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Biomechanic and Hemodynamic Perspectives in Abdominal Aortic Aneurysm Rupture Risk Assessment

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Additional information is available at the end of the chapter

Abstract

Abdominal aortic aneurysms (AAAs) pose a significant source of mortality for the elderly, especially if they go on undetected and ultimately rupture. Therefore, elective repair of these lesions is recommended in order to avoid risk of rupture which is associated with high mortality. Currently, the risk of rupture and thus the indication to intervene is evaluated based on the size of the AAA as determined by its maximum diameter. Since AAAs actually present original geometric configurations and unique hemodynamic and biomechanic conditions, it is expected that other variables may affect rupture risk as well. This is the reason why the maximum diameter criterion has often been proven inaccurate. The biomechanical approach considers rupture as a material failure where the stresses exerted on the wall outweigh its strength. Therefore, rupture depends on the pointwise comparison of the stress and strength for every point of the aneurysmal surface. Moreover, AAAs hemodynamics play an essential role in AAAs natural history, progression and rupture. This chapter summarizes advances in AAAs rupture risk estimation beyond the "one size fits all" maximum diameter criterion.

Keywords: abdominal aortic aneurysm, rupture risk, wall stress, shear stress, wall strength, biomechanics, hemodynamics, intraluminal thrombus, rupture potential index

1. Introduction

Abdominal aortic aneurysms (AAAs) are balloon like dilatations of the abdominal aorta with a diameter exceeding 50% of the diameter of the normal vessel [1, 2]. These are lesions affecting

mostly elderly male patients and have been related to smoking and family history [1, 2]. Patients with AAA are at risk of rupture which is the most devastating complication of this condition and is accompanied by a striking overall mortality of approximately 80% [3, 4]. Therefore, elective repair of AAAs is being performed to avoid the former scenario which of course, similar to any interventional therapy, is not without its own risks. Specifically, surgical treatment of AAAs is followed by a 3–4% periprocedural mortality which is reported to be as low as 1% in centers of excellence but is significantly increased and can reach up to 10% in case of compromised patients [5–8]. Endovascular modalities have significantly reduced operational risks but again carry a significant risk for renal morbidity, continuous need for surveillance with CT imaging with the associated exposure to radiation and a considerable risk for late complications and need for re-interventions in the long run [9, 10]. Therefore, the need for elective repair has to be cautiously balanced against the risk of rupture in order to determine optimal therapeutic management in a patient-specific basis. Currently, the maximum diameter criterion is being used as the sole predictor of rupture risk and the critical determinant of the need for intervention [1, 2]. Large randomized control trials have defined appropriate thresholds for repair which are 55 mm of diameter for male and 52 mm for female patients [11–14]. Nevertheless, this criterion is not always accurate and may frequently lead to therapeutic failures in the management of these patients. Specifically, in a contemporary systematic review, rupture rates for small AAAs, under the threshold for surgical repair, have been reported to reach 1.61 ruptures per 100 person-years [15]. Furthermore, in a more recent report, Laine et al. examining a large cohort of ruptured AAAs indicated that a remarkable 5.6% of men and 11.5% of women presented a maximum diameter under 55 and 52 mm, respectively, which are the thresholds for intervention according to the European guidelines [16].

2. The maximum diameter criterion

Actually, the physical principle behind the maximum diameter criterion is the Law of Laplace which states that the stress exerted on the wall of a pipe is proportional to its radius. Admittedly, this law is valid for cylindrical or spherical shapes with rigid, thin walls [17, 18]. None of these perquisites is valid in the living arterial system and therefore the presumption that maximum diameter can be used as an index to estimate wall stress exerted in the vessel wall is an oversimplification. Specifically, the arterial wall is distensible and not rigid, it has a variable thickness and more importantly AAAs present unique 3D geometric configurations which are original to each patient, presenting myriads of shapes and variable major and minor wall curvatures, not at all resembling simple geometrical shapes [19]. Therefore, relevant tools have subsequently been developed in order to stimulate biomechanical conditions inside AAAs and through computational modeling, calculate the stresses exerted on the arterial wall [20]. This progressively led to the next step of AAAs rupture risk estimation.

3. Wall stress

3.1. General

Stress is a measure of the loading sustained per unit area of the arterial wall, due to systemic pressurization and blood flow [21]. Pressure-induced, in-plane wall stress is orders of magnitude

greater than flow-induced shear stress and is considered the main force that contributes to arterial wall pressurization and the driving force leading to rupture [21]. Peak wall stress (PWS) is the maximum value of stress throughout the surface under evaluation, in other words the maximum stress exerted on the aneurysmal wall during systolic pressurization [22].

Stress acting on the aneurysm sac is estimated through finite element analysis (FEA) which is a numerical method to solve the differential equations of physics [23]. According to this process, any continuous quantity such as wall stress can be approximated by a discrete model composed of a set of simple continuous functions. In other words, in the case of AAAs where the complex geometry precludes a mathematical expression of the behavior of the whole system, one can divide this into a finite number of elements and then study the behavior in a single element or sub-region level. Since these elements have a small size and a simple geometric configuration, the description of their behavior is straightforward. Subsequently, the whole system can be resembled through the description of the behavior of all the elements taken together, since these collectively approximate the shape of the system [23].

