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Pathophysiology of Abdominal Aortic Aneurysm Rupture and Expansion: New Insight on an Old Problem

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1. Introduction

The infrarenal aorta is a region of variable hemodynamics, with low mean and oscillating shear stress, variable secondary flow patterns with vortex formations and consequent high particle residence time (Tang et al, 2006, Dua & Dalman, 2010). Among the biomechanical parameters, wall stress holds a fundamental role, since its distribution and maximum values have been associated with the risk of Abdominal Aortic Aneurysms (AAA) rupture (Fillinger et al, 2003 and Venkatasubramaniam et al, 2004). Rupture can occur where the mechanical forces per unit area of the aortic wall (stress) exceed the local strength, so that reliable rupture risk estimation should take into account both the local distribution of stress and wall strength. Furthermore, high values of wall stress in transition areas of AAAs, ie inflection site between the neck and the AAA sac have been recently reported to differentiate those small AAAs with rapid expansion rate, possibly rendering them amenable to early intervention (Li et al, 2010a).
Computer-enhanced geometric modeling and Finite Element Analysis (FEA) have been used to study the biomechanical behavior of the aorta and the aortic aneurysms (Steinman et al, 2003), contributing in the development of measures to assess AAA rupture risk (Malkawi et al, 2010) and expansion (Li et al, 2010b). This chapter reviews from the clinical point of view the role of wall stress in AAA rupture risk models.

2. Reconstructing the AAA models

Many research groups have evaluated AAA rupture risk with estimation of PWS using the FEA technique, which utilizes small subsections (elements) of a 3-dimentional AAA model, created by segmentation (**Figure 1**) and meshing (**Figure 2**). The stress computations rely on the principles of conservation of mass and momentum for all finite elements of the model. Most researchers acquire information on the 3D AAA realistic geometric configuration using contrast-enhanced high-resolution spiral CT angiography. The acquisition of the two-dimensional CT images for each case is followed in principle by the creation of outlines of the outer and the inner surface of the AAA. Consequently, a stack of contours is reconstructed including the common iliac arteries and the neck of the AAA as fixation

points are required in essential boundary conditions. The latter are needed for the solution the conservation laws. The result is a detailed map of the wall stress values throughout the aneurysm (**Figure 3**).

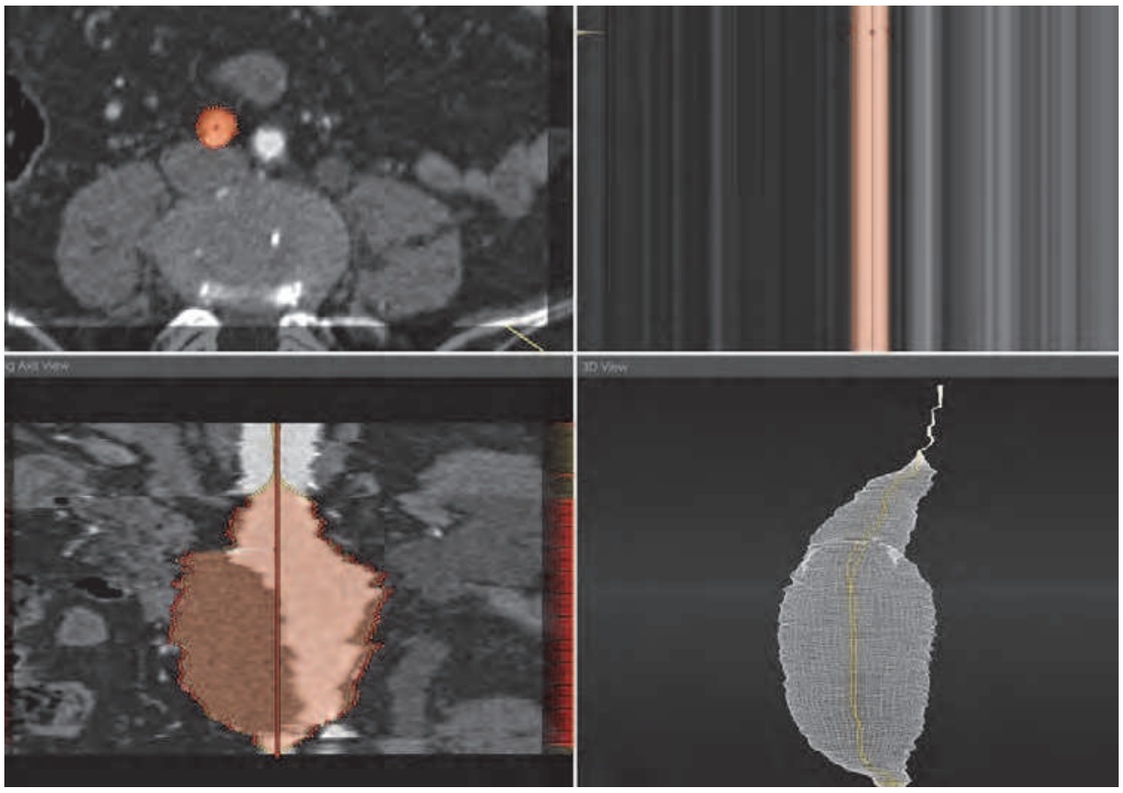

Fig. 1. Reconstructed images of the aneurysm are created from contrast enhanced CT images using purpose-developed software.

