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Biomechanical Determinants of Abdominal Aortic Aneurysm Rupture

David A. Vorp, Jonathan P. Vande Geest

Abstract—Rupture of abdominal aortic aneurysm (AAA) represents a significant clinical event, having a mortality rate of 90% and being currently ranked as the 13th leading cause of death in the US. The ability to reliably evaluate the susceptibility of a particular AAA to rupture on a case-specific basis could vastly improve the clinical management of these patients. Because AAA rupture represents a mechanical failure of the degenerated aortic wall, biomechanical considerations are important to understand this process and to improve our predictions of its occurrence. Presented here is an overview of research to date related to the biomechanics of AAA rupture. This includes a summary of results related to ex vivo and in vivo mechanical testing, noninvasive AAA wall stress estimations, and potential mechanisms of AAA wall weakening. We conclude with a demonstration of a biomechanics-based approach to predicting AAA rupture on a patient-specific basis, which may ultimately prove to be superior to the widely and currently used maximum diameter criterion. (***Arterioscler Thromb Vasc Biol*****. 2005;25:1558-1566.)**

Key Words: abdominal aortic aneurysm ■ biomechanics ■ rupture ■ strength ■ stress

Abdominal aortic aneurysm (AAA) is a focal enlargement of the infrarenal aorta, which occurs over a time course of several years. This condition is present in ≈2% of the elderly population, with ≈150 000 new cases diagnosed each year, and the incidence is increasing.[1,2] If left untreated, AAA will gradually expand until rupture; it is an event that carries a mortality rate of 90% and that is ranked as the 13th most common cause of death in the US.[3] Current AAA repair procedures are expensive and carry significant morbidity and mortality risks.

Open repair of AAA is a major surgical procedure that requires patients to be hospitalized typically for 1 week and to recuperate at home for several more weeks. The mean postoperative mortality for elective repair is ≈5% and for emergency operations 47% (range 27% to 69%).[4] The major drawback of open repair is the compromised quality of life after surgery because of postoperative pain, the prolonged recovery period, and the high costs associated with both the surgery and the recovery.

An alternative approach that avoids the extensive tissue dissection associated with open repair is the minimally invasive endovascular repair procedure. The potential advantages of endovascular AAA repair include reductions in mortality, morbidity, blood loss, hospital stay, intensive care

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Relationship of Size to Rupture in 473 Nonresected AAA

Size, cm	N Ruptured	N Unruptured	Total	% Ruptured
≤5.0	34	231	265	12.8
>5.0	78	116	194	40.0
No size recorded	6	8	14	43.0
Total	118	355	473	24.9

Adapted from Darling et al.

unit utilization, and discomfort.[5] Recovery is faster with the endovascular approach than with the traditional surgical approach.[6] Although at present the cost-effectiveness of endovascular treatment of AAA is debatable, especially in view of the high cost of the graft, endovascular treatment may turn out to be cost-effective in view of the shortened hospital stay. Even with this minimally invasive procedure, which is not devoid of risks and morbidity, careful selection of patients is imperative.[7] In addition, this technique is subject to postprocedural complications, mostly caused by the development of endoleaks or to the mechanical failure of the device, which can occur in 15% to 52% of cases.[8–10]

Given these limitations and risks of current repair techniques, it is important to determine when, during the course of an aneurysm, the risk of rupture justifies repair. That is, only those patients who are at high risk for AAA rupture should be offered repair. Presently, the decision for elective repair of AAA is based on the maximum diameter of the aneurysm. Recent reports by 2 randomized clinical trials suggest that the risk of AAA rupture warrants intervention when the maximum diameter reaches 5.5 cm.[11–13] Whereas these studies support the watchful surveillance of small AAAs (<5.5 cm), other studies suggest that this maximum diameter criterion may not be appropriate. For example, an autopsy study by Darling et al reported a rupture rate of 12.8% for AAAs <5 cm (34/265) and a corresponding rupture rate of 40% for AAAs >5 cm (78/194) (Table).[14] Similarly, Hall et al summarized a group of studies indicating that up to 23% of AAAs rupture at a diameter <5 cm.[15] The apparent discrepancies between these studies and the maximum diameter criterion suggest that surgery based solely on the maximum diameter criterion may be offered too late or may not be necessary for a certain group of patients. Clearly, the ability to reliably evaluate the susceptibility of a particular AAA to rupture on a patient-specific basis could vastly improve the clinical management of these patients.

