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Biological, Geometric and Biomechanical Factors Influencing Abdominal Aortic Aneurysm Rupture Risk: A Comprehensive Review

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Abstract: The current clinical management of abdominal aortic aneurysm (AAA) disease is based to a great extent on measuring the aneurysm maximum diameter to decide when timely intervention is required. Decades of clinical evidence show that aneurysm diameter is positively associated with the probability of rupture, but that other parameters may also play a role in causing or predisposing the AAA to rupture. Biological factors associated with smooth muscle apoptosis are implicated in AAA expansion while geometric and biomechanical factors identified by means of computational modeling techniques have been positively correlated with rupture risk with a higher accuracy and sensitivity than maximum diameter alone. The objective of this review is to examine the factors found to influence AAA disease progression, clinical management and rupture, as well as a patent review that highlights developments in this arena in the past few years.

Keywords: Abdominal aortic aneurysm, biological factor of AAA growth, biomechanical factors of AAA rupture, geometric factors of AAA rupture risk, intraluminal thrombus (ILT), tissue inhibitors of metalloproteinases (TIMP), wall stress.

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a focal abnormal widening of the aorta larger than 3 cm, which is associated with degradation of connective tissue in the arterial wall. The underlying cause for the formation of an aneurysm can be either inherited (i.e., Marfan syndrome or Ehlers Danlos syndrome) or acquired, with risk factors including hypertension, atherosclerosis, and smoking among others. The natural course of the disease is one of progressive enlargements, being the maximum aortic diameter and expansion rate of the strongest predictors of aneurysm rupture [1]. AAAs are potentially life-threatening medical conditions often requiring surgical intervention. The reported incidence of AAA is 4.9%-9.9% in the United Kingdom, accounting for more than 8000 deaths in the United Kingdom [2, 3] and 15000 deaths in the US every year [4]. AAA surgical interventions continue to pose serious risk on patients with a mortality rate of about 5% on patients with stable AAA in the US, and about 1-5% in the best centers in the UK [3]. After AAA ruptures, more than 50% of patients die before reaching the hospital, with emergency repair having about 40–50% mortality [3]. To reduce aneurysm related mortality, several countries have implemented population screening programs among the population with risk factors. Currently, clinical practice is to repair an AAA exceeding 5.5 cm in men, whereas in women a maximum diameter of 5.0 cm is considered since women with aneurysm have an increased risk of rupture [5, 6]. However, it has been reported that only 25% of AAAs rupture in a patient's lifetime [7], and therefore clinicians need start to compare the risk of rupture with the risk of repair, particularly because of the operative mortality in elder patients [8].

Recent research has pointed the unsuitability of deciding a surgical repair based solely on the maximum diameter criterion [7, 9-12]. It is known that small AAAs can rupture and large AAAs can remain stable. Therefore, other rupture risk parameters are needed as alternative to the customary AAA size and expansion rate. A biomechanics based approach may be a viable option. Recent work by Gasser *et*

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al. [13] found that biomechanical parameters such as Peak Wall Stress (PWS) and Peak Wall Rupture Risk (PWRR) were 1.17 and 1.43 times higher in ruptured AAAs compared to those in diameter-matched unruptured aneurysms. McGloughlin and Doyle [14] make a concise review on recent biomechanics-based rupture risk biomarkers for AAA examining their potentiality as clinical decision-making tools.

This manuscript reviews factors involved in AAA development and rupture risk, considering i) biological factors involved in the genesis, development and rupture of AAA; ii) geometric features that discriminate AAA population subsets; and iii) biomechanical factors implicated in the evaluation of rupture risk based on the AAA patient-specific geometry, wall structure and mechanical response.

BIOLOGICAL FACTORS

The pathogenesis of abdominal aortic aneurysms (AAA) is still relatively unknown. Presence of immune reaction factors such as macrophage and lymphocytes, SMC (smooth muscle cell) apoptosis, degraded extracellular matrix (ECM) and neovascularization, and increased concentration levels of certain types of matrix-metallo-proteinases (MMP), are commonly observed in the aneurysmal aorta. These observations suggest that the remodeling process of the wall is on-going, though not in ideal balanced manner. AAA has also been found to be associated with smoking, familial history, and chronic obstructive pulmonary disease (COPD). Many studies point toward unbalanced ECM turnover as a key factor in the development of aneurysms. In this phenomenon, the ECM is broken down, and subsequent alterations in the ECM composition occur that ultimately results in the localized focal dilatation of aorta. This process, however, is triggered or inhibited by many other factors related to AAA (see Fig. **1**), the exact role and activation details of which are not yet completely understood.

Proteolytic Degradation of the AAA Wall

Elastin, collagen types I and III, and vascular smooth muscle cells make up the normal aortic wall. Elastin fibers are present in the media and convey elasticity to the wall, while collagen helps to provide tensile strength. Histological examination shows a thinned aneurysmal aortic wall with decreased levels of medial elastin; an unbalanced proteolytic degradation of these structural constituents results in AAA. It is known that the loss of elastin is associated with aneurysmal dilation, whereas collagen loss is associated with aneurysmal rupture [15]. Indeed, experimental studies have shown that treatment with elastases, enzymes that hydrolyze elastin, leads to arterial dilation, while treatment with collagenases, enzymes that hydrolyze collagen, leads to rupture without dilation [16]. Proteases are a subset of enzymes responsible for hydrolysis action on protein component (proteolysis). They can be further classified into four categories based on the mechanism of action – serine proteases, cystein proteases, aspartic proteases, metalloproteases [17]. Out of these, matrix-metallo-proteinases (MMPs) have been widely implicated in AAA pathogenesis and hence are described in detail in the following section.

Matrix-Metallo-Proteinases (MMPs)

MMPs are zinc and calcium dependent endopeptidases of the metzincin superfamily of proteinases that degrade elastin and collagen. MMP-2, 9 and 12 have all been postulated to have a significant role in aneurysm formation. MMP in its non-activated form is called proMMP and is activated by an outside agent. MMP-9, also known as Gelatinase B or 92kD type IV collagenase, is predominantly produced by macrophages and constitutes the major elastase in human AAAs, while minimal amounts are found in normal aortic tissue. Biopsies of aneurysm walls in patients undergoing open AAA repair have revealed that patients with medium sized aneurysms (5-6.9 cm) had a significantly higher level of MMP-9 activity than did either patients with small aneurysms (< 5 cm) or patients with large aneurysms (> 7 cm) [18]. Experimentation with MMP-9 knockout (MMP-9 KO) mice has shown that MMP-9 is necessary for the initiation of aneurysm formation [19]. MMP-9 knockout and wild-type mice were subjected to intra-abdominal $CaCl_2$ which instigates inflammatory response resulting in an aortic aneurysm formation in wild-type mice, but no significant dilation in the MMP-9 KO mice aortas. Comparison of MMP concentrations in ruptured aneurysms at the site of rupture with those on the anterior aorta showed that concentrations of MMP-8 and MMP-9 were significantly elevated at the site of rupture when compared to a site on the anterior aortic wall [20, 21]. Another study [22] has shown that serum MMP-9 levels first increased after a week and then dropped after a month when measured pre- and post-operatively in a patient that underwent open AAA repair. Peterson *et al.* [23] examined MMP-9 and MMP-2 and their relationship with size and aneurysm rupture. They found that MMP-9 levels were significantly higher in ruptured aneurysms when compared to both large aortic aneurysms and medium sized aneurysms. They also found that MMP-9 activity was inversely associated with diameter in large aneurysms.

Many investigators have also examined the role that MMP-2 (Gelatinase A or 72 kDa type IV collagenease) plays in the developing aneurysm. MMP-2 is expressed by vascular smooth muscle cells and may facilitate the degradation of both elastin and collagen in the aortic wall. Investigators have found elevated levels of both MMP-2 mRNA and protein levels in aneurysmal tissue when compared with normal tissue and atherosclerotic tissue. It is suggested that MMP-2 is responsible for the initial formation of small aneurysms, while MMP-9 is responsible for the growth in moderate sized aneurysms (5 to 7 cm diameter) [24, 25]. Higher MMP-9 expression in the AAA wall relative to Atherosclerotic Occlusive Disease (AOD) samples has been reported elsewhere [26]. It supports the view that AOD and AAA have different pathologies.

