Biomechanical properties of ruptured versus electively repaired abdominal aortic aneurysm wall tissue

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Objective: **The purpose of this study was to evaluate and compare the biomechanical properties of abdominal aortic aneurysm (AAA) wall tissue from patients who experienced AAA rupture with that of those who received elective repair.**
Methods: **Rectangular, circumferentially oriented AAA wall specimens (approximately 2.5 cm × 7 mm) were obtained fresh from the operating room from patients undergoing surgical repair. The width and thickness were measured for each specimen by using a laser micrometer before testing to failure with a uniaxial tensile testing system. The force and deformation applied to each specimen were measured continuously during testing, and the data were converted to stress and stretch ratio. The tensile strength was taken as the peak stress obtained before specimen failure, and the distensibility was taken as the stretch ratio at failure. The maximum tangential modulus and average modulus were also computed according to the peak and average slope of the stress-stretch ratio curve.**
Results: **Twenty-six specimens were obtained from 16 patients (aged 73 ± 3 years [mean ± SEM]) undergoing elective repair of their AAA (diameter, 7.0 ± 0.5 cm). Thirteen specimens were resected from nine patients (aged 73 ± 3 years; P = not significant in comparison to the electively repaired AAAs) during repair of their ruptured AAA (diameter, 7.8 ± 0.6 cm; P = not significant). A significant difference was noted in wall thickness between ruptured and elective AAAs: 3.6 ± 0.3 mm vs 2.5 ± 0.1 mm, respectively ($P < .001$). The tensile strength of the ruptured tissue was found to be lower than that for the electively repaired tissue (54 ± 6 N/cm^2 vs 82 ± 9.0 N/cm^2; $P = .04$). Considering all specimens, no significant correlation was noted between tensile strength and diameter ($R = -0.10$; $P = .55$). Tensile strength, however, had a significant negative correlation with wall thickness ($R = -0.42$; $P < .05$) and a significant positive correlation with the tissue maximum tangential modulus ($R = 0.76$; $P < .05$).**
Conclusions: **Our data suggest that AAA rupture is associated with aortic wall weakening, but not with wall stiffening. A widely accepted indicator for risk of aneurysm rupture is the maximum transverse diameter. Our results suggest that AAA wall strength, in large aneurysms, is not related to the maximum transverse diameter. Rather, wall thickness or stiffness may be a better predictor of rupture for large AAAs. (J Vasc Surg 2006;43:570-6.)**

Clinical Relevance: **Rupture of an abdominal aortic aneurysm is a deadly event that carries an overall mortality of more than 70%. Nonetheless, there exists no reliable criterion to determine the severity of an aneurysm. The wall of an aneurysm progressively weakens as a result of discordant repair/remodeling mechanisms, which can lead to changes in the mechanical properties of the tissue. We demonstrate here that a decrease in stiffness and an increase in thickness of the tissue (both noninvasively measurable) correlate with a decreased strength. Therefore, we believe that an improved risk prediction criterion could be drawn from our data.**

Abdominal aortic aneurysm (AAA) is a vascular pathology that occurs primarily in the elderly.[1,2] A recent study[3] reported that mortality for ruptured AAA (rAAA) is 40% or more. Degradation of extracellular matrix proteins has been indicated as a leading factor in AAA progression and rupture.[4-13] Distinctive features of aortic wall pathology associated with AAA have been described, including upregulation of proteinase enzymes (notably matrix metalloproteinase [MMP]-1, -2, -3, and -9),[9,13-15] elastin and collagen fiber breakdown,[4,6,16] loss of elastin content,[17] and collagen degradation.[9,10,13]

Rupture of AAA represents a mechanical failure of the degenerated aortic wall that occurs when its structural integ-

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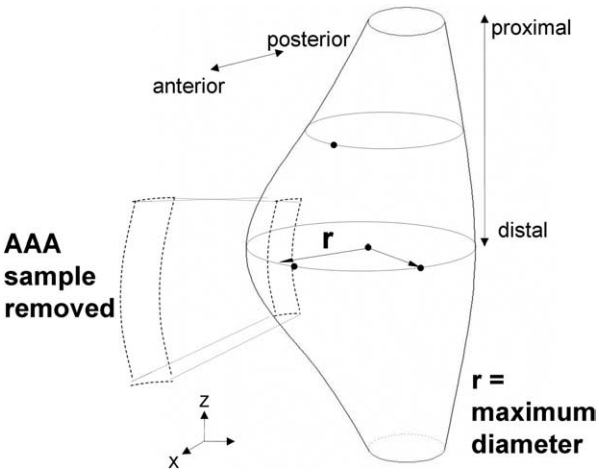

