The risk of rupture in untreated aneurysms: The impact of size, gender, and expansion rate

Peter M. Brown, MD, David T. Zelt, MD, and **Boris Sobolev, PhD,** *Kingston, Ontario, Canada*

Objective: **The purpose of this study was to establish the risk of rupture as related to size of abdominal aortic aneurysm (AAA), gender, and expansion of the aneurysm.**

Methods: **Between 1976 and 2001, 476 patients with conditions considered unfit for surgery with AAA 5.0 cm or more were followed with computed tomographic scans every 6 months until rupture, surgery, death, or deletion from follow-up. Surgery was performed for rupture (n = 22), improved medical condition (n = 37), increase in size (n = 95), symptoms (n = 17), and other reasons (n = 24).**

Results: **Fifty ruptures occurred during the follow-up period. The average risk of rupture (and standard error) in male patients with 5.0-cm to 5.9-cm AAA was 1.0% (0.01%) per year, in female patients with 5.0-cm to 5.9-cm AAA was 3.9% (0.15%) per year, in male patients with 6.0-cm or greater AAA was 14.1% (0.18%) per year, and in female patients with 6.0-cm or greater AAA was 22.3% (0.95%) per year.**

Conclusion: **The risk of rupture in male patients with AAA 5.0 to 5.9 cm is low. The four-time higher risk of rupture in female patients with AAA 5.0 to 5.9 cm suggests a lower threshold for surgery be considered in fit women. The data regarding risk of rupture in patients with AAA 6.0 cm or more may allow more appropriate decision analysis for surgery in patients with unfit conditions with large AAA. (J Vasc Surg 2003;37:280-4.)**

During the past decade, many series have confirmed the minimal risk of rupture of abdominal aortic aneurysm (AAA) of less than 5.0 cm.[1-5] Furthermore, the two randomized trials from the United Kingdom and the US Veterans group[6-8] found no benefit for surgery with AAA of less than 5.5 cm.

There has been a widely shared opinion for many years that 6.0 cm represents the diameter of a large AAA with a significant risk of rupture.[9-13] Despite this consensus, few modern studies have attempted to quantitate the risk of rupture in patients with larger AAA.[14-17] The purpose of this study was to clarify the risk of rupture as related to size of AAA, gender of patient, and expansion rate of AAA in patients with AAA of 5.0 cm or more.

METHODS

Four hundred seventy-six patients were enrolled between 1976 and 2000 with follow-up until April 2002. All had computed tomographic scans every 6 months with review in a follow-up clinic after each scan. All patients had at least two measurements (n = 457) or one scan with an event of rupture or surgery (n = 19). Follow-up continued until rupture (n = 50), surgery for nonruptured AAA (n = 173), death (n = 79), deletion (n = 76), or April 1, 2002. This study is ongoing. Although no precise protocol for recommendation of surgery in this group was possible, elective surgery was usually recommended when it appeared clinically appropriate for increase in size, improved fitness, or symptoms.

Statistical methods. The primary outcome was the rate of rupture. To calculate the annual rate of rupture, we divided the number of ruptures by total number of patient-years in follow-up. Times to rupture were analyzed as prospectively collected observations to compare the rates as related to AAA size. The effect size was measured with relative rate derived from the Cox regression model in which we stratified on age group to avoid the assumption of proportional hazards for this variable. Because the size of aneurysm changed over time, we used models with time-dependent covariates. For example, to examine whether the increase in size to 6 cm increased rupture risk, we used a model variable that takes 1 if the patient had AAA size 6 cm or greater at some point before rupture and 0 otherwise. With fitting this model, we obtained a regression coefficient estimate that was interpreted as relative risk of those with AAA over 6 cm compared with patients with AAA less than 6 cm in diameter. Gender was entered as an independent variable in multivariate regression to assess adjusted effects. All cases removed from the follow-up without rupture were treated as censored observations.

To examine whether the increase in size to 6 cm or more increased the risk of rupture, we first reported the annual rate of rupture in the following four groups: 1, patients from the small AAA program whose AAA reached 5.0 to 5.9 cm; 2, patients from the small AAA program after AAA reached 6.0 cm; 3, patients first seen with unfit conditions with AAA 5.0 to 5.9 cm; and 4, patients first seen with AAA 6.0 cm or greater (Table I). The association

From the Department of Surgery, Queen's University.