3. Role of wall stress in AAA rupture and expansion

Rupture remains the most threatening outcome of an AAA and is related to maximum diameter (Brewster et al, 2003) (**Table 1**).

Max. Diameter (cm)	Annual rupture risk (%)
<4	0
4-5	0.5-5
5-6	3-15
6-7	10-20
7-8	20-40
>8	30-50

Table 1. Annual rupture risk according to diameter (Brewster et al, 2003)

In current clinical practice, aneurysm diameter is one of the primary criteria used to decide when to treat a patient with an abdominal aortic aneurysm (AAA). The current threshold for

treatment is 5.5 cm; however, many surgeons have come across gigantic AAAs (e.g., 11 or 12 cm) that have not yet ruptured, as well as small aneurysms <5.5 cm that have. There is evidence that the simple association of aneurysm diameter with the probability of rupture is not sufficient, and presumably other parameters play a role in causing an aneurysm to rupture or protecting it from rupture. This problem has spawned a need for new methods to reliably predict the actual risk of AAA rupture in the clinical setting.

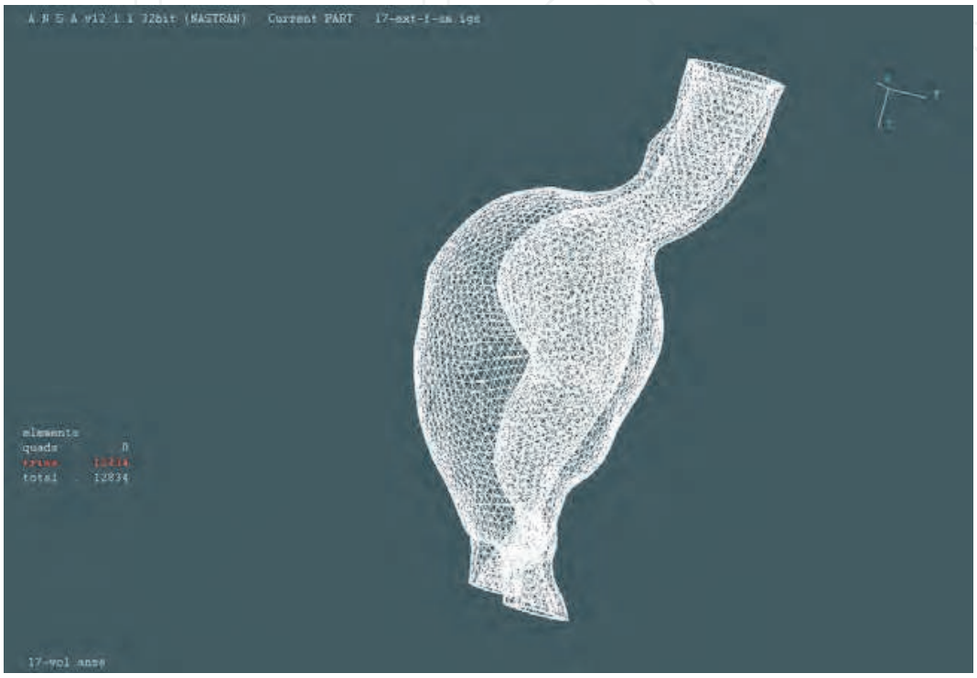

Fig. 2. Creation of the mesh

According to the biomechanical approach, rupture occurs when the stress on the aneurysm wall exceeds its failure strength. Laplace's law can estimate the stress values in ideally thin-walled shapes of simple geometry. However, these assumptions are rarely met in daily routine, since the patent-specific AAA models present variable asymmetry. Therefore, patient-specific knowledge of the magnitude and distribution of AAA wall stress and failure strength are useful measures in assessing the susceptibility to rupture. Stress is a measure of the internal forces induced on a material due to blood pressure and flow (Raghavan et al, 2005). Peak wall stress reflects the mechanical load sustained by the AAA wall during maximal systolic pressurization and depends on the mechanical properties and the geometric configuration of the wall (Raghavan et al, 2005). Arterial wall stress distributions for uniform wall loading, as well as flow-induced non-uniform pressure wall loading, are presented using the von Mises stress, a scalar measure of the stress tensor, proportional to the strain energy density at each point. Von Mises stress is expressed as σ_{VM}:

$$\sigma_{VM} = \sqrt{\tfrac{1}{2}\left[(\sigma_1 - \sigma_2)^2 + (\sigma_1 - \sigma_3)^2 + (\sigma_2 - \sigma_3)^2\right]}$$

where σ_1, σ_2, σ_3 are the principal stresses (Papaharilaou et al, 2007). PWS refers to the mechanical load sustained by the AAA wall during maximal systolic pressurization. Its

value depends on arterial systolic pressure and the mechanical properties and geometric configuration of the material under study. Scotti et al (Scotti et al, 2005) studied virtual aneurysm models of variable asymmetry and wall thickness distribution. They showed that the variability in wall thickness can increase the PWS by 4 times compared with AAA models of uniform thickness. Moreover, they showed that variable thickness and asymmetry affect not only the magnitude but also the distribution of the stress values. Therefore, it is important for modern patient-specific rupture risk assessment to reproduce the specific AAA geometry and wall thickness. Decreasing of wall thickness by 25% causes a 20% increase in PWS and vice versa (Venkatasubramaniam et al, 2004). Therefore, the abovementioned observations depict the limitations of Laplace's law in accurate stress estimation.

Stress analysis has three main components, the study of the geometry under evaluation, the material model that characterizes the mechanical behavior of the aneurysmal tissue and the study of the boundary conditions under observation, eg blood pressure. Peak Wall Stress (PWS) estimation with the Finite element analysis (FEA) technique has been extensively used through the last decade, utilizing a well known mathematical model that describes the biomechanical properties of the AAA wall (Raghavan & Vorp, 2000).

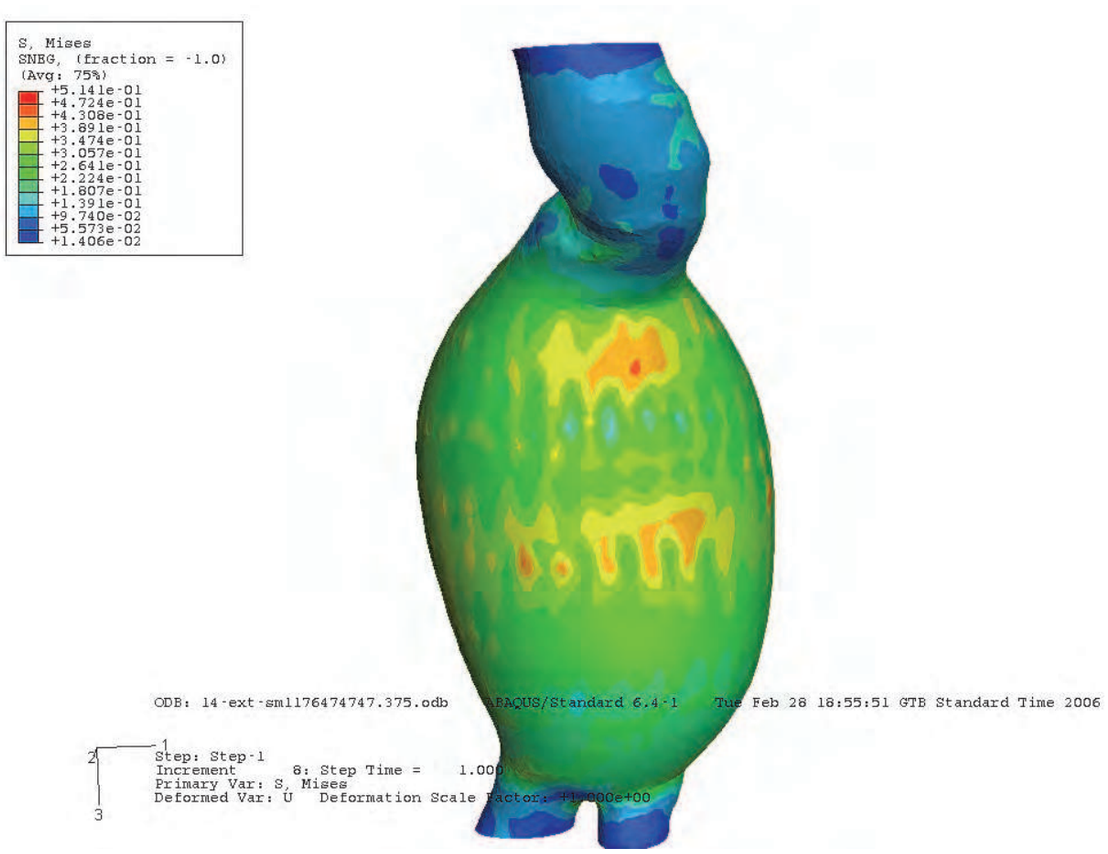

Fig. 3. The detailed map of the wall stress values throughout the aneurysm wall, after Finite Element Analysis. Wall stress values representation is based on a color-scaled climax. The red color depicts the Peak Wall Stress location, whereas blue color represents the sites of lowest wall stress.