In order to perform FEA, information regarding the boundary conditions, the material's constitutive law (stress-strain relationship) and its geometric configuration are required. Then the 3D geometry is loaded with a fixed or patient-specific value of systemic pressure and the mathematical problem is solved taking into account the equations of mechanical equilibrium and conservation of momentum [24].

Another approach is to apply a non-uniform pressure taking into account the pattern of pressure changes and the wall motion during the cardiac cycle. This is called fluid structure interaction (FSI) and provides a more realistic pressure distribution along the AAA luminal surface. Despite being more physiologically sound, such an approach needs increased computational complexity and thus it has not yet been determined if the benefit regarding the accuracy of the results justify the additional burden of complex calculations [25, 26]. Additionally, due to the lack of subject specific wall material properties, its superior accuracy remains a universal question.

Regarding the index geometry, initial studies considered simple representations of AAA shapes which mostly resembled standard geometrical shapes, rather than the complex configuration of real AAAs. Stringfellow et al. as early as 1987 used simple 2D geometries and indicated that aortic size was important in determining wall stress which was also dependent upon aneurysm wall thickness. Maximum longitudinal wall stress was located at the site of aneurysm's maximum diameter [27]. Mower et al. suggested that doubling the diameter of the 2D AAA model resulted in a proportional increase in wall stresses, while the same result was observed in case the wall thickness was reduced in half [28]. Inzoli et al. studied the influence of intraluminal thrombus (ILT) in the wall stress, indicating that this may reduce maximum stress values by up to 30% [29]. Others indicated a significant effect of AAA shape to magnitude and distribution of stress [19]. Actually, the influence of other geometric variables such as vessel asymmetry was found to be similarly important to that of maximum diameter, indicating that similar sized AAAs may in fact present significant differences in wall stresses [30].

With the rapid progression of imaging techniques and computational modeling, the reconstruction of patient-specific rather than idealized anatomies became feasible. Various techniques and softwares were developed in order to post-process medical images and reconstruct individual

anatomies, from simple axial 2D CT images to complex patient-specific AAA models. The process of AAA 3D reconstruction and estimation of wall stresses is displayed in **Figure 1**.

3.2. PWS and rupture risk

Fillinger et al. were the first to indicate that PWS was significantly higher in AAAs that needed emergent repair (ruptured and symptomatic) compared to those that were electively repaired, while no significant differences in maximum diameter or blood pressure were found [31]. In a subsequent study, these authors recorded AAAs progression over time and indicated that baseline PWS was significantly higher in cases that went on to develop symptoms and require urgent treatment compared to those that did not. Despite that baseline diameter was also significantly different between these groups, PWS was far more accurate in predicting adverse outcomes [32]. Other authors confirmed the findings that ruptured AAAs present a significantly higher PWS compared to intact cases [31–44]. These data are summarized in **Figures 2** and **3**.

3.3. PWS and rapid growth

Apart from rupture risk, there are data in the literature to suggest that high PWS may be related to a rapid AAA expansion, as well. Speelman et al. studied 69 paired CTs of AAAs and found that a relatively low AAA wall stress was associated with a lower aneurysm growth rate [45]. The same authors in a subsequent study suggested that AAA growth may be driven rather by ILT accumulation and not PWS. Specifically, in the group of AAAs with rapid growth, a greater ILT volume was recorded along with a lower PWS. Of course, ILT has been found to reduce stresses exerted on the aneurysmal wall which is the reason why many suggest a biomechanical cushioning effect of this structure, which is discussed later [46]. The contradicted data of the two abovementioned studies could be explained by the fact that in the first, the authors did not take into account the presence of ILT during PWS estimation. Others have demonstrated that concentrations of high stresses in the region of the aneurysm shoulder may result in a rapid growth rate. Specifically, baseline AAA shoulder stress was higher in patients with fast growth compared to those with slow and presented a strong and significant correlation with growth rate, whereas AAA diameter did not display any significant effect [47].
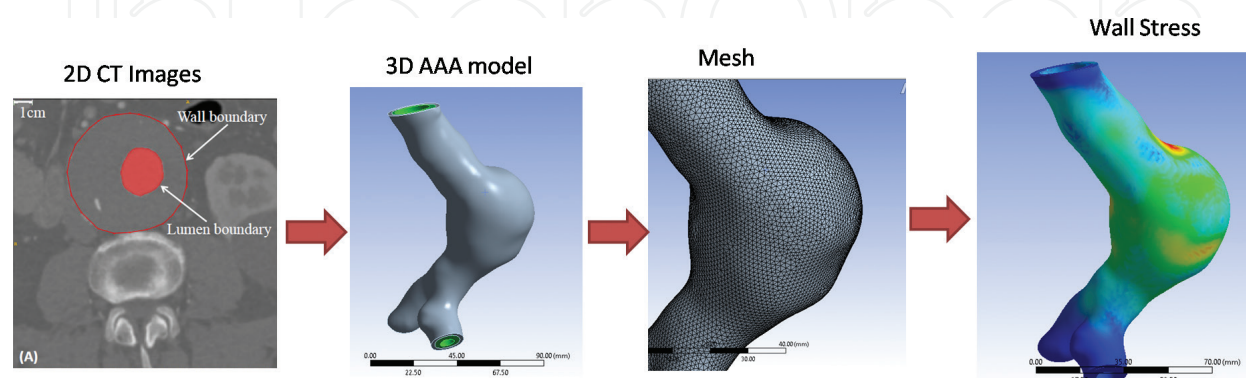

