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The relationship between aortic wall distensibility and rupture of infrarenal abdominal aortic aneurysm

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Objective: **A more accurate means of prediction of abdominal aortic aneurysm (AAA) rupture would improve the clinical and cost effectiveness of prophylactic repair. The purpose of this study was to determine whether AAA wall distensibility can be used to predict time to rupture independently of other recognized risk factors.**
Methods: **A prospective, six-center study of 210 patients with AAA in whom blood pressure (BP), maximum AAA diameter (Dmax), and AAA distensibility (pressure strain elastic modulus [Ep] and stiffness [β]) were measured at 6 months with an ultrasound scan–based echo-tracking technique. A stepwise, time-dependent, Cox proportional hazards model was used to determine the effect on time to rupture of age, gender, BP, Dmax, BP, Ep, β, and change in Dmax, Ep, and β adjusted for time between follow-up visits.**
Results: **Median (interquartile range) AAA diameter was 48 mm (41 to 54 mm), median age was 72 years (68 to 77 years), and median follow-up period was 19 months (9 to 30 months). In the Cox model, female gender (hazards ratio [HR], 2.78; 95% CI, 1.23 to 6.28; *P* = .014), larger Dmax (HR, 1.36 for 10% increase in Dmax; 95% CI, 1.12 to 1.66; *P* = .002), higher diastolic BP (HR, 1.13 for 10% increase in BP; 95% CI, 1.13 to 1.92; *P* = .004), and a decrease in Ep (increase in distensibility) over time (HR, 1.38 for 10% decrease in Ep over 6 months; 95% CI, 1.08 to 1.78; *P* = .010) significantly reduced the time to rupture (had a shorter time to rupture).**
Conclusion: **Women have a shorter time to AAA rupture. The measurement of AAA distensibility, diastolic BP, and diameter may provide a more accurate assessment of rupture risk than diameter alone. (J Vasc Surg 2003;37:112-7.)**

The decision to operate on an asymptomatic abdominal aortic aneurysm (AAA) involves weighing the risks of rupture against those of surgical repair.[1,2] Most surgeons believe that rupture risk is most closely related to maximum diameter. Data from the United Kingdom small AAA trial suggest that elective repair should not normally be considered until maximum diameter exceeds 5.5 cm.[3] However, a significant proportion of ruptured AAAs is less than 5.5 cm. At the same time, it is clear that many patients with larger AAAs die with, rather than of, their aneurysm. A more accurate means of assessing the risk of AAA rupture on an individual patient basis would improve the clinical and cost effectiveness of prophylactic repair. Previous work from our group has suggested that AAA wall distensibility can be reliably measured with an ultrasound scan–based echo-tracking technique[4] and is related to changes in aortic wall structure[5] and to both AAA growth and rupture.[6] The aim of this study was to investigate whether a change in AAA wall distensibility over time is related to rupture risk independently of other recognized risk factors.

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METHODS

Subjects with AAAs not being currently considered for repair were recruited into this prospective, six-center study. Patients were not being considered for AAA repair for one or more of the following reasons: small aneurysm size, comorbidity, or patient unwillingness to consider operative repair. The decision not operate on these patients had been made by the responsible attending surgeon before the patient was approached to take part in this study. The clinical care of the patients in the study was left entirely to the discretion of the attending surgeon and was not influenced in any way by participation in the study. Ethical approval and written informed consent for the study were obtained.

Maximum anteroposterior AAA diameter (Dmax), AAA distensibility (pressure strain elastic modulus [Ep] and stiffness [β]), diastolic and systolic blood pressure (BP), pulse pressure, and mean arterial pressure were collected at baseline and then at least 6 months for a median (interquartile range [IQR]) period of 19 months (9 to 30 months). Brachial artery BP was measured with an automated sphygmomanometer (model 711, Omron Healthcare GmbH, Hamburg, Germany). Dmax and distensibility were mea-

sured with an ultrasound scan–based echo-tracking technique (Diamove, Teltec, Lund, Sweden). The Diamove system has been described in detail previously.[4,6] Briefly, a 3.5-MHz linear array transducer was used to provide a standard real time longitudinal B-scan image of the AAA at the point of Dmax. Cursors locked onto echoes representing the anterior and posterior aortic walls and tracked the movement of both with each cardiac cycle. The longitudinal image was used as experience with the technique and data from formal reproducibility studies indicated that the quality of the data obtained from a longitudinal section was superior to that obtained from a transverse view. At least three pressure-diameter curves were used, together with BP, to determine the Ep and β of the AAA wall at the point of Dmax.