The possible relation of PWS to the risk and the site of rupture in AAAs have been delineated in many studies. PWS has been estimated in ruptured and nonruptured, diameter-matched AAAs and was found to be significantly higher in the rupture group near the time of rupture (Fillinger et al, 2002, 2003, Heng et al, 2008; Venkatasubramaniam et al, 2004; Truijers et al, 2007; Vande Geest et al, 2008, Raghavan et al, 2005a). Moreover, a large prospective study by Fillinger et al (Fillinger et al, 2003) showed that PWS could differentiate AAAs that required urgent repair better than the maximum diameter criterion. In this study, Low-stress aneurysms presented a lower rupture rate whether they were small or large, with high stress aneurysms having a higher rupture rate regardless of size. The PWS values could differentiate more sufficiently than maximum diameter those AAAs prone to rupture over time. The conclusion was that the ruptured AAAs had higher values than the non-ruptured ones and that the elevated values were not simply an acute or incidental event near the time of rupture, but rather a characteristic that could be early recognized, thus gaining a predictive value with respect to the risk of rupture. Though the computational evaluation of PWS with FEA can be a strenuous and time-consuming effort (Leung et al, 2006), the intra- and interobserver variation for PWS is acceptable (Heng et al, 2008), making reliable in studies the utilization of PWS for rupture risk evaluation.

The expansion of the small AAAs is a multifactorial process, where biomechanical and biological factors interact (Dua & Dalman, 2010). It is well documented that cells along the aortic wall can respond biochemically to mechanical stress (Nakahashi et al, 2002). In early stages of AAA enlargement the elastin degradation induced by the wall shear stress (ie. the tangential force exerted by the movement of blood along the axis of flow) elevates the wall stress but accelerates sac enlargement, despite the stress-mediated collagen turnover (Sheidaei et al, 2011).

Slow growth rate in smaller AAAs has been proven to be associated with low stress values, whereas a rapid growth rate in this category seems to depend on the amount of intaluminal thrombus (ILT) rather than on the level of wall stress, which is decreased (Speelman et al, 2010). The presence of ILT promotes elastolytic activity with consequent structural degradation of the adjacent AAA wall (Kazi at al, 2003 and Wiernicki et al, 2010). These findings have been also confirmed recently by Parr et al (Parr et al, 2011), who reported a strong correlation of AAA rapid growth rate with the initial AAA diameter ($r = 0.44$, $P = .006$) and thrombus volume ($r = 0.50$, $P = 0.001$).

4. Evaluating the AAA geometry

PWS has been clearly associated with the risk of rupture. Wall stress has been found to be 12% more specific and 13% more sensitive in rupture prediction than maximum diameter alone and may differentiate ruptured and symptomatic small AAAs from the asymptomatic ones (Truijers et al, 2007; Vande Geest et al, 2008; Fillinger et al, 2003). Its values depend on the mechanical properties and the geometric configuration of the aneurysm wall (Raghavan et al, 2005). PWS estimation requires highly experienced personnel in a process that can require considerable power to run (Leung et al, 2006). Therefore, a useful adjunct tightly related to PWS assessment could provide great help regarding the rupture risk or growth rate estimation. The association of certain geometric parameters with high values of PWS has been demonstrated in many studies. This paragraph summarizes the most important of these studies, underscoring the importance of geometric parameters as potential adjunctive parameters along with maximum diameter and elevated PWS in rupture risk assessment.

Nathan et al (Nathan et al, 2010) studied the differences between saccular and fusiform descending thoracic aortic aneurysms. Although the saccular aneurysms in his study were of smaller diameter than the fusiform ones, the mean PWS was equivalent between the two groups. Since the elevated rupture risk of saccular aneurysms has been well defined in the literature, the abovementioned findings could imply that factors such as aneurysm shape influence the PWS values more effectively than maximum diameter, thus predisposing smaller AAAs having a rupture risk comparable to that of larger AAAs. Complex geometry contributes to equivalently complex stress distribution, with regions of high curvature being associated with high stress values (Sacks et al, 1999). The actual, individualized AAA geometry is the main reason for the non-uniform distribution of stress in the wall. Local anatomy can influence the AAA growth rate 1.5-fold greater than the traditional risk factors (e.g. gender, age, hypertension, heart disease, hypercholesterolemia, renal failure, chronic obstructive pulmonary disease (COPD), smoking, diabetes mellitus and peripheral disease) (Helderman et al, 2010). Furthermore, Pappu et al suggested that an increase in mean tortuosity of the centerline correlated better with rupture of small AAA than an increase in mean transverse diameter (Pappu et al, 2008).

