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Growth Rate and Associated Factors in Small Abdominal Aortic Aneurysms

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Objective. *To study the growth rate and factors influencing progression of small infrarenal abdominal aortic aneurysms (AAA).*
Design. *Observational, longitudinal, prospective study.*
Patients and methods. *We followed patients with AAA <5 cm in diameter in two groups. Group I (AAA 3–3.9 cm,* n=*246) underwent annual ultrasound scans. Group II (AAA 4–4.9 cm,* n=*106) underwent 6-monthly CT scans.*
Results. *We included 352 patients (333 men and 19 women) followed for a mean of 55.2±37.4 months (6.3–199.8). The mean growth rate was significantly greater in group II (4.72±5.93* vs. *2.07±3.23 mm/year;* p<*0.0001). Group II had a greater percentage of patients with rapid aneurysm expansion (>4 mm/year) (36.8* vs. *13.8%;* p<*0.0001). The classical cardiovascular risk factors did not influence the AAA growth rate in group I. Chronic limb ischemia was associated with slower expansion (≤4 mm/year) (OR 0.47; CI 95% 0.22–0.99;* p=*0.045). Diabetic patients in group II had a significantly smaller mean AAA growth rate than non-diabetics (1.69±3.51* vs. *5.22±6.11 mm/year;* p=*0.032).*
Conclusions. *The expansion rate of small AAA increases with the AAA size. AAA with a diameter of 3–3.9 cm expand slowly, and they are very unlikely to require surgical repair in 5 years. Many 4–4.9 cm AAA can be expected to reach a surgical size in the first 2 years of follow-up. Chronic limb ischemia and diabetes are associated with reduced aneurysm growth rates.*

Keywords: Small abdominal aortic aneurysm; Growth rate; Risk factors.

Introduction

The prevalence of abdominal aortic aneurysms (AAA) in the general population is 4–10%.[1–3] Small AAA (<5 cm-diameter) are becoming more common since the introduction of screening programs in different countries. Both the UK small aneurysm trial (UKSAT)[4] and the aneurysm detection and management trial (ADAM)[5] have shown a very small rupture risk in 4–5.5 cm aortic aneurysms, and conservative treatment is currently recommended. However, the widespread use of endovascular repair of AAA has added some controversy to the management of 4–5 cm AAA. The surgical decision is based on the AAA diameter, its expansion rate, the patient's age and risk, the individual center's surgical morbidity and mortality and the local experience of endovascular repair. Predicting the expansion of small AAA and modifying possible risk factors are important for clinical management. Female gender, smoking, hypertension, diabetes mellitus (DM) and peripheral artery disease (PAD) have been reported to influence aneurysm growth in a few published papers, with some conflicting results.[6–15]

The objective of our study was to establish the growth rate of a large series of <5 cm aortic aneurysms. We have also analysed which factors influence the expansion rate.

Patients and Methods

This is an observational, prospective study, ran from January 1988 until August 2004. We followed 352 consecutive patients diagnosed with a small asymptomatic infrarenal AAA. We used the definition of AAA established by McGregor (≥30 mm).[3,17,18] We defined an AAA as small when its initial diameter was 3–4.9 cm. In this report we include all the patients with <5 cm-infrarenal AAA in which we had at least 2 consecutive scans. Our exclusion criteria included:

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≥5 cm AAA diameter; location of the AAA other than infrarenal (juxtarenal, suprarenal, thoracoabdominal aneurysms); follow-up <2 scans; symptomatic aneurysms.

We registered demographic data, clinical characteristics, cardiovascular risk factors (tobacco use, hypertension, diabetes mellitus and hypercholesterolemia), and other comorbidities which could influence the aneurysm growth including chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease (PAD), chronic renal failure, or cancer.

