

Beating a Sudden Killer

When a young woman nearly died from a ruptured aneurysm, the author and the woman's husband began searching for ways to save other aneurysm patients from catastrophe

BY JOHN A. ELEFTERIADES

It was the first beautiful Saturday in spring, and I was in

charge of my children. We were out browsing the stores around our local green when the page came in. Lawrence Cohen, a preeminent cardiologist and my colleague at Yale University, was distraught. Normally a man of few words, Cohen was speaking quickly, almost feverishly. "I need you, John. In the ER. Right away. She's dying, John. She's dying right in front of me."

The situation was particularly distressing because Cohen had been following the woman's condition for three years, ever since her husband had come to teach at Yale. So Carmela Kolman was like a member of the family. She was 32 years old and had Marfan's syndrome, a connective tissue disorder that tends to produce thoracic aortic aneurysms: dangerous swellings in the upper part of the large artery that carries blood from the heart, down through the chest and into the abdomen. Left untreated, these aneurysms can grow until they rupture, an event that is often fatal. The only

intervention is a preemptive operation to replace the damaged regions with artificial components. But the surgery has its own risks, so physicians hold off on making that call until it seems absolutely necessary. Because Carmela's aorta had been only modestly enlarged, Cohen had not recommended surgery.

Yet this Saturday morning Carmela had come to the emergency room complaining of severe chest pain. A computed tomographic (CT) scan and an echocardiogram showed an aortic dissection: blood had seeped through a tear in the inner part of the arterial wall, causing the inner half of the wall to separate from the outer half, down the entire length of the vessel. Dissection alone can be deadly, because it can result in blocked or diverted blood flow, robbing the heart and other organs of essential oxygen and nutrients. But that was not the worst of the story. The scans indicated that Carmela had blood in her pericardium, the sac that sur-

rounds the heart. So the dissection had ruptured. She was drifting in and out of consciousness, her blood pressure was falling, and she was in shock. She needed surgery immediately.

I left the children with a neighbor and rushed to the hospital. There my surgical team and I replaced the weakened part of Carmela's aorta with an artificial vessel made of Dacron, a fabric that is woven into a flexible but sturdy tube. We also traded her damaged aortic valve, which controls the flow of blood as it exits the heart, for a mechanical version. After the surgery, Carmela was very sick. But she clung to life and improved steadily.

Each night on my evening rounds, I spoke with Carmela's husband, John Rizzo, about her condition. As she got better, we found our conversations turning to more scientific topics, particularly issues relating to aortic disease.

Rizzo, it turned out, was an economist working in the epidemiology division of the school of public health and was an expert in data analysis and management. He took a keen interest in my group's work, and in the decade since Carmela's trip to the hospital, Rizzo has helped us compile a database containing the records of all our patients with thoracic aortic aneurysms. As a result, my colleagues and I now have computerized information on more than 3,000 patients with this condition, including some 9,000 images and 9,000 patient-years of follow-up (when our work with all these patients is totaled). We know of no larger organized database on this disorder.

This extensive clinical resource has allowed us to learn more about the be-

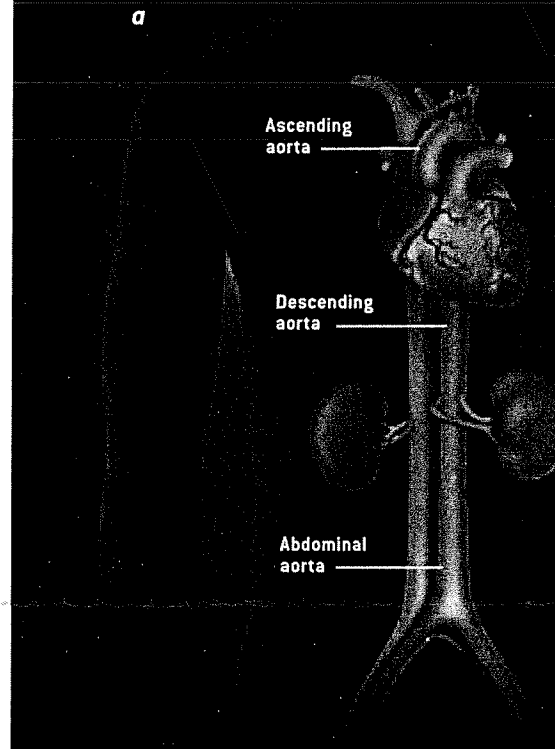
havior of thoracic aortic aneurysms: notably, how fast they grow, how to tell when they are likely to become critical and who is most susceptible to them. These insights have helped physicians decide when to intervene so as to avert the kind of catastrophic event that brought Carmela to the ER that Saturday morning.