The reason that the "5-cm diameter criterion" to evaluate AAA severity is so unreliable is that it does not take into account other individual characteristics of an aneurysm. AAA rupture assessment is not a "one-size-fits-all" process. From a purely mechanical point of view, rupture of AAA occurs when the mechanical stresses (internal forces per unit area) acting on the aneurysm exceeds the ability of the wall tissue to withstand these stresses (ie, the wall's failure strength). Our previous observations show that AAA formation is accompanied by an increase in wall stress,[16] as well as a corresponding decrease in wall strength.[17–19] Despite recent reports,[20,21] it should be noted that evaluation of rupture potential based on only one of these parameters—stress or strength—is not sufficient because a region of the AAA wall that is under elevated wall stress may also have a higher wall strength, thus equalizing its rupture potential. Based on principles of material failure, rupture instead is most likely where the ratio of stress to strength is highest. Nonetheless, it is interesting to note from a recent retrospective study that consideration of even peak wall stress alone may lead to an improvement over the maximum diameter criterion.[20–22] This study showed a statistically significant elevated peak stress for ruptured AAAs (46.8 ± 4.5 N/cm^2) as compared with electively repaired AAAs (38.1 ± 1.3 N/cm^2), even when adjusted for maximum diameter. Clearly, the ability to noninvasively predict the locally acting wall stress and wall strength for AAAs on a patient-specific basis will provide a more appropriate diagnostic tool for isolating those who are at high risk for rupture.

Biomechanical Behavior of AAA Tissue

Understanding the biomechanical behavior of AAA tissue, especially relative to nonaneurysmal aorta or at various stages of the disease, can reveal important information. For example, changes in compliance or vessel wall stiffness may be indicative of gross changes to tissue microstructure or extracellular matrix content. In addition, as stated, AAA wall stress is 1 of 2 important factors when considering aneurysm rupture, and because stress is not a directly measurable quantity, tissue constitutive relations must be used if the state of stress in any body is to be determined. Simply stated, constitutive relations mathematically relate the stress (force per unit area) and strain (deformation) in a material. Constitutive relationships for blood vessels have historically been derived from either in vivo measurements or ex vivo tensile testing, as outlined in the following sections.

In Vivo Mechanical Evaluation

Noninvasive techniques such as ultrasound and computed tomography have long been used in the detection and treatment of AAAs. These techniques have also been used in estimating the mechanical behavior of the AAA wall and intraluminal thrombus (ILT), primarily with the recording of compliance measurements. Länne et al used a phase-locked ultrasound tracking system to show there is a decrease in compliance in patients with AAA as compared with control subjects.[23] MacSweeney et al reported an increase in the pressure–strain elastic modulus in patients with AAA using M-mode ultrasonography.[24] Automated ultrasonographic measurements of the aortic wall and intraluminal thrombus performed in our laboratory demonstrated that the compliance of the AAA wall is decreased as compared with that of the luminal–thrombus interface.[25] The relatively constant area of ILT over the cardiac cycle reported in this study was the first to suggest the incompressibility of this tissue. The results of this work also suggested the possible "mechanical cushioning effect" of the ILT, an observation that has been supported by us and other investigators.[26,27] Sonesson et al investigated the stiffness of the abdominal aorta as well as the common carotid artery in patients with AAA and reported an increase in stiffness for both of these when compared with data reported for healthy subjects.[28] These authors suggest