We only included active smokers in the category of 'tobacco use'. Patients were regarded as hypertensive when they were being treated (diet or medication) or their blood pressure was registered above 140/90 twice in basal conditions. We included complete blood tests in the study of all our patients. Diabetes mellitus was defined if the blood glucose was ≥126 mg/dl or if the patient was being treated by an endocrinologist (diet, oral hypoglucemiants, insulin). Hypercholesterolemia was defined as total basal cholesterol levels ≥200 mg/dl, LDL levels ≥100 mg/dl or the patients were receiving specific medication or a supervised diet.

COPD was diagnosed when maximal voluntary ventilation (MVV) was <80% or the patients were already under treatment. Chronic renal failure was defined as serum creatinine ≥1.5 mg/dl. Peripheral artery disease was diagnosed when the patient complained of ischemic symptoms and had an ankle-brachial index (ABI) <0.90. We routinely performed a carotid duplex-scan on all the patients. We considered that cerebrovascular disease was present when we detected an asymptomatic significant (>50%) carotid stenosis or the patient had a positive history of TIA, minor or major stroke.

We classified the patients according to the AAA size: 3–3.9 cm (group I); 4–4.9 cm (group II). Patients diagnosed with a <4 cm-AAA were followed annually with an abdominal ultrasound (SONOLINE SL-2, SIEMENS) utilizing a 3.5 MHz probe. Aneurysms in group II were followed with an abdomino-pelvic contrast CT-scan every 6 months. We measured the greatest transverse and antero-posterior outer diameters of the infrarenal abdominal aorta. All the scans were performed in the Department of Radiology of our center.

We registered the serial AAA diameters in each patient. We calculated the mean aneurysm growth by dividing the total growth (mm) throughout the follow-up by the number of years of follow-up for every patient. We expressed the mean growth ± standard deviations (SD) in each group. We considered rapid growth when the AAA diameter increased >4 mm/year, because this expansion rate has been related to the likelihood of eventual operative repair of small AAA.[11] We also registered the number and percentage of patients in each group whose AAA reached 5 cm, and we calculated the mean number of months it took to reach this surgical size.

All the patients were followed until surgery or death. The aneurysms were repaired when they reached a 5 cm-diameter or if they expanded >1 cm/year or they became symptomatic. None of the aneurysms included in this series was repaired with endovascular techniques because the endovascular program was introduced in our center in June 2004. No patients were lost to follow-up.

We performed a descriptive statistical analysis, using the mean ± SD for quantitative variables and the number and percentage of patients for nominal variables. The expansion rates follow a normal distribution, as assessed by the Kolmogorov–Smirnov statistical test ($p<0.0001$). Averages were compared with the independent-samples *t*-test, and proportions were compared with the Chi-square test. We also used life tables, Kaplan–Meier and univariant Cox regression. The patient information was introduced into a FileMaker Pro 6 data base and the statistical analysis was performed using the SPSS 10.0 software (www.spss.com). We accepted $p<0.05$ as significant.

Results

We included 352 patients in the study, 333 (94.6%) men and 19 (5.4%) women, with a mean age of 71 years (40–89). The mean initial AAA size was 36.2 ± 5.61 mm (30–49). The mean follow-up period was 55.2 ± 37.4 months (6.3–199.8). During the follow-up 87 patients (24.7%) died, 1 (0.3%) of them because of a ruptured aneurysm, 1 (0.3%) during AAA elective repair. One patient in group I required an urgent surgical procedure because of a 3 cm ruptured iliac aneurysm when the AAA measured 3.7 cm. Two aneurysms ruptured in group II: one of them at a size of 5.6 cm in a patient who was considered unfit for elective surgery due to severe coronary artery disease, the other one at a size of 6 cm in a patient who had not complied with the follow-up protocol. The survival rates were 98.5% at 1 year, 90.6% at 2 years, 80.1% at 5 years and 52.8% at 10 years. The mean expansion rate for the overall group was 2.87 ± 4.39 mm/year.