Fig 1. The location of harvest for the abdominal aortic aneurysm *(AAA)* tissue is indicated on a schematic representation of an aneurysm.

rity is unable to withstand the mechanical load caused by the intraluminal blood pressure. It has been suggested that elastin loss may cause the vessel to enlarge, whereas collagen degradation may initiate wall rupture.[4,18,19] Furthermore, the concomitant action of different MMP enzymes is seemingly needed to achieve aneurysmal wall degradation.[5,19] Despite these recent studies, the exact mechanisms that cause rupture are still unknown.

In this study, we evaluated and compared the biomechanical properties of AAA wall tissue specimens obtained from patients who experienced AAA rupture with that of those who received elective repair. We looked at intrinsic properties of the aneurysm tissue by performing mechanical tests on harvested pieces with standard techniques used in material characterization.

MATERIALS AND METHODS

Human aortic tissue specimens. All human aortic tissue specimens were obtained according to the guidelines of our institutional review board. Segments of AAA were obtained fresh from the operating room from patients undergoing surgical repair. The specimens were all taken from the same area located across the midline on the anterior surface of the aneurysm at the point of maximum diameter (Fig 1). The aneurysm diameter was recorded from patient charts as assessed from computed tomographic scans. No bias to AAA patient selection was made with respect to age or sex. All tissue specimens were placed in saline, refrigerated at 4°C, and tested within 48 hours of procurement.[20] Age and sex as reported in the patient's clinical chart were collected for all specimens.

Tensile testing. Rectangular specimens (approximately 2.5 cm × 7 mm) were cut in the circumferential orientation with respect to the intact aorta. The specimen width and thickness were measured for each specimen in a noncontacting fashion with a laser micrometer (Beta LaserMike, Inc, Dayton, Ohio), and length was measured with a manual caliper. The tissue specimens were placed in a previously described uniaxial tensile testing system[21] and continuously wetted with saline solution at 37°C. After a short thermal equilibration period, the specimen was stretched until failure (rupture) of the tissue was reached, as the force was measured continuously. Corresponding deformation was calculated from the known strain rate of 8.5%/min, data acquisition rate (1 Hz), and specimen length previously described.[21] A representative stress-stretch curve obtained from the tensile tests is shown in Fig 2.

Data analysis. The Cauchy stress was calculated as the applied force normalized by the deformed cross-sectional area, and stretch was calculated as the deformed length normalized by the original length of each specimen (see Raghavan et al[21] for details). The maximum tangential modulus (TM_{max}) was taken as the maximum slope of each stress-stretch curve; the ultimate tensile strength (UTS) was taken as the peak stress obtained before specimen failure; and the ultimate stretch (UStr) was taken as the peak stretch ratio at failure (Fig 2). A custom routine written in Mathematica (version 5.0; Wolfram Research Inc, Champaign, IL) was used to calculate the average tissue tangential modulus (TM_{avg}) as the average of all tangential moduli computed by using a fixed window size of data points on the stress-stretch curve. The ratio between the maximum and average tangential modulus was calculated for each curve (TM_{max}/TM_{avg}) to provide a quantitative indication of the nonlinearity of the stress-stretch curve. That is, as the ratio approaches the value of 1.0, TM_{avg} approaches a value equal to TM_{max}, thus indicating that the stress-stretch curve is close to linear. Conversely, if the ratio is much less than 1.0, the curve is highly nonlinear. In addition, another tangential modulus (TM_{100}) was calculated at the stress predicted by the law of Laplace corresponding to a pressure of 100 mm Hg:

$$\sigma_{100} = \frac{PD}{2t},$$

where P is pressure, D is the maximum diameter of that particular aorta and t is the undeformed thickness of the specimen. All parameters used in the statistical analysis are reported in Fig 2.