Fontaine *et al.* [27] proposed that intraluminal thrombus absorbs blood components and stores, releases and participates in the activation of proteases involved in aneurysmal evolution. Spontaneous clotting of the blood was found to induce the release of pro-MMP-9 into serum that is 4 folds higher than the paired control plasma and that fibrinolysis progressively releases more MMP-9 in a time dependent manner. They also report that leukocytes are the main source of MMP-9 during clot formation. This is in agreement with the clinically observed fact that patients with

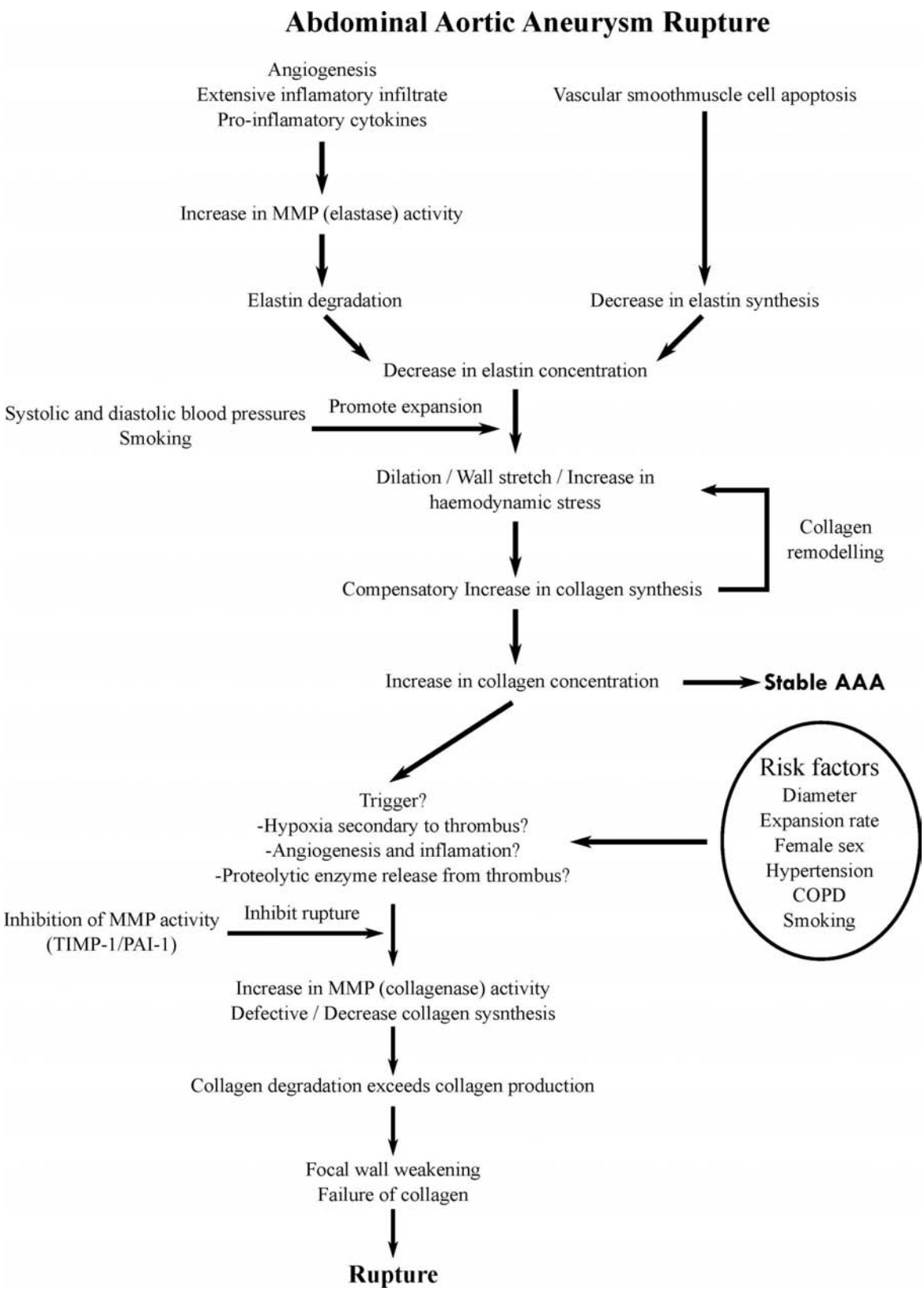

Fig. (1). Succession of biological events related to AAA rupture. Reproduced from [16] with permission.

previously stable AAAs had a seemingly high rate of early rupture after undergoing an unrelated operation [28].

MMP-12's role in aneurysm formation is much less defined. Some studies have shown increased MMP-12 protein expression in AAA, but without MMP-12 mRNA expression. Pyo *et al.* [29] performed a study on MMP-12 knockout mice that puts into question its role in aneurysm formation. They studied MMP-12 knockout mice, MMP-9

knockout mice and MMP-12/MMP-9 knockout mice together, and found that MMP-9 knockout mice were protected from artificial aneurysm formation, while MMP-12 knockout mice developed aneurysm dilation. Longo *et al.* [30] found after artificially inducing aneurysm in MMP-12 knock out and wild type mouse that the increase in aorta diameter was about 26 ± 14 % in MMP-12 knock out mouse against the 63 ± 5% increase in the normal wild type mouse. They suggest that the macrophage recruitment was reduced due to absence of MMP-12 resulting in smaller dilation.

MMP-1 and -8 are metalloproteinases associated with the degradation of collagen in aortic tissue. Higashikata *et al.* [31] showed elevated levels of these MMPs in aneurysmal tissue when compared to normal aortic tissue. Even though MMPs predominantly are involved in fibrinolysis, enzymes other than matrix-metalloproteinase such as cystein proteases have been implicated in fibrinolysis process [32]. Abisi *et al.* [26] compared cystein protease activity in the AAA wall with that in the AOD wall using a bio-immunosorbent assay and observed that members of cathepsin family are overexpressed in the aneurysmatic wall and their inhibitor cystatin C is downregulated. Activity of MMP-9 was found to correlate positively with cathepsin L and negatively with cystatin C. This could have implications for a pharmacological pathway to control wall degradation by upregulating cystatin C artificially.

Tissue Inhibitors of Metalloproteinases (TIMP)

TIMPs are predominant inhibitors of MMP activity. In the normal human aorta, a balance in the tissue levels of MMP and TIMP helps to create equilibrium in the ECM between synthesis and degradation. TIMP-1 is a specific inhibitor of MMP-9. Eskandari *et al.* [33] subjected both TIMP-1 KO mice and wild-type mice to intra-aortic infusion of elastase to stimulate aneurysm growth. The TIMP-1 KO mice demonstrated a significant increase in aortic diameter when compared to the wild-type variety. It is also reported that TIMP-1 deficiency contributes to a reduction in atherosclerotic plaque size but promotes aneurysm [34]. It should be noted that it is the difference between degradation and repair activities of the vascular wall that results in aneurysm formation and not the degradation activity alone.

Macrophage and Lymphocyte Presence

Histologically, it has been observed that macrophages and lymphocytes are present in the aneurysmal wall. What triggers the penetration of these immune system cells into the wall is still unknown. Elastin degradation products are proposed to be chemo-attractant proteins for the macrophages [35]. Kazi *et al.* [36] have observed the chemotaxis and have verified the presence chemo-attractant proteins within the wall covered by intra-luminal thrombus. The observed deposition of immunoglobulin (IG) in the aneurysmatic aortic wall also substantiates the fact that the pathogenesis of AAA may have origin in the autoimmune response. Macrophages and lymphocytes secrete a cascade of cytokines that results in activation of many proteases (see Fig. **2**). Also, 55% of the aneurysmatic population has been found infected with chlamydiae pneumonia [37]. A recently applied Positron Emission Tomography (PET) imaging method for detecting metabolic activity in aneurysm is based on the fact that macrophage is engaged in significant glycolysis activity on its surface. The positron emitting chemical marker called fluorodeoxyglucose (F18 FDG) was used to trace glycolysis activity on aneurysm surface [38-40].

Mast cells (MC), which are an integral part of the immune system, are also implicated in AAA pathogenesis [41]. This fact is supported by previously reported findings that MC deficient rats and mice are protected from AAA. Structurally and functionally, MCs are very close to basophils in that they carry histamine and heparin in form of granules and are born in bone marrow. However, dislike basophils that leave bone marrow only at maturity, mast cells enter blood flow and mature at the tissue site where they get planted. Mayranpaa *et al.* [42] reported association of mast cells and neovascularization with AAA. High densities of neovessels and MCs were observed in the media layer of the artery wall and also in thrombus-covered AAA samples. MCs were found in close apposition to neovessels making it a possibility that mast cells participate in the neovascularization process. MCs are also involved in proteolysis of extra-cellular-matrix.

