Abdominal aortic aneurysm: A general defect in the vasculature with focal manifestations in the abdominal aorta?

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Purpose: It has been suggested that abdominal aortic aneurysms (AAA) develop as a result of an alteration in the systemic connective tissue metabolism. This might change wall mechanics and diameter, not only in the AAA but also in the rest of the vascular system. This hypothesis was tested by studying the mechanical properties of AAAs as well as the common carotid artery (CCA) in the same patient population.

Methods: AAA and carotid artery stiffness (β) was studied in 121 individuals (101 men, 20 women) who were admitted for elective repair of AAA. Stiffness (β) was calculated from diameter and pulsatile diameter change determined noninvasively from an ultrasonic echo-tracking system and blood pressure obtained by the auscultatory method. The results were compared with those of healthy individuals of corresponding age and gender published elsewhere.

Results: The stiffness of the AAA was increased in both men and women ($p = 0.0001$). The increase was more pronounced in women compared with men ($p = 0.0003$) to a mean of 435% and 189% of the normal predicted values, respectively. In the CCA, the stiffness was increased in men ($p = 0.027$) and in women ($p = 0.0001$) to a mean of 131% and 149% of the normal predicted values, respectively. A significant correlation between stiffness in the aneurysm and in the carotid artery was seen ($p = 0.0031$). The carotid diameter was unchanged in men ($p = 0.924$) and in women ($p = 0.070$) if adjusted for the difference in blood pressure between the individuals with AAAs and control subjects. There was no correlation between stiffness and diameter of the aneurysm in men ($r = 0.16$, $p = 0.119$) nor in women ($r = 0.12$, $p = 0.598$).

Conclusions: This investigation demonstrated altered mechanical properties of the aneurysmal wall as well as in the CCA in individuals with AAAs. The normal age- and gender-related differences seen in the healthy aorta and CCA vanished. The results suggest that AAA is a generalized process of the vasculature with focal manifestation in the abdominal aorta. (J Vasc Surg 1997;26:247-54.)

The etiologic mechanism of abdominal aortic aneurysms (AAAs) is probably multifactorial and is no longer regarded as a random variant of atherosclerosis that occurs at a weakened site of the aortic wall. There are genetic,[1,2] anatomic,[3,4] mechanical,[5] biochemical,[6-11] and acquired (smoking)[12] factors that contribute to the development of AAAs and to ultimately rupture. From a mechanical point of view, AAAs could be regarded as a case of material failure, where the applied load is excessive, the tensile strength of the material is inadequate, or a combination of both. The mechanical properties of the arterial wall are mainly determined by the matrix components of the wall. These are predominantly elastin, collagen, and smooth muscle cells. Thus changes in the composition and structure of the wall will alter its mechanics.

Earlier investigations have shown an increased stiffness of the wall in AAAs, both in vitro[6,13] and in vivo,[14,15] but did not address the issue of whether there were gender-related differences as observed in the healthy aorta.[16,17]

Because it has been suggested that aneurysms develop as a result of an alteration in systemic con-

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Table I. Demographic data of individuals with aneurysms

	Men	*Women*
No.	101	20
Age (yr)	71 ± 7	68 ± 9
Age ranges (yr)	55-83	49-84
Weight (kg)	76 ± 12	60 ± 10
Height (cm)	177 ± 6	164 ± 7
AAA diameter (mm)	56 ± 11	54 ± 12
AAA diameter range (mm)	38-93	38-80
Hypertension (n)	41	10
Diabetes (n)	7	3

nective tissue metabolism,[18] this might change wall mechanics and diameter not only in the AAA but also in the rest of the vascular system. An associated generalized dilating diathesis has been proposed, but the studies that confirm this are few.[19,20] Furthermore, studies of wall mechanics are lacking.

The aim of the present investigation was to study the mechanical properties of the aneurysmal aorta and assess whether there are any gender differences, and to study the mechanical properties of the common carotid artery (CCA) as an indicator of a general arterial defect in individuals with AAAs. These results were compared with those of a healthy age- and sex-matched reference population published elsewhere.[15,16,21]

METHODS

The investigation was performed on 121 individuals (101 men, 20 women) who were admitted for elective repair of an AAA from 1991 to 1996. Individuals who had previously undergone carotid artery surgery or had a stenosis of the common carotid artery (CCA), as well as individuals with cardiac arrhythmias that made it impossible to obtain ultrasonic pulsatile diameter changes of adequate quality, were excluded. Each subject gave informed consent to the studies. The results from the subjects with AAAs were compared with the results from the previous published healthy reference population regarding normal diameter and wall mechanics of the abdominal aorta and carotid artery.[15,16,21] The error of measurement was evaluated in 30 of the individuals with AAAs. The investigation was approved by the Ethics Committee, Lund University, Sweden.

