Novel Measurement of Relative Aortic Size Predicts Rupture of Thoracic Aortic Aneurysms

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Background. **Optimal operative decision making in thoracic aortic aneurysms requires accurate information on the risk of complications during expectant management. Cumulative and yearly risks of rupture, dissection, and death before operative repair increase with increasing aortic size, but previous work has not addressed the impact of relative aortic size on complication rates.**

Methods. **Our institutional database contains data on 805 patients followed up serially with thoracic aortic aneurysms. Body surface area information was obtained on 410 patients (257 male, 153 female). We calculated a new measure of relative aortic size, the "aortic size index," and examined its ability to predict complications in these patients.**

Results. **Increasing aortic size index was a significant predictor of increasing rates of rupture ($p = 0.0014$) as well as the combined endpoint of rupture, death, or dissection ($p < 0.0001$). Using aortic size index, patients were stratified into three risk groups: less than 2.75 cm/m^2 are at low risk (approximately 4% per year), 2.75 to 4.24 cm/m^2 are at moderate risk (approximately 8% per year), and those above 4.25 cm/m^2 are at high risk (approximately 20% per year).**

Conclusions. **This study confirms that (1) thoracic aortic aneurysm is a lethal disease, (2) relative aortic size is more important than absolute aortic size in predicting complications, and (3) a novel measurement of relative aortic size allows for the stratification of patients into three levels of risk, enabling appropriate surgical decision-making.**

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Historically, operative decision making in patients with thoracic aortic aneurysms (TAAs) has relied primarily on anecdotal data and personal clinical experience. The considerable risks involved in medical management of thoracic aortic disease as well as those traditionally associated with surgical repair necessitate an accurate understanding and balancing of both risks.

The threats of an unoperated aneurysm include rupture, dissection (with subsequent end-organ ischemia), and death. In contrast, the risks of surgery include paraplegia, stroke, bleeding, and death. Despite the armamentarium of modern perioperative and postoperative cardiac surgical care, the operative mortality after elective aortic surgery ranges from 3% to 9% [1–5]. In contrast mortality for emergent repair is much higher, from 16% to 59% [2, 3, 6]. This emphasizes the need for appropriate timing of surgical intervention, before the occurrence of complications.

Our group has previously demonstrated that both the cumulative and yearly risks of aortic dissection and rupture increase with aneurysm size [3, 7]. While our data emphasized the risk present as aneurysms rise above 5 cm in maximal diameter, in multivariate analysis, we also found that women had a higher likelihood of rupture or dissection. Similarly, in univariate analysis, Juvonen and colleagues [8] found a higher percentage of women among patients who ruptured, although this was not apparent in their elegant multivariate model. Although we speculated that these results reflect the fact that a specific size aneurysm represents proportionately greater aortic dilatation in smaller female patients [7], changes in risk based on patient size have never been demonstrated. We therefore undertook the current study to define the impact of body surface area on risk of aortic complications, and to determine whether the added risk of female sex was simply a surrogate for patient size.

Patients and Methods

Patient Population

Our database includes information on 1,326 patients with TAAs. There are 5,918 total patient-years of follow-up and 1,615 patient-years of follow-up preceding surgical repair from which natural history can be assessed. We have analyzed 5,438 radiographic studies (2,246 computed tomographic scans, 585 magnetic resonance imaging scans, 257 transesophageal echocardiography studies, 2,011 transthoracic echocardiographs, and 339 angiographic studies).

Inclusion criteria for this study were aortic size at least

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Table 1. Demographic Data on 410 Patients With Thoracic Aortic Aneurysms

Variable	Number	%	Mean	Median	Range
Sex (male)	257	62.9			
Age at presentation (yrs)			61.9	65.2	8.8 to 92.8
Body surface area (m^2)			1.93	1.94	1.09 to 2.74
Initial aortic size (cm)			5.2	4.9	3.5 to 11.0
Initial aortic size					
3.5 to 4.4 cm	129	31.5			
4.5 to 5.4 cm	155	37.8			
5.5 to 6.4 cm	68	16.6			
6.5 to 7.4 cm	32	7.8			
≥ 7.5 cm	26	6.3			
Final aortic size (cm)			5.7	5.3	3.6 to 12.0
Initial aortic size index (cm/m^2)			2.75	2.50	1.38 to 10.07
Initial aortic size index					
< 2.00 cm/m^2	58	14.2			
2.00 to 2.74 cm/m^2	195	47.6			
2.75 to 3.49 cm/m^2	88	21.5			
3.50 to 4.24 cm/m^2	47	11.5			
4.25 to 4.99 cm/m^2	13	3.2			
≥ 5.00 cm/m^2	9	2.2			
Final aortic size index (cm/m^2)			3.02	2.79	1.52 to 10.07
Radiologic follow-up (months)			31.4	6.3	0.0 to 327.4
Marfan syndrome	23	5.6			
Nonsyndromic family history (n = 305)	51	16.9			
Body surface area					
< 2.00 m^2	239	58.3			
≥ 2.00 m^2	171	41.7			
Aneurysm location					
Ascending	315	76.8			
Arch	20	4.9			
Descending	41	10.0			
Thoracoabdominal	34	8.3			
Hypertension (n = 356)	238	66.9			
Cardiac disease (n = 349)	119	34.1			
Tobacco Use (n = 349)	127	36.4			
Pulmonary disease (n = 353)	83	23.5			
Carotid disease (n = 345)	32	9.3			
Renal disease (n = 352)	27	7.7			
Coronary artery disease (n = 410)	95	23.2			
Congestive heart failure (n = 410)	22	5.4			
Stroke or transient ischemic attacks (n = 410)	23	5.6			
Abdominal aortic aneurysm (n = 410)	38	9.3			