Figure 1. The process of biomechanical analysis is displayed. From 2D CT images, with manual or automated segmentation, 3D AAA models are reconstructed. Then a mesh is constructed and finite element analysis is performed. The final map of wall stress distribution is finally obtained.
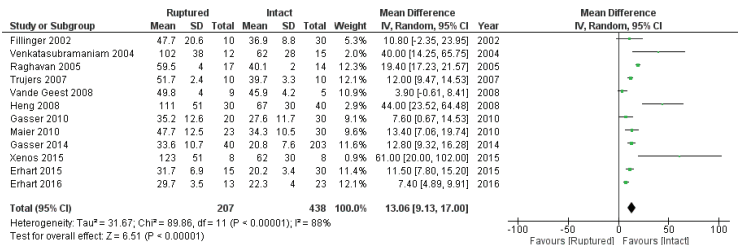
Study or Subgroup	Ruptured Mean	SD	Total	Intact Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Fillinger 2002	47.7	20.6	10	36.9	8.8	30	5.3%	10.80 [-2.35, 23.95]	2002
Venkatasubramaniam 2004	102	38	12	62	28	15	2.0%	40.00 [14.25, 65.75]	2004
Raghavan 2005	59.5	4	17	40.1	2	14	12.3%	19.40 [17.23, 21.57]	2005
Trujers 2007	51.7	2.4	10	39.7	3.3	10	12.1%	12.00 [9.47, 14.53]	2007
Vande Geest 2008	49.8	4	9	45.9	4.2	5	10.9%	3.90 [-0.61, 8.41]	2008
Heng 2008	111	51	30	67	30	40	2.9%	44.00 [23.52, 64.48]	2008
Gasser 2010	35.2	12.6	20	27.6	11.7	30	9.1%	7.60 [0.67, 14.53]	2010
Maier 2010	47.7	12.5	23	34.3	10.5	30	9.6%	13.40 [7.06, 19.74]	2010
Gasser 2014	33.6	10.7	40	20.8	7.6	203	11.6%	12.80 [9.32, 16.28]	2014
Xenos 2015	123	51	8	62	30	8	0.9%	61.00 [20.00, 102.00]	2015
Erhart 2015	31.7	6.9	15	20.2	3.4	30	11.4%	11.50 [7.80, 15.20]	2015
Erhart 2016	29.7	3.5	13	22.3	4	23	12.1%	7.40 [4.89, 9.91]	2016
Total (95% CI)			207			438	100.0%	13.06 [9.13, 17.00]	

Heterogeneity: Tau² = 31.67; Chi² = 89.86, df = 11 (P < 0.00001); I² = 88%
Test for overall effect: Z = 6.51 (P < 0.00001)

Figure 2. Metanalysis of the studies examining PWS in ruptured and intact AAAs. A consistent finding is that ruptured cases present significantly higher values of PWS compared to elective cases. The high heterogeneity between studies is due to differences in methodology (differences in assumptions for FEA, loading of the AAA model with patient-specific or standard values of pressure, inclusion of ILT in the final model, etc.). In many of the studies there were significant differences in maximum diameter between ruptured and intact AAAs which could have confounded results. This metanalysis has been performed by the authors for the purposes of this chapter only and has not been published elsewhere.
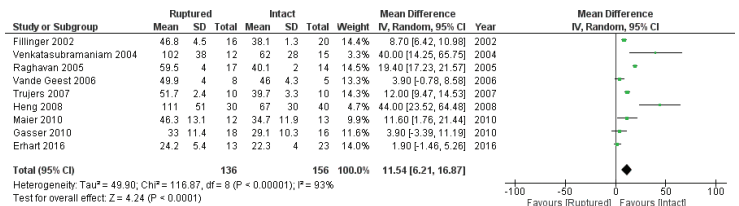

Study or Subgroup	Ruptured Mean	SD	Total	Intact Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Fillinger 2002	46.8	4.5	16	38.1	1.3	20	14.4%	8.70 [6.42, 10.98]	2002
Venkatasubramaniam 2004	102	38	12	62	28	15	3.3%	40.00 [14.25, 65.75]	2004
Raghavan 2005	59.5	4	17	40.1	2	14	14.5%	19.40 [17.23, 21.57]	2005
Vande Geest 2006	49.9	4	8	46	4.3	5	13.3%	3.90 [-0.78, 8.58]	2006
Trujers 2007	51.7	2.4	10	39.7	3.3	10	14.3%	12.00 [9.47, 14.53]	2007
Heng 2008	111	51	30	67	30	40	4.7%	44.00 [23.52, 64.48]	2008
Maier 2010	46.3	13.1	12	34.7	11.9	13	9.9%	11.60 [1.76, 21.44]	2010
Gasser 2010	33	11.4	18	29.1	10.3	16	11.6%	3.90 [-3.39, 11.19]	2010
Erhart 2016	24.2	5.4	13	22.3	4	23	14.0%	1.90 [-1.46, 5.26]	2016
Total (95% CI)			136			156	100.0%	11.54 [6.21, 16.87]	