Silent Stalker

AS A CARDIAC SURGEON, I focus on disorders that can damage the heart, such as thoracic aneurysms. But aneurysms can arise in any artery. A good number occur in the lower, or abdominal, aorta: the section that runs from the diaphragm to the area above the pelvis, where the artery branches to carry blood to the legs. Research by other investigators has revealed that the mechanisms underlying the growth, dissection and rupture of abdominal aortic aneurysms are similar to those that control the behavior of aneurysms in the chest.

Aneurysms that strike the aorta are the most life-threatening. Every year more than 15,000 people in the U.S. die when an aneurysm in the chest or abdomen bursts or dissects—more people than die from AIDS. Albert Einstein, Olympic volleyball star Flo Hyman, Florida State University basketball player Ronald Pierce, and actors Lucille Ball, George C. Scott and John Ritter were all killed by thoracic aortic aneurysms. Individuals with Marfan's syndrome are especially susceptible. Medical historians have suggested that Abraham Lincoln might have had this disorder, a condition that, before surgery became feasible, killed most victims by

The normal aorta (a) is shaped like a candy cane and is roughly as wide as a garden hose. An aneurysm, which can occur anywhere along the tube, is a ballooning of the wall (b), which thins



middle age. Thus, it is possible that our 16th president would have died early even if he had not been assassinated.

Aortic aneurysms are insidious because they are silent stalkers. The vessel can balloon without causing pain. Indeed, most people discover their aneurysms while being tested for something else: a physician will spot the telltale bulge while performing an ultrasound to investigate a heart murmur or a CT scan to evaluate a chronic cough. Pain most often occurs only when an aneurysm ruptures or dissects. And it is severe: the knifelike tearing sensation that accompanies the crisis is described by patients as being orders of magnitude worse than the agony of childbirth or kidney stones.

Survival after such an event tends to be poor. Ruptures usually kill instantly. In some fortunate cases, however, neighboring tissues can press up against the rent in the aorta and hold the structure

Overview/Aneurysms

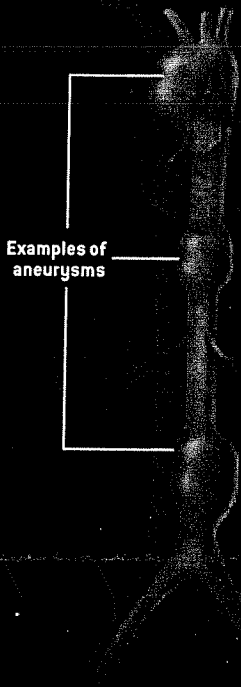
- Clinicians have classically been unsure when to operate on an aortic aneurysm—a swelling in the large artery that carries blood from the heart. Left alone, an aneurysm could fatally rupture or dissect, the inner layer peeling away from the vessel wall. But the only proven intervention, replacement of the damaged aorta with artificial parts, is itself risky.
- Detailed analyses of thousands of patients have now led to guidelines for the best time to operate.
- Weight lifters with aneurysms are in particular danger of sudden death while exercising and should take special precautions.

THE PERILS OF ANEURYSMS

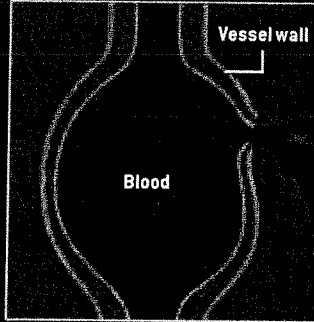
and weakens as it enlarges. The condition can be fatal if the tissue ruptures [c] or dissects [d and photograph], or both. Dissection, the separation of the inner and outer parts of the vessel wall, results when blood seeps into the middle of the wall through a tear of the inner lining.

By analyzing thousands of cases, the author and his colleagues have learned how to predict when an aneurysm is highly likely to rupture or dissect. Such information can help determine when the need for corrective surgery outweighs the substantial risks of the procedure.