Echo-tracking ultrasonography for measurements of wall mechanics. The method for calculation of vessel wall stiffness and noninvasive monitoring of pulsatile diameter changes in the distal abdominal aorta has been described previously.[17] Briefly, we use an electronic echo-tracking instrument (Diamove, Teltec AB, Lund, Sweden) interfaced with a real-time ultrasound scanner (EUB-240, Hitachi, Tokyo) and fitted with a 3.5 MHz (aorta) or 5 MHz (carotid artery) linear array transducer. All examinations were performed with the subjects in the supine position and after at least 15 minutes of rest. The AAAs was insonated from the epigastrium. Measurements were made at the maximum anterior-posterior diameter of the aneurysm. The CCA was insonated from the neck behind the sternocleidomastoid muscle and visualized as proximal as possible to the truncus brachiocephalica to exclude any proximal stenosis. Differences in indirect blood pressure between the left and right arm were excluded before the investigation. Measurements were made 2 cm proximal to the bifurcation with the transducer held against the skin with a minimum of pressure to avoid distortion of the configuration of the artery. If plaques were present in the bifurcation, measurements were made proximal to these in a disease-free area. The arteries were visualized in a longitudinal section on the real-time image. Two electronic markers, each representing one tracking gate, were aligned with and locked on the echoes from the posterior interface of the anterior wall and the anterior interface of the posterior wall, respectively. The echo-tracker measures the distance between the vessel walls perpendicular to the longitudinal axis of the vessel. A data acquisition system, containing a personal computer type 386 (Express, Tokyo) and a 12-bit analogue-to-digital converter (Analogue Devices, Norwood, Mass.), was included for on-line monitoring of pulsatile vessel diameter. In the system used for the study, the smallest detectable movement is 7.8 μm.[22,23] The repetition frequency of the echo-tracking loops is 870 Hz, and the consequent time resolution is approximately 1.2 milliseconds.

The wall mechanics can, in general terms, be described as distensibility or stiffness. Distensibility means the ease with which the wall is distended, whereas stiffness is the inverse.

Calculations of various distensibility indexes are based on the pressure/diameter relationship of the arterial wall, which is nonlinear, with a more distensible part at smaller than at larger distention.[17] This means that pressure has impact on the obtained distensibility value, that is, on which part of the pressure/diameter curve the systolic/diastolic diameter variation is measured. This must be taken into account when different study populations with different blood pressures are compared. To overcome the problem with pressure dependence when calculating distensibility, Hayashi et al.[24] constructed a relation

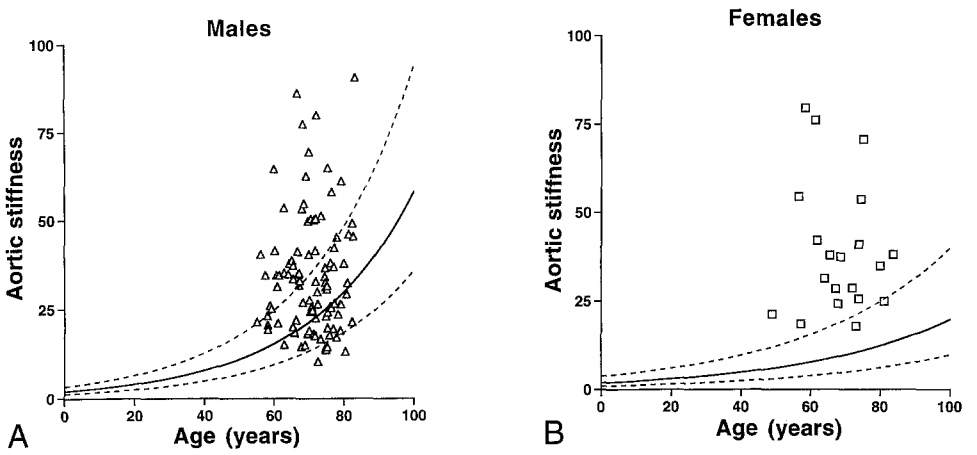

Fig. 1. Stiffness (β) of abdominal aortic aneurysms in men (**A**) and women (**B**) compared with normal aorta in reference population. *Solid line* represents mean, and *dotted lines* represent upper and lower 95% CI for reference population. Stiffness of aneurysm was increased in both men and women ($p = 0.0001$), respectively.