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Reprint requests: Peter M. Brown, MD, Department of Surgery, Victory 3, Kingston General Hospital, 76 Stuart St, Kingston, Ontario, Canada K7L 2V7.

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Table I. Number of patients, ruptures, time at risk, annual rate (and standard error), and relative risk (and 95% CI) according to gender and aneurysm size

Description	*No. of patients*	*No. of ruptures*	*Time at risk (y)*	*Annual rate (standard error)*	*Relative risk (95 CI)*
Men, 5.0 to 5.9 cm	333	6	607	1.0% (0.01%)	1.0
Women, 5.0 to 5.9 cm	89	5	128	3.9% (0.15%)	4.0 (1.2,13.0)
Men, 6.0 cm or greater	186	28	198	14.1% (0.18%)	14.3 (5.9,34.5)
Women, 6.0 cm or greater	48	11	49	22.3% (0.95%)	22.6 (8.4,61.1)

Table II. Rupture rates when sudden deaths are considered to represent rupture

	No. of patients	*Ruptures*	*Sudden death*	*Total*	*Annual rate (standard error)*	*Relative risk*
Men, 5.0 to 5.9 cm	33	6	5	11	1.8% (0.01%)	1.0
Women, 5.0 to 5.9 cm	89	5	1	6	4.7% (0.20%)	2.6
Men, 6.0 cm or greater	186	28	3	31	15.6% (0.20%)	8.6
Women, 6.0 cm or greater	48	11	4	15	30.5% (1.10%)	16.8

between rupture risk and aneurysm size then was modeled with hazards ratio in the Cox proportional hazards regression. Because the size of aneurysm changed over time, we used models with a time-dependent covariate: 1 if the patient had AAA size 6 cm or greater at some point before rupture and 0 otherwise. In the analysis, we adjusted for gender to assess the proportionate hazards for this variable.

RESULTS

Four hundred seventy-six patients (377 male and 99 female), with a mean age of 73.4 years, with conditions considered unfit for surgery, were enrolled into the prospective monitoring program.[3] Seventy-six patients were deleted from that follow-up because of refusal (n = 37), advanced age (n = 16), terminal malignant disease (n = 14), move to another location (n = 4), and other reasons (n = 5).

Fifty ruptures occurred during 982 patient-years of follow-up. The risk of rupture stratified according to aneurysm size at last sizing and gender is shown in Table I. Note that the total number of patients in this table of 656 is greater that 476 because 180 patients had expansion from the 5.0-cm to 5.9-cm group to the 6.0-cm or greater group. The average risk of rupture in male patients with AAA 5.0 to 5.9 cm was low at 1.0% per year. The average risk of rupture in women with AAA 5.0 to 5.9 cm was four times as high as in men (relative risk, 4.0; $P < .001$). The average annual risk of rupture in men with AAA 6 cm or greater was 14.1% and in women was 22.3%.

The association between aneurysm size (as derived from the Cox regression model with a time dependent factor) showed a progressive relative risk of rupture with increasing size. In comparison with the 5.0-cm to 5.9-cm group, relative risks (95% CI) for the following size groups were: 6.0 to 6.9 cm, 5.2 (2.3 to 11.7); 7.0 to 7.9 cm, 8.0 (3.0 to 21.6); and 8.0 cm or greater, 31.3 (11.1 to 88.4).

In this group of 476 patients, there were 173 elective operations with eight deaths (3.8%). Seven of these 173 patients had endovascular repairs. Reasons for operation included improved medical condition (n = 37), increase in size (n = 95), symptoms (n = 17), and other reasons (n = 24). Of the 50 ruptures, 22 had surgery with 11 operative deaths. Twenty-eight patients died of rupture without surgery. Diagnosis of ruptured AAA in the nonsurgical group was clinical (n = 18), computed tomographic scan (n = 7), and autopsy (n = 3).

The 79 deaths in the follow-up group were cardiac (n = 30), pulmonary (n = 16), malignant disease (n = 9), stroke (n = 6), gastrointestinal (n = 4), motor vehicle accident (n = 1), and sudden unknown (n = 13). All unknown deaths had severe cardiac disease. The distribution of these patients with sudden deaths according to gender and size of AAA is shown in Table II. If one takes the most extreme approach that all of these patients with sudden death were ruptures, the annual risk changes only modestly as shown in Table II. The annual risk of rupture or unknown sudden death (possibly rupture) in men with 5.0-cm to 5.9-cm AAA is low at 1.8% (standard error, 0.01%).