Statistical methods. The statistical package SigmaStat 3.0 (SPSS Inc, Chicago, Ill) was used for statistical analysis. A multiple t test procedure was considered for the two groups of rAAA and elective AAA (eAAA) specimens. A total of eight t tests were performed to compare differences in age, diameter, wall thickness, UTS, UStr, TM_{max}, TM_{max}/TM_{avg}, and TM_{100} between the two groups with a familywise significance level set to $\alpha = .05$. As is standard practice in multiple testing, the appropriate significance level at which each of the planned tests was to be conducted was determined through the Bonferroni correction, and the value of significance level to be used in each test was set to $\alpha' = \alpha/8 = .006$.

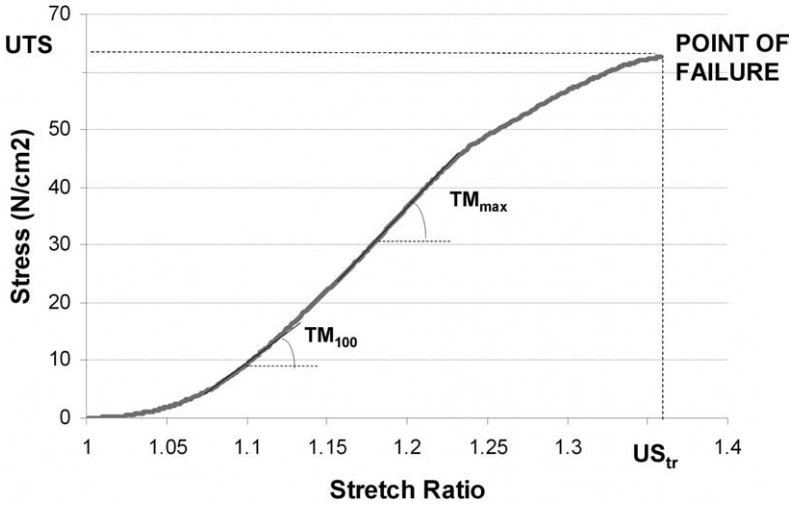

Fig 2. Stress-stretch curve for one generic tensile test. *UTS,* Ultimate tensile strength; TM_{max}, maximum tangential modulus; TM_{100}, tangential modulus corresponding to a pressure of 100 mm Hg; *UStr*, ultimate stretch.

Table I. Parameters used in the statistical analysis

Variable	*Description*
Age	Age of the patient at the time of surgery
Diameter	Maximum diameter of the aneurysm
Wall thickness	Thickness of the sample
TM_{max}	Maximum slope of the stress-stretch curve (Fig 2)
TM_{max}/TM_{avg}	Ratio between the maximum and average slope of the stress-stretch curve (indicates the nonlinearity of the stress-stretch curve: close to 1, linear; close to 0, nonlinear)
TM_{100}	Slope of the curve at the stretch corresponding to 100 mm Hg (Fig 2)
UTS	Ultimate stress value at rupture (Fig 2)
UStr	Ultimate stretch ratio at rupture (Fig 2)

TM_{max}, Maximum tangential modulus; TM_{avg}, average tissue tangential modulus; TM_{100}, tangential modulus corresponding to a pressure of 100 mm Hg; *UTS,* ultimate tensile strength; *UStr,* ultimate stretch.

The χ^2 test of statistical significance was used to test bivariate tables, such as the male vs female population of patients. Spearman rank order correlation coefficients were used to test correlations among all variables for all aneurysm specimens (AAAs and rAAAs).

To take into account the effect of harvesting multiple specimens from the same patient and to evaluate whether the results might change if only one value for each parameter was considered for each patient, all statistical analyses were performed by first considering all specimens tested and then averaging values from multiple specimens obtained from the same patient to yield one value per patient. Data are reported as mean ± SEM.