b

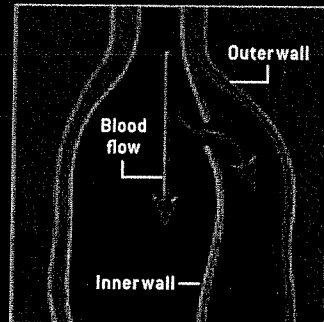


c



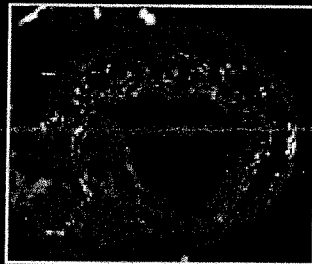
RUPTURE

d



DISSECTION

Cross-sectional view of dissected aneurysm



together long enough for the patient to get to the hospital. For dissections, survival depends on the location. If left untreated, those that begin in the ascending aorta—the segment that emerges from the heart—are fatal within hours or days. Tears in this area can unseat the aortic valve, causing shock, or occlude the coronary arteries, triggering a heart attack. Dissections in the descending aorta, which runs down the back of the chest, are not as threatening: they rupture less frequently than those in the ascending aorta and do not share the same complications.

Surgery can prevent rupture or dissection, but the operation to replace the aorta is very serious and as invasive as procedures get. The operation involves stopping the heart and shunting the blood through a heart-lung machine. In some cases, depending on the location of the aneurysm, surgeons must shut down

blood flow entirely and cool the patient from 37 to 18 degrees Celsius to slow metabolism and prevent brain damage while they repair the aorta. Although most people do very well after the surgery, the operation carries risks of stroke, paralysis and death.

To assess whether such a dangerous intervention is warranted, a physician must know how likely it is that an aortic aneurysm will rupture or dissect. In general, a large aneurysm is more dangerous than a small one. But specific data were sorely lacking when Carmela fell ill. Although more than 300 papers had been written on how to operate on the aorta, we could find precious little information on how aortic aneurysms behave before surgery, namely, how fast they expand and how likely they are to burst or tear at any given size. Carmela's aorta, for example, had dissected at 4.8 centimeters in diameter, a relatively modest size—

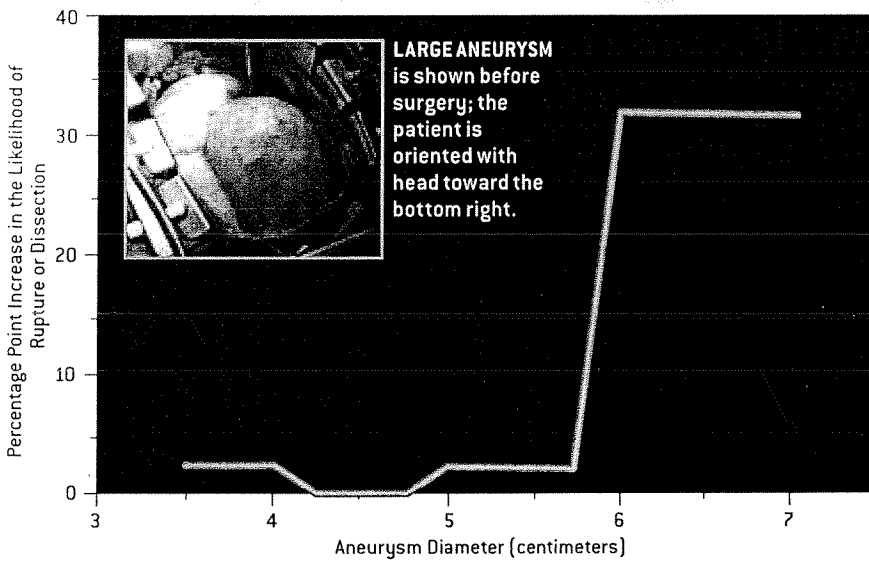
which was why the event was so unexpected. (The normal thoracic aorta is typically about 2.5 to 3.5 centimeters.) Thus, questions regarding aneurysm growth and stability, we reasoned, were a good place to begin our investigations.