Group I consisted of 246 patients with AAA sized 3–3.9 cm, and group II 106 patients with 4–4.9 cm-AAA. The cardiovascular risk factors and comorbidities of each group are shown in Table 1. The mean

growth rate was significantly greater in group II (4.72±5.93 *vs.* 2.07±3.23 mm/year; $p<0.0001$; *t*-test) (Fig. 1). Group II also had a greater percentage of AAA with rapid expansion (>4 mm/year) (36.8% *vs.* 13.8%; odds ratio-OR 3.63; CI 95% 2.12–6.3; $p<0.0001$; Chi-square). Rapid expansion was significantly associated with reaching a 5 cm-size and undergoing surgical repair in groups I and II ($p<0.0001$ for both; Chi-square). No expansion (0 mm) was observed in 25.2% of the AAA in group I and 17.9% in group II ($p=0.14$; Chi-square). Thirty-six (14.6%) aneurysms reached 5 cm in group I, and 72 (67.9%) in group II (OR 12.35; CI 95% 7.19–21.28; $p<0.0001$; Chi-square). The freedom from expansion to ≥5 cm were 100 and 74.4% after 1 year; 97.6 and 44.2% after 2 years; 82.4 and 18.4% after 5 years, respectively, for groups I and II (Fig. 2). The likelihood of the aneurysm reaching ≥5 cm was 11 times greater in group II than in group I (OR 11.09; CI 95% 7.29–16.89; $p<0.0001$; univariant Cox regression). The time it took for the AAA to reach a surgical size was significantly shorter in group II (22.4±19.6 *vs.* 49.7±21.6 months; $p<0.0001$; *t*-test).

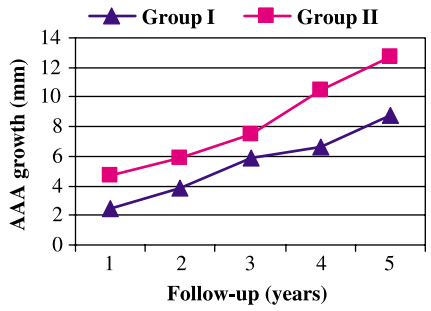
We observed a greater expansion in bigger AAA within group I (Table 2). We analysed the influence of the cardiovascular risk factors and comorbidities on the AAA growth rate in each group (Tables 3 and 4). Both gender and the classical risk factors (smoking, hypertension, DM, hypercholesterolemia) had no influence on AAA growth in group I. PAD was associated with a smaller growth rate (≤4 mm/year) (35.3 *vs.* 53.8%; OR 0.47; CI 95% 0.22–0.99; $p=0.045$; Chi-square). Patients with chronic renal failure had a higher AAA growth rate and more rapid expansion (>4 mm/year) (29.4 *vs.* 13.7%; OR 2.63; CI 95% 1.14–6.06; $p=0.02$; Chi-square) (Table 3).

AAA within group II had similar growth rates irrespective of their initial sizes (Table 2). Diabetic

Table 1. Cardiovascular risk factors and comorbidities in groups I and II (statistical analysis: *t*-test, Chi-square)