Heterogeneity: Tau² = 49.90; Chi² = 116.87, df = 8 (P < 0.00001); I² = 93%
Test for overall effect: Z = 4.24 (P < 0.0001)

Figure 3. Metanalysis of the same outcome as in **Figure 2**. Only studies which performed matching for maximum diameter or in which differences were not significant are included. The results are similar with the overall comparison, so PWS seems superior to maximum diameter in differentiating ruptured from intact AAAs. This metanalysis has been performed by the authors for the purposes of this chapter only and has not been published elsewhere.
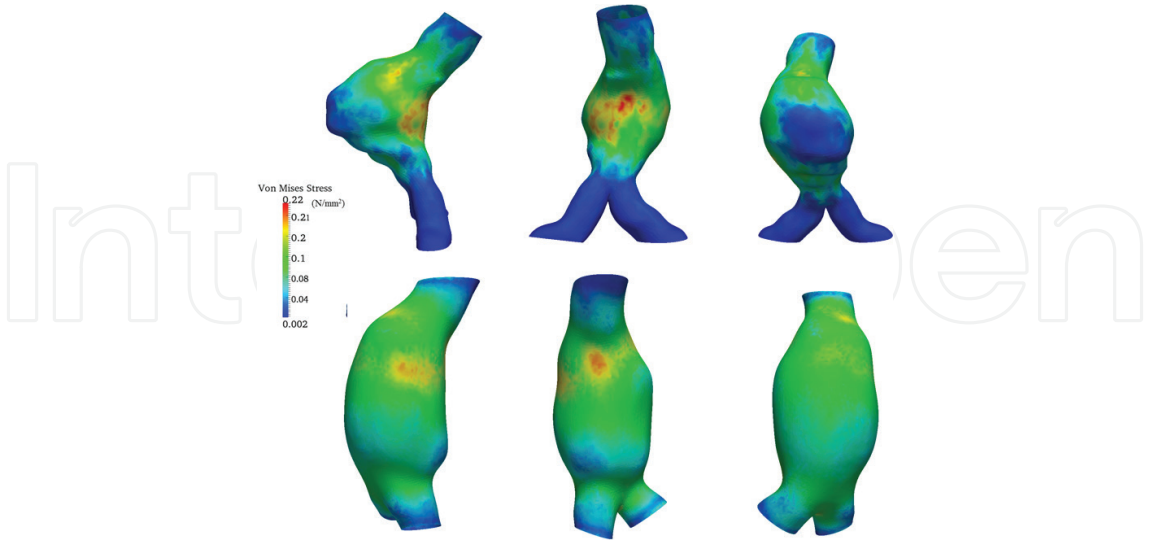

Figure 4. Lateral, posterior and anterior views of the stress distribution in two AAAs are displayed. Case in the first row presented a rapid growth rate while that in the second a much slower one. The difference in stress distribution can be observed. In the rapidly growing AAA high stresses are concentrated in the posterior wall, while in the case with relatively stable size, this is more uniform. According to Metaxa et al. [48] higher posterior wall stress may foretell a potential for rapid expansion.

Shang et al. in a contemporary study also indicated that there is a strong and statistical significant correlation between PWS and AAA growth rate. This is a particularly important finding since rapid growth has been shown to foretell a high rupture risk. Therefore, a high baseline PWS could identify lesions in risk for such adverse outcomes [48]. Moreover, Metaxa et al. divided their patient cohort into fast and slow growth rate subgroups and observed a significant variability in the distribution of stresses along the AAA surface: the fast growth rate group presented significantly higher wall stresses in the posterior portion of the AAA sac compared to the slow growth rate group [49]. Interestingly, they did not record any significant differences in the PWS between those groups. A representative example is presented in **Figure 4**. Finally, Martufi et al. studied a cohort of AAAs taking into account the baseline and a follow-up CT scan and quantified regional growth by dividing the two 3D AAA models in 100 cross sections and registering each section of the initial phase with the corresponding one from the final state. They indicated that for the aortic wall not covered with ILT, the local growth rate was strongly related with the local values of wall stress. The high stress sensitivity of non-dilated aortic walls suggests that wall stress could initiate AAA formation and expansion [50].