A Threshold Emerges

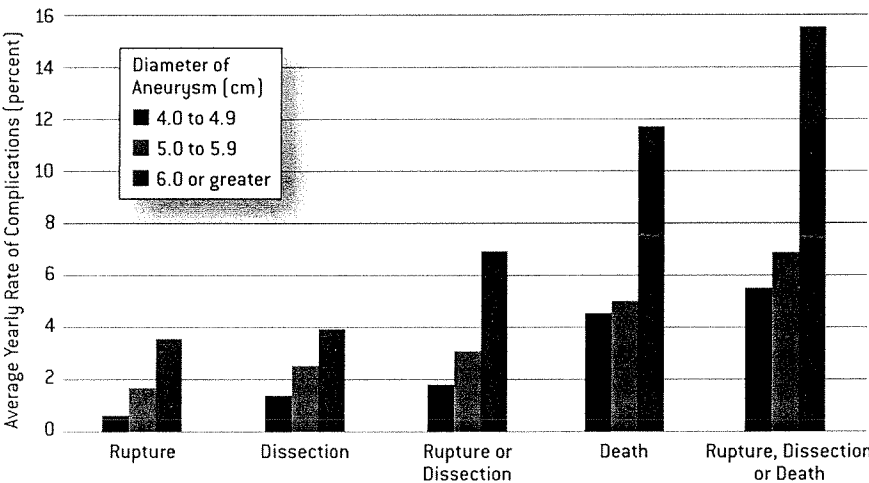
TO HELP DRAW this information from our clinical database, Rizzo first developed sophisticated statistical techniques that allowed us to determine accurately the growth rate of aneurysms. We found that most grow inexorably and surprisingly slowly: only about 0.12 centimeter per year. Thus, an aneurysm will generally take a decade to grow one centimeter. This finding suggests that aneurysms detected in middle-aged adults probably began growing when the patients were young adults or earlier.

A statistical method devised by Rizzo also permitted us to assess the probabil-

RELATION OF SIZE TO RISK OF COMPLICATIONS



YEARLY RISK OF COMPLICATIONS



PROBABILITIES that rupture or dissection will occur have been calculated for aortic aneurysms in the chest. In one study, the author and his colleagues plotted risk relative to that posed by small aneurysms of 4.0 to 4.9 centimeters. They found a dramatic surge in danger when aneurysms reach six centimeters in the ascending aorta (*top graph*) or seven centimeters in the descending aorta (*not shown*). Another study (*bottom graph*) revealed that the likelihood of rupture, dissection or death within the coming year also jumps sharply for aneurysms that reach six centimeters or higher. (The rates indicated for "Rupture or Dissection" and for "Rupture, Dissection or Death" are lower than the sum of the rates in individual categories because patients with multiple complications were counted only once in the combined categories.) Based on such information, the investigators have determined that many patients with aneurysms in the ascending aorta need corrective surgery when the artery balloons to 5.5 centimeters.

ity of rupture or dissection for thoracic aneurysms of different sizes. We were amazed by the definitiveness of the results. According to our data, the probability of rupture or dissection skyrockets when an aneurysm in the ascending aorta reaches a diameter of about six centimeters, roughly that of a soft drink can. More than 30 percent of patients whose aneurysms reached that size experienced

a devastating complication, either rupture or dissection. In the descending aorta, the risk shoots up most dramatically at about seven centimeters.

These numbers represent a lifetime risk of complication: the chance that an aneurysm of a given size will rupture or dissect, although the figures do not indicate when the crisis will happen. But patients who discover that they have an

aneurysm are more interested in numbers that predict the yearly rate of complication: in other words, whether their aneurysm might harm them in the near future.

Determining such probabilities requires a large number of cases, and we have recently amassed enough data to begin the appropriate statistical analyses; this data set combines information from patients with aneurysms anywhere in the thoracic aorta, although about two thirds of the patients were affected in the ascending region. We see a trend of gradual increase in the probability of adverse events within the coming year as the aneurysm grows from 4.0 to 5.9 centimeters and then a sharp jump in risk once the aorta reaches six centimeters [see *bottom graph* in illustration at left]. For instance, we find that for a thoracic aneurysm of six centimeters or greater, the risk of rupture, dissection or death within a year soars to a staggering 15.6 percent. Many forms of cancer do not carry as great an annual probability of mortality.

Based on these observations, we recommend that aneurysms in the ascending aorta be surgically removed well before the defect grows to six centimeters. For most people with no family history of aneurysms, we suggest operating at 5.5 centimeters. For the descending aorta, we might perform surgery at six centimeters if a patient is healthy enough to withstand it, but we sometimes delay until about 6.5 centimeters if the patient is frail. We operate at smaller sizes than those listed above for patients with Marfan's or a family history of aneurysm-related disorders, as aneurysms in these people tend to become life-threatening earlier. Using these criteria, we believe, should prevent the vast majority of ruptures and dissections without exposing patients unduly or prematurely to the dangers of aortic surgery. Before an aneurysm warrants going under the knife, doctors may attempt to protect the aorta with medicines that control blood pressure and slow the heart, to limit the stress that is exerted on the ballooned wall.

The abdominal aorta is normally

ALISON KENDALL (graphs); JOHN A. ELEFTERIADES (photograph); LINE GRAPH SOURCE: M. A. COADY ET AL. IN JOURNAL OF THORACIC CARDIOVASCULAR SURGERY, VOL. 113, NO. 3, PAGES 476-491, MARCH 1997; BAR GRAPH SOURCE: R. B. DAVIES ET AL. IN ANNALS OF THORACIC SURGERY, VOL. 73, NO. 1, PAGES 17-27, JANUARY 2002.