3.5 cm and age older than 6 years at presentation, absence of congenital aortic malformations (for example, aortic coarctation), and at least one size measurement before operative repair. In all, 1,106 patients met these criteria. Among these patients, 301 had preexisting chronic dissection at presentation and were excluded from the analysis because dissection was an endpoint to this portion of the study.

Since 2003, height and weight have been collected in a prospective fashion; for patients accrued before 2003, height and weight information was obtained from hospital chart review and patient interview. Four hundred ten patients had accurate data from which body surface area could be calculated, and they form the study group for this analysis.

Hospital chart review was conducted on each identified patient, and the data were entered into a computerized database. Data recovered from hospital records and computer files were cross-referenced with hospital discharge abstract data monitored by the Connecticut Hospital Association and the Connecticut State Mortality Records as well as the Social Security Death Index (available at: http://sssdi.rootsweb.com). The patient database is maintained as part of the ongoing studies at the

Table 2. Logistic Regression Analysis of Factors Predicting the Combined Endpoint of Rupture, Dissection, or Death Before Operative Repair (Dependent Variables)[a]

Regression Analysis Variable[b]	Parameter Estimate	Standard Error	*p* Value	Odds Ratio[c]
Intercept term	−2.0435	0.3118	<0.0001	
Aortic size index				
< 2.00 cm/m^2	0.4508	0.4567	0.3235	1.570 (0.641 to 3.841)
2.75 to 3.49 cm/m^2	0.6996	0.3686	0.0577	2.013 (0.977 to 4.146)
3.50 to 4.24 cm/m^2	0.1075	0.5087	0.8327	1.113 (0.411 to 3.018)
4.25 to 4.99 cm/m^2	1.2971	0.6616	0.0499[d]	3.659[d] (1.000 to 13.381)
≥ 5.00 cm/m^2	1.6395	0.7455	0.0279[d]	5.153[d] (1.195 to 22.213)
Aneurysm location (desc/TA)	0.5761	0.3544	0.1040	1.779 (0.888 to 3.564)
Sex (male)	−0.4374	0.3053	0.1519	0.646 (0.355 to 1.175)
History of abdominal aortic aneurysm	0.5669	0.4340	0.1914	1.763 (0.753 to 4.127)

[a] This variable equals 1 if the patient incurred a rupture, dissected, or died before operative repair and 0 otherwise. [b] Variables removed from model in backward fashion, aortic sie index was. Criteria for assessing model fit: −2 Log L: intercept only, 348.351; intercept and covariates: 324.465; χ^2 for covariates (likelihood) ratio): 23,8864 with 8 DF ($p = 0.0024$). [c] 95% confidence intervals on odds ratios are given in parentheses. Odds ratios for aortic size index are given in relation to aneurysms with size index 2.00 to 2.74. [d] Statistically significant at $p < 0.05$ level.

desc/TA = descending or thoracoabdominal.

Yale Center for Thoracic Aortic Disease, a major referral center for southern New England. Patients were recruited and followed up between 1985 and 2005.

Statistical Methods

Statistical methods were used to identify and estimate risk factors for the following outcomes: cumulative incidence of major negative events, survival free from these events, and overall long-term survival. Measurements of cumulative incidence tend to overestimate risk in patients followed up for long periods of time while underestimating risk in patients followed up for short time periods; therefore, the survival free from negative events is a better estimate of true risk.

Body surface area (BSA) was calculated using the Dubois and Dubois formula [9]:

$$\text{BSA} = 0.20247\left(\text{wgt}^{0.425} * \left(\frac{hgt}{100}\right)^{0.725}\right)$$

It was used both as a continuous variable and stratified into two groups: less than 2.00 m^2 and 2.00 m^2 or more. In addition, the interaction between BSA and aortic size was evaluated using the aortic size index (ASI) which was calculated as: ASI = aortic diameter (cm) divided by body surface area (m^2).

When analyzing smoking history, hypertension, and the presence of cardiac, pulmonary, or renal disease, patients were stratified according to established criteria of risk for complications from vascular disease [10], and the analysis was performed both with the stratified severity levels and with a dichotomous variables indicating the presence of disease of any severity. Of note, all patients diagnosed with hypertension received treatment with antihypertensive medications during follow-up. Results are not shown for the analysis with stratified levels because they did not provide any additional information.

