

**JUSTIN HURIE, MD:** Basically, I'm the vascular surgeon here at Wake Forest University Hospital. Today's topic is modern treatment of abdominal aortic aneurysms. So this is an overview of the topics that I plan on covering over the next 40 minutes, which will leave time for the questions and discussion at the end.

Given the variety of people in the audience today, we will briefly review definitions and pathophysiology of aneurysms. We will then tackle epidemiology and risk factors for the development of aneurysms. Next, we move on to the natural history and clinical presentation of patients with abdominal aneurysms. Finally, we will discuss treatment options and outcomes including newer technologies, such as fenestrated endografts.

The slide on the right is an image of our first fenestrated endograft performed at Wake Forest University Hospital earlier this year. We're only one of two centers in North Carolina performing this procedure, and the only center in the triad.

The word aneurysm comes from the Greek language, where it means to dilate. We consider a vessel that is greater than 1 and 1/2 times its normal size to be an aneurysm. It is considered ectatic if it is enlarged, but below this cut off.

As you can see from the image on the right, the average diameter of the adult aorta is up to approximately 2 centimeters, which means that we consider an aneurysm beginning at 3 centimeters. Now, abdominal aortic aneurysm was first described by Fernel in 1581 as "the dilatation of an artery full of spiritous blood." For those of you who have seen an open abdominal aneurysm repair, you know that still holds true today.

The first modern repair of an abdominal aortic aneurysm was performed by Charles Dubost in 1951. I have a correction on my slides. It was actually Cid Dos Santos who performed the first iliac endarterectomy four years earlier.

So the normal aortic wall as illustrated on the top image, is well-organized, and composed of the intima, media, and adventitia. The destruction of elastin is believed to play a large role in the development of aneurysms. Elastin is a load-bearing protein that is sometimes thought of as resisting aneurysm formation.

The elastin content of the aortic wall is variable with the highest concentration found in the ascending aorta. The decrease in elastin between the supra- and infrarenal aorta may partially explain the propensity for aneurysm formation in the infrarenal segment compared to the suprarenal aorta. Elastin is not synthesized in the adult aorta and its half-life is 40-70 years, which partially explains the higher rate of aneurysm formation in the elderly.

This is compared to collagen, which can be synthesized throughout life. Collagen acts as a safety net and its loss can play an important role in aneurysm rupture. The lower slide demonstrates the loss of elastin and the presence of inflammation within aneurysms.

The formation of abdominal aortic aneurysm is a complex process that appears to be the result of inflammation, proteolysis, loss of smooth muscle cells and the formation of mural thrombus. Chronic inflammation has been found to be due to mechanical and oxidative stresses. Patients with an abdominal aortic aneurysm have been found to have elevated levels of angiotensin II, tumor necrosis factor alpha, interleukin 1 and 6, as well as interferon gamma.

As we discussed earlier, the formation of abdominal aortic aneurysm is dependent on degradation of elastin and collagen. Patients have been found to have markers of proteolysis, including elevated levels of matrix metalloproteinases 2 and 9. These proteins are believed to be crucial for aneurysm formation, as prior studies have demonstrated that MMP-2 and 9 knockout mice are resistant to aneurysm formation.

Formation of abdominal aortic aneurysm appears to involve apoptosis of smooth muscle cells within the media. Smooth muscle cells appear to play an important role in repairing damage caused by proteolysis and inflammatory processes. Finally, the formation of mural thrombus appears to be related to hypoxia within the media, which contributes to inflammation and neovascularization.

Well, that's enough pathology for the day. When you talk about epidemiology, you always have to discuss prevalence and incidence. Prevalence refers to the number of people in a population that have a condition. Abdominal aortic aneurysms are relatively common with a prevalence of 4-9% in men over 65, and around 1% in women over 65. Large aneurysms are more rare, with the rate of around a 0.5% in men 50 to 79.