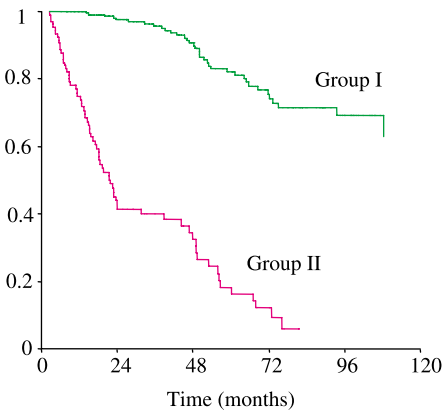
	Group I ($n=246$)	Group II ($n=106$)	OR (95% CI)	*p*
Age (years)	70±8.7 (40–89)	73±7.6 (53–89)	–	0.001
Gender (M/F)	235 (95.5%)/11 (4.5%)	98 (92.5%)/ 8 (7.5%)	1.74 (0.68–4.47)	0.24
Tobacco use	83 (33.7%)	30 (28.3%)	1.29 (0.78–2.12)	0.32
HT	123 (50%)	60 (56.6%)	0.77 (0.48–1.21)	0.26
Diabetes mellitus	43 (17.5%)	15 (14.2%)	1.29 (0.68–2.43)	0.44
Hypercho-lesterolemia	61 (24.8%)	32 (30.2%)	0.77 (0.48–1.21)	0.29
CAD	94 (38.2%)	49 (46.2%)	0.72 (0.45–1.14)	0.16
COPD	69 (28%)	45 (42.5%)	0.53 (0.33–0.85)	0.008
CRF	39 (15.9%)	21 (19.8%)	0.76 (0.42–1.37)	0.37
PAD	126 (51.2%)	36 (34%)	2.04 (1.27–3.28)	0.003
Carotid artery disease	45 (18.3%)	20 (18.9%)	0.96 (0.54–1.73)	0.9
Neoplasia	49 (19.4%)	29 (27.4%)	0.66 (0.39–1.12)	0.12

n, number; OR, odds ratio; CI, confidence interval; M/F, male/female; HT, arterial hypertension; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; PAD, peripheral artery disease.



AAA growth (mm)	Group I ($n=246$)	Group II ($n=106$)	*p*
1 year	2.45+/-4.26	4.7+/-5.13	**0.001**
2 years	3.87+/-4.08	5.89+/-5.94	**0.006**
3 years	5.85+/-5.39	7.5+/-7.72	0.202
4 years	6.64+/-6.5	10.43+/-6.3	**0.017**
5 years	8.8+/-7.69	12.77+/-8.58	0.095

Fig. 1. AAA growth rates in groups I and II in the first 5 years of follow-up (statistical analysis: *t*-test).



AAA <5 cm	Group I ($n=246$)	Group II ($n=106$)	*p*
1 year	100%	74.4%	
2 years	97.6%	44.2%	**<0.0001**
5 years	82.4%	18.4%	

Fig. 2. Life-table analysis of the AAA which have remained small (<5 cm) in groups I and II (statistical analysis: univariate Cox regression).

Table 2. AAA expansion variables within groups I and II (statistical analysis: *t*-test, Chi-square)

Group I ($n=246$)	3–3.4 cm ($n=155$)	3.5–3.9 cm ($n=91$)	OR (95% CI)	p
AAA growth rate (mm/year)	1.65±2.41	2.8±4.19	–	0.007
Expansion > 4 mm/year	17 (11%)	17 (18.7%)	0.54 (0.26–1.11)	0.091
No expansion (0 mm)	48 (31%)	14 (15.4%)	2.47 (1.27–4.79)	0.007
AAA reach 5 cm	14 (9%)	22 (24.2%)	0.31 (0.15–0.65)	0.001
Group II ($n=106$)	4–4.4 cm ($n=62$)	4.5–4.9 cm ($n=44$)		P
AAA growth rate (mm/year)	4.5±5.38	5.02±6.69	–	0.66
Expansion > 4 mm/year	24 (38.7%)	15 (34.1%)	1.22 (0.55–2.73)	0.63
No expansion (0 mm)	9 (14.5%)	10 (22.7%)	0.58 (0.21–1.57)	0.28
AAA reach 5 cm	39 (62.9%)	33 (75%)	0.57 (0.24–1.33)	0.19

n, number; OR, odds ratio; CI, confidence interval; AAA, abdominal aortic aneurysm.

patients in this group experienced a significantly lower mean AAA growth rate than non-diabetics ($p=0.032$; *t*-test). No other cardiovascular risk factor or comorbidity influenced AAA expansion (Table 4).