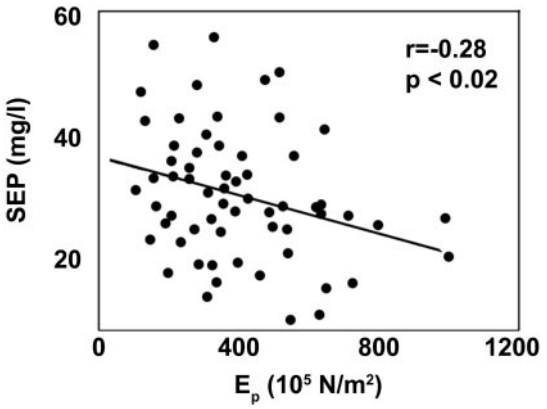

Figure 1. Relationship between stiffness (Ep) of the AAA wall and serum elastin peptides (SEP). Adapted with permission from Wilson et al.[30]

that aneurysmal formation is a system-wide phenomenon with a localized manifestation in the abdominal aortic region. Later work by this group showed that ultrasonographically measured stiffness did not significantly differ in patients whose AAA eventually ruptured as compared with those who were electively repaired.[29] Wilson et al investigated the relationship between compliance, maximum diameter, and growth rate, and concluded that large aneurysms tended to be less compliant, or stiffer.[30] This group later investigated serum markers in AAA and concluded that increased elastolysis is associated with decreased AAA wall stiffness[31] (Figure 1). More recently this group has shown that the female gender, higher blood pressure, a decrease in the pressure strain elastic modulus (Ep), and a larger maximum diameter have a significant influence on time to AAA rupture.[32] Although the stiffness and compliance of AAAs can be investigated noninvasively using ultrasound techniques, this method cannot be used to derive the continuum-based constitutive models that are required when analyzing patient-specific local wall stresses on AAA using finite element analysis.

Ex Vivo Tensile Testing

Most early ex vivo studies on the biomechanical properties of AAA were focused on understanding the effect of the extracellular matrix derangements found in aneurysms on basic properties such as wall stiffness.[33–35] He and Roach displayed a stiffer and less distensible uniaxial response for AAA as compared with nonaneurysmal tissue along with an associated decrease in volume fraction of elastin in AAA. Our laboratory previously reported a decrease in AAA wall strength for AAA specimens tested uniaxially as compared with nonaneurysmal tissue.[17,18] More recently, we formulated a hyperelastic, continuum-mechanics based model for the AAA wall to be used in the finite element models of AAA.[36] Thubrikar et al[37] has since reported their important observation that the biomechanical properties (eg, yield stress) of a given AAA vary spatially. Their results underscore our belief that the spatial variations in wall stress and wall strength must be taken into account on a patient-specific basis.

Whereas other work has suggested the anisotropy of aortic tissue,[38–43] work performed by our group[44] appears to be the first to directly assess the anisotropy of human abdominal aortic tissue using planar multiaxial experimental methods. Most of the previous work investigating the material symmetry of aorta has been performed on animal tissue or involved uniaxial tensile testing, which is unable to conclusively assess the anisotropic response of this tissue. There has been very little published work involving the biaxial experimentation of human aortic tissue,[45,46] and none for AAA tissue. Biaxial tensile testing of AAA recently completed by our laboratory has demonstrated that aneurysmal formation is associated with an increase in circumferential stiffness (830 ± 120 N/cm^2 versus 330 ± 60 N/cm^2 for the AAA and AA, respectively [$P=0.03$]).[47] The constitutive relation derived in this work is, to our knowledge, the first anisotropic constitutive relation reported for AAA tissue.[47]

Di Martino et al first published the uniaxial tensile properties of intraluminal thrombus, modeling it as a linear isotropic material.[48] Our laboratory later used uniaxial tensile tests to develop a hyperelastic isotropic constitutive relation for the ILT.[49] This work also highlighted the heterogeneity of the ILT as 3 distinct layers were found to have distinct mechanical properties. More recent work in our laboratory has shown that the luminal layer of ILT behaves as an isotropic material.[50]