4. Wall strength

According to the biomechanical approach, rupture of AAAs follows the basic principles of failure applying in any given material. Therefore, material failure occurs when the mechanical stress exerted on that material surpasses its strength. Accordingly, rupture depends on the pinpoint comparison of the wall stress and strength for every point throughout the aneurysmal surface. Therefore, and taking into account that a significant regional variation of mechanical properties and strength of the AAAs' wall has been shown, a means to quantify the local arterial wall strength non-invasively and provide a map of its distribution similar to that of wall stress was required in order to provide a sound biomechanical rupture risk estimation [51]. Vande Geest et al. in a landmark study that they published in 2006 recorded several demographic and morphometric information of AAA cases and identified significant predictors of wall strength values by relating those to the tensile testing of surgically procured AAA wall specimens. Using this methodology, a four-parameter statistical model was developed, in which the significant predictors that were included were sex, family history, ILT thickness and normalized transverse diameter. Demonstrative application of the model resulted in an original, complex distribution of wall strength over the aneurysmal surface [52].

$$\text{STRENGTH} = 71.9 - 37.9 \times (\text{ILT1/2} - 0.81) - 15.6 \times (\text{NORD} - 2.46) \\ - 21.3 \times \text{HIST} + 19.3 \times SEX \tag{1}$$

These authors also suggested a new biomechanical index to estimate rupture risk which was the Rupture Potential Index (RPI). This integrated information about wall stress and strength and was basically the *stress:strength* ratio for any given point of the aneurysm wall. This ranged from 0 (low stress exerted in aneurysms with high wall strength) to 1 (high stress exerted in AAAs with low wall strength). **Figure 5** illustrates color maps for the distribution of wall stress, wall strength and RPI in a patient-specific AAA model. Subsequently, the same
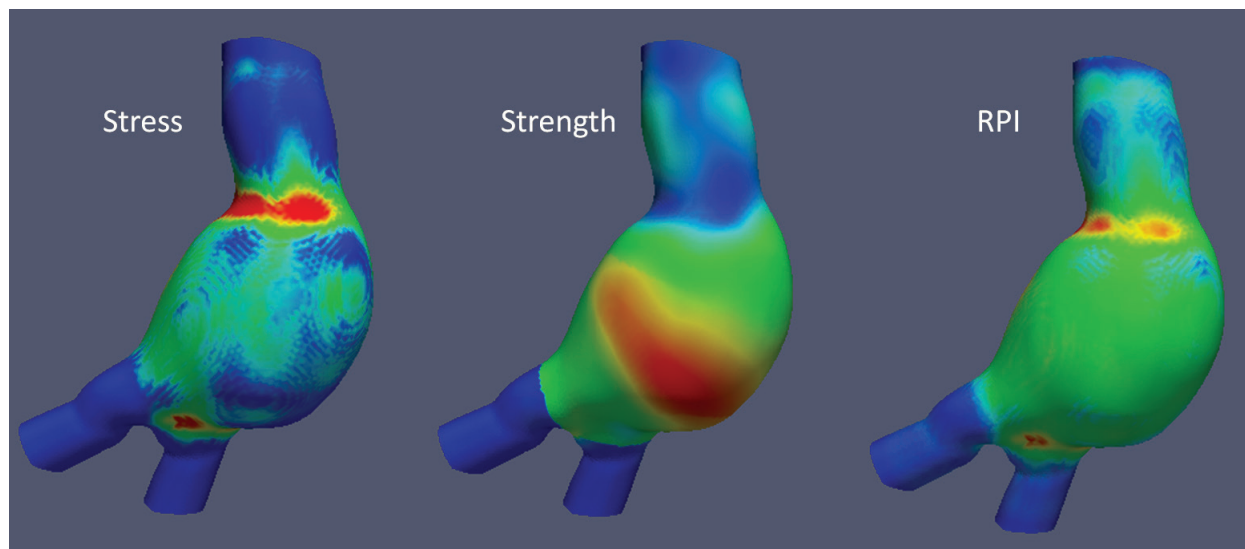
Figure 5. A patient-specific AAA model is presented where distribution of stress, strength and RPI can be seen. It can be observed that a weak region (decreased strength) at the site of maximum diameter results in a comparatively high RPI value, while at the same site a low stress value had been recorded. The implementation of strength in biomechanical calculations with the introduction of RPI seems superior than using wall stress alone.

authors compared between a small cohort of ruptured and non-ruptured AAAs indicating that RPI was superior in differentiating these groups than PWS alone. Due to small sample size, statistical significance was not reached. Other studies that included this marker in the biomechanical estimation of AAAs rupture risk consistently showed that RPI could improve risk prediction. Gasser et al. examined a diameter-matched cohort of 18 intact and 16 ruptured AAAs and indicated that both PWS and RPI were significantly higher in the former group of patients. Similar results were obtained when cases were matched for maximum diameter and blood pressure values. Overall, these authors suggested that RPI reinforces PWS as a biomechanical rupture risk index [39]. In a larger population including 203 intact and 40 ruptured AAAs, the same authors indicated that both PWS and RPI were significantly different between groups and that a linear relation existed between PWS and maximum diameter, while an exponential one fitted the relation between RPI and maximum diameter [41]. Erhart et al. analyzed CTA data from 13 asymptomatic AAAs experiencing rupture at a later stage who had imaging during the time of rupture as well. FEA was performed to calculate PWS and RPI and identify location of those values in the pre-rupture state. A statistical comparison was performed between the pre-rupture state and that at the time of rupture. Moreover, this group was compared with a 23-patient diameter-matched asymptomatic AAA control group that underwent elective surgery. The AAAs that subsequently went on to rupture displayed significantly higher values of RPI at the pre-rupture state compared with the diameter-matched group of asymptomatic AAAs, while the differences of PWS were not significant. Regarding in-group comparisons between the AAAs at the pre-rupture state and at the time of rupture, again RPI displayed significant differences, while PWS alone did not [44]. Overall, according to published data, RPI seems to advance rupture risk estimation and provide a more accurate biomechanical prediction compared to PWS alone. Studies examining RPI are summarized in **Table 1**.