Ep ($10^5 Nm^{-2}$) was defined with the equation:

$$\frac{133.3\ (\text{BP systolic} - \text{BP diastolic})}{(\text{Dmax systolic} - \text{Dmax diastolic})/\text{Dmax diastolic}}$$

β (arbitrary units) was defined by the equation:

$$\frac{\text{natural logarithm (BP systolic/BP systolic)}}{(\text{Dmax systolic} - \text{Dmax diastolic})/\text{Dmax diastolic}}$$

As the AAA wall became stiffer (less distensible), both Ep and β increased.[7-11] The reproducibility of Ep and β has previously been examined.[4] The coefficients of variation of method error for intraobserver variability were 21.2% for Ep and 17.6% for β. Patients with a ruptured AAA were identified with death certificate information from the Information and the Statistics Division of the National Health Service or from hospital records.

Statistical methods. Statistical analysis was carried out with SPSS version 10 and SAS release 6.12 (SAS Institute, Cary, NC).[12,13] Wilcoxon signed rank test was used to compare patient values of BP, Dmax, and distensibility between baseline and last follow-up visit. The Mann-Whitney *U* test was used to compare patients whose aneurysms went on to rupture and those that did not in terms of BP, Dmax, and distensibility at baseline and at last follow-up visit. Measurement of these variables could not be taken at each follow-up visit for every patient, and therefore, only those follow-up visits where measurements could be taken were included in the analysis. For example, for various reasons, 16 patients could not have measurements taken at baseline (13 no waves and three not fit), so data from a subsequent follow-up were used as their baseline visit instead. All 210 patients had information collected on BP, Dmax, and distensibility on at least one occasion and were followed up until a study event (rupture, surgery for AAA, non-AAA related death) occurred or until February 29, 2000. For the univariate analyses, medians and IQRs were quoted. However, because the distributions were skewed, for all variables except age, their natural logarithms were used in the modeling. A Cox proportional hazard regression model[14] was used to determine which factors were significant independent predictors of time to rupture (number of days from baseline to rupture). Those patients whose aneurysms did not rupture had "censored" data (we knew rupture did not occur up to a certain point in time) and were still used in the analysis. The assumption of proportional hazards held when baseline variables were examined. Time-dependent variables were used in the model, which meant that at each follow-up visit, the values for each patient's risk factors changed in the model. It was anticipated that the changes in Dmax, Ep, and β could be important predictors of rupture. However, because Dmax, Ep, and β were not collected at the precise time of rupture, time of operation, time of death, or at the end of the observed study period (February 29, 2000), their change in the final period (after the last follow-up visit) was not known. Therefore, final Dmax, Ep, and β needed to be estimated. Linear regression models were used to predict the values of Dmax, Ep, and β at a particular follow-up visit from the previous follow-up visit, after taking into account the time difference between visits. The resultant models for each follow-up were similar, and hence, the model that predicted the third follow-up visit from the second follow-up visit was used to predict Dmax, Ep, and β at the time of rupture, operation, death, or end of study, which was a compromise between the maximum number of patients completing a particular follow-up visit and use of data from the latest follow-up. For the Cox regression, change in Dmax, Ep, and β over the next period could then be calculated for each follow-up visit (including the final study period). This methodology takes into account the time between successive follow-up visits with the following formula to estimate the "change per month" on the natural logarithmic scale:

$$\frac{(\text{logarithm of value at follow-up} - \text{logarithm of value at previous follow-up}) \times 365.25/12}{\text{number of days between two follow-up visits}}$$

