Detection, Management, and Prospects for the Medical Treatment of Small Abdominal Aortic Aneurysms

Janet T. Powell, Anthony R. Brady

Abstract—Small abdominal aortic aneurysms, up to 5.5 cm in diameter, are very common. Ultrasonography is the most cost-effective method of detecting these aneurysms and keeping them under surveillance, because the natural history is 1 of continued expansion. The expansion rate is in the range 0.25 to 0.35 cm/y and is fastest in current smokers. From a study of expansion rates, it has been possible to formulate guidelines for the intervals at which surveillance should occur. Although the evidence from randomized trials indicates that early, open, elective surgery for small aneurysms does not save lives, when aneurysms exceed 5.5 cm in diameter, either open or endovascular surgery is recommended. To prevent small aneurysms reaching the 5.5-cm threshold, new treatments to reduce the expansion rate by \( \frac{1}{2} \) need to be designed, based on the underlying pathologic processes: proteolysis and inflammation. Any proposed treatments, including statins, will need to be tested in clinical trials. (Arterioscler Thromb Vasc Biol. 2004;24:241-245.)

Key Words: aneurysms  aorta  smoking  ultrasonography

Abdominal aortic aneurysm (AAA) too often is a silent disorder, without symptoms until the catastrophic events of aneurysm rupture. In this respect, there are similarities with hypertension, also often silent until a major event, such as stroke, occurs. The similarities stop at this point. Most advanced health economies have family medicine (general practice)—based screening programs for hypertension. There are a variety of effective therapeutic strategies based on our scientific knowledge about blood pressure regulation. Effective drug and lifestyle treatments of hypertension reduce the risks of stroke and other cardiovascular events. In contrast, AAA screening programs are not widespread, and current scientific knowledge about the processes that drive aneurysm expansion and eventual rupture has not been sufficient to support drug development and/or clinical trials to prove therapeutic efficacy.

Detection of AAAs

AAAs, particularly large AAAs, can be detected by manual palpation of the abdomen, although this becomes difficult with obese patients, and estimation of the transverse AAA diameter is inaccurate. Small AAAs, defined as a maximum infrarenal aortic diameter of \( \leq 3 \) cm, often go undetected by physical examination. Formal evaluation has shown that abdominal palpation has neither the sensitivity (at best 68%) nor specificity (75%) needed for a screening program.1 The sensitivity is highest in patients with an abdominal girth \( <100 \) cm and increases with AAA diameter.1 Physical examination has reasonable sensitivity (82%) for detecting AAAs \( \geq 5 \) cm in diameter but is poor for smaller aneurysms.1 Ultrasonography is a relatively inexpensive, noninvasive method of high sensitivity (\( >98\% \)) and specificity (almost 100%) for the detection of AAAs.2 Ultrasonography measures the abdominal aortic anterior-posterior diameter more accurately and reproducibly than the transverse diameter. Even so, unless ultrasonographers are trained very carefully, the repeatability of anterior-posterior diameter measurements might be as high as \( \pm 8 \) mm.3 The neck of the aneurysm and suprarenal aorta might be more difficult to visualize with ultrasonography, and most ultrasound screening studies report only the maximum
anterior-posterior diameter. However, ultrasonography (Figure 1) also can provide information about the size and shape of the luminal thrombus in an AAA and the presence of iliac aneurysms.

Ultrasonography is the detection method of choice for AAA screening: it is cheap and noninvasive and can be used easily in a community setting. A randomized trial to evaluate the efficacy of screening for AAA, in men aged 65 to 79 years, used ultrasonography for detection. Most screening-detected AAAs were small (3 to 5.9 cm in diameter), in the range where surveillance is a safe policy. Although screening halved aneurysm-related deaths within 4 years, there was no associated reduction in total mortality. With the possibility of national screening programs being discussed, studies have evaluated the efficacy of screening men aged 65 years only. Although the prevalence of AAA increases with age, the evidence suggests that all those who go on to develop an AAA will have an aortic diameter >2.5 cm at age 65 years. For those men with an aortic diameter <2.6 cm at age 65 years, rescreening 10 years later detected no further AAA, and no interventions for AAA or deaths from AAA had been recorded.

The screening trial recruited only men, and 4.9% were identified as having an AAA ≥3 cm in diameter. Health economic analysis of the screening trial, wherein AAA screening costs were on per-person basis, suggested that screening white men, with high acceptance rates for screening, was on the margins of cost-effectiveness. Cost-effectiveness might be achieved by the introduction of more selective screening. In contrast, screening in areas of socioeconomic deprivation, where acceptance of screening is low, could lead to screening becoming cost-ineffective. Although medical history, including a history of never smoking, might suggest that some men do not need screening, there has been no formal evaluation of using screening criteria other than sex. The prevalence of AAA in women >65 years is only 1.6%, and there is no suggestion that the sensitivity of ultrasound detection is lower in women than in men.