The methods of statistical analysis included χ^2 test for comparisons of dichotomous risk factors with negative outcomes (rupture, dissection, death); Mantel-Haenszel χ^2 test for comparisons taking into consideration disease severity (cardiac disease, pulmonary disease, progressively larger aneurysms, and so forth); and the Wilcoxon test for comparisons of continuous variables with negative outcomes ($p < 0.05$). Logistic regression analysis of the cumulative incidence was used to evaluate the influence of risk factors for rupture or dissection. Product-limit estimates (Kaplan-Meier) were calculated using the LIFETEST procedure of SAS 9.1 for Windows (SAS Institute, Cary, North Carolina) with the log-rank test for difference between strata. Yearly rates of complications were calculated as the mean yearly rate over the first 5 years. The Cox regression model (using the PHREG procedure) was used to identify the most predictive variables.

After univariate analysis, variables were entered into the models using three selection criteria: forward, forward stepwise, and backward. All variables predictive of the outcome in univariate analysis were entered into regression analyses; certain variables were included in all analyses independent of univiariate prediction because of their significance in previous publications, specifically pulmonary disease, sex, and age [3, 7, 8]. Models were compared using the −2 Log L score and the Wald score for significance; in all cases the most predictive model is presented. Threshold for entry into the model for both logistic regression and Cox regression was *p* less than 0.20, except that all categories of aortic size index were included in the models in order to assess the impact of this variable on outcomes.

Event Rates

The incidence of acute dissection or rupture (or both) before operative repair was evaluated by both descriptive and multivariable analyses. Rupture and dissection were

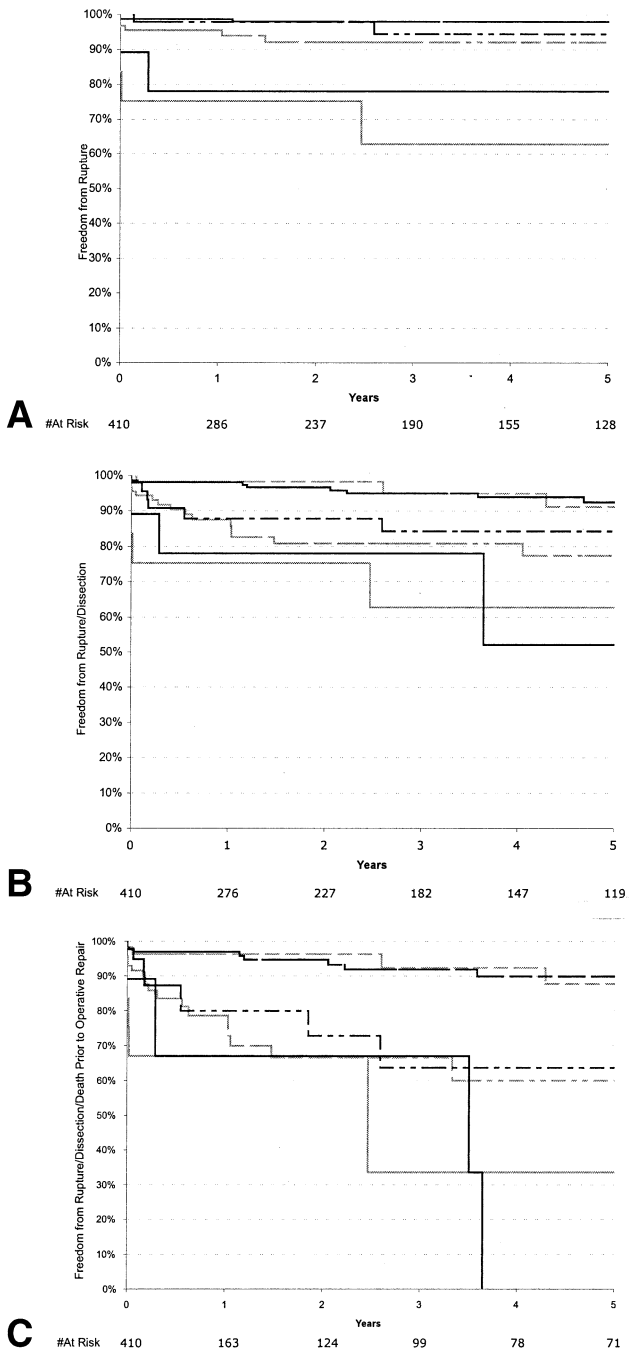

Fig 1. Kaplan-Meier cumulative survival free from (A) rupture, (B) rupture or dissection, and (C) rupture, dissection, or death before operative repair. Five-year complication-free survival is illustrated for patients as a function of initial aortic size index. Higher initial aortic size index is associated with decreased survival in all three categories: (A) $p = 0.0014$, (B) $p = 0.0015$, and (C) $p < 0.0001$. (Light dashed line = less than 2.00; dark dashed line = 2.00 to 2.74; light dot/dash line = 2.75 to 3.50; dark dot/dash line = 3.50 to 4.24; light solid line = 4.25 to 5.00; dark solid line = 5.00 or more.)

confirmed by at least one of the following: autopsy, operation, death certificate, or computed tomography or magnetic resonance imaging.