Autoimmune Response

T-cells are suggested to have an influence on the production of MMP by macrophage activation. The type-1 T helper cells (Th-1) tend to release proinflammatory cytokines. This was proven due to elevated levels of the cytokines associated with the Th-1 cell immune response in the blood and aortic tissue of AAA patients [43]. An advanced stage of AAA growth also reveals type-2 T helper cells (Th-2) associated with cytokines IL-4 and IL-10. However, experimental findings suggest that these cytokines restrain aneurysmal degradation [43]. Conversely, Schonbeck *et al.* [44] suggest that Th-1 cytokines govern atheroma while Th-2 cytokines govern AAA expansion. Hence, it is argued that the Th-2 activity directs the atheroma to AAA formation.

Xiong *et al.* [45] reported that mice lacking IL-10 developed larger aneurysms than wild-type controls. They also reported that the larger aneurysms occur in CD4 deficient and IL-4 deficient mice. Since Th-1 cytokines are IFN-γ, IL-2, IL-12, IL-15, and IL-18 whereas Th-2 cytokines are IL-4, IL-5, and IL-10, the aforementioned experimental observations substantiate the proinflammatory action of Th-1 and the inhibitory action of Th-2 cells. Experimentally, it was found that the mouse with absent CD4+ T-cells exhibited aneurysm formation. IL-6 and IL-8 were found to have an inflammatory action whereas IL-10 is anti-inflammatory [46]. A correlation between AAA surface area and mean plasma IL-6 levels was reported by Dawson *et al.* [47], suggesting prominent IL-6 generation in the aneurismal aorta. An investigation into the genetic basis of interleukins concluded that an allele of genotype IL-10-1082 is more common in AAA patients compared to the control group [48]. However, independent association of IL-10 with AAA could not be established when other risk factors such as smoking, gender, etc., were considered. This fact supports the possibility that the IL-10-1082 genotype may have an

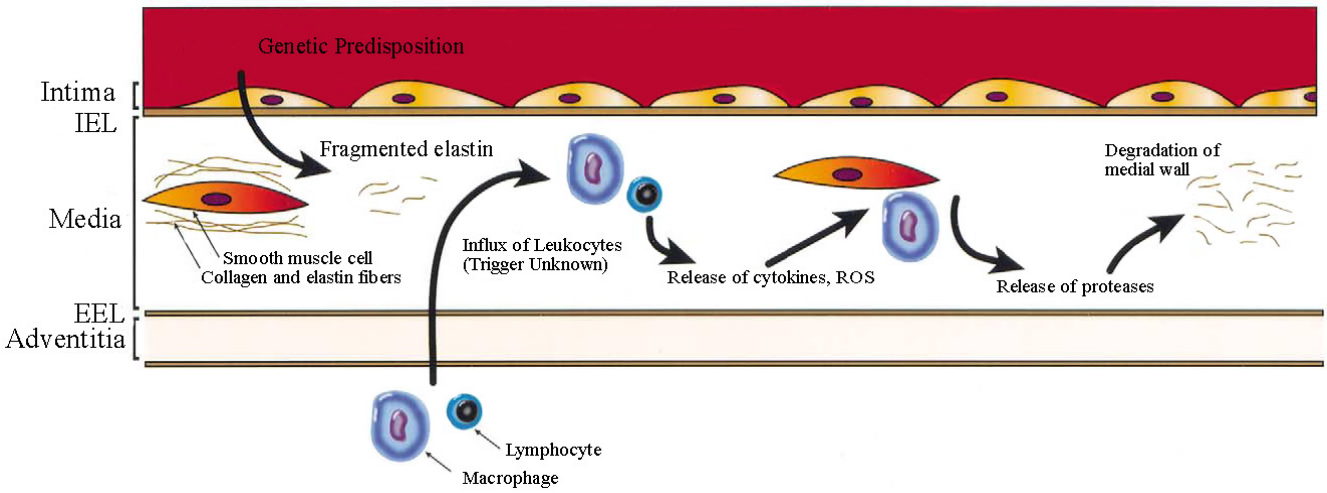

Fig. (2). Localized stresses, fragmented medial proteins, and genetic predisposition, likely attract inflammatory cells into the aortic wall. Released chemokines, cytokines, and reactive oxygen species by these inflammatory cells, result in further influx of leukocytes, and further medial degradation. Reproduced from [37] with permission.

association with various AAA risk factors and not to AAA formation directly.

Reactive Oxygen Species (ROS)

In vitro studies suggest that ROS activate MMP [49], thereby having an important role in AAA pathogenesis. ROS are also found to cause apoptosis of the vascular smooth muscle cells, contributing to wall weakening. High levels of DNA fragmentation are found in aneurysmal medial smooth muscle cells; they are a marker for SMC apoptosis. The wall, though under degradation because of protease action, is simultaneously being synthesized because of protein generation by SMCs. ROS accelerate the wall degradation by promoting MMP action as well as decreasing protein synthesis by SMC apoptosis and damage to the structural integrity of the wall. It is hypothesized that ROS activate the pro-MMPs by covalently modifying the sulfur group of the cysteine switch [50].

Miller *et al.* [51] observed [O_2^-] levels by lucigenin-enhanced chemoluminescence and confirmed that they are 2.5 times higher than the neighboring non-aneurysmal region of the same aorta, i.e. ROS in the AAA wall are locally elevated. They state that the ROS levels are enhanced in aneurysmal tissue compared to an atherosclerotic one and that increased [O_2^-] levels are predominantly produced by SMC, though both SMC and phagocytes generate [O_2^-]. This outcome was based on three observations: (i) the [O_2^-] levels were diffusely increased throughout the medial layer and not restricted to areas of macrophages or monocytes; ii) the phagocyte form of the oxidase predominantly used NADPH (nicotinamide adenine dinucleotide phosphate-oxidase) whereas the vascular oxidase used both NADH (nicotinamide adenine dinucleotide) and NADPH. NADH-stimulated [O_2^-] levels were increased in the AAA; iii) NADPH subunits in the AAA were not confined to the region of leukocytes.

Alternative studies have focused on molecules such as inducible nitric oxide synthase (iNOS) and Endothelial Nitric Oxide synthase (eNOS), and their role in inflammation and the pathogenesis of AAA. iNOS promotes formation and activity of peroxynitrite resulting in an oxidative action [52]. Conversely, eNOS, also known as NOS3, helps in vasodilation and has a role in atherosclerosis [46]. eNOS and iNOS are responsible for the synthesis of nitric oxide; iNOS is Ca^{2+} insensitive whereas eNOS is not. At high levels, nitric oxide can become toxic and helps to degrade elastin in the wall. Johanning *et al.* [53] infused rat aorta with elastase, which produced elevated levels of iNOS. They then selectively inhibited iNOS, which significantly reduced aneurysm size. A study with human subjects found that iNOS expression was present in the AAA wall whereas virtually no iNOS expression was found in the normal aorta [52].

C-Reactive Protein (CRP)

CRP, produced mainly by hepatocytes in the liver, has been established as an important factor in atherosclerosis pathology [46]. Increased high-sensitive-C-Reactive Protein (hsCRP) has been observed in AAA patients [54]. This observation was supported by Wiernicki *et al.* [55] as they found a correlation between haptoglobin polymorphism and AAA, and elevated CRP levels in the AAA patients. However, growth rate was found not to have a significant association with CRP levels in a multivariate analysis.

Dyslipidemia

The association of lipids found in abnormal concentrations in the blood with AAA is highly debated. Baumgartner *et al.* [56] studied 68,236 human subjects in 44 countries and reported no association between hypercholesterolemia and AAA; this outcome is supported by Schlosser *et al.* [57]. However, surprisingly it has been reported that patients taking lipid lowering drugs have about 1.2 mm per year lower growth rate of AAA compared to that of the non-users of lipid lowering drugs [57]. It is reported by Golledge *et al.* that the AAA has no association with low-density-lipoproteins (LDL). However, AAA is associated with high-density-lipoproteins (HDL). The discrepancy in

these findings can be attributed to the fact that there is no clear definition of dyslipidemia and the fact that on-going lipid modifying treatments may have confounding influence on the findings. Also, it is important to interpret significance of the lipid factor relative to other predominant AAA risk factors in future work pertaining to the subject. Total cholesterol level is reported to have decreased overall amongst population from 1980's to end of 1990's by Wanhainen *et al.* [54].