Discussion

We have analysed the outcome and expansion rates of a large series of <5 cm AAA. Ultrasound scanning is the method routinely used for the diagnosis and follow-up of small AAA, it is simple, safe, reliable, inexpensive and readily accesible. However, the measurement of infrarenal aortic diameter by ultrasound can differ ±2 mm compared to CT.[16] AAA of <4 cm-diameter are associated with a negligible risk of rupture. CT measurements are appropriate for follow-up of faster growing 4–4.9 cm AAA, which are very likely to reach a surgical size in the short-term.

Table 3. Analysis of AAA growth rate (mm/year) according to gender, cardiovascular risk factors and comorbidities in group I ($n=246$) (statistical analysis: *t*-test)

	Male	Female	p
Gender	2.07±3.25	2.08±2.74	0.99
	Yes	No	p
Tobacco use	1.87±2.03	2.18±3.69	0.47
HT	2.07±2.68	2.08±3.7	0.99
Diabetes mellitus	1.72±2.34	2.15±3.38	0.42
Hypercholesterolemia	2.15±2.54	2.05±3.43	0.84
CAD	2.09±2.47	2.06±3.62	0.95
COPD	2.01±2.35	2.1±3.51	0.85
CRF	3.63±6.16	1.78±2.2	0.001
PAD	1.69±2.35	2.48±3.91	0.053
Carotid artery disease	1.87±2.46	2.12±3.38	0.64
Neoplasia	2.4±5.22	1.99±2.51	0.43

HT, arterial hypertension; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; PAD, peripheral artery disease.

Table 4. Analysis of AAA growth rate (mm/year) according to gender, cardiovascular risk factors and comorbidities in group II ($n=106$) (statistical analysis: *t*-test)

	Male	Female	p
Gender	4.92±6.07	2.19±2.99	0.21
	Yes	No	p
Tobacco use	4.42±5.56	4.84±6.1	0.75
HT	5.24±7	4.03±4.12	0.30
Diabetes mellitus	1.69±3.51	5.22±6.11	0.032
Hypercholesterolemia	3.64±5.32	5.18±6.16	0.22
CAD	5.02±6.27	4.46±5.67	0.63
COPD	4.57±6.32	4.82±5.68	0.83
CRF	4.34±4.77	6.24±9.28	0.19
PAD	4.34±6.5	4.91±5.66	0.64
Carotid artery disease	3.22±5.67	5.07±5.97	0.21
Neoplasia	5.1±5.56	4.57±6.1	0.69

HT, arterial hypertension; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; PAD, peripheral artery disease.

The behaviour of AAA strongly depends on the AAA diameter.[6,10,12,15,17,18] AAA 3–3.9 cm expand slowly, with a mean growth rate of 2.07 mm/year, and none has ruptured throughout the follow-up. Over 25% did not expand at all over a mean follow-up of 3.5 years. Some series have reported expansion rates of 1.1–7 mm/year with 11.4–34% absence of AAA growth.[6,10–14,17–25] The UK SAT estimated 3–3.9 cm-AAA rupture risk to be 0.9 per 100 person-years.[4,6] These are often young patients with high long-term survival rates who can be safely managed conservatively. Less than 20% of the patients will need a surgical repair of their AAA in the first 5 years of follow-up. The finding that larger AAA within this group (3.5–3.9 cm) show a greater growth rate than smaller ones (3–3.4 cm) (2.8 *vs.* 1.65 mm/year) has also been reported by other authors (1.5–4.1 *vs.* 0.9–3.3 mm/year),[11,18] but Solberg recently reported a similar growth rate in both subgroups (1.75 *vs.* 1.8 mm/year).[7] AAA smaller than 3.5 cm are stable, <10% reached 5 cm during the whole follow-up period. Larger 3.5–3.9 cm-AAA are more important and in our series 24.2% reached a surgical size. Santilli reported similar results with 0 and 27% AAA reaching 5 cm, respectively.[11]