	N		RPI		P-value	Dmax	Conclusions
	Intact	Ruptured	Intact	Ruptured			
Vande Geest [52]	5	8	0.36	0.48	0.10	Similar	The peak RPI may be better identify those AAAs at high risk of rupture than maximum diameter
							or peak wall stress alone
Gasser [39]	16	18	0.61	0.84	0.016	Matched Dmax	RPI reinforces PWS as a biomechanical rupture risk index.
Maier [40]	30	23	0.33	0.47	<0.001	No	In the diameter range where surgical indication is not obvious, the RPI holds great potential for improvement of clinical decisions.
	13	12	0.32	0.47	0.009	Matched Dmax	
Gasser [41]	203	40	0.49	1.03	<0.001	No	From different FEA parameters RPI distinguishes most precisely between asymptomatic and symptomatic AAAs. If elevated, this value may represent a negative prognostic factor for asymptomatic AAAs.
Erhart [43]	30	15	0.46	0.83	<0.001	No	From different FEA parameters RPI distinguishes most precisely between asymptomatic and symptomatic AAAs.
Erhart [44]	23	13	0.5	0.7	<0.001	Matched Dmax	The location of the RPI predicted future rupture sites in several cases. RPI is superior than PWS in identifying cases that will go on to rupture.

Table 1. Studies that examine RPI during biomechanical analysis are presented, along with absolute values and statistical significance of the differences between intact and ruptured cases and main authors' conclusions.

5. Equivalent diameters

Despite the fact that the abovementioned data provide consistent evidence of the superiority of stress and stress/strength calculation over the maximum diameter criterion for the evaluation of AAAs rupture risk, clinical applicability of these findings remain limited. A possible explanation could be the complexity of the process along with the requirement of sophisticated software, increased computational time and specially trained personnel. Indeed, computational modeling and mathematical algorithms that may be required in order to perform biomechanical calculations are often puzzling and confusing to clinical doctors. In order to deal with this problem and translate biomechanical indices into a more relevant clinical variable, the concept of "equivalent diameters" has been recently introduced. According to this approach, the PWS and RPI values are determined from a reference population of intact AAAs and these are plotted against the maximum diameter to obtain a graphical representation of
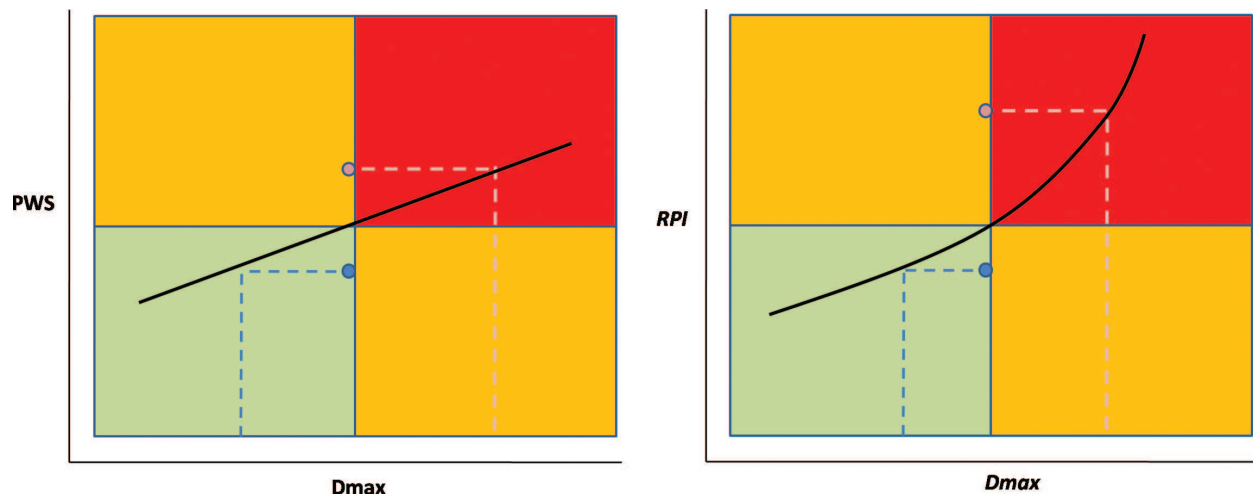
Figure 6. A graphical representation of the concept of equivalent diameters is presented. According to that, the equivalent diameter is determined based on the PWS or RPI value of a given AAA which is related to the diameter of the average AAA with similar PWS or RPI values. For example, it can be seen from these figures that two AAAs with the same maximum diameter, may present large differences in their equivalent diameters depending on biomechanical analysis.

their relationship. Subsequently, the values of PWS and RPI for any given AAA are related to those of an average AAA and the diameter of the latter is nominated "equivalent diameter".