Age and gender were considered to be important confounders and thus were included in the Cox model. Dmax, systolic BP, diastolic BP, mean arterial pressure, pulse pressure, Ep, β, and change over the next follow-up period for Dmax, Ep, and β were entered into the model. A stepwise procedure was used with variables entered and leaving the model at the 5% significance level. The units for the hazards ratios were modified so that they reflected a 10% change in the original units and a 10-year change in age. For ease of description, the hazards ratios are frequently referred to as risks, but the reader should be aware that this is not strictly speaking semantically correct. The usual Kaplan-Meier survival curves could not be produced because the covariates were time dependent. However, with the parameter estimates from the Cox model, it was possible to produce modified survival curves to illustrate the effects of a change in one risk factor (while using the median values for all other factors). Separate figures were produced for male and female patients as the risk of rupture differed substantially between the genders.

Table I. BP, Dmax, and distensibility at baseline and last follow-up for all 210 patients

Variable	*Baseline*	*Last follow-up*	*Change*	*Wilcoxon signed rank test,* P *value*
Diastolic BP (mm Hg)	80 (72-90)	82 (74-90)	0 (-2 to 8)	.017
Systolic BP (mm Hg)	140 (128-160)	145 (130-161)	0 (-8 to 11)	.404
Dmax (mm)	47.8 (41.0-53.5)	51.5 (45.3-58.6)	3.2 (0.0 to 7.4)	.001
Ep (10^5 Nm^{-2})	2.93 (2.06-4.38)	3.35 (2.28-4.66)	0.00 (-0.26 to 1.00)	.015
β (arbitrary units)	20.2 (15.0-29.5)	22.2 (15.9-30.4)	0.0 (-2.6 to 5.3)	.051

Values are medians (IQRs).

Table II. BP, Dmax, and distensibility at baseline visit in those subjects whose aneurysms did and did not go on to rupture

Variable	*Rupture (n = 28)*	*Nonrupture (n = 182)*	*Mann-Whitney U test,* P *value*
Diastolic BP (mm Hg)	86 (80-90)	80 (72-90)	.031
Systolic BP (mm Hg)	141 (120-150)	140 (130-160)	.552
Dmax (mm)	53.4 (46.6-63.6)	47.7 (40.1-53.0)	.001
Ep ($10^5 Nm^{-2}$)	2.61 (1.97-3.50)	2.93 (1.99-4.43)	.244
β (arbitrary units)	16.5 (13.5-23.2)	19.8 (14.5-19.5)	.116

Values are medians (IQRs).

Table III. BP, Dmax, and distensibility at last follow-up visit in those subjects whose aneurysms did and did not go on to rupture

Variable	*Rupture (n = 28)*	*Nonrupture (n = 182)*	*Mann-Whitney U test,* P *value*
Diastolic BP (mm Hg)	88 (83-95)	80 (74-90)	.013
Systolic BP (mm Hg)	145 (136-156)	145 (130-162)	.829
Dmax (mm)	57.6 (49.0-64.0)	50.8 (44.6-57.3)	.006
Ep ($10^5 Nm^{-2}$)	3.32 (2.14-4.37)	3.35 (2.30-4.70)	.789
β (arbitrary units)	20.4 (14.5-29.8)	22.4 (16.1-30.4)	.524

Values are medians (IQRs).

RESULTS

The 210 subjects (163 male; 47 female) had a median (IQR) age of 72 years (68 to 77 years). Thirty-eight patients (18%) had an initial AAA size of greater than 5.5 cm, and the figures were similar for males (n = 30; 18%) and females (n = 8; 17%). The median (IQR) period of follow-up was 19 months (9 to 30 months), and the 38 patients who had a follow-up period of less than 9 months had a genuine reason for a short follow-up period (eight died and 30 had surgery). Considering the cohort as a whole, there was a significant increase in diastolic BP and Dmax and a significant decrease in distensibility (increase in Ep and β) between baseline and last follow-up visit (Table I). The AAAs of 28 patients (13%; 17 male [10%] and 11 female [23%]) ruptured during the follow-up period. Only five of these patients (18%) had emergency surgery (two male, one of whom survived, and three female, who all survived). Therefore, the overall death rate from rupture was 11% (24/210). The median (IQR) follow-up period for the 28 patients whose AAAs ruptured was 16 months (7 to 27 months), compared with 29 months (18 to 51 months) for those patients whose AAAs did not rupture. Of the remaining 182 patients whose AAAs did not rupture, 54 had elective surgery (and were asymptomatic), 10 had elective surgery because they were symptomatic, 36 died from non–AAA-related causes, and 82 patients were followed up until the end of the study (February 29, 2000). The median (IQR) time to rupture after the last follow-up visit was 102 days (63 to 268 days).