The prevalence of an abdominal aortic aneurysm based on autopsy studies illustrates the variation based on location and gender. As you can see from the slide on the right, the increase in aneurysm prevalence in men appears to start in their 60s; while there's an increasing prevalence in aneurysm formation in women, especially in their '70s.

In order to discuss the number of ruptured aneurysms, we have to talk about incidence. Incidence refers to the number of new events within a certain time period. For example, we use incidence to discuss the number of people that have flu in a certain year.

In the slide on the right, there appears to be an increase in the incidence of ruptured aneurysms over the study time period, granted that most of them ended in the late 1980s. The other item of note on the slide is the high mortality rate of patients with a ruptured aneurysm. Despite improving technology, ruptured aneurysms still have a mortality rate in the 80% to 90% range. The good news is that ruptured aneurysms are relatively rare, even with a rate of 21 per 100,000 people years.

As we discussed earlier, most patients that are incidentally found have an aneurysm have a small aneurysm that measures less than 5 centimeters. The first question from a patient is usually about the natural history of aneurysms. Unfortunately, 98% of aneurysms grow over time; but the growth rate tends to be slow, especially at small diameters.

Abdominal aortic aneurysms that are 3 to 4 centimeters grow at approximately 0.2 centimeters per year. Most patients have a variable growth pattern so periodic surveillance is recommended, even for small aneurysms.

Pictured on the right is a CAT scan of a patient with an infrarenal aneurysm that has been reconstructed to three dimensions. This technique allows us to more accurately measure the dimensions of an aneurysm.

The goal of aneurysm surgery is to prolong and improve quality of life. The most commonly used techniques for determining rupture risk is based on aneurysm size. As you can see on the left, the risk of aneurysm rupture increases significantly above 5 centimeters. The image on the right is of a patient with a large ruptured aneurysm we were able to treat with an endograft.

When talking with patients about aneurysms, I like to divide the list into reversible and irreversible categories. In terms of irreversible risk factors, aneurysm formation is associated with being male, advanced age, family history and heart disease. The reversible list is much shorter and basically comes down to smoking. While quitting smoking will not reverse an aneurysm, it has been shown that patients that continue to smoke have an elevated growth rate compared to patients that have quit.

The first major risk factor we discuss is age. As you can see from the slide, the prevalence of patients with an abdominal aortic aneurysm increases steadily with age. In male patients that are less than 55, there is approximately a 1% risk of having an aneurysm, and even less having a large aneurysm. By the time a male patient is 80, 10% of patients will have an aneurysm.

The second major risk factor is gender. And as we saw earlier, men have a higher rate of aneurysm formation than women. Some have hypothesized that the difference may be due to the fact that women on average have smaller aortic diameters.

Despite having fewer women with aneurysms, it has been found that women appear to rupture their aneurysms at a smaller aortic diameter, usually measuring at 1/2 to 1 centimeter smaller than men. This has contributed to some physicians using a 5 centimeter cut off for repair of an abdominal aortic aneurysm, especially in a healthy woman.

As you can see from the slide, smoking is the strongest risk factor for the formation of an abdominal aortic aneurysm. The correlation between smoking and aneurysm formation includes duration of smoking and active tobacco use. Furthermore, there's evidence that continued smoking increases the growth rate by about 20% compared to nonsmokers.

Minor risk factors for aneurysm formation include patients with claudication, coronary artery disease, cerebrovascular disease, and hypertension. There are a number of similarities between patients with atherosclerosis and aneurysms. Family history of an aneurysm is also relatively common with about 10% to 20% of patients with a first degree relative having an aneurysm, even without an identifiable genetic predisposition such as Marfan syndrome.

There are a few protective factors as well. There appears to be a lower rate of aneurysm formation in African Americans, as well as women. There may be also a lower rate of aneurysm formation in patients with diabetes. There's some evidence that diabetes may modify collagen and decrease matrix metalloproteinase activity, making the aortic wall stiffer and less prone to aneurysm formation. Unfortunately, it doesn't serve as a good treatment strategy.