AAA of 4–4.9 cm-diameter expanded twice as fast in our series. Other authors have reported similar results, with mean growth rates of 3–6.9 mm/year.[10,14,17–20,22–25] The risk of rupture of

these AAA has been estimated to be 0.6–2.1% per year.[5,17,26] In contrast to our series, Solberg found an increased growth rate in the larger AAA in this group (4.5–4.9 *vs.* 4–4.4 cm: 3.36 *vs.* 2.31 mm/year).[7] Two thirds of the AAA reached 5 cm in a mean time of 2 years. Brown calculated that patients with 4.5–4.9 cm-AAA were 6.8 times more likely to require surgical repair than those with 3–3.4 cm at entry; 52% of their 4.5–4.9 cm-AAA underwent surgery with a mean follow-up of 2.2 years.[10] In the ADAM study 27% of 4–5.5 cm-AAA randomized to the surveillance group had undergone surgical exclusion at 2 years' follow-up, and over 60% at 5 years.[5] Young age and larger AAA size at the initial evaluation increased the likelihood of surgical repair during the follow-up.[15] AAA of 4.5–4.9 cm-diameter expand quite rapidly and are expected to reach a surgical size in 2–3 years. So, patients should be evaluated and surgical treatment could be offered to fit patients, considering of course every case individually. It is safe to follow AAA <4.5 cm-AAA.

We routinely perform an abdominal ultrasound scan in all our patients with PAD as part of their vascular evaluation, and we have found a high incidence of AAA in these patients (13%), most of them (70.9%) <4 cm in size.[27] This explains why there is a significantly higher percentage of PAD in patients with 3–3.9 cm AAA. PAD has proved to be a protective factor against rapid expansion in our series. Its effect on AAA expansion rates shows a very strong trend ($p=0.053$), which can virtually be considered significant. And its influence on the rate of rapid expansion is statistically significant ($p=0.045$), which reinforces the validity of the association. It was also associated with slower AAA expansion in the UK SAT, with growth rates reducing by 0.2 mm/year for each fall of 0.2 in ABI.[6] In contrast, chronic renal failure has been associated with a mean growth rate twice that of patients with normal renal function. Chang and Englund found a correlation between older age, recent stroke and cardiac disease with rapid AAA growth,[13,14] results which have not been confirmed in our series. Beta-adrenergic blockade has also been correlated with slower AAA growth.[14] Some authors have reported an association between hypertension and greater expansion rates[8,11,15] while others have not confirmed this point.[6,9,14] Smoking has also been associated with higher expansion rates of small AAA in most but not all series.[6,9,12–14] We only considered current smokers in our analysis because we believe only active smoking can have an effect on the disease. Other series have included both current and previous smokers, with a global prevalence of over 90%. The prevalence of both previous and current smokers in our series was 80.1% ($n=282$) and we are fairly successful in achieving smoking cessation. All this might help explain the difference in our results on the impact of smoking compared to other series. Hypercholesterolemia seems to play a minor role in the pathogenesis and expansion of small AAA.[6,9,12,13] A slower AAA growth rate has been observed in diabetic patients, with a crude reduction of over 30%.[6,11] This may be explained by the modification of collagens and decreased synthesis and activity of metalloproteinases induced by diabetes.[28] In our series, only diabetes was significantly associated with slower expansion in 4–4.9 cm-AAA.

The data reported in this and other published series can provide a useful guideline of the likelihood of growth of small AAA, and it can be of value in making operative decisions on individual patients. Our series confirms the fact that the expansion rate of small AAA increases with the AAA diameter. Our follow-up protocol, which is widely used in several countries, is safe. AAA smaller than 4 cm expand slowly, they are very unlikely to require a surgical repair in 5 years. However, many 4–4.9 cm AAA can be expected to reach a surgical size in the first 2 years of follow-up, so the patients can be conveniently prepared for elective repair. Some patients with specific risk factors, like chronic renal failure or 4.5–4.9 cm AAA size, should be monitored closely to determine the appropriate time for aneurysm repair.

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