Mycotic Aneurysms

Aneurysms originating from microorganism infections are known as mycotic aneurysms. Most of such cases are predominantly reported from East Asian countries and the majority of these patients had diabetes [58]. Three predominantly involved microorganisms in AAA are *salmonella* (15%), *staphylococcus* (28%), and *streptococcus* (10%) [59]. There has been a case reported by Morrow *et al.* [60] where the infection is said to have migrated from appendicitis to infrarenal segment non-contagiously.

Genetic Aspects

Genome wide association studies have consistently reported associations between a region on chromosome 9p21.3 and a broad range of vascular diseases, such as coronary artery disease (CAD), aortic and intracranial aneurysms and type-2 diabetes (T2D) [61]. Ethnic association of AAA disease and frequently observed familial history has established genetic link of AAA by now [5, 46, 56, 62, 63]. In 15% of AAA patients, it is found familial history [46]. This emphasizes the need to explore genetic aspects involved in AAA. Marfan syndrome (MFS) and Thoracic Aortic Aneurysm and Dissection (TAAD) have been well characterized for their genetic links compared to AAA [46]. However, genome wide studies have made advances in recent year to finger point the location on chromosomes related to AAA disease. Shibamura *et al.* [63] reported loci of the AAA to be 19q13 (AAA1) and 4q31 (AAA2). Recently, Elmore *et al.* [64] reported the AAA loci to be 3p12.3. Genetic link relating some of the individual risk factors has also been explored. Functional MMP-9 polymorphism (C-1562T) was found common in AAA patients [65]. Interleukin genotype IL-10-1082A allel was found to be frequent amongst AAA patients. A recent genome-wide study involving 1292 individuals with AAA and 30,503 controls found that A allele of rs7025486 on 9q33 was found to associate with AAA, with an odd ratio (OR) of 1.21 and $P = 4.6 \times 10^{-10}$ [66].

Miscellaneous Factors

Gender dependence of the AAA and association with smoking was highlighted in the UK Small Aneurysm Trial that based its finding on 1090 patients (UKSAT) [5]. The trial found that female patients have less occurrence of AAA, however, chances of rupture of AAA were found higher in female patients. Biomechanical aspects were explored from gender perspective by Larsson *et al.* [67], however, differences found were not statistically significant. Their relatively smaller pool of patients could be the culprit. Also, chances of occurrence of AAA in the family of female patients were found higher than that in case of the male patients. Association of smoking has been debated since many of the studies that include the smoking as a variable in patient trial have not taken into account the COPD as a separate fact [16].

Influence of diabetes on AAA is debated. Baumgartner *et al.* [56] report inverse association. Diabetic patients with Haptoglobin polymorphisms Hp 2-1 and Hp 2-2 phenotype are reported to have lower elasticity compared to those with Hp 1-1 phenotype. However, in most of the mycotic aneurysms *diabetes mellitus* is found to be common [58]. Inhibition of platelet activation is reported to have reduced aneurysm diameter, thrombus development, platelet CD41 expression, leukocyte infiltration and elastic degradation of the aortic wall in experiment with rat model [68]. Platelet activating factor is phospholipids activator produced by neutrophils, basophils, platelets, epithelial cells. It plays a role in leukocyte functioning and platelet aggregation. It promotes MMP activity and migration of macrophages and leukocytes into the vessel wall thereby promoting aneurysmal deterioration. Species such as plasmin, plasminogen and tissue plasminogen inhibitor (tPA) which are involved in fibrinolysis have also been implicated in AAA etiology. Plasminogen is inactive form of an enzyme plasmin which actively breaks downs blood clot. In presence of tissue plasminogen activator (tPA) plasminogen produces plasmin for fibrolysis. Plasminogen Activator Inhibitors regulate plasminogen activator action. tPA is reported to be present in increased mass concentration, in contrast to relatively smaller concentration of tPA/PAI-1 complex in blood plasma samples of AAA patients [69]. Angiogenesis Converting Enzyme inhibitors (ACE inhibitor) were associated with aneurysm growth rate by Sweeting *et al.* [70]. However, previously it has been reported that use of ACE inhibitors reduces aneurysm rupture risk [71, 72]. These two observations leave us with an interesting possibility that though ACE inhibitors increase growth rate they also increase material strength or reduce inhomogeneity in aortic wall or reduce hypertension thereby reducing risk of rupture.

According to the aforementioned discussion, AAA etiology can be summarized as follows:

1. Some unknown event attracts the attention of leukocytes to the infrarenal segment of aorta;
2. Penetration of the leukocytes into the wall of aorta;
3. Macrophages start secreting chemokines, ROS, pro-MMPs in extracellular fluid;
4. pro-MMP gets activated;
5. TIMP presence may attempt to neutralize the MMP activity;
6. MMP activity dominates the TIMP resistance. Thus, net result is degradation of structural matrix proteins;
7. Over a period the activity continues. The loss of elastin reduces the stiffness of the wall. Therefore, the aorta begins to bulge out in form of an aneurysm;
8. Collagen degradation weakens the wall;

9. Smooth muscle cells undergo apoptosis. This hampers the rebuilding activity of wall structural proteins;
10. Interstitial collagen distribution becomes disorganized;
11. Aneurysm increasingly expresses T cells, B cells, and plasma cells. This highlights the momentum of the autoimmune system;
12. Th-1 cells are encouraging the inflammatory action and thereby aneurysm whereas Th-2 cells try to suppress the same.

GEOMETRIC FACTORS

Currently, the clinical management of AAAs is based on maximum diameter and expansion rate of an aneurysm [1, 2]. However, reports show that these two metrics are not a reliable measure of individual rupture risk. This is evident by the small aneurysms (diameters less than 5.0 cm) that do rupture and the larger aneurysms that have exceeded the threshold size for elective intervention that do not rupture. In an autopsy study of four hundred and seventy-three non-resected aneurysms [73], 13% of the aneurysms with a maximum diameter less than 5.0 cm ruptured and 60% with diameters greater than 5.0 cm remained intact. Other studies report similar findings of small aneurysms rupturing, indicating that the current use of the maximum diameter or expansion rate may be insufficient in that it underscores the variable behavior of individual aneurysms. In an interesting study by Solberg *et al.* [74], where 4265 subjects with a normal sized aorta resulted in 116 AAAs diagnosed after 7 years, a statistical analysis revealed that the baseline diameter was a highly significant ($p < 0.001$), strong (95% CI: 7–76 times higher risk) and gender-independent risk factor for developing AAA. They also found that median diameter increases less with age compared to mean diameter, indicating that there was less increase in diameter for people with smaller aorta in the beginning. Another interesting finding of the study was that when adjusted for age and aortic diameter, male sex was not significantly associated with AAA. It implies that geometry matters more than gender and hence biological differences. These findings are in agreement with previously reported fact that growth rate of larger non-aneurysmatic aorta was higher than the smaller non-aneurysmatic aorta [75]. These findings emphasize the role of size as a geometric factor involved in the aneurysmatic condition of the aorta and progression of disease.

The mechanics of the AAA wall and the resulting distribution of wall stress are primarily determined by the individual shape, not size, of the aneurysmal aorta. While precise soft tissue characterizations of the wall and thrombus, as well as patient-specific blood flow velocity measurements, are important to achieve accurate computational predictions of the flow-induced wall stresses, the native AAA geometry is the most important feature to consider in evaluating the wall mechanics. Limiting the characterization of geometry to the measurement of maximum diameter or expansion rate from medical images is not the best strategy to address the at-risk status of aneurysms on an individual basis. AAA shape is complex; most aneurysms are generally tortuous, asymmetric, and with amorphous multi-layered ILT [7]. Moreover, the implementation of patient-specific non-uniform thickness of the arterial wall in the analysis is a complex task, due primarily to limitations in the current technology to measure this parameter non-invasively.

Early studies report on the power of shape measures to distinguish between normal and abnormal brain surface shapes and to establish a relationship between the shape of the human brain surface and the function of the underlying tissue [76]. Recent studies describe the derivation of a set of global indices for the size and shape of cerebral aneurysms for assessment of their rupture potential and choosing the appropriate clinical treatment modality [77, 78]. A quantitative tortuosity index may be used to quantify AAA shape as a function of the orthographic projection of the aortic centerline about its central axis [79]. Ruptured AAAs seem to be less tortuous and have a larger cross-sectional diameter asymmetry [80], which is consistent with FEA studies showing that the highest wall stress is obtained in AAAs with an asymmetric geometry [81]. The evidence for geometric asymmetry is further supported by the finding that peak wall stress is localized near the aorta-aneurysm inflection point where the aneurysm curvature changes [10]. Moreover, the location of maximum stress at the posterior wall seems to coincide with peaks in the magnitude of the Gaussian curvature [82]. Idealized fusiform and saccular models have also shown that wall stress increases with bulge diameter and asymmetry [81, 83].