We compared the expansion rate of AAAs that ruptured with nonruptured AAAs, as shown in Table III. In both the 5.0-cm to 5.9-cm group and the 6.0-cm or greater group, there was significantly greater mean expansion in the ruptured group. Median rate of expansion was also greater, as measured with the ratio at median, in ruptured AAA at both 5.0 to 5.9 cm and 6.0 cm or greater at entry, although with less statistical significance.

Because of the United Kingdom small AAA and Veterans group size limit of 5.5 cm, we analyzed our 5.0-cm to 5.9-cm group, looking for differences in risk of rupture in the 5.0-cm to 5.4-cm group and the 5.5-cm to 5.9-cm group (Table IV). Risk of rupture in men with AAA 5.0 to 5.4 cm and 5.5 to 5.9 cm was identical at 0.8% per year. There were no ruptures in the group of women with AAA 5.5 to 5.9 cm with 58 patients, although there were five ruptures in the group of women with AAA 5.0 to 5.4 cm.

Table III. Mean (standard error) and median (25th, 75th percentile) expansion rate (cm/y) among patients with ruptured and nonruptured AAA, according to gained size of aneurysm

	Gained size			
	5.0-5.9 cm		*6.0 cm or greater*	
	Mean	*Median*	*Mean*	*Median*
Ruptured	0.44 (0.03)	0.33 (0.13,0.53)	0.84 (0.32)	0.55 (0.22,0.75)
Nonruptured	0.21 (0.09)	0.12 (0.05,0.20)	0.39 (0.04)	0.27 (0.10,0.51)
	t test: $P < .05$	Ratio at median: $P < .1$	*t* test: $P < .01$	Ratio at median: $P < .1$

Table IV. Number of patients, ruptures, time at risk, annual rate according to gender, and aneurysm size

Description	*No. of patients*	*No. of ruptures*	*Time at risk (person-years)*	*Annual rate (standard errors)*
Men, 5.0 to 5.4 cm	301	4	500	0.8% (0.01%)
Women, 5.0 to 5.4 cm	71	5	60	5.1% (0.23%)
Men, 5.5 to 5.9 cm	217	2	226	0.8% (0.04%)
Women, 5.5 to 5.9 cm	58	0	97	-

CONCLUSION

Although the United Kingdom and Veterans group trials suggest that follow-up is appropriate until 5.5 cm,[6,8] several controversial areas remain with larger AAA. First, the use of a fast expansion rate as an indication for surgery "makes sense but has never been validated."[18] Limet, Sakalihassan, and Albert[19] in a study of 19 AAA ruptures found an expansion rate of 5% greater than median in ruptured AAA and suggested that risk of rupture was not only related to final size but to relative change in size of the aneurysm. We found increased mean and median expansion rates in patients with ruptured AAA (mean, 0.84 cm/y in those ruptured 6.0 cm or greater) as compared with nonruptured (mean, 0.39 cm/y in nonruptured 6.0 cm or greater). Lederle et al[17] also found a significantly greater mean AAA expansion rate in patients with probable rupture.

Another area of controversy relates to the management of female patients with AAA. Virtually all protocols, including our own,[2,3] the United Kingdom trial,[6] and the Veterans group trial,[8] managed both male and female patients with an identical threshold for surgery. Very few women were in the Veterans group trial (only 34 total, with four having AAA of 4.0 cm or greater),[20] allowing limited conclusions regarding women from this study. Within the United Kingdom study, however, women had a three-fold higher risk of rupture than men when their 1167 nonrandomized patients were included.[21] Furthermore, the mean diameter preceding rupture was smaller in women (5.0 ± 0.8 cm) than in men (6.0 ± 1.4 cm) in the United Kingdom trial.[21] We found the risk of rupture in women with AAA 5.0 to 5.9 cm to be four times that of men with AAA 5.0 to 5.9 cm, corresponding to an annual risk of rupture in women of 3.9% (standard error, 0.15).

This relative risk of rupture is identical to the relative risk of 4.0 times found in the long-term outcomes review of the United Kingdom small aneurysm trial.[7] On the basis of our results and the United Kingdom study, we would recommend that the threshold for surgery for women should be lower than for men and no higher than 5.0 cm in fit individuals when a low operative mortality can be shown.