[LAUGHTER]

There are 9,000 to 17,000 deaths from aneurysms yearly in the United States. Based on a 2010 population of 648,000, there'd be expected to be approximately 26 ruptured aneurysms per year in Winston-Salem, although this estimate may be artificial low as there's a high mortality rate and most patients are asymptomatic prior to rupture. Aneurysms are the 13th leading cause of death and responsible for 0.8% of all deaths. In an effort to decrease the number of aneurysm deaths, there are approximately 45,000 aneurysm repairs per year in the United States alone.

So, diagnosis. The screening modality of choice for an abdominal aortic aneurysm is ultrasound. It's noninvasive and doesn't involve contrast exposure. The sensitivity is greater than 95% and specificity is nearly 100%.

Sensitivity is the ability of the test to identify patients with disease, so the ultrasound is able to identify at least 19 of 20 patients that have an aneurysm. Specificity, on the other hand, is the ability of the test to identify people without the disease. As you can see on the slide, the majority of patients that are identified in screening tests have small aneurysms and require periodic surveillance.

The United States Preventive Services Task Force has issued guidelines regarding the screening of patients for an aneurysm. They recommend a one-time screening of men who are 65 to 75, who have ever smoked, which is considered to be greater than 100 cigarettes. Based on this definition, 70% of men in this age group are eligible for screening.

This recommendation is partly based on the finding in a mass trial performed in the United Kingdom. This trial found that screening halves the rate of aneurysm related mortality within four years, although did not change overall mortality rates. The recommendation against screening for women is a result of the relatively low number of women that develop an aneurysm. Unfortunately, it does not take into account family history or other risk factors for aneurysm formation.

As you can see from this slide, there appears to be a beneficial effect of statin use for patients with a small aneurysm. There been a large number of observational studies that are compiled in this meta analysis that appear to indicate a slower rate of growth for patients on statins.

One potential mechanism of action is that statin use has been shown to decrease MMP9 levels within the aneurysm wall itself. Unfortunately, there have been no randomized studies to confirm these findings. An additional benefit of statin use relates to the high cardiac morbidity associated with aneurysm repair. There's a high prevalence of coronary artery disease in patients with an aneurysm, which was well-documented by Dr. Norman Hertzner from the Cleveland Clinic.

There have been multiple studies which have demonstrated a beneficial effect of decreasing death from cardiovascular causes in patients with an aneurysm. All together, it appears the patient's with an aneurysm likely benefit from statin use. And I would probably benefit from a drink of water.

[LAUGHTER]

So there also appears to be preliminary evidence that patients taking an angiotensin converting enzyme inhibitor may have a lower rate of aneurysm rupture. This comes from a large administrative database in Ontario, Canada. To the contrary, a subgroup analysis of the patients in the UK small aneurysm trial found no difference in the rate of aneurysm expansion with an ACE inhibitor. These conflicting results indicate the need for additional study to evaluate the role of ACE inhibitors for patients with an aneurysm.

There's some evidence that doxycycline may decrease the rate of aneurysm expansion. Initially, the use of doxycycline began in response to the high rate of chlamydia pneumoniae, which was found within the wall of aneurysms themselves. Baxter and colleagues found that a 100 milligram dose twice a day was useful in decreasing the rate of aneurysm expansion over a three-month period.

A more contemporary mechanism of action is related to doxycycline decreasing rates of MMP expression in patients with aneurysms. There's some difficulty tolerating doxycycline, so it's not more universally used.

There's preliminary evidence from animal studies that beta blockers also decrease the rate of aneurysm growth. The beneficial effect of beta blockers appeared to be corroborated by retrospective series, although there were two perspectives trials that failed to show a benefit. In the Propranolol Aneurysm Trial, which you see here, the investigators found that patients with a small aneurysm did not have a decreased rate of aneurysm growth. Thank you.