A common feature in most AAAs is the presence of an intra-luminal thrombus (ILT). ILT is known to alter the stress distribution in the aneurysmal wall [68, 75, 76] and directly affect AAA growth and rupture [5, 21, 68, 74, 78, 84] making it important in AAA biomechanics. Despite ILT's impact on aneurysm disease, from a biomechanics perspective, thrombus development and its relation to aneurysm rupture is still not clearly understood. Whether it increases or decreases the risk of aneurysm rupture, i.e., reinforces proteolytic activity [79], which weakens the wall [80] or buffers against wall stress [81], is still subject to debate.

A factor of significant importance in AAA rupture risk prediction is the non uniformity of the wall thickness. Fig. (**3**) shows an estimation of AAA wall thickness distribution obtained from an AAA CT scan [85]. Di Martino *et al.* [86], using a laser micrometer, measured the thickness of AAA wall specimens, obtained fresh from the operating room from patients undergoing surgical repair. A significant difference was found in wall thickness between ruptured (3.6 ± 0.3 mm) and electively repaired (2.5 ± 0.1 mm) aneurysms, as well as an inverse correlation between wall thickness and local tissue strength. The tensile strength of ruptured AAA tissue was found to be lower than that for electively repaired tissue (54 N/cm^2 *vs* 82 N/cm^2). In the same study, it was found that AAA rupture is associated with aortic wall weakening, but not with wall stiffening. Since AAA wall strength in large aneurysms did not correlate positively with maximum transverse diameter, wall thickness would be a better predictor of rupture for large AAAs. In an autopsy study, Raghavan *et al.* [87] analyzed the tissue

properties of three un-ruptured and one ruptured AAA revealing that all aneurysms had considerable regional variation in wall thickness and there was a significant reduction in wall thickness near the rupture site. Similarly, Mower *et al.* [88] demonstrated that the wall thickness represents a major parameter influencing wall stress distribution, rather than aneurysm maximum diameter alone.

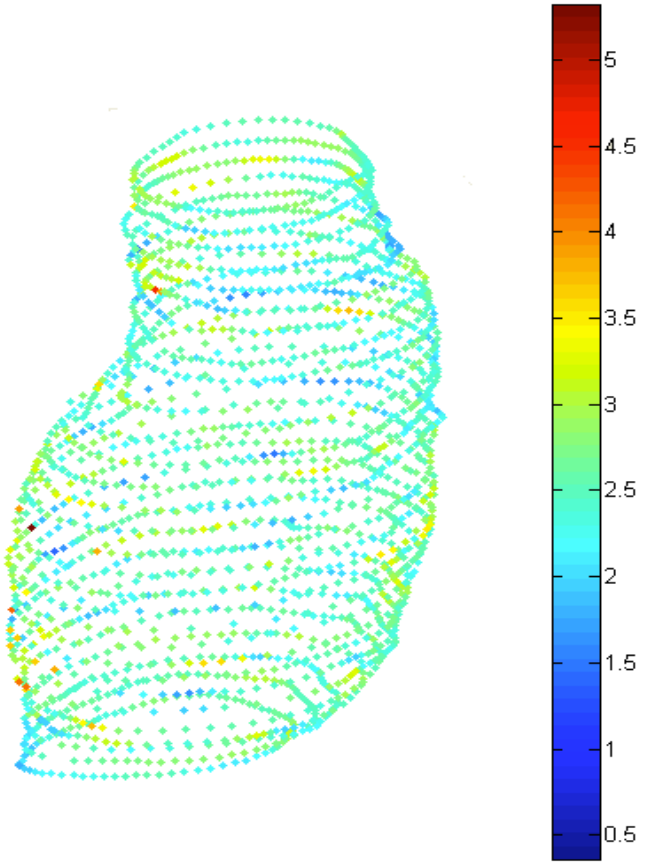

Fig. (3). Estimated wall thickness distribution (in mm) in a point cloud resulting from a segmented CT dataset.

Geometric features have been shown to be significant predictors of peak wall stress (PWS) and subsequent risk of rupture or tendency [9, 10, 89]. Multiple regression analysis was performed on 39 patients and 17 features to assess the influence of the features on the peak wall stress ([90]). Among the geometrical parameters, PWS was correlated with the mean centerline curvature, the maximum centerline curvature, and the maximum centerline torsion of the AAAs, with mean centerline curvature as the only significant predictor of PWS and subsequent rupture risk resulting from the multiple regression analysis. A multivariate analysis of 40 variables of 259 aneurysms revealed that ruptured aneurysms tend to be less tortuous and have a greater cross-sectional diameter asymmetry (Fillinger *et al.* [91]).

Current research had been concerned with identifying features in aneurysm morphology that are correlated with peak wall stress, and therefore rupture. Georgakarakos [92] developed a linear model to associate PWS and geometric parameters. They report that the optimal predictive model can be formulated as follows: *PWS = 8.791 + 2.3953*MaxDiameter + 25.2923*IntTortuosity* [92]. Shum *et al.* developed a quantitative pipeline consisting of image segmentation [85, 93] and geometry quantification to compute 64 features that describe the size, shape, wall thickness, and curvature for a subset of ruptured and unruptured aneurysms (see Fig. **4**). Utilizing these features, a decision tree model (see Fig. **5**) was trained on 76 AAAs and a prediction accuracy of 87% for sac length, surface area, tortuosity, and the ratio of ILT to AAA volume was obtained (Shum *et al.* [94]).

In addition to linking geometric features to rupture potential, five "*geometric biomechanical factors*" (deformation rate, asymmetry, saccular index, relative wall thickness, and growth rate) were recently combined to obtain a *rupture risk qualitative indicator* (Vilalta *et al.* [95]). This index was defined to monitor the evolution of patients with aneurysms by integrating geometric information obtained from periodic checkups in an effort to improve the accuracy of rupture risk assessment. Validation studies were only performed on one clinical case and three cases obtained from the literature, and a broader study enrolling more patients is currently in progress. Results show that the deformation rate and growth rate are more influential on the rupture potential of aneurysms than the maximum diameter, and that a rupture risk qualitative indicator greater than 0.64 (nondimensional, based on the weighted averages of the five geometric biomechanical factors) indicates elective repair should be considered.

BIOMECHANICAL FACTORS: FEA, CFD AND FSI ANALYSES

From a purely biomechanical viewpoint, aneurysm rupture is a phenomenon that occurs when the mechanical stress acting on the dilating inner wall exceeds its failure strength. Therefore, a criterion for repair based upon quantifying aneurysm stress and strength could facilitate a better method to determine at-risk AAAs. Unfortunately, obtaining *in vivo* patient-specific measurements of tissue stresses or strength non-invasively is currently not feasible. However, mathematical and computational models that accurately compute the aneurysmal wall stress can be utilized to evaluate the AAA biomechanical environment at the organ scale. In addition, recent research has pointed the unsuitability of deciding a surgical repair based solely on the maximum diameter criterion [7, 9-12]. Therefore, alternative rupture risk parameters need to be proposed as alternative to the classical AAA size and expansion rate [14].