RESULTS

Twenty-six eAAA specimens were obtained from 16 patients (aged 73 ± 3 years; AAA diameter, 7.0 ± 0.5 cm). Thirteen rAAA specimens were resected from nine patients (aged 72 ± 3 years; P = not significant; AAA diameter, 7.8 cm ± 0.5; P = not significant) during repair of their rAAA. Most AAA patients were male (12/16 [60%] for AAAs and 8/9 [80%] for rAAAs; χ^2 = not significant), which is consistent with findings of other reported studies.[22]

Table II. Patient data and results for eAAA and rAAA specimens

Variable	*eAAA specimens*	*rAAA specimens*	P *value*
Age (y)	74 ± 2	73 ± 2	.76
Diameter (cm)	7.0 ± 0.5	7.8 ± 0.6	.34
Wall thickness (mm)	2.5 ± 0.1	3.6 ± 0.3	<.001*†
TM_{max} (N/cm^2)	315 ± 69	202 ± 32	.27
TM_{max}/TM_{avg}	0.53 ± 0.01	0.59 ± 0.02	.13
TM_{100} (N/cm^2)	235 ± 22	214 ± 36	.6
UTS (N/cm^2)	82 ± 9	54 ± 6	.04†
UStr	1.5 ± 0.04	1.6 ± 0.09	.4

Data are mean ± SEM.

TM_{max}, Maximum tangential modulus; TM_{avg}, average tissue tangential modulus; TM_{100}, tangential modulus corresponding to a pressure of 100 mm Hg; *UTS,* ultimate tensile strength; *UStr,* ultimate stretch ratio; *eAAA,* elective abdominal aortic aneurysm; *rAAA,* ruptured abdominal aortic aneurysm.

*Significant difference after Bonferroni correction.

†Significant difference with significance level set to $\alpha = .05$.

A significant difference was noted in wall thickness between eAAA and rAAA: 2.5 ± 0.1 mm vs 3.6 ± 0.3 mm ($P < .001$; Table II). The tensile strength of the rAAA tissue was found to be lower than that for the eAAA group (54.2 ± 5.6 N/cm^2 vs 82.9 ± 9.1 N/cm^2, respectively; $P = .04$; Table II). However, when the Bonferroni correction for multiple tests was applied to the significance level and the corresponding $\alpha = .006$

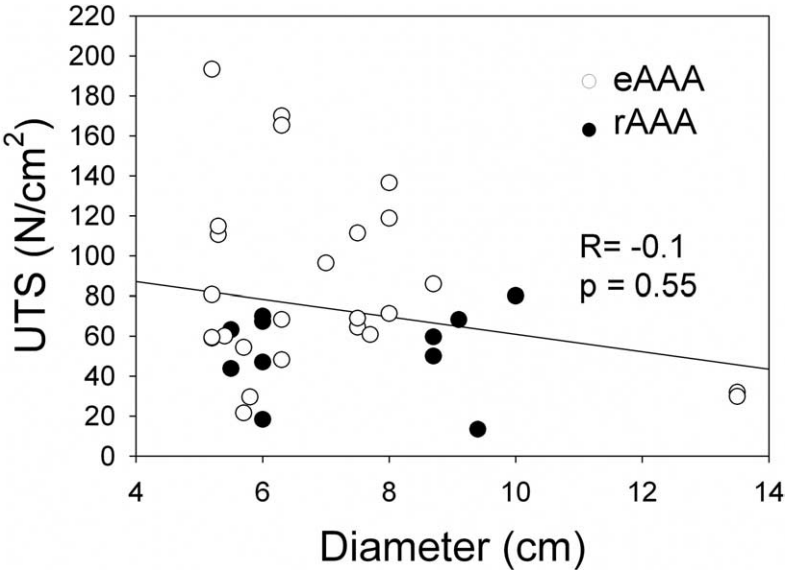

Fig 3. Correlation between the diameter of the aneurysm and the ultimate tensile strength *(UTS)*. The Spearman correlation coefficient showed no statistical significance ($P = .55$). The regression line is shown for all data in the plot. *eAAA,* elective abdominal aortic aneurysm; *rAAA,* ruptured abdominal aortic aneurysm.