The most significant finding was the difference between permanent withdrawal of the study medication, which you can see on the graph on the left. Twice as many patients in the Propranolol group discontinued the use of the study medication compared to patients in the placebo group. There was also a significant decrease in quality of life of patients taking beta blockers.

So it appears the beta blockers were poorly tolerated and there was little benefit in terms of decreasing the rate of aneurysm growth. That being said, a lot of patients are on beta blockers for other reasons and that's obviously beneficial to continue in the perioperative period.

So on to indications for repair. In terms of indications for repair, some are obvious, such as a patient with a mycotic aneurysm or patients with a ruptured aneurysm. Patients with rapid growth or symptoms of abdominal pain are believed to be at increased risk of aneurysm rupture, and therefore benefit from repair.

The final criteria for aneurysm repair depends on diameter. As we saw earlier, there's a direct correlation between aneurysm diameter and the risk of rupture. About 5 and 1/2 centimeters, there appears to be a significant increase in the risk of rupture. Aneurysms that are less than 5 centimeters remain at a low risk of rupture and generally require ultrasound surveillance every three to six months.

Aneurysms that are between 5 and 5 and 1/2 centimeters remain a gray zone and require an individualized treatment plan. The image on the right is an angiogram of a ruptured aneurysm that we treated with an endograft.

So, why do I say 5 to 5 and 1/2 centimeters is a gray zone. There are two randomized studies that have compared open surgery versus surveillance for patients with small aneurysms. There was no difference in survival between the two groups, although there was a high rate of cross over to the intervention group. There was about 2/3 of patients ended up having an aneurysm repair, despite being in the surveillance group.

The UK small aneurysm trial, which had a high mortality rate associated with surgery, which you see there on the left, contributed to the question of whether or not endovascular repair would be more favorable in this patient population.

So there are two widely cited studies that evaluated the morbidity and mortality of endovascular repair compared to open surgical repair. In both studies, there was a lower mortality rate with patients treated in the endovascular group during the first two years. There was a higher rate of re-intervention in the endovascular group and a loss of survival benefit after four years. Given the choice, the majority of patients will choose the less invasive option and undergo an endovascular aneurysm repair.

So in 2012, the first fenestrated endograft was approved for use in the United States. This is an image of the device that demonstrates the key features of the new graft. These devices are custom-made for the patient and include holes in the fabric that allow us to place the grafts higher in the aorta and maintain blood flow to critical vessels such as the renal and mesenteric vessels.

The results of this advancing technology is our ability to treat more patients with a minimally invasive option if they're not good candidates for open repair. Approximately 10% to 15% of patients are eligible for this technique that otherwise would not be eligible for an endovascular repair.

This is the study which the approval was based on. Within this carefully selected group of patients, there have been no aneurysm-related deaths. There's been no aneurysm growth and no evidence of serious endoleaks. The most worrisome aspects of the grafts appear to be renal artery stenosis or occlusion, which as you can see occurred in approximately 13% of the trial population.

Another exciting development that we will be a part here at Wake Forest University Hospital is the upcoming trial of an iliac branch device. We will be one of the first centers in the country to use this device to maintain perfusion of the internal iliac artery while treating patients with a common iliac artery aneurysm. Approximately 25% of patients with an abdominal aortic aneurysm also have an iliac aneurysm.

While most patients tolerate coverage of one internal iliac artery, some develop severe buttock claudication, or even colonic ischemia. As you can see on the image on the left, the patient has bilateral common iliac artery aneurysms. On the right is the completion angiogram that demonstrates preserved flow to both internal iliac arteries.

So in review, we electively repair patients with an abdominal aortic aneurysm between 5 and 5 and 1/2 centimeters, depending on the characteristics of the patient and their preferences. There's some role for aspirin and statin medication in patients with small aneurysms, as well as doxycycline. We have an increasing number of minimally invasive tools in order to treat your patients.

And I'd like to thank you for your attention.

[APPLAUSE]