Other imaging techniques, such as computed tomography, angiography, and magnetic resonance angiography, are used to define the extent of the AAA, anatomy of the neck, and the location and patency of branching arteries in preparation for aneurysm repair but not for routine detection of AAA.

Management of AAAs
Randomized, controlled trials have shown that a policy of early, elective surgery for small AAA (4.0 to 5.5 cm in diameter) does not save lives. These trials also showed that a policy of surveillance until the AAA diameter exceeded 5.5 cm (approximately 3 times the normal aortic diameter) was safe and associated with a very low rate of AAA rupture, ≤1% per annum. Although the total operative mortality rate at 30 days for combined elective and emergency repair was 5.8% in the British trial, the American trial showed that even with a lower mortality rate (2.7%), early, elective surgery still did not save lives. The current level 1 evidence with respect to the management of AAAs is summarized in Figure 2. This evidence has persuaded surgeons that for men, in the absence of symptoms referable to the aneurysm, surgical intervention should not be considered until the AAA diameter exceeds 5.5 cm. Delaying surgery until the diameter exceeds 5.5 cm appears not to be associated with an increased operative
mortality risk, despite the aging of the patient. The decision to operate on larger AAAs (>5.5 cm) is based on convention, not evidence, but the risk of rupture appears to increase to 25% per annum for AAAs ≥6 cm in diameter. After an aneurysm reaches 8 cm in diameter, the risk of rupture rises to 26% within 6 months.

Only 1 of the 2 small aneurysm trials contained a sizeable proportion of women. AAA is a male-dominated disorder, but 17% of the UK Small Aneurysm Trial patients were women. These women had a 4-fold increase in the risk of AAA rupture compared with men, and aneurysms ruptured at smaller diameters (mean, 5 cm vs 6.2 cm in men). Since Dubost et al. pioneered the approach in 1951, the decision has stood the test of time and produced a durable result. Under general anesthetic, the aorta is approached and occluded by the graft, a femorofemoral crossover graft is used. The aorta is clamped proximally below the renal arteries proximal to the aneurysm and distal to the aneurysm. The aneurysm sac is opened and thrombus is removed before a polyester (Dacron) inlay tube graft is sutured into the normal-diameter aorta above and below the aneurysm. The graft is oversewn with the aneurysm sac before proceeding to closure of the approach incision. In a minority of cases, it is necessary to use a trouser-shaped graft, with the distal limbs sutured into the iliac arteries. This is a major surgical procedure: patients stay in hospital for ~7 days after the operation, and there is significant mortality associated with the procedure, ~5% in population-based studies. In population studies, operative mortality in men and women might be similar. However, in the longer term (beyond 30 days), women appear to have worse survival than age-matched controls in the general population.

In 1986, Volodos and colleagues first described endovascular repair of an AAA with a stent-graft device introduced through the femoral artery. The technology has advanced rapidly, and today several devices are available commercially. The Dacron graft is introduced through the femoral artery and positioned under fluoroscopic control before the proximal end is fixed against the aortic wall with a balloon-expandable stent: hooks and barbs might be used for increased adherence. Some devices have fenestrations to permit fixation above or across the renal arteries. Most contemporary endovascular devices are aortouniiliac, with the distal limb also being held in place with a balloon-expandable stent. Because the contralateral iliac artery is occluded by the graft, a femorofemoral crossover graft is performed to continue perfusion of the contralateral limb. This procedure is less invasive than open surgery and can be performed under epidural or even local anesthesia. Patients recover rapidly and might leave hospital as soon as 2 days after the procedure, operative mortality being ~2%. Such advantages might be offset by several factors. The technique might be suitable for less than half of patients with AAA, the principal exclusion criteria being short aortic necks and angulated or tortuous iliac arteries. These contraindications appear to be particularly common in women. Several devices have had major complications and have been withdrawn from the market, the trials and tribulations of new technologies. The durability of endovascular repair is uncertain; continued postprocedural surveillance by computed tomography is common. Usually, the AAA sac shrinks, sometimes endoleaks are observed, and the rupture rate after endovascular repair is 1% per annum, similar to that for AAAs <5.5 cm. The generalizability and durability of endovascular repair versus conventional open repair is being tested in clinical trials. These trials have operative mortality, late mortality, and costs as their primary outcome measures but are unlikely to report until late 2004 or beyond.
Prospects for Medical Therapy to Limit Aneurysm Expansion