that was less pressure-dependent. It was later modified and applied in vivo by Kawasaki et al.[25] and called stiffness (β). The reduced pressure dependence of stiffness (β) has also been confirmed by our studies,[15,16] and it is therefore used in this study.

$$\text{Stiffness } (\beta) = \frac{\ln (\text{P systolic}/\text{P diastolic})}{(\text{D systolic} - \text{D diastolic})/\text{D diastolic}}$$

In the equation, P systolic (mm Hg) and P diastolic (mm Hg) are the maximum systolic and end-diastolic blood pressure levels measured, respectively. D systolic (mm) and D diastolic (mm) are the vessel diameters that correspond with those levels. Mean arterial blood pressure was taken as the diastolic pressure plus one third of the pulse pressure. Stiffness is a nondimensional index.

Arterial blood pressure was measured by the auscultatory method with a sphygmomanometer on the left arm immediately after measurement of the pulsatile diameter change. Brachial cuff pressure was approximated as systemic blood pressure in the abdominal aorta and common carotid artery. The pressure in the blood stream of the aneurysm was assumed equal to the transmural pressure of the aneurysmal wall.[26]

Ideally, arterial pressure and pulsatile diameter change should be measured at the same site where stiffness (β) is estimated. Brachial arterial cuff pressure, however, is more accessible and was therefore approximated as the blood pressure in the abdominal aorta and in the common carotid artery. This assumption could be questioned because pulse pressure increases from the aorta towards the periphery. This is a result of wave reflection from the periphery, which augments the peak of pressure wave in peripheral arteries close to the reflection site. This has been described to occur mainly in young and healthy individuals. With increasing age, however, the pulse wave velocity increases so that the pressure wave augmentation also occurs in central arteries. Thus these differences in central and peripheral pressures are reduced and disappear in middle-aged and elderly persons.[27] Further, pressure measured by the auscultatory method in the brachial artery rather than direct in the abdominal aorta in the middle-aged and elderly show no age or gender differences.[17] However, pulse pressure is systematically underestimated by approximately 16%, leading to underestimation of β by 15% to 20%.[17] Thus we believe that our assumptions regarding pressure are acceptable.

Each individual was examined three times with calculation of β from the corresponding diameter, pulsatile aortic diameter change, and blood pressure. The interobserver and intraobserver variability of pulsatile diameter changes in the healthy aorta and CCA with the system used was 10% to 15%, and compiled with blood pressure measurements in calculating β the variability slightly increased to 15% to 20%.[28] Regarding the variability for the aneurysm, please see the Results section.

Statistics. Analyses of nonlinear regression with 95% confidence intervals for individual prediction

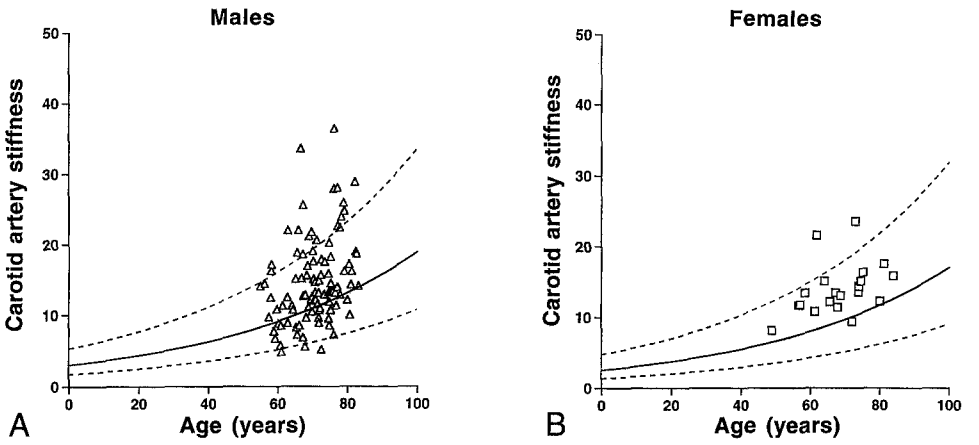

Fig. 2. Stiffness (β) in common carotid artery in men **(A)** and in women **(B)** with AAAs compared with normal common carotid artery in reference population. *Solid line* represents mean, and *dotted lines* represent upper and lower 95% CI for reference population. Stiffness was increased in both men ($p = 0.0272$) and women ($p = 0.0001$).