Advanced patient-specific computational models can be used to assess the correlation between PWS and 3D geometric features. Giannoglou et al (Giannoglou et al, 2006) reported a strong relationship between PWS values and the centerline curvature in AAA models, whereas Doyle et al (Doyle et al, 2010) advocated a correlation between PWS and centerline asymmetry. Both studies were based on computational models without taking into account the presence of thrombus. Others have reported a correlation between PWS and centerline tortuosity in AAA models with ILT (Georgakarakos et al, 2010). While the major difference in the abovementioned studies is whether or not ILT was integrated into the model, they all agree that geometric features will play a significant role in prospective studies estimating the risk of AAA expansion or rupture. While the correlation of these 3D geometric features with maximum diameter (making them dependent variables) reduces the impact of these findings, they may be used as adjuncts to diameter.

Geometric parameters can affect the hemodynamic behavior of AAAs, which in turn could have an important implication regarding the prognosis of rupture or the estimation of the aneurysm distension rate. Li and Kleinstreuer showed that an AAA neck angle substantially impacts flow fields, causing strong irregular vortices in the AAA sac, remarkably influencing wall stress distribution (Li & Kleinstreuer, 2006). Furthermore, Xenos et al (Xenos et al, 2010a) showed that the peak value of von Mises stress increases as the iliac angle increases. Specifically, the increase in the iliac bifurcation angle is associated with constantly high stress values of Von Mises stress values in this area; yet, when these blood stagnation points were exluded, an overall decrease of the mean stress values in the rest of the AAA wall (ie. sac wall) was revealed.

As small AAAs enlarge, a variety of geometrical changes can take place, including the length and angulation of AAA neck, the asymmetry of the centerline, the tortuosity of iliac arteries and the angulation of the iliac bifurcation (Georgakarakos et al, 2011b). Certain geometric changes, especially in the iliac bifurcation, have been postulated to mirror an adaptation response during the aneurysmal progression disease, in an attempt to alter the wall stress distribution patterns and decline the stress values, in favor of rupture risk attenuation and AAA growth deceleration. The increase in iliac angulation seems to lower the stress values in the AAA wall with instantaneous increase in iliac bifurcation stress values (blood stagnation site), trying to re-distribute the mechanical load at sites less prone to rupture (**Figure 4**), being the iliac site (Xenos et al, 2010).

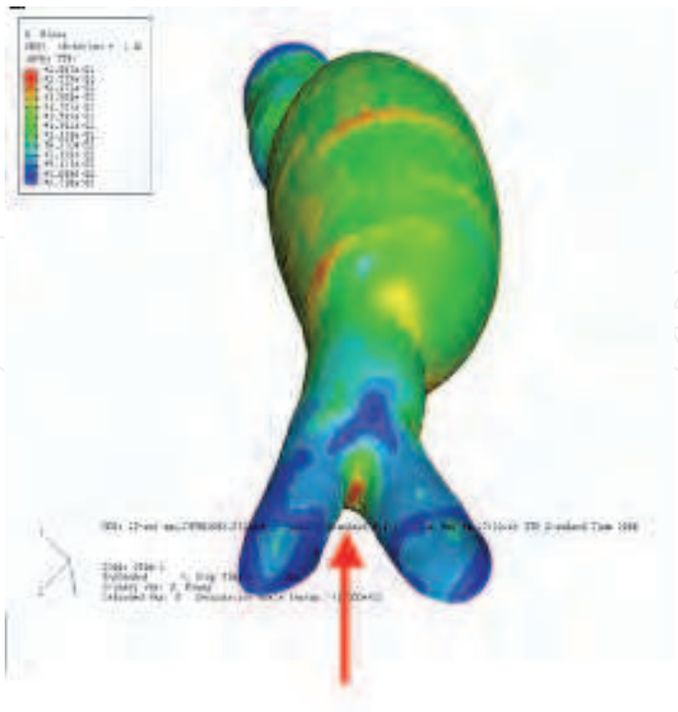

Fig. 4. The iliac bifurcation is generally assumed to be a site less susceptible to rupture. In the early stages of AAA enlargement, accumulation of high stress values in this area by certain geometrical adaptations can be considered as an adaptation response, in order to reduce stress in other wall areas.