The multivariable analysis specifies a logistic regression model relating event occurrence to each of the following: initial aortic size (both stratified and unstratified), initial ASI (both stratified and unstratified), final aortic size (both stratified and unstratified), final ASI (both stratified and unstratified), aneurysm location, age at presentation, sex, Marfan syndrome, presence of a nonsyndromic family history of aortic or aneurysmal disease, cardiac status, hypertension, pulmonary disease, renal disease, history of smoking, and a history of abdominal aortic aneurysm, coronary artery disease, congestive heart failure, or stroke.

Event-Free Survival and Long-Term Survival

Five-year survival estimates were calculated by product-limit estimates (Kaplen-Meier). For these analyses, patients were entered into the analysis at the time of presentation. For the event-free survival analysis, patients were censored when they were lost to follow-up, underwent surgical correction, or died without rupture or dissection. Only two major complications—rupture, dissection, or both—were considered in analyzing event-free survival. For the long-term survival analysis, patients were censored when they were lost to follow-up or underwent surgical correction. Yearly event rates for subgroups were estimated from the Cox regression analysis using the BASELINE statement of PROC PHREG (SAS 9.12 for Windows) and represent the mean event rate for each year during the first 5 years after diagnosis.

The specific factors tested for survival differences included initial and final aortic size (both stratified and unstratified), ASI (both stratified and unstratified), aneurysm location, age at presentation, sex, Marfan syndrome, presence of a nonsyndromic family history of aortic or aneurysmal disease, cardiac status, hypertension status, pulmonary disease, renal disease, history of smoking, and history of abdominal aortic aneurysm, coronary artery disease, congestive heart failure, or stroke.

Results

Patient and Aneurysm Characteristics

The distribution of aneurysms by initial aortic size and ASI is shown in Table 1. Aneurysms in the ascending aorta were more common than in the aortic arch, descending, or thoracoabdominal regions. Characteristics for patients with Marfan syndrome as well as those with nonsyndromic family history of aortic or aneurysmal disease were similar to the remaining population, including mean initial aortic size, ASI, and BSA. However, patients with Marfan syndrome were significantly younger (37.7 years versus 62.6 and 63.1 years, $p < 0.0001$).

Patients with ascending or aortic arch aneurysms were significantly younger at presentation than those with descending or thoracoabdominal aneurysms (60.1 years versus 69.0 years, $p < 0.0001$); and ascending/arch aneu-

Table 3. Proportional Hazards Regression of Factors Predicting Rupture or Dissection (Dependent Variables)[a]

Regression Analysis Variable[b]	Parameter Estimate	Standard Error	*p* Value	Hazard Ratio[c]
Initial aortic size index				
< 2.00 cm/m^2	0.61558	0.46582	0.1863	1.851 (0.743 to 4.612)
2.75 to 3.49 cm/m^2	0.77014	0.37995	0.0427[d]	2.160[d] (1.025 to 4.549)
3.50 to 4.24 cm/m^2	0.38646	0.48015	0.4209	1.472 (0.574 to 3.772)
4.25 to 5.00 cm/m^2	1.46162	0.57268	0.0107[d]	4.313[d] (1.404 to 13.251)
≥ 5.00 cm/m^2	1.23764	0.64803	0.0562	3.447 (0.968 to 12.277)
Aneurysm location (desc/TA)	0.71542	0.31512	0.0232[d]	2.045[d] (1.103 to 3.793)
Age (yrs)	0.01488	0.01014	0.1422	1.015 (0.995 to 1.035)

[a] This variable equals 1 if the patient incurred a rupture or dissection and 0 otherwise. [b] Variables removed from the model is backward fashion. Criteria for assessing model fit: −2 Log: intercept only: 555.772; intercept and covariates: 531.249; χ^2 for covariates (likelihood ratio): 23.7623 with 6 DF ($p = 0.0013$). [c] 95% confidence intervals on hazard ratios are given in parentheses. Hazard ratios for aortic size index are given in relation to aneurysms with size index of 2.00 to 2.74 cm/m^2. Hazard ratio for age indicates the additional hazard for each additional year in age. [d] Statistically significant at $p < 0.05$ level.

desc/TA = descending or thoracoabdominal.

rysms were smaller at initial presentation (5.0 cm versus 6.0 cm, $p < 0.0001$).

