. reviewed the concept of the study, drafted and critically revised the manuscript.

Competing interests. We have no competing interests.

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