Estimation of AAA Wall Stress

The earliest predictions for AAA wall stress used the Law of LaPlace,[26,51–53] which assumes that the AAA wall geometry is a simple cylinder or sphere with a single radius of curvature. However, the AAA wall is complexly shaped with both major and minor wall curvatures.[54] To use only the maximum diameter to predict wall stresses in AAA, therefore, ignores the significant contributions of local complex wall surface shapes.[55] In fact, it has been shown by our laboratory[16,27,55,56] and others[20–22,51] that the stresses acting on a AAA are not evenly distributed and cannot be adequately described by the Law of LaPlace. Therefore, AAAs with equivalent diameters and pressures (and thus LaPlace-predicted wall stress) could have largely different stress distributions. Other early mechanical wall stress models for AAA were rather crude, using inappropriate tissue constitutive models, idealized geometries, and/or 2-dimensional stress analyses.[26, 48, 51–53, 57] The use of the theory of linearized elasticity or other inappropriate tissue constitutive models in AAA stress models[26,48,51–53,55,57] can also lead to erroneous stress distribution predictions.[16] Each of the aforementioned approaches, although providing useful information on the general factors influencing AAA wall stress, are unable to provide realistic stress distributions in patient-specific AAA.

Accurate wall stress analysis of AAAs requires information regarding aortic geometry, wall thickness variability, applied forces and boundary conditions, governing equations representing the relevant physical laws (momentum balance and conservation of mass), constitutive models, material parameters, and a means to solve the resultant system of partial differential equations. It should also be noted that continuum-based constitutive relations provide the easiest

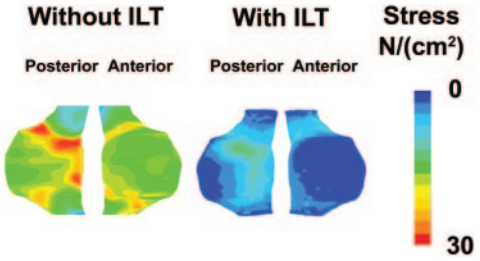

Figure 2. Effect of intraluminal thrombus on the wall stress in a representative patient-specific AAA. Adapted with permission from Wang et al.[27]

implementation into computational stress analyses, as parameter-based (eg, see Raghavan et al[18]) equations are not easily adapted to 3-dimensions. We first used a continuum-based constitutive model in the finite element analyses of patient-specific aneurysms[16] to demonstrate the complex stress distributions in AAA, with localized regions of high and low stresses (range of peak stress, 29 to 45 N/cm^2). In addition, the stresses on nonaneurysmal aorta were found to have more evenly distributed lower peak stress values (peak stress, 12 N/cm^2).

Other laboratories have subsequently used similar methods using patient-specific geometries and nonlinearly elastic, experimentally established tissue models to evaluate wall stresses in AAA. Fillinger et al[21,22] and Venkatasubramaniam et al[20] each recently performed stress analyses on AAA, which did not account for the presence and effect of the ILT. However, it has been suggested via idealized geometries and finite element analysis that ILT acts to reduce peak wall stress by up to 30%.[26,48,57] Subsequent research by our laboratory has shown that not including the commonly found ILT into finite element analyses can lead to significant errors in both the magnitude and the distribution of AAA wall stresses[27,58] (Figure 2). For this reason, our methods now routinely include the ILT.[27] More recent work in our laboratory has allowed the improvement of AAA stress estimation technique by the incorporation of experimentally determined tissue anisotropy into our models.[47,59] Kyriacou and Humphrey showed that the stress distribution in cerebral aneurysms is markedly different when incorporating an anisotropic model versus a simplified isotropic model,[60] and we have made similar preliminary observations for AAA.

In addition to the aforementioned concerns, there are several improvements that can still be made to the stress analysis of AAAs. For example, it is known that the AAA wall does not have a uniform thickness. Recent work has demonstrated that the inclusion of a variable wall thickness into stress analyses of AAA may better estimate the location of rupture.[61] Likewise, incorporation of patient-specific wall calcifications may also lead to an improved estimation of wall stresses.[62] In addition, all stress simulations to date assume that the unloaded stress free configuration is that taken from computed tomography imaging. The effect of this assumption on AAA stress distributions has yet to be quantified in the literature. Only experimental evidence will determine the degree of complexity appropriate for AAA failure modeling, but the penalty for false or inaccurate assumptions will be great.