5. Association of mechanical stress and biomarkers

Mechanical and biological factors have been implicated in the growth rate of the small AAAs, apart from the aforementioned clinical factors. Increased levels of Metalloproteinase-2 (MMP-2) have been implicated in the degradation of elastine in the small AAAs wall, leading to their generation and expansion, whereas the increased expression of MMP-9 leads to accelerated expansion of the larger AAAs and rupture (Choke et al, 2005).

AAA wall degeneration or alteration of integral properties induced by biochemical factors such as metalloproteinases (MMPs) and mechanical loading constitute a field to focus on, since there has been growing evidence of pathogenic correlation between these factors. The mechanical loading of the AAA wall, as expressed by PWS, has been implicated in the expansion of small AAAs, since a relative low wall stress was associated with a lower aneurysm rate, as reported by Speelman et al (Speelman et al, 2010a). The ratio of wall stress to the maximum diameter of the AAA has been postulated to be a valuable index for predicting AAA growth. Interestingly, the latter study reconfirmed also the positive relation of MMP-9 to increased growth rate, despite the fact that no correlation between MMP-9 and wall stress was found, implying that AAAs in patients with high wall stress/max Diameter values may undergo more rapid growth and wall damage than those with low wall stress/max Diameter values. AAA growth is most likely a multifactorial phenomenon, possibly combining biological and mechanical effects, as well as dynamic flow effects through the AAA (Khanafer et al, 2007).

Rahman et al studied the levels of MMPs in areas of low and high wall stress values in the AAA wall (Rahman et al, 2011). Finite Element Analysis was used to estimate the values and distribution areas of low and peak wall stress (PWS) on the wall of AAAs before surgery. These areas were accordingly mapped out and excised intraoperatively, providing tissue samples for MMPs analysis. Elevated levels of MMP levels were detected at areas of PWS compared to areas of low stress, despite that fact that no statistical significance was reached (possibly attributed to type 2 statistical error). Moreover, small AAAs with rapid growth rate can be differentiated from small ones of slower growth rate by the high values of wall stress at the area of inflection between the neck and the AAA sac (Li, 2010a and Li et al, 2010b). Localized geometric abnormalities correlate with high PWS values (Sacks et al, 1999) which can induce an increased inflammatory reaction (Xu et al, 2010) and overexpression of MMPs, thus attenuating the structural integrity of the sac wall. The abovementioned findings underscore the importance of interconnection between biomechanical factors and bioengineering tools for the study, identification and prediction of small AAAs prone to rapid growth and/or rupture.

6. Mechanical properties of the wall

The computational estimation of PWS with Finite Element Analysis models relies strongly on the material properties data input into these models. In most studies the AAA wall has been assumed to be hyperelastic, incompressible and isotropic material (Georgakarakos et al, 2011a). The values of these parameters represent mean data derived from large-scale population tissue mechanical studies. However, there is increasing evidence of the anisotropic properties of the AAA wall, ie the preferential stiffness of the wall in one plane compared to the other, as a result of heterogeneous mechanical behavior of the structural substrate, depended on the orientation of the collagen fibers (Rissland et al, 2009 and Rodríguez et al, 2008, 2009). Whether the adaptation of the anisotropic wall properties in the computational models yields statistically significant difference in the evaluation of the PWS values and distribution, thus affecting the rupture risk computation, remains to be delineated in large-scale studies.

Moreover, rupture risk estimates or expansion-rate predictions should be obtained in a patient-specific basis, since mechanical parameters in AAAs such as segmental dilation and compliance, stiffness and pressure strain elastic modulus vary among AAAs from different patients and variable maximum diameters (Long et al, 2004, 2005; Wilson et al, 2003). AAA rupture is associated with aortic wall weakening as a result of discordant repair / remodeling mechanisms, mirrored by an increase in thickness and a decrease in stiffness, correlated with decreased strength (Di Martino et al, 2006). Since different AAA of the same maximum diameter can have different strength levels, it seems that noninvasive techniques to estimate mechanical properties of the AAA wall would be a helpful adjunct for prediction of AAA rupture risk.

Strength is calculated from a mathematical type which takes into account the square root of the ILT thickness, the presence of positive family history, the gender, smoking status and age of the patient and the normalized diameter (Vande Geest et al, 2006a), strength = 71.9 – 37.9 ($ILT^{1/2}$ – 0.81) – 15.6 (NORD – 2.46) – 21.3 HIST + 19.3 SEX, where ILT is the local attached ILT thickness in cm; NORD is the local diameter normalized to the diameter of the non-aneurysmal aorta (infrarenal) estimated form the patient's age and sex (Raghavan et al, 2000); HIST is the family history (1/2 with history, -1/2 without history); and SEX is patient's gender (1/2 male, -1/2 female).