were used to define the normal ranges for stiffness, diameter, and blood pressure in the healthy reference population according to age and gender. The results from the male and female subjects with AAAs were compared with these confidence intervals. The analysis of covariance was then used to compare stiffness, diameter, and blood pressure from the subjects with AAAs with those of the reference population. Differences between groups were adjusted for age and blood pressure. The results were also expressed as a percentage of individually predicted values. A multiple linear regression model was used to analyze the correlation between stiffness of the aneurysm and its diameter. The error of measurement in the aneurysms was evaluated according to Bland and Altman,[29] and the coefficient of variation was calculated. Differences between groups were assessed using the Mann-Whitney U test. The statistical package used was SAS system (SAS Institutes, Cary, N.C.).

A p value less than 0.05 was considered significant. Data are presented as the mean value ± SD, if not otherwise indicated.

RESULTS

Data on age, sex, diameter, and other demographic data on the individuals with aneurysms are compiled in Table I. Hypertension was defined as requiring antihypertensive medication. Diabetes was defined as requiring insulin, antidiabetic medication, or diet. Smoking was defined as smoking or stopped smoking less than 1 month. Data on the healthy reference population regarding normal values of the aorta and common carotid artery have been given earlier.[15,16,21]

Error of measurement of the ultrasonic echotracker. The error of measurements for pulsatile diameter change in the AAAs was 0.0045 mm (95% confidence interval [CI], −0.0098 to 0.0078 mm), and the coefficient of variation (CV) was 22%. The corresponding values for β were 5.7 (95% CI, −9.6 to 12.7) and the CV 18%.

Stiffness of the aneurysm. Fig. 1 shows that β of the AAAs was increased in both men and women compared with the reference population ($p = 0.0001$). This was true also when adjusted for differences in blood pressure between individuals with AAAs and control subjects. In the men with AAAs there was wide range of stiffness from normal values to clearly above the upper CI limit. Approximately one third of the men had values above, in contrast to the women, almost all of whom had values above the upper CI limits. The increase in stiffness was more pronounced in women compared with men ($p = 0.0003$) to a mean of 435% and 189% of the normal predicted values, respectively. When the stiffness values for men (34.3 ± 16.7) were compared with those in the women (39.4 ± 18.6), no significant difference was observed ($p = 0.213$), and thus the normal gender-related difference vanished.

Stiffness in the common carotid artery. Fig. 2 shows that stiffness β in the CCA was increased in both men ($p = 0.014$) and women ($p = 0.0001$) compared with AAAs compared with the reference population. When the statistical analysis was adjusted

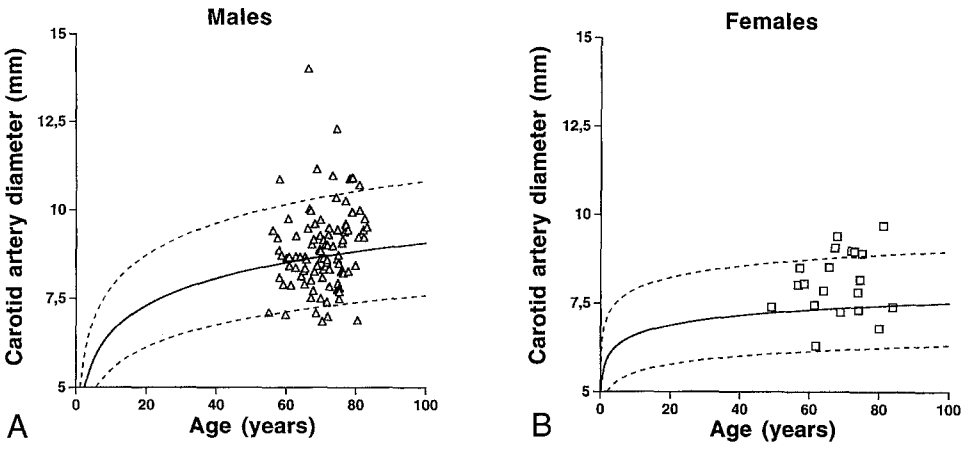

Fig. 3. Diameter of common carotid artery in men **(A)** and women **(B)** with AAAs compared with normal common carotid artery. *Solid line* represents mean, and *dotted lines* represent upper and lower 95% CI for reference population. Diameter was essentially unaltered in men (p = 0.9239). In women, diameter was slightly increased, but if adjusted for difference in blood pressure increase is not significant (p = 0.0696).

for the difference in blood pressure between the individuals with AAAs and control subjects, the corresponding p values were p = 0.027 (men) and p = 0.0001 (women). The carotid stiffness values in the men and in the women were a mean of 131% and 149%, respectively, of the predicted normal values. When the stiffness values in the men (14.8 ± 6.2) were compared with those in the women (14.0 ± 3.8) no significant difference was observed (p = 0.966), and thus the normal gender-related differences vanished.