Early studies used Laplace's law to correlate AAA diameter and rupture [15]. However, this approach ignores the complex geometry and boundary conditions as well as the presence of the ILT. In this regard, calculation of the peak wall stress by using finite element analysis was first applied to a 2 dimensional simple geometric shape of AAA by Stringfellow *et al.* [84]. Their work showed that AAA models with the same diameter but different geometry had different wall stress pointing to the importance of AAA shape and the non adequacy of Laplace's law even for an idealized approximation of complex geometries. This work was later corroborated by Elger *et al.* [96]. In addition, the study by Thubrikar *et al.* [89] indicates a considerable transmural variation of the maximum principal stress, for which 3D continuum models or advanced shell models are required. A diameter matched approach was used by Gasser

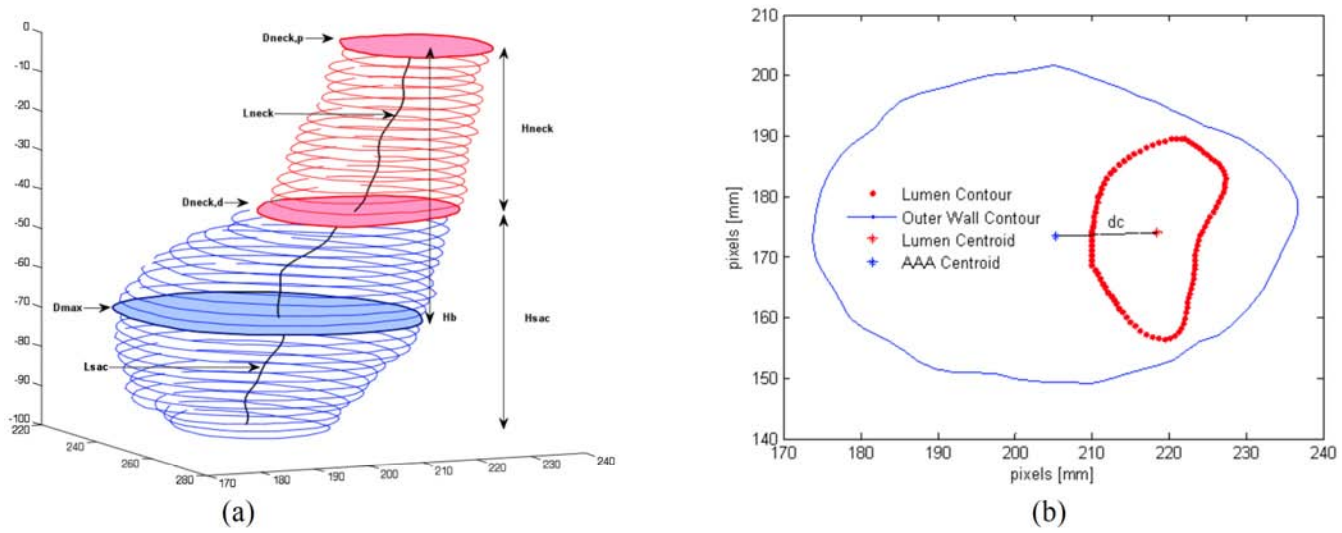

Fig. (4). (**a**) 1-D size indices: maximum diameter (Dmax), proximal neck diameter (Dneck,p), distal neck diameter (Dneck,d), sac height (Hsac), neck height (Hneck), sac length (Lsac), neck length (Lneck), bulge height (Hb); (**b**) 1-D size index: centroid distance at the maximum diameter (dc).

et al. [13] to emphasize inclusion of ILT in analysis for better ability to distinguish ruptured and non-ruptured aneurysms.

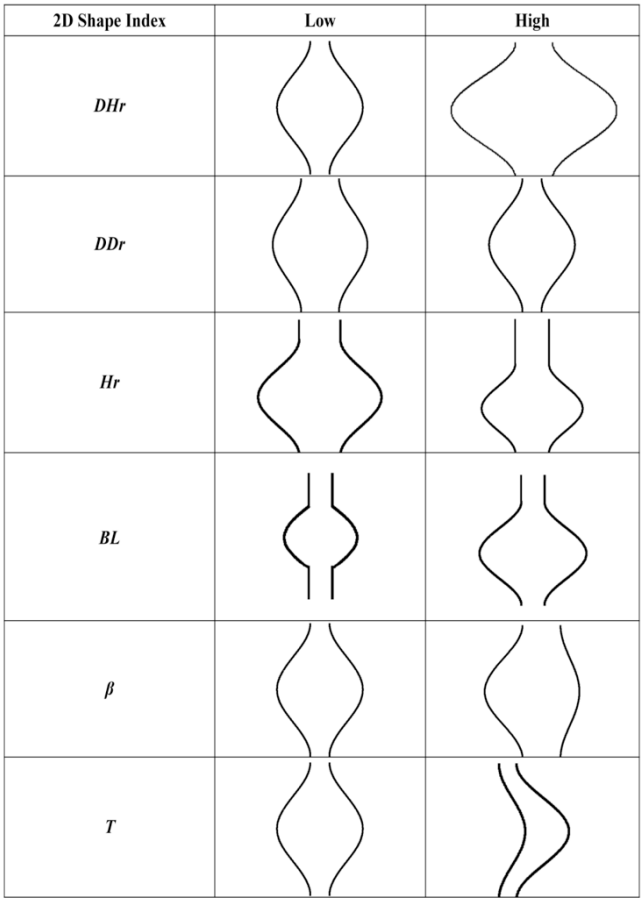

Fig. (5). Schematic of 2D shape indices providing an approximate measure to construe the global AAA shape: diameter to height ratio (DHr), diameter to diameter ratio (DDr), height ratio (Hr), bulge location (BL), asymmetry (β), and tortuosity (T).

Fillinger *et al.* [9, 10] showed the feasibility of using finite element analysis (FEA) for patient-specific wall stress calculations and reported statistically significant differences in peak stress for ruptured/symptomatic AAAs (46.8 N/cm^2) in comparison with those electively repaired (38.1 N/cm^2). They also demonstrated that maximum wall stress correlated more closely with the risk of rupture than maximum diameter [10]. In their study, wall stress was calculated by using FEA applied to a population of 103 patients, from which wall stress at a threshold of 44 N/cm^2 had 94% sensitivity and 85% accuracy in predicting rupture, compared to 81% sensitivity and 73% accuracy with the maximum diameter at a threshold of 5.5 cm. A similar study was undertaken by Venkatasubramaniam *et al.* [89] with 27 patients, from which 15 AAAs ruptured. They found that ruptured AAAs had significantly higher peak wall stress than non-ruptured AAAs (77 N/cm^2 *vs* 55 N/cm^2). Both studies [10, 89] found a strong correlation between areas of high stress and the rupture site, based on quasi-static computational solid stress calculations applying a uniform intraluminal pressure directly on the wall.

AAA Material Behavior and Constitutive Models

An accurate and reliable stress analysis of AAA requires not only a precise three-dimensional description of the aneurysm but also an appropriate constitutive law for the material. Most of the earlier studies on AAA have relied on isotropic models [9, 10, 84, 86, 96-100] assuming an incompressible behavior for the arterial wall. Such models have limited accuracy for AAA stress analysis since *ex vivo* biaxial experiments on human AAA tissue conducted by Vande Geest *et al.* [101] demonstrated that the aneurysmal degeneration of the aorta leads to an increase in mechanical anisotropy, with the circumferential direction being the preferential stiffening direction. A number of anisotropic constitutive models have been proposed for AAA tissue [83, 102-104]. In general, using anisotropic constitutive model results in significantly higher peak wall stress in both

idealized and patient-specific geometries [83, 105, 106]. In this regard, anisotropic model results are more sensitive to changes in geometric parameters such as symmetry and aneurysm length. A recent study conducted by Gasser *et al.* [13] indicates that ILT has a major impact on AAA biomechanics and rupture risk, and hence, needs to be considered in meaningful FE simulations. In addition, they also claim that inter-patient variability might reduce the importance of considering anisotropic behavior, whereas the geometry is the most critical property to be considered on a structural analysis.

Influence of ILT on Peak Wall Stress

An intraluminal thrombus (ILT) is found in most AAAs of clinically relevant size. The role of ILT on AAA is quite significant and some authors have suggested that ILT growth and volume may be related to AAA risk of rupture [107]. Some studies have suggested that hypoxia in the AAA wall covered by ILT causes degradation of the extracellular matrix and subsequent wall weakening, being one of the precursors for AAA bulging [108]. On the contrary, the ILT influences mechanical stress distribution on the underlying vessel wall and is usually regarded as an elastic body that redistributes stress and buffers the arterial wall from mechanical stress [109, 110]. In this regard, Georgakarakos *et al.* [111] have found reduction in the peak wall stress in patient-specific geometries including the ILT modeled using linear material properties (Young modulus E = 0.11 MPa and Poisson ratio 0.45) and wall modeled by using hyperelastic material proposed by Raghavan and Vorp [112]. These observations have also been corroborated by other studies [102, 110, 113]. However, there is still some concern regarding the protective role of the ILT. On a recent study, Polzer *et al.* [114] have found that ILT fissures locally increase the mechanical stress in the underlying wall up to a 30% which could possibly cause AAA rupture. In addition, *in vivo* measurements of intraluminal pressure pointed out that the presence of ILT did not significantly reduce the transmission of intraluminal pressure on the AAA wall [115, 116]. From a mechanical point of view, ILT is usually considered as a homogeneous incompressible hyperelastic solid [110, 117, 118]. However, recent developments prefer describing ILT constitutive behavior using nonlinear viscoelasticity [118], an observation also supported by the recent work by Gasser *et al.* [119]. In this work they also found ILT to be vulnerable against cycling loads with the ILT material showing significant decreasing strength with respect to the number of load cycles increasing the likelihood of ILT failure and the consequent overstress of the AAA wall as found in [114].