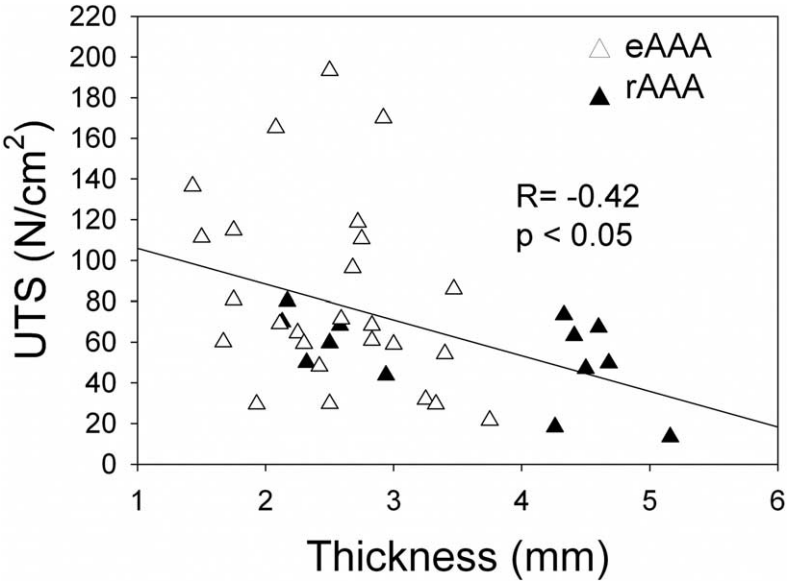

Fig 4. Correlation between tissue thickness and ultimate tensile strength *(UTS)*. The regression line is shown for all data in the plot. *eAAA,* elective abdominal aortic aneurysm; *rAAA,* ruptured abdominal aortic aneurysm.

was used, the test was nonsignificant. No difference was noted between the two groups in terms of UStr (1.54 ± 0.04 vs 1.60 ± 0.09; $P = .9$). TM_{max} and TM_{100} were not significantly different between the two groups, although both were lower on average for the rAAA group (TM_{max}: 277 ± 36 N/cm^2 for eAAA vs 202 ± 32 N/cm^2 for rAAA, $P = .19$; TM_{100}: 235 ± 22 N/cm^2 for eAAA vs 214 ± 36 N/cm^2 for rAAA; $P = .6$; Table II). Conversely, TM_{max}/TM_{avg} was higher, on average, for the rAAA group. All comparisons were performed by averaging data from specimens obtained from the same patient to yield a single value for each patient, and the results showed no difference with respect to what was found by considering each specimen separately.

No correlation was found between UTS and diameter ($R = -0.1$; $P = .55$; Fig 1) or between UTS and age ($R = 0.13$; $P = .44$). UTS, however, had a positive correlation with TM_{max} ($R = 0.76$; $P < .01$) and a weak negative

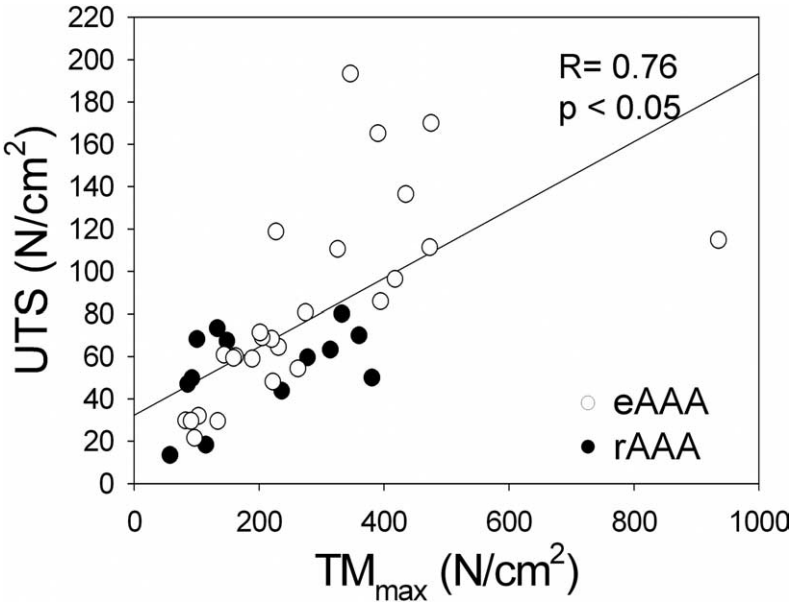

Fig 5. Correlation between maximum tangential modulus *(TM_{max})* and ultimate tensile strength *(UTS)*. The regression line is shown for all data in the plot.

correlation with wall thickness ($R = -0.42$; $P < .01$) (Abstract) and (Figs 3-5).