Diameter of the common carotid artery. Fig. 3 shows the diameter of the CCA in men and women with AAAs. It was essentially unaltered in men with AAAs (p = 0.924) compared with the reference population. In women the diameter was increased (p = 0.005). However, when the statistical analysis was adjusted for difference in blood pressure between the individuals with AAAs and control subjects, the increase in diameter in women became insignificant (p = 0.07). The diameter of the common carotid artery in men and in women was a mean of 101% and 109% of the predicted normal values, respectively.

Correlation between aneurysm diameter and stiffness of the aneurysm. There was no correlation between the diameter and the stiffness of the aneurysm in men (r = 0.16; p = 0.119) or in women (r = 0.12, p = 0.599) adjusted for age.

Correlation between stiffness in the aneurysm and the carotid artery. There is a correlation between the stiffness in the aneurysm and carotid artery adjusted for age (r = −0.27, p = 0.0031).

Blood pressure. The mean arterial blood pressure in the men was a mean of 107% of the predicted normal value (p = 0.022), and in the women the mean arterial pressure was a mean of 116% of the predicted normal value (p = 0.0001). Systolic pressure showed no difference compared with the reference population in men (105% of predicted normal value; p = 0.073), but in women it was increased, with a mean of 123% of the predicted value (p = 0.0001). Diastolic pressure was increased in men, with a mean of 109% of the predicted normal value (p = 0.0002), and in women, with 109% of the predicted normal value (p = 0.007) compared with the reference population.

DISCUSSION

The present investigation demonstrates an alteration of the mechanical properties of the aneurysmal aorta as well as in the common carotid artery in individuals with AAAs. The results suggest that AAA is a generalized process in the vasculature with focal manifestations in the abdominal aorta.

The mechanical properties of large arteries are mainly determined by the matrix components of the wall. These are predominantly elastin, collagen, and smooth muscle cells. Elastin and collagen determine the passive mechanical properties,[30] whereas smooth muscle cells produce extracellular matrix and have the potential to modulate wall mechanics.[26,31] The latter function is not of any practical importance in the aorta[26,32,33] and probably neither in a large elastic artery as the common carotid artery.[26] Thus it is clear

that the collagen-to-elastin ratio is the principal determinant of wall mechanics.[26,34,35]

In healthy arteries, stiffness increases with age as a result of an increase in the collagen-to-elastin ratio of the walls, with men having stiffer arteries than women.[16,21] Further, these age- and gender-related differences are most marked in the aorta. Thus changes in the composition and in the structure of the arterial wall will alter its mechanics.

The wall of the aneurysm was stiffer in both men and women compared with the normal aortic wall in the reference population (Fig. 1). However, in the men there was a wide range of stiffness values from normal to clearly above the upper CI limit in contrast to the women, where almost everyone had values above CI limits. The variation in result could only to a small part be attributed to the variability in the method because the coefficient of variation for β was 18%. The change of wall mechanics from normal to aneurysmal aorta in women is more marked compared with men ($p = 0.0003$). Furthermore, in the AAAs the age- and gender-related difference in wall mechanics of the healthy aorta[16,17] vanishes.

Previous investigations in vitro[6,13] and in vivo[14,15] have also shown an increased stiffness of AAAs but have not reported gender-related changes in aneurysmal wall mechanics.

The alteration in the mechanical properties of the aneurysms may be related to the changes in structure and composition. Histologic examinations of AAAs reveals a disrupted thin media with a lack of elastic fibers, fibrosis, and thickening of the adventitia and neointima.[11] The elastin content is decreased,[6,10,13,14] whereas collagen content has been reported as increased[10,11,13,36] or unchanged.[37] These changes may be a result of the reported increased proteolytic activity of collagenase[7,36] and elastase,[38,39] whereas at the same time lower antiprotease activity has been detected.[40] Together these factors will raise the collagen-to-elastin ratio and alter the wall structure, resulting in changed wall mechanics.