For example, a 45 mm AAA could correspond to a stress equivalent 65 mm AAA, if a higher PWS or RPI is calculated. The concept of equivalent diameters relates results of biomechanical analysis to currently accepted diameter thresholds being determined from large clinical AAA trials, and hence manifests a sound clinical interpretation of biomechanical results [41]. The number of studies that have used this concept remains limited at the moment, but a consistent finding of larger equivalent diameters in ruptured compared with intact AAAs even when diameter matching was performed has been consistently reported [41, 43, 44]. As already mentioned, the relation between the maximum diameter and PWS is a linear one while that between diameter and RPI is exponential. This is because while stress is expected to increase as a function of diameter, in the case of RPI, strength has been shown to decrease as a result of an increased diameter too. Therefore, in that instance, a larger aneurysm size results in both higher stress values and lower strength values which are displayed in the exponential form of the relation between the RPI and the maximum diameter. A graphical representation of this concept is presented in **Figure 6**.

6. Wall shear stress

The wall shear stress (WSS) is the tangential force acting on the arterial wall due to blood flow. This traditionally had been considered to play a negligible role in AAAs expansion and progression to rupture for several reasons. Specifically, not only AAAs almost universally contain ILT which acts as an impediment between the blood flow and the endothelial layer of the arterial wall, but also it has been suggested that AAAs mostly lack a proper intimal layer that would

be affected by shear stress [20]. More importantly, the flow-induced shear stress acting on the AAA wall is orders of magnitude smaller than the in-plane pressure-induced wall stress, which until recently was believed to be the only force that could impair structural integrity of the wall leading to rupture. Specifically physiological values of wall stress is about 10^4 orders higher than WSS (wall stress is measured in 10^4 Pa, whereas WSS in Pa) [53].

Nevertheless, lately there have been data in the literature, to indicate a role of WSS in the natural history of AAAs. The main variable that seems to be related to WSS is the accumulation of ILT. Specifically, it has been suggested that ILT deposition has a significant negative relation with WSS. In other words thrombus tends to accumulate in regions where WSS is minimal. WSS typically ranges from 1.5 to 4 Pa [53]. Tzirakis et al. used longitudinal data for AAA patients and related initial hemodynamic parameters with subsequent ILT accumulation during follow-up, using an original technique that divided AAA surface into patches, in order to achieve registration between the initial and the final state. They indicated that a low local WSS was related with later ILT formation, with a value <0.5 Pa be indicative of a higher probability for thrombus deposition [54]. Representative AAA cases are presented in **Figure 7**. Similarly, Arzani et al. examined the relationship between changes in ILT and hemodynamic indices at mid-aneurysm cross section and suggested that thrombus growth mainly occurred in regions where WSS displayed values between 0.2 and 0.3 Pa [55]. To provide an answer to the obvious contradiction that intracranial saccular aneurysms, despite presenting low WSS, almost never exhibit thrombus accumulation, Gasser et al. suggested that initial platelet activation inside a proximal recirculation zone, such as the aneurysm neck, where relatively high-shear stresses act long enough to activate platelets, must precede their convection toward the wall at the distal portion of the sac, in order to initiate the cascade that ultimately results in ILT deposition [56]. Moreover, the rate of ILT accumulation has been reported to be similar to that of AAA expansion, while AAAs with thrombus exhibited a significantly faster enlargement compared to those without, with the former group presenting lower values of WSS. These
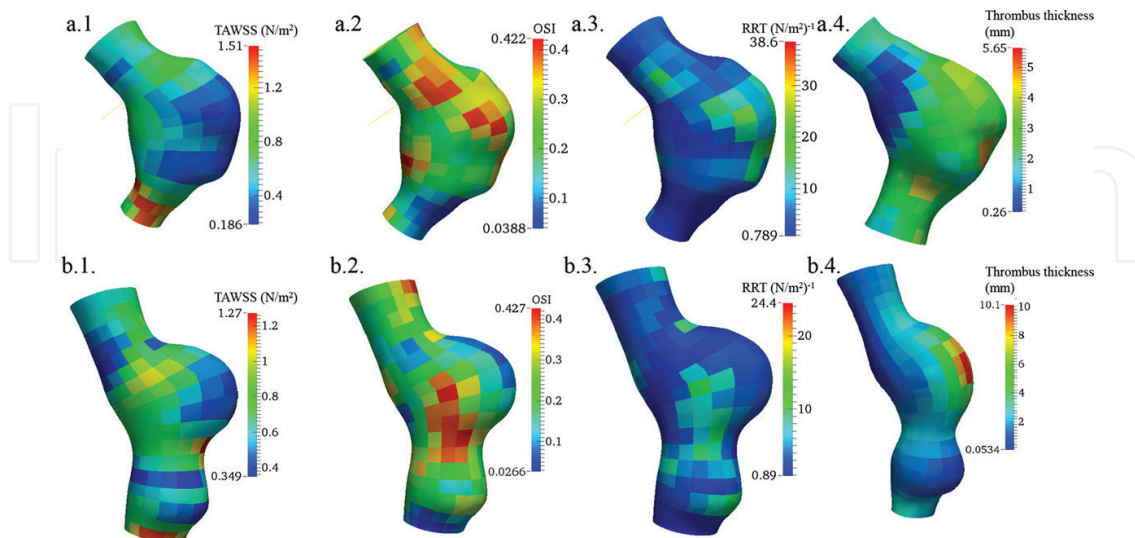

Figure 7. Initial hemodynamics (Time Average Wall Shear Stress-TAWSS, Oscillatory Shear Index-OSI, Relative Residence Time-RRT) and thrombus deposition thickness at follow-up for two cases. Adapted with permission from Tzirakis et al., [54].

findings imply a causal relation between low WSS and rapid AAA growth which could be mediated by the accumulation of ILT [57]. Finally, a recent study indicated that WSS independently predicted the growth of AAA volume and these investigators suggested that since aneurysmal wall lacks endothelial cells, blood flow properties could only indirectly influence AAA growth through stimulation of the biochemical environment within the ILT [58].