DISCUSSION

In this study, we compared the biomechanical properties of rAAA vs eAAA tissue. We found that tensile strength was on average lower for rAAA tissue, which also had significantly thicker walls than the eAAA tissue specimens (Table II). The various modulus values considered here showed no significant difference between these two groups (Table II). These results are consistent with a previous study that compared the in vivo stiffness values of eAAA vs rAAA.[23] Our results also showed a significant correlation between ultimate tissue strength and tissue stiffness (Fig 5), whereas no correlation was found between ultimate tissue strength and maximum AAA diameter (Fig 3).

It is well known that extensive extracellular matrix changes are present within the AAA wall,[24,25] and these are believed to be associated with inflammatory cell infiltration and MMP activity.[26-28] Petersen et al[28] studied the presence and activation of MMP-2 and MMP-9 in medium rAAAs (5-7 cm) and large eAAAs (>7 cm). They found that MMP-9 was significantly higher in rAAA than eAAA tissue but that MMP-2 was significantly higher in eAAAs. Moreover, MMP-9 was negatively correlated with diameter, whereas MMP-2 was positively correlated with diameter. This suggests that MMP-2 may be involved in aneurysm enlargement, whereas MMP-9 may be involved in aneurysm rupture. Wilson et al[29] demonstrated a positive correlation between tissue elastolytic activity and arterial distensibility in an aneurysm. Because the strength of an aneurysm has been linked to the continued loss of structural integrity of the elastin and collagen network, these data would suggest that a reduction in AAA wall strength is accompanied by an increased compliance. Indeed, in a subsequent study, Wilson et al[30] showed that AAAs that went on to rupture tended to be more distensible compared with those that did not rupture during follow-up. These findings were corroborated by our direct measurements of aortic stiffness ex vivo. We found that both TM_{max} and TM_{avg} were positively correlated with the ultimate strength, thus suggesting that AAAs that are less stiff are weaker and therefore more prone to rupture.

It is generally believed that the thickness of an AAA diminishes as the diameter increases, as would the thickness of a cylinder (or a sphere) while it enlarges under the effect of internal pressure. However, AAAs enlarge with time, and remodeling plays an important role in aneurysm progression. Although some AAA tissue walls do present, as expected, as very thin specimens, we found that, on average, the thickness of AAA tissue was 2.9 mm. Measurements performed with a manual caliper may underestimate thickness because the value is taken while the specimen is compressed. To avoid this problem, we used an optical method (laser) to measure thickness. There is variability in thickness among specimens from the same patients, and this variability is hard to measure because only two specimens per patients were obtained at most. When comparing eAAAs vs rAAAs, we found a significant difference in the specimen thickness, which may be due to the documented increased inflammatory infiltration found in the latter.[31]

The procedure by which specimens were collected was standardized, and the surgeon harvested only tissue samples that came from the same area (located axially at the level of the maximum diameter and circumferentially across

the midline on the anterior surface of the AAA). This choice is dictated in part by surgical reasons; in fact, current surgical procedures require that the AAA wall be sutured on top of the prosthesis after AAA content is removed. Our procedure was such that it did not interfere with the standard care of the patient, and, therefore, only tissue from the anterior surface of the aorta (that the surgeon cuts before suturing the aortic wall) was available to be tested. None of the specimens was collected at the site of rupture, which is in general retroposterior. Although our procedure limits the appreciation of the regional variability of mechanical properties in AAA and prevents, for the most part, the rupture site tissue from being harvested, it provides a standardization of the site of harvest and eliminates the location of harvest from the variables to be considered in the statistical analysis.

Recognizing that the aortic wall in the presence of an aneurysm is nonhomogeneous,[32] we concentrated our study on local measures of intrinsic properties of the aortic tissue in the presence of an aneurysm, such as the local stiffness and local thickness, as opposed to global measures, such as the diameter of the aneurysm. As a consequence, we chose to test multiple specimens when available. We found that thickness was inversely correlated with the local strength of the material and that stiffness was directly correlated with strength, even within the same patient. This finding further demonstrates the nonhomogeneity of the aortic wall in the presence of an aneurysm and may imply that there are changes at the local tissue level that change the mechanical properties and the thickness of the wall as the aneurysm progresses.[32]

The use of ex vivo aortic specimens limited our study to patients who received surgical treatment. Therefore, we cannot infer the propensity for rupture of the eAAA patients studied here, which may explain why no significant difference was found between eAAA and rAAA tangential moduli, although a significant correlation was found between the tangential modulus and strength of the tissue. However, our method allows a direct assessment of the mechanical properties of the tissue, as opposed to only estimation, as with in vivo measurements. Furthermore, in vivo measurements can not assess tissue strength; only destructive ex vivo methods can be used for that assessment.