The mechanical properties of the CCA were also altered in both men and women with an increase in stiffness (β; Fig. 2). As in the AAAs, the gender difference in wall mechanics seen in the normal reference population[21] also vanished.

A tentative explanation to our findings is that the matrix components of the vascular wall are altered. This might be a result of the fact that individuals with AAAs have a general defect of connective tissue in the vasculature. Data from other groups for comparison are at the moment not available. In Marfan syndrome, a general connective tissue disease with a defect in fibrillin that causes abnormal elastic fibers,[41] vascular wall mechanics are altered.[42] In analogy a significant correlation between AAA and carotid stiffness ($r = -0.27$, $p = 0.0031$) was found. The lack of a stronger correlation might be a result of the fact that when the aorta starts to become aneurysmal several other factors accentuate the degeneration and alter the collagen/elastin ratio, and thus wall mechanics. The aneurysmal aorta represents probably the end stage of aortic wall degeneration.

Several factors, such as smoking, diabetes, and atherosclerosis, may affect the outcome of our measurements. Many individuals with AAAs are heavy smokers. However, a recent study by us has shown that the chronic effects of heavy cigarette smoking on wall mechanics only gives minor changes on stiffness (unpublished data).

Diabetes might be a confounding factor that increases wall stiffness. However, only a few of the individuals with AAAs had diabetes, so this does not affect the main outcome.

Atherosclerosis is common in individuals who have AAAs and might be another factor involved in the stiffening of the arterial wall. A large number of studies, however, favor the opinion that the increase in wall stiffness is independent of atherosclerosis.[27,43-48] One explanation is that the distribution of atherosclerosis is usually patchy and localized to intima-subintima, whereas wall mechanics are determined by the media. It is possible that the vessel compensates by means of increased distensibility in disease-free areas. Only when calcification is extensive with circumferential plaques the vessel becomes stiffer.[43,48] Thus because our measurements were made in a plaque-free area, we believe that the outcome is not affected by atherosclerosis.

An associated dilating diathesis of the common carotid artery was not found either in men or in women when corrected for differences in blood pressure compared with the reference population (Fig. 3). This is in contrast to Ward,[20] who found a small (0.6 mm) but significant increase in the diameter of the common carotid artery in individuals who had AAAs. However, the data of the patients with AAAs were not adjusted for blood pressure differences compared with the data of the control subjects.

In other peripheral arteries, a general dilating diathesis has been found by Ward[20] as well as by Tilson and Dang.[19] The extreme is represented by the rare and probably special entity of individuals who have diffuse aneurysmal disease and arteriomegaly, as reported by Hollier et al.[49] The investigations by Tilson and Dang[19] and Ward[20] are quite

small, and further investigations have to be conducted to establish the relation between AAA and a general dilating diathesis of peripheral arteries.

It has been proposed that a combination of local hemodynamic factors, as well as factors that affect wall strength (proteolytic activity, antiproteases, genetic factors, inflammation), are needed in the development of AAAs in most cases. Our results suggest that aneurysmal disease is a generalized process with focal manifestations. Is the difference in hemodynamic force acting on the vessel wall in the infrarenal aorta compared with the carotid artery one of the reasons why the infrarenal aorta is a common site for aneurysm formation, whereas this is very rare in the carotid artery? It is known that the largest pulsatile load of any vessel in the body is localized in the infrarenal aortic region, resulting in a local high-pressure zone.[26,50,51]

When addressing the issue of risk of aneurysm rupture, the law by Laplace is commonly discussed. This law describes the relation between intraluminal pressure (p), vessel radius (r), wall thickness (h), and wall tension (T) and is expressed as $T = p$. The tension increases with increasing intraluminal pressure and aneurysm diameter. One would expect that the tension increases and the aneurysm wall becomes stiffer with increasing size of the aneurysm. However, we found no correlation between the stiffness of aneurysm wall and aneurysm size. This corroborates the well-known fact that aneurysms of equal size may or may not rupture, and that even if the size of the aneurysm still remains as the most important predictor of rupture,[52] even small AAAs may rupture.[53]

CONCLUSION

This investigation demonstrates altered mechanical properties of the aneurysmal wall, as well as in the CCA, in individuals with AAAs. The normal age- and gender-related differences seen in the healthy aorta and CCA vanish. The results suggest that AAA is a generalized process of the vasculature with focal manifestation in the abdominal aorta.

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