Cumulative Event Rates

AORTIC RUPTURE. Increasing initial aortic size was associated with an increased risk of aortic rupture ($p = 0.0320$). A stronger association was seen with increasing ASI ($p = 0.0022$). While there was a steady increase in risk with increasing aortic size, analysis with ASI showed a dramatic step-up in risk above 4.25 cm/m^2; initial ASI of 4.25 to 4.99 cm/m^2 was associated with a sevenfold increase in the incidence of rupture (odds ratio [OR] 7.9577, $p < 0.001$). Other univariate predictors of rupture included aneurysm location in the descending or thoracoabdominal aorta (OR 3.281, $p = 0.004$) and a history of abdominal aortic aneurysm (OR 3.484, $p = 0.009$). There was a trend toward larger aortic size at rupture among patients with descending or thoracoabdominal aneurysms (6.8 cm versus 5.8 cm, $p = 0.2452$). Nineteen patients ruptured at ASI less than 4.25 cm/m^2. This comprised 76% of all ruptures. Predictors of rupture in this subgroup did not differ significantly from those who ruptured at higher ASI, nor did they differ significantly from patients with small ASI who did not rupture.

Multivariate analysis confirmed the increased risk of rupture associated with increasing ASI ($p = 0.0032$); ASI 4.25 to 4.99 cm/m^2 was associated with an 13-fold increase in the cumulative risk of rupture (OR 13.765, 95% confidence interval [CI]: 3.048 to 62.171). Other significant predictors of rupture in this multivariate model included ASI of 5.00 cm/m^2 or greater (OR 7.577, 95%CI: 1.167 to 48.932) and aneurysms located in the descending or thoracoabdominal aorta (OR 2.581, 95%CI: 1.012 to 6.584) When ASI was removed from the model and replaced with aortic size, lower BSA emerged as a significant predictor of rupture ($p = 0.0202$).

AORTIC DISSECTION. Increasing ASI also predicted a higher incidence of dissection ($p = 0.0215$), but the association was less pronounced than with rupture. Aortic dissection was more strongly associated with aortic size independent of BSA ($p = 0.0094$ versus 0.0215), and BSA less than 2.00 m^2 did not predict a lower incidence of dissection (OR 0.6781, 95%CI: 0.3197 to 1.4385). Aneurysms in the descending or thoracoabdominal aorta were more likely to dissect (OR 2.4453, 95%CI: 1.1298 to 5.2924), while male sex was protective against dissection (OR 0.4063, 95%CI: 0.1974 to 0.8363).

When rupture or dissection are considered together, size index remains highly predictive of negative events. Other significant predictors of rupture or dissection include: aneurysm location in the descending or thoracoabdominal aorta (OR 3.105, 95%CI: 1.6498 to 5.8498) and history of AAA (OR 2.3745, 95%CI: 1.0536 to 5.3515). Both BSA greater than 2.00 m^2 (OR 0.5249, 95%CI: 0.2781 to 0.9909) and male sex (OR 0.5029, 95%CI: 0.2800 to 0.9032) were protective against the combined endpoint of rupture or dissection.

Logistic regression confirmed the importance of female sex in predicting dissection ($p = 0.0085$). Despite the inclusion of BSA in the analysis, female sex was most predictive of dissection before operative repair (OR 2.329, 95%CI: 1.122 to 4.838). Similar results were obtained when rupture and dissection were considered together (data not shown).

Mortality Before Operative Repair

Increasing ASI was highly predictive of the combined endpoint of rupture, dissection or mortality before operative repair ($p = 0.0008$). Other univariate predictors of the combined endpoint were similar to each endpoint considered alone with a history of AAA and aneurysms located in the descending or thoracoabdominal aorta carrying significantly higher risk (OR 2.5643 and 2.5368, $p = 0.013$ and 0.002). Results of the multivariate analysis are given in Table 2.

Incidence of Rupture, Dissection, or Death as a Function of Time

UNIVARIATE ANALYSIS. Five-year event-free survival is shown in Figure 1. Larger initial ASI predicted worse event-free survival in all categories. Patients with descending or thoracoabdominal aneurysms had higher

Table 4. Proportional Hazards Regression of Factors Predicting Rupture (Dependent Variables)[a]

Regression Analysis Variable	Parameter Estimate	Standard Error	*p* Value	Hazard Ratio[c]
Using aortic size index (ASI, cm/m^2)[b]				
Initial aortic size index				
$<$ 2.00 cm/m^2	1.08300	0.67468	0.1084	2.954 (0.787 to 11.082)
2.75 to 3.49 cm/m^2	1.09260	0.60758	0.0721	2.982 (0.906 to 9.810)
3.50 to 4.24 cm/m^2	0.50292	0.76178	0.5091	1.654 (0.372 to 7.359)
4.25 to 5.00 cm/m^2	2.40316	0.68929	0.0005[d]	11.058[d] (2.864 to 42.698)
$\geq$ 5.00 cm/m^2	1.90791	0.86786	0.0279[d]	6.739[d] (1.230 to 36.925)
Aneurysm location (desc/TA)	0.96188	0.45276	0.0336[d]	2.617[d] (1.077 to 36.925)
Using aortic size (cm)[e]				
Initial aortic size				
3.5 to 4.4 cm	−0.41541	0.58127	0.4748	0.660 (0.211 to 2.062)
5.5 to 6.4 cm	0.35126	0.54754	0.5212	1.421 (0.486 to 4.155)
6.5 to 7.4 cm	−0.84354	1.07308	0.4318	0.430 (0.053 to 3.524)
$\geq$ 7.5 cm	1.04947	0.59481	0.0777	2.856 (0.890 to 9.164)
Aneurysm location (desc/TA)	0.84893	0.47299	0.0727	2.337 (0.925 to 5.906)
History of abdominal aortic aneurysm	0.84300	0.50777	0.0969	2.323 (0.859 to 6.285)