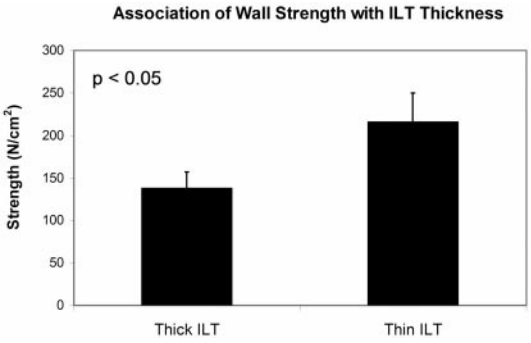

Figure 3. Association of AAA wall strength with adjacent ILT thickness. Adapted with permission from Vorp et al.[19]

AAA Wall Strength

Estimation of AAA Wall Strength

Though using patient-specific stress simulations is useful to determine localized regions of high stress within a given AAA, the rupture risk of an aneurysm is also a function of the wall strength. In other words, the AAA wall will rupture when the strength of the wall is unable to withstand the stresses acting on it. Therefore, the noninvasive estimation of wall strength is required to accurately predict AAA rupture risk. To our knowledge, there is currently no published noninvasive technique for determining the localized AAA wall strength on a patient-specific basis. Our laboratory has previously investigated the ultimate tensile strength of aneurysmal tissue, reporting a significant 50% decrease in strength of the AAA wall versus nonaneurysmal aorta.[17] More recent work in our laboratory suggests that the wall strength of ruptured (n=13) AAA wall is significantly lower (P=0.02) than electively repaired (n=26) AAAs (54.2±5.6 N/cm^2 versus 82.3±9.0 N/cm^2, respectively).[63] We also previously reported the influence of local ILT thickness on AAA wall strength; ie, that the tensile strength for AAA wall adjacent to a thick layer of ILT is significantly weaker than wall in the same AAA adjacent to a thinner or no ILT (Figure 3).[19] Thubrikar et al and Raghavan et al have also recently reported the spatial variation of wall thickness and tensile strength in an excised AAA.[37,61] These studies are to our knowledge the only reporting AAA wall strength and support the idea that evaluation of AAA wall stress distribution alone is insufficient to predict rupture because one cannot assume that the wall strength is the same from point-to-point in a given aneurysm or from patient-to-patient.

Preliminary work in our laboratory has investigated the use of statistical methods to noninvasively predict local wall strength distribution in a given AAA (Wang[65] and Wang DHJ, Makaroun MS, Webster MW, and Vorp DA, unpublished data, 2005). Specifically, multiple linear regression methods were used to derive a statistical model based on experimental measurements of AAA wall strength and possible predictor variables. The significant predictor variables included "global" parameters (ie, those that do not vary

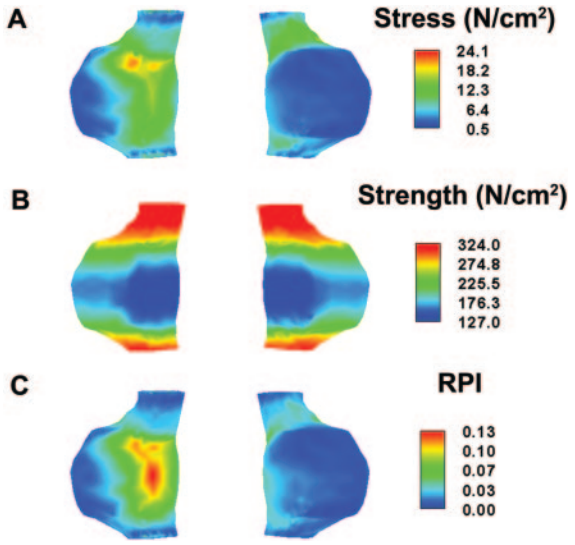

Figure 4. The stress, strength, and rupture potential index (RPI) for a representative patient-specific AAA. Adapted with permission from Wang et al.[65]