Influence of Initial AAA Configuration

Most computational geometries used for AAA finite element analysis, i.e. the arterial wall and lumen, are typically generated from multiple CT images acquired at one instant (gated) or multiple instants of the cardiac cycle, hence these geometries do not correspond to the geometry in the unloaded state or corresponding to zero internal pressure. Thus the application of physiological pressure boundary condition to these geometries may have significant effect on the wall stress distribution results. Ideally the physiological pressure conditions should be applied to the unloaded geometry or zero pressure geometry to get physiological stress results. A number of numerical techniques have been developed and applied to recover approximately the zero pressure configurations from an aneurysm reconstructed from gated CT images [120, 121]. Some of the results from these studies are contradictory. The works by de Putter [122] and Speelman [123] conclude that not accounting for the zero pressure configuration may lead to an overestimation of the maximum peak wall stress, whereas Raghavan *et al.* [120] and Lu *et al.* [124] arrive to the opposite conclusions. It is worth mentioning that in all previous works pertaining to retrieval of zero pressure configuration, the presence of the ILT has been neglected in the calculations and the AAA wall has been modeled as an isotropic material. In our laboratory, a new algorithm has been developed and applied to patient-specific models of AAA including the ILT and the wall thickness [125]. Preliminary results obtained assuming a nonlinear isotropic behavior for both the AAA wall and the ILT for 3 patient-specific AAA models (AAA-1, AAA-2 and AAA-3) show that not accounting for the unloaded configuration may overestimate the maximum displacement of the AAA, and underestimate the peak wall stress by as much a 20% (see Fig. **6**).

Hsu *et al.* [126] also proposed an iterative procedure for obtaining a prestress model for vascular fluid-structure interaction simulation, where they modified the solid modeling procedure of the fluid-structure interaction (FSI) formulation to account for the tissue prestress by employing an additive decomposition of second Piola-Kirchoff stress tensor. Their results suggest that the model without prestress tends to over inflate resulting in a significant difference in the wall shear stress and wall tension.

Effect of Blood Flow

Most of the wall stress distribution on AAA has been obtained from structural analysis of AAA models by applying a uniform pressure on the inner surface of aneurysm sac. The limitation of this approach is that the hemodynamics of the blood flow through the aneurysm and the compliant nature of the AAA wall are not accounted for. One of the pioneering works that account for the effect of blood flow on the peak wall stress of AAA was conducted by Di Martino *et al.* [99]. Their fluid-structure interaction (FSI) analysis of a realistic aneurysm aorta model showed that the complicated hemodynamics would considerably affect the stress distribution, but also reported the cushioning effect of ILT on the AAA wall. However, in their work, the wall and ILT were considered linear elastic and isotropic in behavior. The nonlinear behavior of the wall and ILT as well as more complex flow conditions has been considered in a series of works conducted by Scotti *et al.* [127-129]. These studies have demonstrated the importance of considering the nonlinear elastic behavior of the structure. Also the comparative study between FSI (coupled and decoupled) and Computational Solid Mechanics (CSM) analysis of patient-specific AAA performed by Scotti *et al.* [130] show that the non uniform pressure distribution in the inner surface of the AAA due to the flow yielded a maximum peak wall stress up to 20% higher compared to that obtained with static wall stress analysis when a uniform systolic pressure of 117

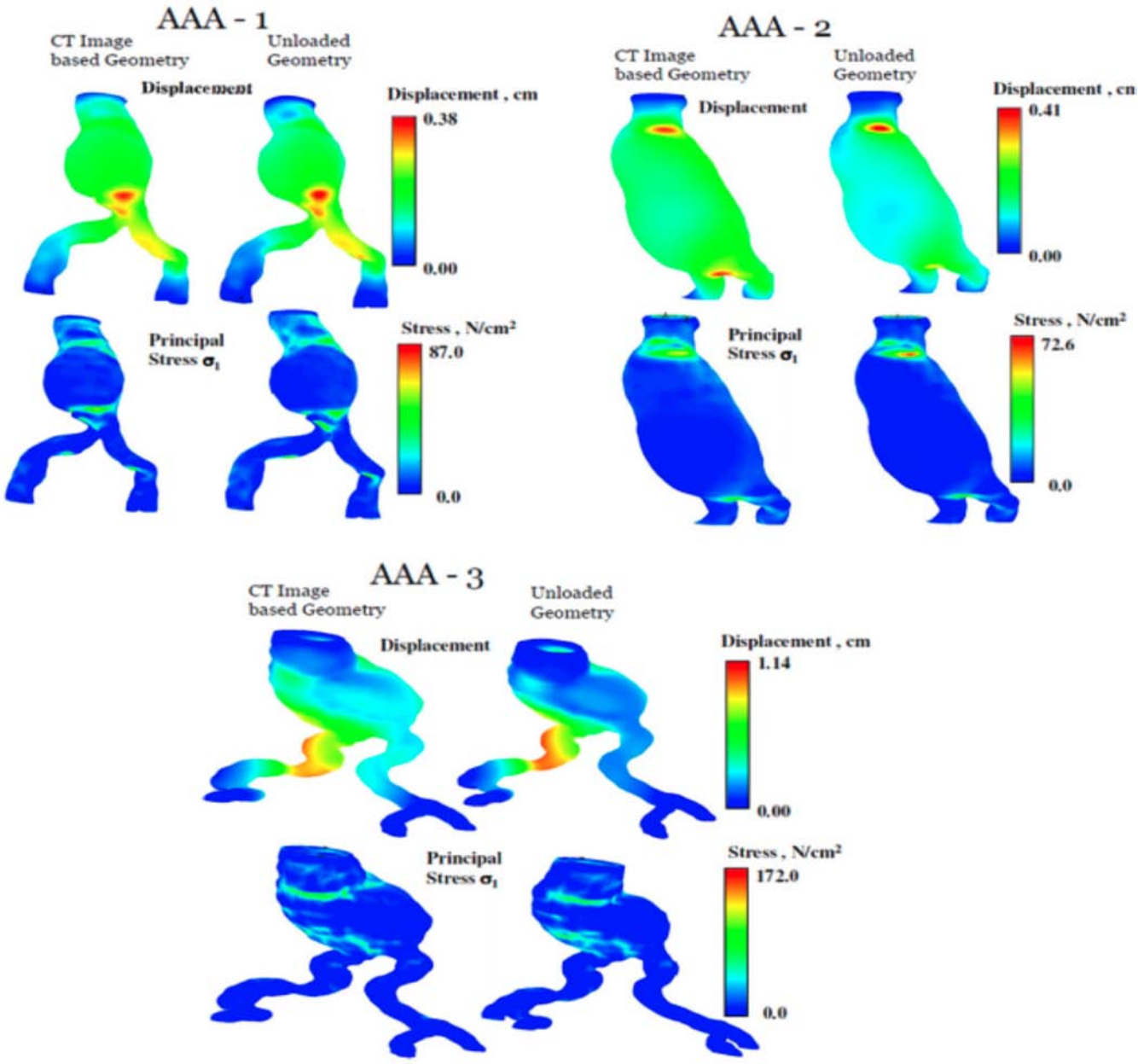

Fig. (6). Displacement and stress distribution in three patient-specific geometries for both the CT image based analysis and the zero pressure configuration. Analysis based on the zero pressure configuration yielded a larger peak wall stress (unpublished data).

mmHg is applied. In these studies it is concluded that FSI analysis has the potential to capture the fluid dynamics inside a complex AAA structure accurately and hence is a better approach for calculating the wall stress and studying rupture risk. Leung *et al.* [131] also compared the stress results obtained from fluid-structural interaction (FSI) model and computational static structural (CSS) model and reported that the addition of fluid flow and compliant wall can change the local stresses slightly but has negligible effect on the peak wall stress. However, they did not consider the presence of ILT in their analysis. One of the main conclusions that can be extracted from these studies is that using a non-uniform pressure distribution on the AAA sac can substantially improve structural analysis avoiding computationally extensive FSI analysis for determining AAA rupture risk. Results from Scotti *et al.* [127, 132], as well as the importance of considering ILT in FSI analysis were corroborated by subsequent authors [133-135]. A recent study by Chandra *et al.* [136] demonstrated the effect of MRI derived inlet flow boundary conditions on the fluid-structure-interaction modeling of a patient-specific AAA model with ILT. Comparison of results obtained from fully coupled FSI simulations, decoupled FSI simulations and transient FEA simulations revealed that the stress-strain variations follow the inlet velocity boundary condition rather than the pressure outlet boundary condition and further emphasize on the fact that peak systolic pressure does not provide the phase for peak stress and strain (see Fig. **7**).