The mean growth rate of small AAAs (\( \leq 5.5 \) cm in diameter) is 2.6 mm/y, increasing with aneurysm diameter, when assessed with flexible multilevel modeling for patients referred to vascular surgeons.\(^{22}\) This likelihood-based approach avoids the upwards bias of linear regression modeling when the growth series is truncated because of an observed measurement, as happens when surgery is undertaken when the aneurysm diameter is \( > 5.5 \) cm.\(^{21}\) The use of multilevel modeling suggests that AAA expansion rates are lower than previously suggested in a cohort of patients identified through screening.\(^{13}\) A realistic therapeutic goal is to reduce the expansion rate of a 4.0-cm AAA from 2.6 mm/y to 1.3 mm/y, so that the time taken for the AAA to exceed the 5.5-cm threshold for consideration of surgery is increased from 5 to 6 years to \( > 10 \) years. Therapeutic strategies should be based on understanding the pathologic process (Figure 3). For those who believe that aneurysms are caused by atherosclerosis, it would be prudent to focus on cardiovascular risk factor reduction, a strategy that might have additional health benefit. There has been only 1 adequately powered, randomized, clinical trial of the effect of medical therapy (\( \beta \)-blockers or antibiotics) on AAA expansion. Propranolol was shown to have no effect on the expansion rate of small AAAs, which contradicts the suggestions of observational studies.\(^{24,25}\) Moreover, propranolol was poorly tolerated, and patients allocated to active drug treatment had a worse quality of life than did placebo controls. Neither systolic blood pressure nor serum cholesterol concentration is associated with AAA expansion.\(^{22}\) None of the statin trials have reported on aortic diameters. In addition, atherosclerotic burden, as measured by reduced ankle pressures, was associated with slower AAA expansion rates.\(^{22}\) Smoking cessation might be an effective approach to reducing AAA expansion rates. Several studies have shown that expansion rates are faster in current smokers than ex-smokers,\(^{26,27}\) but expansion rates are likely to be reduced by only 25% or less. Additional therapeutic strategies will be needed, and these should be focused on the biology of proteolytic connective-tissue remodeling or neutralization of inflammatory cascades in the AAA wall.\(^{28}\)

Most of the focus on proteolytic enzymes in the aneurysm wall has centered on the matrix metalloproteinases MMP-2, MMP-3, and MMP-9.\(^{29–31}\) These enzymes are not unique to arterial tissue and are involved in the normal processes of connective-tissue turnover and repair. Doxycycline is an effective inhibitor of MMPs and has been used to repress AAA formation in several animal models.\(^{32–34}\) Although phase II studies have shown the safety of doxycycline therapy, results from large clinical trials are not yet available.\(^{35}\) However, doxycycline will inhibit all metalloproteinases, including those needed for tissue repair and remodeling, and there are indications that long-term inhibition of MMPs might lead to increased enzyme abundance in the longer term.\(^{36}\) In addition, inhibition of MMPs might unmask the role of other classes of proteases (serine and cysteine) that participate in aneurysm development and expansion.\(^{37,38}\) Selective MMP inhibitors are being developed,\(^{39}\) and such an approach would offer a more effective therapeutic strategy if pivotal enzymes can be identified. Evidence for the role of the serine protease urokinase plasminogen activator (uPA) is supported by gene deletion studies in mice.\(^{40,41}\) uPA is inhibited by the serpin plasminogen activator inhibitor 1 (PAI-1). Further support for the role of uPA might come from the association of functional gene polymorphisms with a phenotype of rapid AAA expansion, a logical strategy to identify proteases associated with AAA expansion. The feasibility of this method has been demonstrated for the uPA inhibitor PAI-1. Patients of the PAI-1 \(-675 \) 5G5G genotype (associated with the lowest plasma levels of PAI-1) had AAA expansion rates 0.5 mm/y higher than did patients with the 4G5G and 4G4G genotypes.\(^{42}\) This is a small effect (<20%), and candidate genes will have to be selected carefully so that chance associations of genotype with AAA expansion can be avoided.

Alternatively, therapeutic strategies could be directed at preventing the destructive inflammatory cascades of the aneurysm wall. Although nonsteroidal anti-inflammatory drugs can limit experimental AAA formation and might attenuate AAA expansion in humans, more selective drugs targeted to the site of pathology are likely to be required.

Summary

Good-quality evidence is now available to guide the detection and management of small AAAs. In contrast, there are golden opportunities for vascular biologists and drug designers to improve the prospects for the medical management of this condition.

References


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