Since the wall strength presents a spatial distribution along the AAA wall, an accurate method to estimate rupture-risk on a patient-specific model should take into account not only PWS, but also the local wall strength variation (Vorp et al, 2005). The Rupture Potential Index (RPI) estimates the ratio of local PWS to local wall strength, RPI = Local wall stress (N/cm^2) / Local wall strength (N/cm^2). The importance of simultaneous incorporation of the wall strength in the rupture risk prediction is underscored in a recent retrospective study, where the rupture risk indices between 15 men and 15 women were compared. Taken into account the reported higher rupture risk for women, it was interesting to note that though PWS values did not differ between the 2 groups, the difference in peak wall rupture risk between the groups almost approached statistical significance (P = .06), suggesting also that differences in biomechanical properties could contribute to the higher rupture risk reported for women.
Small patient series have provided promising results regarding the utility of RPI in the prediction of rupture as well as the detection of the rupture site (Xenos et al, 2010b). Larger-scale prospective clinical trials are needed for validation of RPI as a predictive tool for rupture, before this tool can be sufficiently incorporated into routine clinical practice.

7. The intraluminal thrombus

ILT is generated by activated platelets that aggregate toward the AAA wall. For the generation of ILT the following seem to be essential a) a proximal recirculating zone, with b) high values of wall shear stress (WSS), so that the platelets can sustain the WSS long enough, to get activated and aggregate (Biasetti et al, 2010). The aggregation sites are preferably located in areas of low WSS. The frequently observed asymmetric ILT distribution (**Figure 5A**) can be attributed to the asymmetry and complexity of the flow in asymmetric AAAs (**Figure 5B**), (Ekaterinaris et al, 2006 and Bluestein et al, 2009).

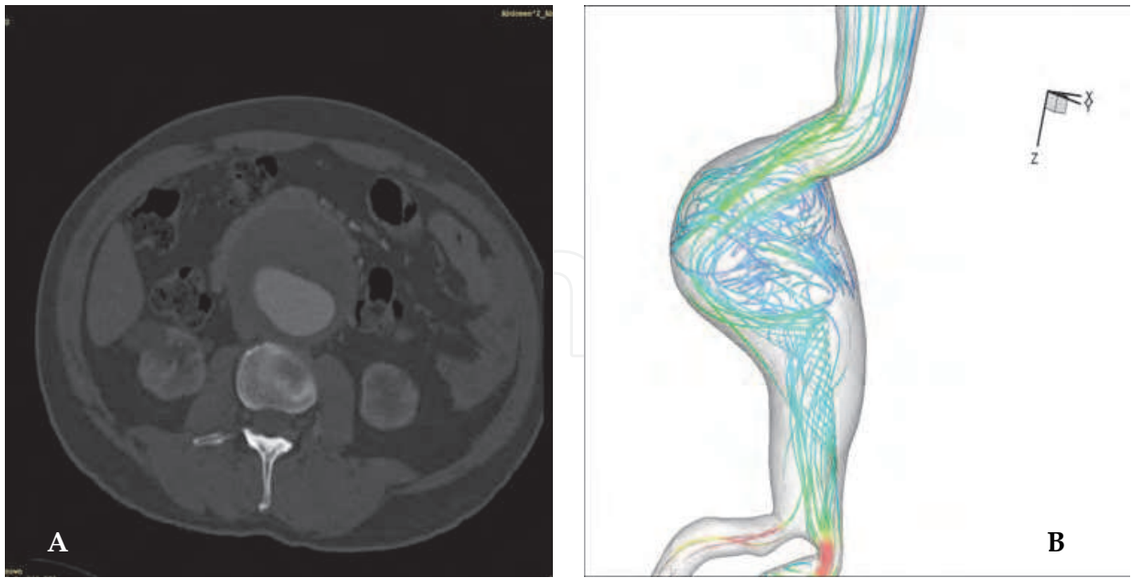

Fig. 5. A) Aneurysm sac with asymmetric distribution of intraluminal thrombus (eccentric, anterior). B) Complex flow ribbons in the AAA lumen. The inferiorly-anteriorly located thrombus causes narrowing of the lower sac, which in turn, induces the complex flow pattern above.

The integration of intraluminal thrombus (ILT) on the FEA models plays a crucial role in the estimation of wall stress values and stress distribution (Georgakarakos et al, 2009 and Wang et al, 2002). ILT consists of 3 layers (abluminal, medial and luminal) with marked differences in mechanical properties and structure (**Figure 6A**). The luminal layer (**Figure 6B**) consists of a network of fibrin fibers, with Young's modulus values 54 and 57 N/cm^2 in the longitudinal and circumferential directions, respectively (van 't Veer et al, 2008). The medial layer shows some degree of degeneration of the fibrin fibers and presents a 33 and 27 N/cm^2 in the longitudinal and circumferential directions, respectively (Wang et al, 2001). Finally, the abluminal layers appear too degenerated (**Figure 6C**) to be tested on vitro for determination of the mechanical properties. Vande Geest et al performed planar biaxial testing on the luminal layer of ILT and estimated the maximum tangential modulus to be 23.1 and 20.1 N/cm^2 in the longitudinal and circumferential directions, respectively (Vande Geest et al, 2006b). Di Marino et al (Di Marino et al, 1998) estimated the range of ILT Young's modulus to be 5-20 N/cm^2, whereas Hinnen et al (Hinnen et al, 2007) 1.3-5.9 N/cm^2.