[a] This variable equals 1 if the patient incurred a a rupture and 0 otherwise. [b] Variables removed from the model in backward fashion. Criteria for assessing model fit: −2 Log L: intercept only: 265.126; intercept and covariates: 244.199; χ^2 for covariates (likelihood ratio): 20.9261 with 6 DF (p = 0.0019). [c] 95% confidence intervals on hazard ratios are given in parentheses. Hazard ratios for aortic size index are given in relation to aneurysms with size index of 2.300 to 2.74 cm/m^2. Hazard ratios for aortic size are given in relation to aneurysms with size of 4.5 to 5.5 cm. Hazard ratio for age indicates the additional hazard for each additional year in age. [d] Statistically significant at $p < 0.05$ level. [e] Variables removed from the model in backward fashion. Criteria for assessing mode fit: −2 Log L: intercept only: 265.126; intercept and covariates: 248.882; χ^2 for covariates (likelihood ratio): 16.2433 with 6 DF (p = 0.0125).

desc/TA = descending or thoracoabdominal.

rupture rates (1- and 5-year rupture-free survival 94.9% and 83.0% versus 97.2% and 97.2%, p = 0.0009). Aneurysms in these locations also had higher risks of the two combined endpoints: rupture or dissection (p = 0.0001), and rupture, dissection, or death (p = 0.0005). Female patients had significantly higher rates of dissection (p = 0.005; 1- and 5-year event-free survival 90.3% and 84.3% versus 99.1% and 94.4%), but not of rupture. Patients with a history of abdominal aortic aneurysm also had a significantly higher rate of rupture (p = 0.0291). Other variables analyzed demonstrated no ability to predict higher rates of negative events.

MULTIVARIATE ANALYSIS. Proportional hazard regression demonstrates that the hazard function for rupture or dissection is more than three times worse for patients with aortic size indexes above 4.25 cm/m^2 than for those with size index between 2.00 and 2.75 cm/m^2. Again, as with the univariate analysis, descending and thoracoabdominal aneurysms were associated with increased risk (OR 2.380, 95%CI: 1.321 to 4.290; Table 3).

Results of the proportional hazard analysis of rupture alone are shown in Table 4. The risk of rupture is 11 times higher with aortic size index 4.25 to 4.99 cm/m^2 than with size index 2.00 to 2.74 cm/m^2. In comparison, when aortic size without reference to BSA is used in the same regression, the increased risk with increased size is not nearly as dramatic (Table 4).

Graphic illustration of the event-free survivor function estimates is shown in Figure 2. Predicted 5-year rupture-free survival for patients with ASI less than 2.00 cm/m^2 was 97.6% versus 82.2% in those with ASI 5.00 cm/m^2 or more. There are two marked step-ups in yearly event rates: at size index above 2.75 and again for size index of 4.0 or greater (Fig 3).

Long-Term Survival

Five-year survival irrespective of operative repair was only 44.4% in patients with the largest aortic size index, compared with 94.7% in those with ASI less than 2.00 ($p < 0.0001$). Long-term survival was better for nondissected than dissected aortas (5-year survival 73.6% versus 63.7%, $p < 0.0001$), and for ascending and aortic arch aneurysms compared with those in the descending and thoracoabdominal aorta (76.2% versus 59.2%, $p < 0.0001$).

Comment

Examining the natural history of TAA presents several challenges. Because patients with high rates of growth and large aneurysm size are selected out for surgery, following the natural history of the disease in an unbiased manner is difficult. Assessment of cumulative risks will tend to underestimate the risk of larger aneurysms (where patients are followed up for very short periods of time) and overestimate risk of smaller aneurysms (where patients may be followed up for years).

We previously identified female sex as a significant predictor of negative events, in particular the combined endpoint of rupture or dissection [7]. We hypothesized that this might be due in part to differences in mean body size between males and females, with a given aortic dimension representing proportionally greater diameter