A widely accepted indicator for risk of aneurysm rupture is the maximum transverse diameter,[33,34] but our results suggest that the AAA wall strength is not related to the maximum transverse diameter. Rupture is the final event that occurs when the tissue stress exceeds the tissue ability to sustain stress (tissue strength). Diameter is definitely a factor in wall stress in any tubular or spherical structure, because wall stress increases with diameter. Therefore, because stress is ultimately what causes rupture, it is correct to infer that larger aneurysms are more prone to rupture. Our results concern large aneurysms; in fact, there was no significant difference between the eAAA and rAAA groups in terms of diameter, and the average diameter was 7 cm. Although it is accepted that a large aneurysm is at greater risk of rupture than a smaller one, we show that factors other than diameter only could be considered and used to better discriminate the risk of rupture and could explain why, in some cases, the diameter rule fails. The recent advances in diagnostic images provide noninvasive means to estimate the stiffness of an artery and could therefore be used to add one diagnostic piece of information to the clinical decision.

In conclusion, our data suggest that aneurysm rupture is associated with aortic wall weakening, but not with wall stiffening. Moreover, our results suggest that AAA wall strength, in large aneurysms, is not related to the maximum transverse diameter. Rather, wall thickness or stiffness may be a better predictor of AAA rupture.

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AUTHOR CONTRIBUTIONS

Conception and design: E.S.D.M, N.G, M.S.M, D.A.V
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Statistical analysis: E.S.D.M
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INVITED COMMENTARY

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The clinical predictors of abdominal aortic aneurysm (AAA) expansion and rupture have recently been better delineated in randomized trials, but the dominant factor for rupture risk remains aortic diameter. Indeed, an aortic diameter of >5.5 cm is the cutoff for risk benefit-ratio for operative repair.[1] Many large AAAs do not rupture, and it would be ideal to have additional patient-level information that might better predict the risk of an AAA rupture. It is now clear from recent sophisticated computed tomography imaging studies that geometry and wall stress play a significant role in local aortic wall stress. For example, significant aortic tortuosity and asymmetric geometry confer a greater AAA rupture risk.[2]

The study by Martino et al highlights a correlative measure of aortic wall strength and thickness in humans. Specifically, comparison was made of wall thickness and tensile strength between ruptured AAA and elective AAA tissue. The authors show that mean aortic wall thickness was greater in ruptured compared with nonruptured tissue. Further, tensile strength of the ex vivo specimen was lower in ruptured aortic tissue than nonruptures ($P = .04$, noncorrected). Although this study is limited by its small patient number, lack of a normal aorta control group for biomechanical parameters and imaging, and heterogeneity of specimens, this study is intriguing and hypothesis generating.

While it is not counterintuitive that ruptured AAA tissue specimens may have weaker tissue than intact AAAs, it is important to note that the tissue analyzed was not from the site of rupture but the anterior wall. Thus, patients with any given size AAA may have intrinsically weaker walls throughout the aorta. Supportive of this, but not necessarily intuitive, is the finding that ruptured AAAs have thicker walls. This is consistent with greater inflammatory processes in these aortas. The molecular pathologic remodeling process was not evaluated in this study, but likely involves leukocyte-driven matrix breakdown via matrix metalloproteinase activity. Complementary studies with gene array and single nucleotide polymorphism analysis hold further promise to elucidate these mechanisms.

The current paper adds to our understanding of end-stage AAA pathophysiology in humans. These data require further validation in larger patient imaging studies, particularly to determine a threshold thickness of aortic wall as a prognostic variable. In addition to the well known risk factors of AAA growth including size, smoking, diastolic, hypertension, and emphysema, we should now also consider the finer points of imaging analysis.

REFERENCES

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