In fact, ILT has been suggested to play an active role in AAAs' natural history. Most researchers believe that it has a negative effect through its proteolytic activity and promotion of inflammation. ILT thickness has been associated with vascular smooth muscle cell apoptosis and elastin degradation, while it is positively associated with the concentration of proteolytic enzymes in the underlying wall [59]. Moreover, segments of the AAA sac under a thick layer of ILT have been recorded to be hypoxic and present significantly more neovascularization compared to those covered by no or minimum ILT. More importantly, regions of thicker ILT presented a decreased wall strength, which could make them more susceptible to rupture [60]. Additionally, there are longitudinal and computational AAA studies that also suggest a negative effect of ILT in AAAs progression. Speelman et al. recorded a higher growth rate in AAAs containing larger amounts of ILT despite the fact that those presented significantly lower values of PWS [46]. In a contemporary study which recorded regional growth of AAAs, it had been demonstrated that the local growth was positively related to local values of wall stress only in cases where ILT was absent. On the other hand, in the presence of ILT, local growth was dependent on local ILT thickness but not wall stress [50]. Therefore, these data may imply that ILT plays a more imminent role in AAAs progression than wall stress. Additionally, it has been suggested that larger ILT deposition may be related to AAA expansion, rupture and even with cardiovascular events [61–63]. On the other hand, it should also be mentioned that biomechanical analysis has demonstrated a cushioning effect of thrombus which acts as a buffer reducing stresses exerted on the wall. Many studies have examined this effect recording a reduction in PWS values up to 30% [64]. Therefore, there is wide consensus that ILT should be included in computational simulations in order to have a realistic and accurate estimation of stress magnitude and distribution. Additionally, while there is general agreement that ILT plays an active role in AAAs progression, not being an "innocent bystander" its exact role is still debatable, but most evidence points to a negative overall effect of ILT. All in all, taking into account the definitive role of ILT in AAAs progression and its well established relation with the shear stresses and the overall hemodynamic environment inside the aneurysm sac, a significant impact of hemodynamic forces in the AAAs' natural history has started to become evident.

7. Clinical implications

All the abovementioned indices and diagnostic methods point toward developing a predictive model that will be able to estimate AAAs rupture risk in an individualized, patient-specific basis. This would allow identification of patients with small AAAs presenting a higher than average rupture risk, thus being suitable for prompt elective repair at a lower diameter, but also those with larger aneurysms and low rupture potential who would benefit from conservative treatment. Subsequently, optimization of patients' management with the selection

of the most appropriately suited treatment (i.e. conservative or interventional/surgical) for each patient would reduce rupture rates of AAAs at the same time obviating unnecessary procedural risks of patients that do not actually need to undergo surgical intervention. A new promising tool that will probably receive much attention in the near future and will have an upgraded role in AAAs' diagnostics is ultrasonography which is a cheap and readily available bedside imaging modality which has recently been used to estimate biomechanical variables of AAAs with promising results [65].

8. Limitations

Despite the fact that biomechanical analysis seems to have advanced rupture risk prediction which is a consistent finding of all relevant studies, this approach is not without limitations. Specifically, the stresses and strains which are obtained are dependent on several model assumptions taken into account during FEA. For example inclusion or not of the ILT, consideration of the arterial wall as isotropic or anisotropic, linear or non-linear material properties, consideration of the pre-stress state as well as accuracy of the 3D reconstruction, meshing and number of finite elements used, all can have a great influence on calculated values. As a consequence, interpretation of results in many studies can be difficult since these are often not comparable. Differences in PWS due to different model assumptions can be up to 210% in extreme cases. Overall, in order for comparisons between individual reports to be valid, information about preconditions and model assumptions should be provided [26]. Moreover the need for special software and/or highly trained special personnel to make these complex calculations along with the fact that data are not directly comparable with information from randomized trials which have taken into account the maximum diameter criterion alone limit applicability of biomechanical analysis in the every-day clinical practice.

9. Conclusion

Despite the fact that currently therapeutic management of AAAs is based on the maximum diameter criterion, there is evidence that this can often be inaccurate. New methods have been developed in order to advance rupture risk estimation. Biomechanical indices of wall stress and rupture potential index have been consistently shown to be superior to maximum diameter in this regard. The concept of equivalent diameters may provide a comprehensive means to translate results of biomechanical analysis into a simple clinical index which may be appropriate for use in a clinical setting. An important role of hemodynamic conditions which can have a significant effect on AAAs progression, mainly through its relation with ILT accumulation, has recently started to become evident as well.

Conflict of interest

None to declare.

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