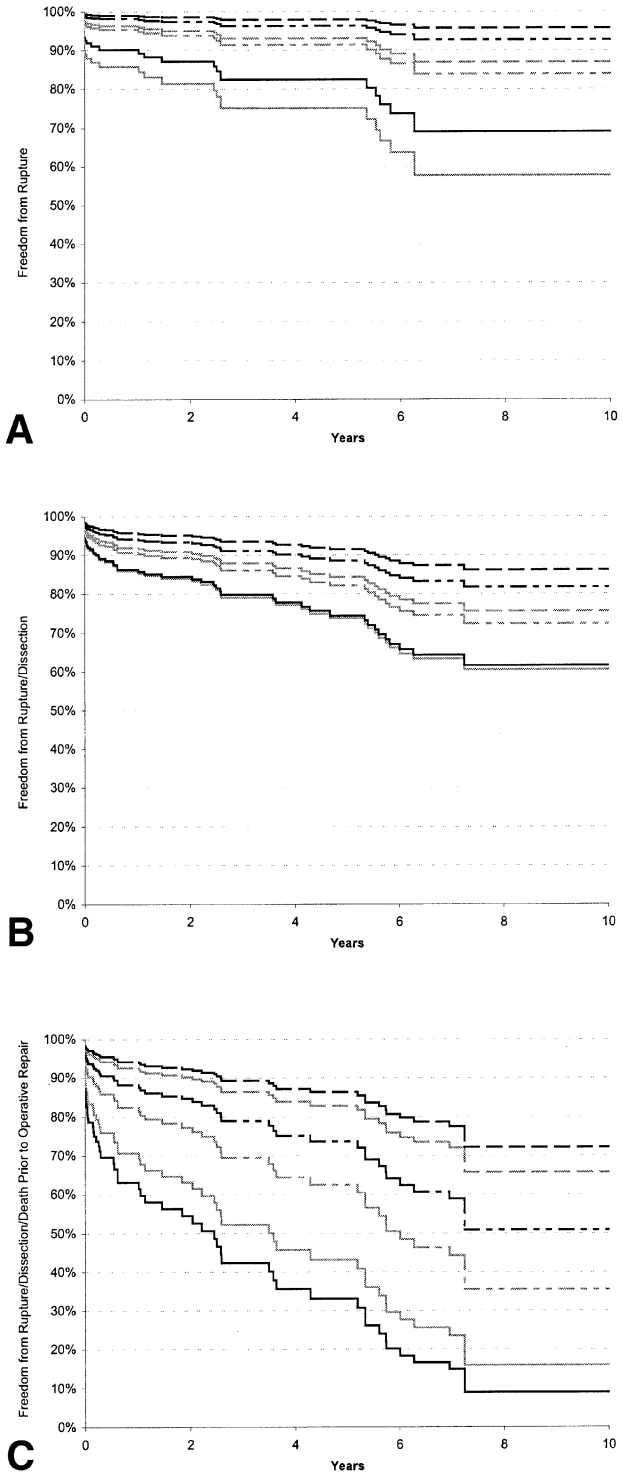

Fig 2. Ten-year event-free estimated survival function (calculated using Cox proportional hazards regression) stratified by aortic size index. The estimated survival function for each size index is illustrated for (A) freedom from rupture ($p = 0.0005$ for Cox regression model), (B) freedom from rupture or dissection ($p = 0.0014$), and (C) freedom from rupture, dissection, or death before operation ($p < 0.0001$). (Light dashed line = less than 2.00; dark dashed line = 2.00 to 2.74; light dot/dash line = 2.75 to 3.50; dark dot/dash line = 3.50 to 4.24; light solid line = 4.25 to 5.00; dark solid line = 5.00 or more.)

in smaller women. Here we demonstrate that lower BSA is associated with a higher incidence of negative events including rupture, dissection, and death.

To more accurately assess the risk of negative events, we developed a new measurement, the aortic size index (ASI) which takes into account both aortic diameter and BSA. Throughout all methods of analysis, ASI was a better predictor of negative events than maximal aortic diameter. This study confirms that TAA is an intrinsically lethal disease and that aortic diameter, corrected for body surface area, is an important predictor of rupture, dissection and death.

In particular, we found that using ASI, patients could be stratified into three categories of risk (Fig 3). Those with ASI less than 2.75 cm/m^2 are at low risk for negative events, with a yearly incidence of approximately 4%, those with ASI between 2.75 and 4.25 cm/m^2 are at moderate risk with yearly incidence of approximately 8%, whereas those with ASI above 4.25 cm/m^2 have yearly rates of rupture, dissection, or death as high as 20% to 25%. These data are summarized in Table 5. These differences in yearly rates were reflected in the Cox proportional hazards regression where the OR for rupture is more than 11 times higher in patients with aortic size index greater than 4.25 cm/m^2.

We anticipate that this information will be useful in counseling individual patients regarding the risks of nonoperative management of aneurysms. These data confirm that, consonant with our previous reports, most patients should receive operative correction before aneurysm size reaches 6.0 cm [3, 7]. However, smaller patients may benefit from operative repair at even smaller sizes (Table 5).