It is clear that there is a wide variation in the mechanical properties of ILT. The mechanical properties of the thrombus vary not only within the ILT volume of a given AAA but also between different ILTs (Ashton et al, 2009; van Dam et al, 2008). Consequently, the hemodynamic load on the AAA wall can be modified by the variations in local thickness, shear modulus and volume of ILT (Speelman et al, 2010b). Moreover, the varying mechanical properties of the thrombus account for the large variability in its compressibility (Truijers et al, 2009), which could influence its protective role against AAA rupture or sac enlargement. Furthermore, fissures in ILT can breach the ILT "cushion" effect, resulting in increase in wall stress in the underlying AAA wall (Polzer et al, In Press).

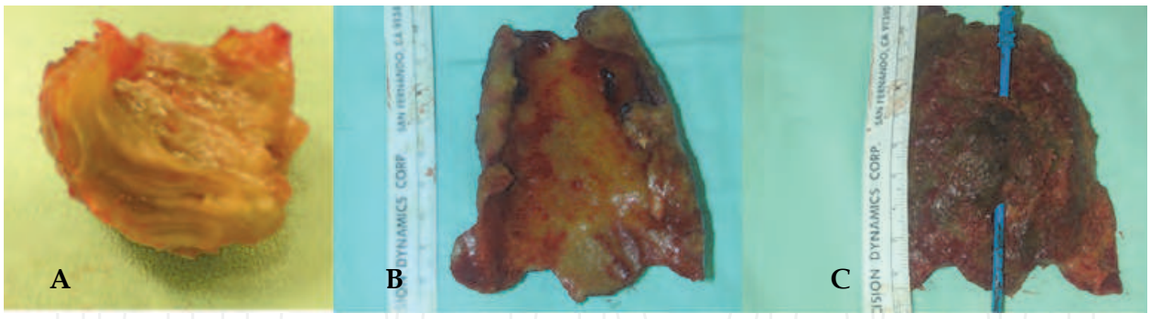

Fig. 6. A) The different layers of intraluminal thrombus (ILT), B) The luminal surface of ILT, C) The abluminal surface of ILT.

8. Conclusion

AAA rupture is a matter of deficient wall strength and increased hemodynamic loading. Therefore, reliable rupture risk estimation should take into account both the local distribution of wall stress and wall strength. Refinements in computational methods of these parameters could lead to identification of high-risk aneurysms, patient-specific risk assessment, detailed geometric characterization of AAAs and precise follow-up of aneurysm growth. The development of hybrid models that would take into account the geometric, biomechanical and biologic factors in a patient-specific basis is awaited with

great interest. Furthermore, advances in ultrasound and dynamic MRI imaging are expected to provide us with important information regarding the material properties of ILT over the cardiac cycle, the spatial variance of compliance, stiffness and distensibility of the AAA wall and, finally a detailed mapping of the AAA wall thickness. The aforementioned elements are necessary for improvement of accurate, reliable patient-specific prediction models of rupture risk.

9. References

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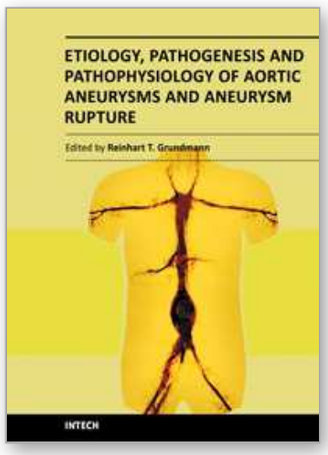

Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture

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This book considers mainly etiology, pathogenesis, and pathophysiology of aortic aneurysms (AA) and aneurysm rupture and addresses anyone engaged in treatment and prevention of AA. Multiple factors are implicated in AA pathogenesis, and are outlined here in detail by a team of specialist researchers. Initial pathological events in AA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species. AA development is characterized by elastin fragmentation. As the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process, but resulting in a less distensible vessel. Proteases identified in excess in AA and other aortic diseases include matrix metalloproteinases (MMPs), cathepsins, chymase and others. The elucidation of these issues will identify new targets for prophylactic and therapeutic intervention.

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