spatially within a given AAA) such as the patient's age (in years), sex (0=male, 1=female), smoking status (0=smoker, 1=nonsmoker), family history (0=without, 1=with), and AAA size (in cm). Significant "local" predictor variables included ILT thickness (in cm) and local normalized transverse diameter. Regression techniques were performed to identify which of these parameters were significant predictors of AAA wall strength given our data set. The final regression-based model was

$$\text{Strength} = 141.26 - 17.16 \times \text{ILT} + 3.39 \times \text{Age} - 257.30 \times \text{Nord} - 69.5 \times \text{Hist} + \epsilon$$

where strength is in N/cm^2, ILT (thickness) is in centimeters, age is in years, and normalized transverse diameter, being the ratio of local transverse diameter to maximum transverse diameter, is dimensionless. The ϵ term in equation 1 represents the error or residual in strength that is not accounted for by the other independent variables. The application of this model is demonstrated for a representative AAA for which a comparison stress analysis was performed (Figure 4 A and 4B). It should be noted that equation 1 and Figure 4 B are preliminary in nature and are presented here simply for demonstrative purposes. As discussed, development of such a noninvasive technique may allow an accurate, biomechanics-based prediction of AAA rupture, which would improve patient management immensely.

Potential Mechanisms of AAA Wall Weakening

Whereas it is well-established that biomechanical changes occur with AAA formation,[17,18,34,36,37,47,48] and that these properties are spatially variable,[19,37,61] little is known about the mechanisms involved. Our previous data demonstrated that the tensile strength of AAA tissue progressively decreases with increasing diameter.[17,18] More recently, we demonstrated that the wall strength distribution within any particular AAA is spatially variable,[19] and this was corroborated by Thubrikar et al, who also demonstrated spatial variation in tissue stiffness.[37] These observations support the hypotheses that local factors (eg, biomechanical wall stress and/or hypoxia) may promote tissue degeneration in AAA. Sumner et al[33] found that aneurysmal portions of human aorta were stiffer and contained less elastin and collagen than nonaneurysmal aorta, and these findings were, in part, corroborated by a more recent study.[34] Dobrin[35] studied the biomechanical changes associated with experimental enzymatic degradation of structural proteins in arterial segments ex vivo and suggested that AAA expansion is primarily related to elastolysis, whereas rupture involves failure of the remaining collagen mesh. He further suggested that the strength of the aneurysmal wall and the forces it is subjected to are primary factors for AAA rupture. It is clear from these and other studies that the biomechanical derangements in AAA are related to changes in extracellular matrix (ECM). Based on all of these observations, we discuss here 2 possible mechanisms for changes in the ECM of AAAs: stress-mediated and hypoxia-mediated wall weakening.

Stress-Mediated or Strain-Mediated Wall Weakening

Mechanical forces or deformations are considered to be paramount to maintenance of microstructure in normal tissue. Sakalihasan et al found a decreasing quadratic relationship between elastin concentration and diameter for nonaneurysmal aortas, as well as AAAs of increasing diameter.[66] Because the Law of LaPlace indicates that vascular wall stress is proportional to its diameter, these changes may reflect a response to elevated wall stress. Similarly, Hunter et al made note of focal saccular outpouchings, or "blebs," found within the walls of some AAA and conjectured that they may represent sites of potential rupture.[67] Studies by our group[55] and others[60] indicate that such asymmetrical outpouchings result in focal stress concentrations. That the blebs were characterized by a decreased procollagen expression and decreased elastin content as compared with the adjacent AAA wall[68] again gives rise to the possibility that increased mechanical forces alter local ECM synthesis. This possibility is strengthened by findings that mechanical forces alter ECM production by smooth muscle cells (SMCs),[69] endothelial cells,[70] and other cells[71] in culture. Mechanical forces may also act to alter ECM synthesis in an indirect manner by stimulating cellular release of cytokines such as tumor necrosis factor-α,[72] which inhibits procollagen expression in human aortic SMCs.[73] In sum, these studies support the idea that stress concentrations in the AAA wall may lead to altered ECM synthesis.