The influence of material anisotropy in FSI simulations has been investigated by Rissland *et al.* [137] and Xenos *et al.* [138]. In their work, Rissland and colleagues introduced a

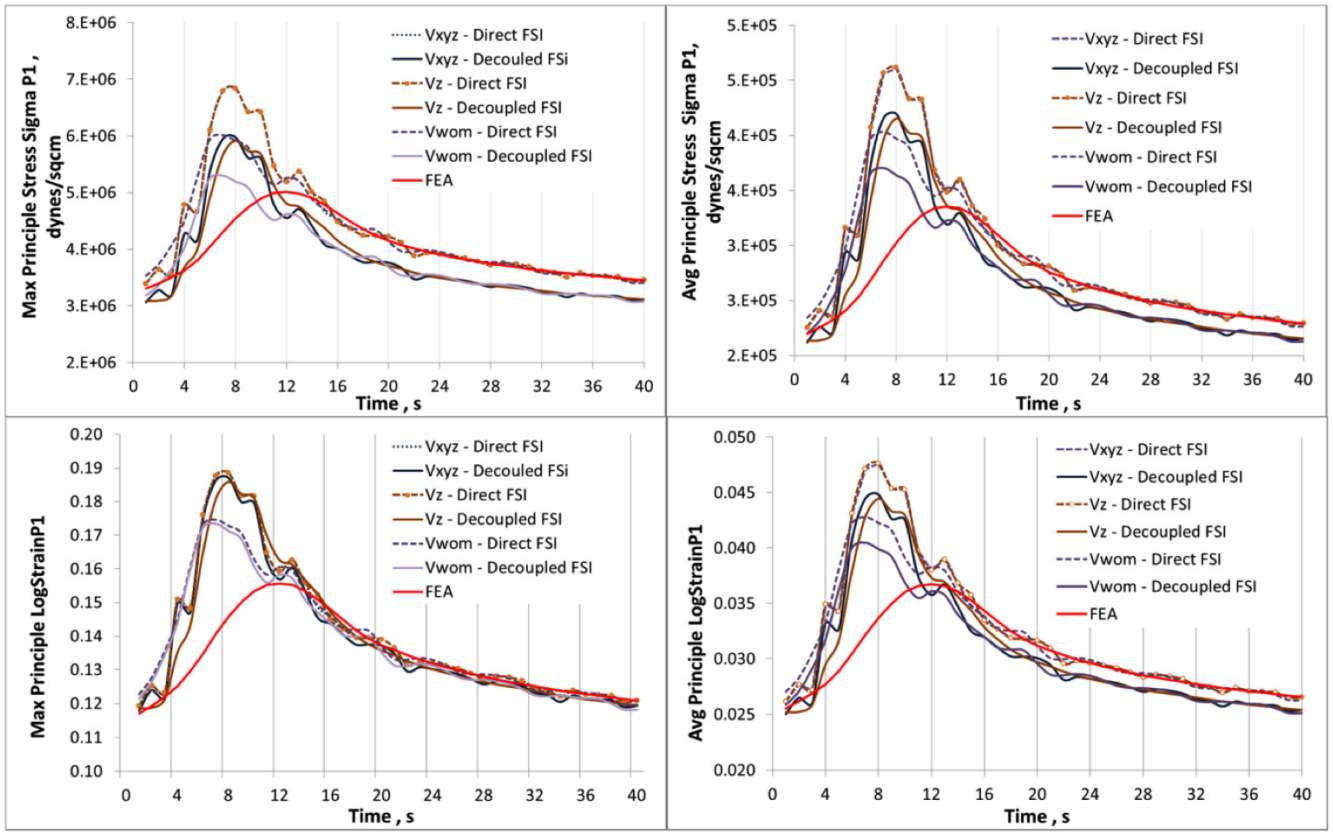

Fig. (7). Maximum and average principal stress and strain waveforms for a patient-specific AAA obtained using direct FSI, uncouple FSI and transient FEA. The stress and strain follow the inlet velocity waveform rather than the pressure waveform boundary condition (unpublished data).

new anisotropic material model of AAA wall to perform FSI simulations of patient-specific AAA geometries in order to develop more reliable predictor for risk of rupture. The ILT was still modeled as a linearly elastic compressible material. The results clearly indicate that the isotropic material properties have less stress values than anisotropic model resulting in underestimating the risk of rupture.

CURRENT & FUTURE DEVELOPMENTS

Previous sections have discussed factors behind the genesis of the AAA, and different criteria that determine the criticality level of a given lesion and determines final the decision of performing a surgical intervention. To date, traditional surgery has been used for a longer period of time to treat AAA disease. However, in the last fifteen years, endovascular stent graft repair has attracted the attention as a potential alternative to surgery, in those cases that the lesion allows for this alternative treatment. In an endovascular procedure, a stent is used to obtain and maintain the patency of a vessel while maintaining the integrity of the vessel. In the case of AAA, the function of the device is to internally reline the abdominal aorta, including the bifurcation, isolating the aneurysm from blood circulation, and therefore preventing the injury from bursting.

Current available stent grafts are constructed from self expanding stainless steel or nitinol stents and a lining material that could be either polyester or ePTFE. Most stent grafts differ in the shape of the metallic stent pattern as well as how the stent is assembled, i.e., as a continuous tube-like structure (AneuRX stent graft) or as independent stent rings (Gore Excluder, Zenith Flex or the Anacond stent grafts). These stent graft designs have been tested for over ten years becoming quite reliable in clinical practice. However, there are still known problems to these implants particularly related to migration of the prosthesis, or twisting and kinking during deployment [139]. In this regard, current efforts are focusing on improving the delivery system as well as stent pattern to prevent kinking and twisting as well as facilitating positioning even in difficult geometries [139, 140, 141, 142]. Another area of active development in stent technology is the use of novel materials for stents. In particular, the use of biopolymers to build self-expanding stents with high recoverability ratio and Chronic Outward Force (COF) values similar to commercially available stent models [143], or the development of tissue engineered endovascular stents impregnated with cells in order to favor a secure anchoring of the stent to the damage tissue to reduce migration and endoleaking [144].

CONCLUDING REMARKS

There is a clear need to revisit the use of size alone for clinical rupture risk assessment of AAAs. Biological factors along with geometric and biomechanical parameters derived from computational modeling techniques have emerged as promising adjuncts to maximum diameter and expansion rate. However, lacking a convincing clinical validation based

on a large multi-site study will likely detract vascular surgeons and interventional radiologists from implementing these parameters in their clinical toolkit. The accuracy of patient-specific AAA computational modeling is dependent on the resolution and accuracy of the clinical imaging modality. Therefore, the feasibility of implementing geometric and biomechanical parameters for rupture risk assessment is subject to advancements in dynamic imaging techniques that limit radiation exposure while providing a detailed characterization of the patient's abdomen. To this end, the implementation of high resolution, non-contrast magnetic resonance imaging is a promising alternative to the current standard of care computed tomography angiography. Improved dynamic MRI protocols would allow researchers to accurately estimate regional distributions of time-dependent wall thickness and individualized material properties of aneurysmal tissue, which will be key contributions to the development of geometric models as well as tissue growth and remodeling constitutive equations. While the accurate characterization of geometry and wall mechanics has a promising future for the clinical management of AAA disease, the identification of biological factors and development of an improved *in vivo* (animal) model can lead to a better understanding of aneurysm progression. In particular, an *in vivo* model that can replicate intraluminal thrombus formation and wall calcification concomitant with collagen and elastin turnover will be imperative for the discovery of pharmaceutical agents that can decrease the rate of AAA expansion or prevent the disease altogether. The localized delivery of such agents, however, will be the key to bridging the gap between experimental research and clinically feasible therapies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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