At baseline, patients whose AAAs went on to rupture had higher diastolic (but not systolic) BP and larger AAA diameter (Table II). AAAs that went on to rupture also tended to be more distensible (lower Ep and β) at baseline, although this difference did not attain statistical significance. At the last follow-up visit, patients who went on to rupture had significantly higher diastolic BP and larger AAA diameter, but there was no significant difference with regard to systolic BP or distensibility (Table III).

In the Cox proportional hazards model, after adjustment for age and gender, Dmax ($P = .002$), change in Ep

Table IV. Significant independent predictors of time to rupture with Cox proportional hazards regression model

Factor	*Parameter estimate*	*Standard error*	*P value*	*Hazards ratio (95% CI)*	*Shorter time to rupture for those:*
Age	0.06	0.04	.108	1.82 (0.88-3.79)	who were 10 years older
Gender	1.02	0.42	.014	2.78 (1.23-6.28)	who were female
Log Dmax	3.26	1.06	.002	1.36 (1.12-1.66)	with 10% larger Dmax
Log change Ep	−3.42	1.34	.011	1.38 (1.08-1.78)	with 10% decrease in change in Ep
Log diastolic BP	4.06	1.41	.004	1.47 (1.13-1.92)	with 10% higher DBP

Hazards ratio and associated CI relates to 10% change in original scale for variables on logarithm scale and 10 years for age. Variables considered for entry into model via stepwise procedure: age, gender, diameter (log Dmax, log change in Dmax/mo), blood pressure (log diastolic BP, log systolic BP, log mean arterial pressure, log pulse pressure), and distensibility (log β, log change in β/ mo, log Ep, log change in Ep/mo).

($P = .011$), and diastolic BP ($P = .004$) were significant independent predictors of time to rupture (Table IV). Women had a shorter time to rupture than men for any given age, change in Ep, Dmax, and diastolic BP. There was a shorter time to rupture for older patients, but the result was not statistically significant at the 5% level. A patient with a larger aneurysm diameter than another patient, assuming all other risk factors stayed the same, had an increased risk of rupture (Fig 1). The same was true for a patient with a higher diastolic BP (data not shown). Patients with a larger proportionate monthly decrease in Ep (increase in distensibility) had a shorter time to rupture for any gender, age, Dmax, or diastolic BP than patients with no change in Ep or those who showed an increase in Ep (Fig 2). Although a change of 20% in Ep over 6 months, at first sight, appears relatively large, 26% of the 759 Ep changes (in the Cox model) were more than a 20% increase and 32% were more than a 20% decrease.