McMillan et al[74] demonstrated increased matrix metalloproteinase (MMP)-9 mRNA in AAA correlating with increasing aneurysm size. Other studies show that the degree of elastolysis increases in the AAA as it enlarges.[66] The Law of Laplace indicates that this move toward ECM degradation may reflect a response to elevated wall stress. Other proteolytic enzymes have also been identified in the AAA wall,[75] and their expression may be enhanced by locally acting forces. In support of this idea, an upregulation of MMP-1 has been reported in mechanically stimulated SMCs,[76] aortic endothelial cells,[77] and fibroblasts[78] in culture. Similarly,

expression of several other MMPs, tissue plasminogen activator, and urokinase plasminogen activator is enhanced by mechanical stimulation of SMCs and/or fibroblasts.[76,79] We are especially intrigued by macrophages present in the AAA wall[19,80] because they anchor themselves to the surrounding ECM and would hence "feel" any stress that is transmitted locally. It appears that these cells, when subjected to local stress concentrations, may produce greater levels of proteolytic enzymes than when under lower stress.[81] This possibility is strengthened by observations of Lee et al,[82] who showed that elevated mechanical stress zones in atherosclerotic plaques contain macrophages and express significantly greater levels of MMP-1 than the lower stress zones. Similarly, Lendon et al[83] showed that the mechanical strength of plaque caps is reduced with increased presence of macrophages. These studies suggest that macrophages may play an important role in reducing the strength of AAA via force-mediated expression of proteolytic enzymes.

In whole vessel segments, where many cells act synergistically with one another, proteolytic enzyme production may be even more sensitive to mechanical stimulation. MMP-2 and MMP-9 have been found to increase in human saphenous veins as a result of mechanical manipulation during surgical preparation.[84] Altered expression of other genes has also been demonstrated by us and others for arterial segments in response to biomechanical stresses,[85,86] and it was determined that an increase in wall stress (as opposed to increases in intraluminal pressure or flow, for example) is a sufficient stimulus for these changes.[87] These observations suggest that elevated mechanical stress can act as a stimulant to the cells within the AAA wall to produce proteolytic enzymes.

In summary, these previous investigations support the idea that locally acting forces (and therefore wall stresses) play an important role in the pathophysiology of aneurysmal disease. Specifically, the degeneration of the aneurysmal wall may in fact be coupled with local increases in mechanical stresses resulting in changes in the ECM that, in turn, could result in a compromised structural integrity of the AAA wall.

Hypoxia-Mediated Wall Weakening

Much like mechanical stimulation, hypoxia may also play a significant role in AAA wall weakening by upsetting the normal balance between ECM synthesis and degradation. Studies have shown that hypoxia influences ECM synthesis both directly[88–90] and indirectly by mediating cytokines such as tumor necrosis factor-α[91]. For example, aortic endothelial cells[89] cultured in hypoxic conditions exhibit a decrease in collagen synthesis, whereas hypoxic arterial SMCs exhibit a decrease in both collagen synthesis[90] and tropoelastin mRNA expression and synthesis[88] (Figure 5). Other cells associated with the arterial wall, such as fibroblasts, are similarly affected by hypoxic stimulation.[92] These previous observations suggest that local hypoxia would contribute to AAA wall weakening by inhibiting ECM synthesis.