There have been recent studies regarding risk of rupture in larger aneurysms as related to size. Jones, Cahill, and Gardham[14] reported "the largest series of untreated aneurysms 5 cm or greater" consisting of 57 patients in 1998. Unfortunately, these patients were not prospectively sized after entry and a median interval of 20 months existed between entry and rupture in the seven patients with AAA 5.0 to 5.9 cm. It is not clear that any of these patients had AAA less than 6.0 cm at rupture. Conway et al[15] reported a series of 106 patients with AAA greater than 5.5 cm who were turned down for surgery. Again, serial measurements were not taken so that more precise risks of rupture according to size were not possible. Powell and Brown[16] reported the risk of rupture in the United Kingdom trial patients along with another 1167 patients not randomized. They suggested that the "risk of AAA 5.0 to 5.9 cm in diameter is low but appears to escalate sharply for aneurysms greater than 6 cm in diameter."[16] None of these three studies allow estimates of risk of rupture according to size in patients with AAA over 5 cm.

Lederle et al[17] reported the Veterans group experience of rupture rate of large AAA in patients refusing or unfit for elective repair. Surprisingly, the risk of rupture in the 5.5-cm to 5.9-cm group was no different than the 6.0-cm to 6.9-cm group, with 1-year rupture risks of approximately 10% in both groups. The risk of rupture in our 333 male patients with 607 years of follow-up was only 1.0%. If all sudden deaths were included as ruptures, the risk in this group was only 1.8% annually. Furthermore, if one compared the rupture risk in men with AAA 5.0 to 5.4 cm with those with AAA 5.5 to 5.9 cm, the annual rate would be identical in our series at 0.8%.

The apparent discrepancy in the Veterans group results with our results will be critical to resolve. If there truly is a 1-year risk of rupture of almost 10% in men with AAA 5.5 to 5.9 cm, can one justify withholding treatment in the group just minimally smaller at 5.0 to 5.4 cm as suggested by the two randomized trials?

Surveillance programs for AAA may become increasingly important with an increasing threshold for aneurysm surgery. In the Veterans group screening program, 913 AAA of 5.0 to 5.9 cm were detected as compared with only 320 of 6.0 cm or greater.[22] The appropriate thresholds for fit men and women remain controversial, with those for women as low as 5.0 cm and those for men as high as 5.9 cm. Patient preferences may also be a critical issue, especially for fit patients, because the "issue of small AAA repair is only a question of when not if."[23]

Although surgical decision regarding elective aneurysm surgery remains complex, recent information from large prospective series will change the practice of aneurysm surgery with benefits to both patient morbidity and mortality and hopefully to patient satisfaction. The recent clarification of natural history of AAAs has lagged far behind therapeutic advances and yet may be equally important to our overall management of this quintessential peripheral arterial diagnosis.

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DISCUSSION

Dr John W. Hallett, Jr (Bangor, Me). These data are very important data as I think has been implied by Tom O'Donnell. Two questions for you.

When you choose to follow someone, there has to be an understanding that the patient will comply to that follow-up program. What was your compliance rate over time? And does that compliance rate vary depending on the age of the patient?

The second question, has the overall rupture rate in your community changed over the years because you are more interested in aneurysms? We know that about seven of 10 aneurysm patients in this country with a ruptured AAA did not know that they had an aneurysm until the day they ruptured. Has the total rate of rupture in your community changed at all in this long period of time?

Dr Peter M. Brown. Well, the first question, if you look at the number of patients who are deleted in the high-risk group, we encourage these patients to be followed. And they were all informed that this information was very important to us even though that surgery might not be forthcoming. And the average follow-up rate was about 4 years. So, we did what we could do to encourage this follow-up.

The rupture rate, even though we have had a known interest in aneurysm surgery, has remained steady over the last decades.

Dr Yaron Sternbach (Toronto, Ontario, Canada). I am a little perplexed by the differential risk of rupture for both men and women. I wonder if you can comment as to the relative size of the normal aorta in the men and women and whether you looked at a ratio of their aneurysm size to their normal aorta at any point?

Dr Brown. It is an interesting question. It is actually another study I am doing right now though, and I do not have those data. But all I can do is guess. And I am looking at both L2 transverse lumbar diameters and aortic size at the SMA. My guess is that there is about a 0.8-cm difference. I want to able to equate what 6 cm in men is to women, and I suspect it will be about 5.2 cm. I do not think there is anything that will be that much more provocative than simply women are smaller than men.