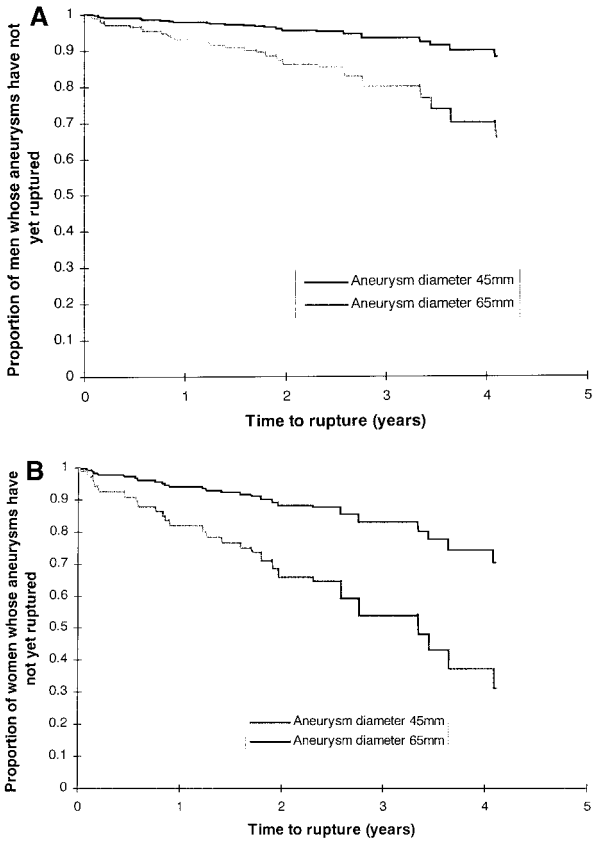

Fig 1. A, Modified survival curve for men shows effect on time to rupture of Dmax of 45 mm compared with Dmax of 65 mm. All other factors in Cox model take median value: 73 years of age, 80 mm Hg diastolic BP, zero change in Ep over 6 months. **B,** Modified survival curve for women shows effect on time to rupture of Dmax of 45 mm compared with Dmax of 65 mm. All other factors in Cox model take median value: 73 years of age, 80 mm Hg diastolic BP, zero change in Ep over 6 months.

DISCUSSION

The principal novel finding of this prospective, multicenter study is that a reduction in AAA distensibility over time is associated with a significant reduction in time to rupture independently of other risk factors. Specifically, for any given gender, age, AAA diameter, and BP, a 10% decrease in Ep over time was associated with a 28% increase in rupture risk when compared with no change in Ep. Over the same period, a 10% increase in maximal diameter, the variable most frequently used to predict risk of rupture, was associated with a 36% increase in rupture risk. In other words, an increase in distensibility over time appears to be almost as powerful a predictor of rupture risk as does change in diameter. The study has also confirmed that female gender and diastolic BP are risk factors for AAA rupture.[3,15,16]

The current data indicate that most aneurysms become progressively less distensible as they increase in diameter.[6] This is presumably because of remodeling of the wall, involving the laying down of collagen, in response to the increase in wall tension predicated by the Law of Laplace.[5] Such remodeling appears to protect against rupture, and importantly, failure of such remodeling as indicated by the increase in distensibility observed in this study appears to significantly increase the risk of rupture. The actual factors that determine at what point AAA remodeling fails, and distensibility increases, are unknown but presumably vary between patients.

Data on the natural history of medium-sized aneurysms are sparse because most patients with AAAs considered to be at risk of rupture undergo operative repair. This study could only have been performed in a cohort of patients who

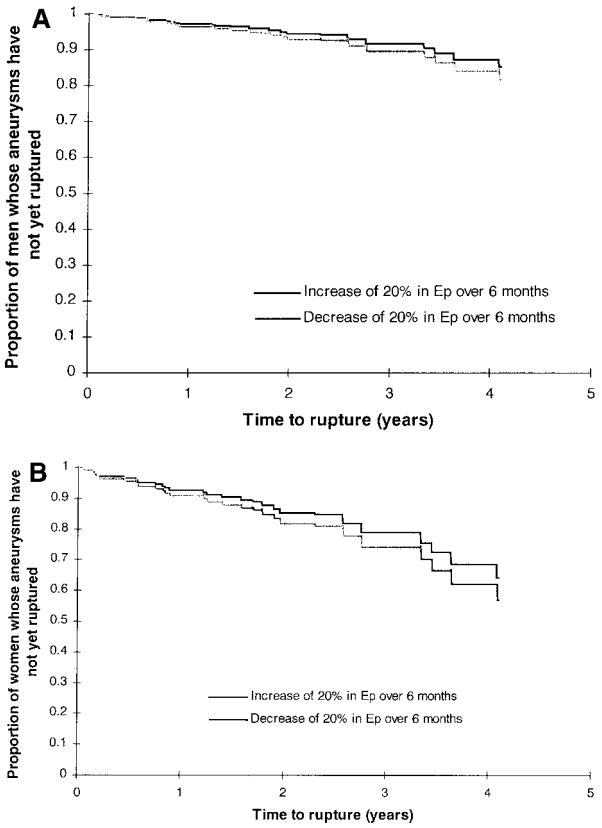

Fig 2. A, Modified survival curve for men shows effect on time to rupture of increase in Ep of 20% compared with decrease of Ep of 20% over period of 6 months. All other factors in Cox model take median value: 73 years of age, 80 mm Hg diastolic BP, 55-mm Dmax. **B,** Modified survival curve for women shows effect on time to rupture of increase in Ep of 20% compared with decrease of Ep of 20% over period of 6 months. All other factors in Cox model take median value: 73 years of age, 80 mm Hg diastolic BP, 55-mm Dmax.