Hypoxia also influences vascular cell expression of genes related to ECM degradation.[88,93] For example, exposure of macrophages to hypoxia is known to enhance their gene expression, including that of MMP-7[93] as well as their release of elastase[94] and cytokines.[91] We have provided data that

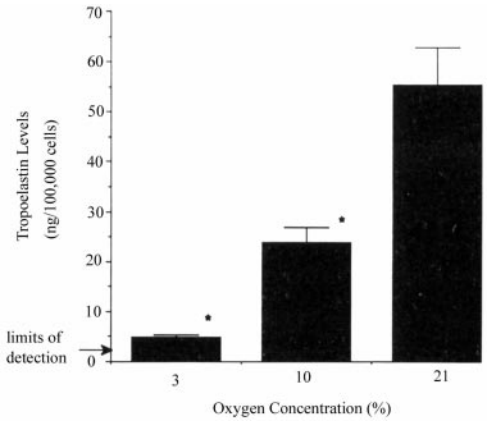

Figure 5. Tropoelastin protein production by calf pulmonary artery smooth muscle cells grown under various levels of hypoxia for 120 hours. Taken with permission from Durmowicz et al.[88]

suggest that some portions of the AAA wall are under a state of hypoxia caused by the presence of an ILT layer.[19] As a consequence, the mural cells within these zones likely respond to this environment. Kazi et al recently demonstrated that AAA wall adjacent to ILT was thinner, contained fewer SMCs, and contained more macrophages and other inflammatory cells than AAA wall adjacent to no ILT.[80] Perhaps not coincidentally, the AAA wall adjacent to ILT also exhibited greater degree of apoptosis and contained fewer elastin fibers. Similarly, the observations of Lendon et al[83] that the mechanical strength of plaque caps is reduced with increased presence of macrophages may be caused by the stimulation of these cells by a local hypoxic environment,[95] causing them to release MMPs[82,93,94] or other proteolytic enzymes. Our laboratory has demonstrated that macrophages are present within the ILT[96] and are exposed to a hypoxic environment.[19,97] The observation by Jean-Claude et al that elevated levels of plasmin are present in the inner layers of the AAA wall near the interface with intraluminal thrombus is a possible consequence of this.[98] All of these considerations suggest that hypoxic conditions may stimulate the cells within the AAA wall and ILT to express ECM degrading factors, thereby contributing to local aneurysm wall weakening.

In summary, these previous investigations outline the potential importance of hypoxia in upsetting the local balance of protein degradation and synthesis in the AAA wall. The observed local hypoxic environment in AAA may therefore lead to a decrease in the overall structural integrity of the wall and its eventual rupture.

Biomechanics-Based AAA Rupture Prediction: The Future?

Ever since AAA repair became the mainstay of the vascular surgeon's practice in the latter half of the 20th century, clinicians have attempted to develop means to accurately predict the risk of aneurysm rupture. All of the criteria that have been proposed have been based on empirical data with less emphasis on sound physical principles. The most commonly used criterion is the maximum diameter criterion, which is based on a cutoff value of 5.5 cm for the maximum

diameter. Though most physicians do not use this 5.5-cm cutoff as an "end all" for determining when a patient should have surgery, this method can be improved as it has resulted in a rupture rate of 1% per year for patients under observation.[11–13] Other parameters that have also been proposed as potential predictors of AAA rupture include the AAA wall stiffness,[29] increase in intraluminal thrombus thickness,[99] wall tension,[15] and peak AAA wall stress.[20–22] All of these approaches have their own limitations and may lead to errors in decisions pertaining to clinical management of AAA. We believe that taking into consideration both the wall stress and the wall strength will greatly improve the ability to identify those AAAs who are at highest risk for rupture. Toward this end, we recently introduced the concept of a "rupture potential index," which is defined as the locally acting wall stress divided by the local wall strength.[65,100] This definition for rupture risk provides a numerical value that ranges from 0 to 1 and would be highest when the mechanical stresses acting on the aneurysm are large in comparison to the locally acting wall strength. Shown in Figure 4C are preliminary 3-dimensional distributions of rupture potential index for a representative AAA using the aforementioned techniques for the noninvasive predictions of patient-specific wall stress (Figure 4A)[16,27] and wall strength (Figure 4B) (Wang[65] and Wang DHJ, Makaroun MS, Webster MW, and Vorp DA, unpublished data, 2005) distributions. Clearly, to determine the usefulness of this approach and a critical value of rupture potential index for which AAAs are considered to have a high risk of rupture, a rigorous clinical validation study must be completed.

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