Certain limitations of these data can be enumerated. By analyzing the subset of patients with accurate BSA measurements, we have selected a population of patients more likely to have undergone operative repair. Patients presenting to the emergency room moribund after aortic

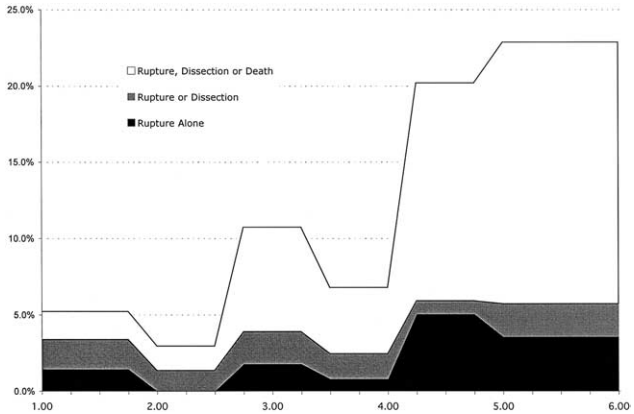

Fig 3. Average yearly rates of negative outcomes: rupture, dissection, and death. These estimates represent the average rate during the first 5 years after presentation calculated based on the Cox proportional hazards regression for each size index group. (Black area = rupture only; gray area = rupture or dissection; white area = rupture, dissection, or death.)

Table 5. Risk of Complications by Aortic Diameter and Body Surface Area With Aortic Size Index Given Within Chart

	Aortic Size (cm)									
	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0
BSA										
1.30	2.69	3.08	3.46	3.85	4.23	4.62	5.00	5.38	5.77	6.15
1.40	2.50	2.86	3.21	3.57	3.93	4.29	4.64	5.00	5.36	5.71
1.50	2.33	2.67	3.00	3.33	3.67	4.00	4.33	4.67	5.00	5.33
1.60	2.19	2.50	2.80	3.13	3.44	3.75	4.06	4.38	4.69	5.00
1.70	2.05	2.35	2.65	2.94	3.24	3.53	3.82	4.12	4.41	4.71
1.80	1.94	2.22	2.50	2.78	3.06	3.33	3.61	3.89	4.17	4.44
1.90	1.84	2.11	2.37	2.63	2.89	3.16	3.42	3.68	3.95	4.22
2.00	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50	3.75	4.00
2.10	1.67	1.90	2.14	2.38	2.62	2.86	3.10	3.33	3.57	3.80
2.20	1.59	1.82	2.05	2.27	2.50	2.72	2.95	3.18	3.41	3.64
2.30	1.52	1.74	1.96	2.17	2.39	2.61	2.83	3.04	3.26	3.48
2.40	1.46	1.67	1.88	2.08	2.29	2.50	2.71	2.92	3.13	3.33
2.50	1.40	1.60	1.80	2.00	2.20	2.40	2.60	2.80	3.00	3.20

□ = low risk (~1% per yr); ▒ = moderate risk (~8% per yr); ■ = severe risk (~20% per yr).

White area indicates low risk, light gray area indicates moderate risk, and dark gray area indicates severe risk.

BSA = body surface area.

rupture were unlikely to have accurate height and weight information available in the chart. Over the past year we have been collecting this data prospectively, but the patient population as a whole remains skewed toward those reaching operative repair. Thus, the survival in patients with BSA data available was significantly better than in those without such information ($p < 0.0001$). Second, definition of rupture, dissection and aneurysm-related death was strict, requiring in-hospital documentation by imaging study, operative findings or postmortem examination. The true rupture rate is likely higher. Third, patients we followed up were operated on electively when they reached size criteria, underwent periods of rapid growth, or became symptomatic, eliminating them from further analysis. These two factors: elective repair in patients at high risk and strict definition of rupture mean that the yearly rupture rates reported here likely underestimate the true rates, which will lie between the estimated rate and the mortality rate, as unoperated rupture is a lethal event.

Although size was a significant predictor of poor outcome, it is interesting to note the small but significant risk of rupture among patients with smaller aneurysms. Even the "safest" group had yearly rates of approximately 2% to 3%. As more patients have aneurysms in this smaller size range, as many as 25% of ruptures occur where ASI is less than the median of 2.50 cm/m^2 and below what most would consider appropriate operative intervention criteria. Possible explanations for rupture at small size include differing immunologic responses to aortic injury or variation in the morphology of the aneurysm.

Despite the inclusion of BSA in the analysis, multivariate models of endpoints that included dissection still included a protective effect of male sex. This finding may indicate that differences other than size account for some of the increased risk in women. Possible contributing factors include changes in the activity of inflammatory mediators in the presence of higher estrogen levels [11] and increased proximal thoracic aortic stiffness in elderly women [12].

Consonant with our previous report, we were unable to demonstrate a significant effect of pulmonary disease on rupture and dissection rates [7]. This contrasts with the findings of several other investigators [8, 13, 14] and may represent differing definitions of pulmonary disease. As has been found previously [7, 8], hypertension was not predictive of negative events, likely because a diagnosis of hypertension usually implies treatment; accurate serial measurements of blood pressure in these patients will be required to delineate the role of hypertension in aortic disease.

This study permits the following conclusions. Thoracic aortic aneurysm is a lethal disease with yearly event rates in the highest risk patients above 20%. Absolute aneurysm size is predictive of negative events, but relative aortic size as measured here with ASI better predicts the occurrence of rupture and death before operative repair. We recommend elective operative repair before the patient enters the zone of moderate risk with ASI greater than 2.75 cm/m^2.

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