were not to be considered for surgery despite being at significant risk of rupture. So, by definition, the current cohort of patients are likely to be different, primarily in terms of comorbidity, from the generality of patients with AAA who are offered surgery. Although the authors see no clear reason why the current data should not be representative of AAAs in general, this potential source of bias needs to be kept in mind.

Because measurements of BP, Dmax, Ep, and β could not be taken at each follow-up for every patient, we only included follow-up visits where measurements could be taken in the final analysis. For 16 patients, baseline measurements were not available, and therefore, data from their subsequent visit were used as their baseline values. Potentially, this meant that the smoking and comorbidity data that were collected at baseline could have changed in the meantime. However, smoking and comorbidity data were examined in detail and no significant effects on rupture were noted. Therefore, we did not analyze the impact on these variables in this paper, and hence, the conclusions are not affected by this decision.

Changes in Dmax, Ep, and β were thought to be important for the prediction of rupture. However, the only way change could be added to the Cox model was if change could be calculated between all time periods. Because the Dmax, Ep, and β were not known at the endpoint (whether this was rupture, death, surgery, or end of study period), we had to estimate them. Linear regression was in our judgement the best option, and different models were considered on the basis of prediction of the values at each subsequent follow-up on the basis of the values at the previous follow-up. Ultimately, the regression equation that predicted the third follow-up visit from the second follow-up value was used. In addition, because time-dependent variables were added in the model, data from all follow-up visits were used in the analysis and not just from the last follow-up or change in the final period. Nevertheless, it is possible that change in the final period between last follow-up and event is not the same for the four groups (rupture, death, surgery, and followed up to end of study without an event) or that the resultant model was not as good for patients with fewer follow-up visits. Therefore, it is possible that the estimation of Dmax, Ep, and β at the time of the event has not been precisely estimated. Because we have no way of knowing whether this is true, it must be borne in mind when interpreting the findings.

The Diamove system has a number of important limitations that detract from its potential utility as a clinical, as opposed to a research, tool. First, informative pressure-diameter curves cannot be obtained from a significant minority of patients because of obesity, bowel gas, arrhythmia, and inability to lie flat or hold the breath. Second, the technique is associated with a significant learning curve and moderate interobserver and intraobserver variation.[4] Third, the Diamove system cannot measure distensibility simultaneously in different parts of the wall. In this study, distensibility at the point of maximal AAA diameter in longitudinal section was chosen because it was shown to offer the most reproducible measurement site and because it may be a site of high stress and strain. However, clinical experience suggests that AAAs do not always rupture at this point. As indicated by Vorp, Raghavan, and Webster,[17] AAAs are not spheric or cylindric and points of high strain are likely to be predicated by differences in geometry. Although the echo-tracking technique used in this study provides an overall assessment of distensibility at the widest point of the AAA, it is unable to localize or quantify high stress points predicted with computer modeling.[18] We are currently evaluating a more sophisticated ultrasound scan–based system that allows simultaneous measurement of wall movement along the length of the AAA, and at its interface with the normal proximal and distal aorta.

Notwithstanding the technical challenges yet to be overcome in developing a tool that can be used in day-to-day clinical practice, this study has produced further evidence to support the paradigm that change in distensibility is a significant predictor of AAA rupture risk independently

of aneurysm diameter. The study has also reemphasized female gender and diastolic hypertension as highly significant risk factors for rupture. The latter is open to therapeutic intervention, and the presence of the former may suggest a lower threshold for elective repair. An AAA surveillance program that uses distensibility, gender, and BP in addition to maximum diameter seems likely to provide a more accurate prediction of rupture risk for individual patients than one based on size alone and may better inform decisions regarding prophylactic surgery.

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