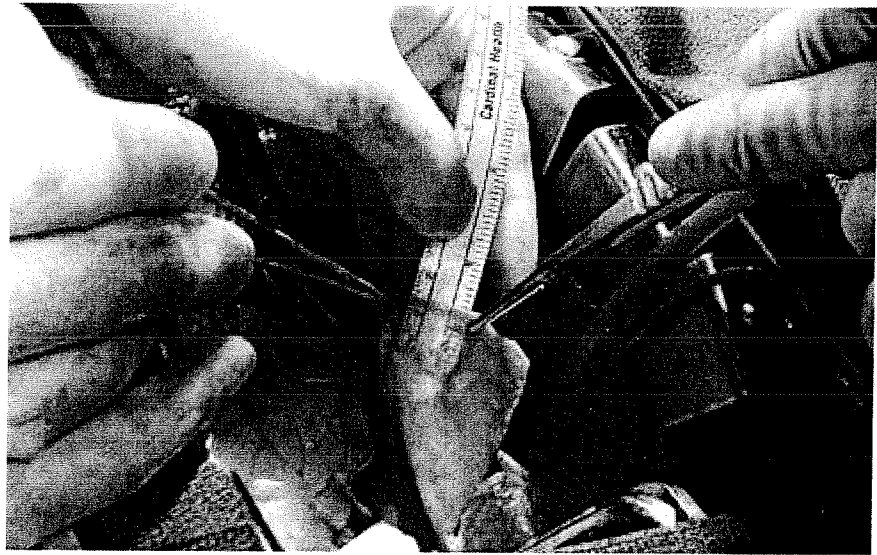
smaller than the thoracic aorta, and rupture of the abdominal aorta usually occurs at smaller sizes than in the thorax. Accordingly, physicians usually intervene surgically at smaller sizes for abdominal aortic aneurysms. Some authorities recommend intervention at four centimeters for women and five centimeters for men, as rough general guidelines.

All in the Family

TO SAVE MORE LIVES, doctors would benefit from knowing which asymptomatic individuals are at risk for aneurysms, so that the condition could be detected early, monitored closely and treated promptly. Marfan's syndrome is a well-known warning; many with the condition wind up having aortic aneurysms. But people with Marfan's account for only 5 percent of all aneurysm patients. The remaining 95 percent of cases are idiopathic—their cause is not yet known.

Physicians once believed that aneurysms were caused by atherosclerosis—the accumulation of plaque (fatty gunk) in the arterial wall. But we have found that patients with aneurysms in the ascending aorta are actually less susceptible to atherosclerosis than the general population, so plaque deposition probably is not causal in their cases. Aneurysms in the descending and abdominal areas, on the other hand, are often accompanied by plaque throughout the aorta and in its branches, which suggests that atherosclerosis probably does contribute to those aneurysms.

Our database has revealed that most thoracic aneurysms have a strong genetic component of some kind—and the same appears to be true for aneurysms in the abdominal aorta and in the brain. Reviewing family histories, we were astounded to discover how often people with aneurysms report having a relative with one or a family member who died suddenly or unexpectedly at a young age. The latter occurrence is often chalked up to cardiac arrest, but in many instances an autopsy would have revealed a ruptured aneurysm. In the 500 families whose pedigrees we have analyzed, approximately 20 percent display some his-



WALL OF AORTA became so thin in a six-centimeter aneurysm that a ruler placed behind it can be seen through the tissue. New findings indicate that aneurysms are caused in part by excessive activity of enzymes known as metalloproteinases (MMPs), which digest proteins that are needed for the elasticity of the artery wall.

tory of aneurysm. In most families, the trait appears to be dominant—in other words, an individual need only inherit an “aneurysm gene” from one parent to be affected; in one of these families, the father passed on aortic disease to all four of his children. Other families showed different patterns of inheritance, suggesting that more than one gene can play a role in susceptibility.

If genetic markers that signify increased susceptibility could be identified, physicians might someday use a simple blood test to pinpoint those who need close monitoring—say, by CT scans or echocardiograms—to catch aneurysms early and determine the best time for surgery. And if the actual genes at fault could be found, researchers might even be able to develop therapies that specifically counteract their ill effects—potentially slowing or preventing the growth of aneurysms by blocking the undesirable activities of the proteins encoded by those genes.

With better detection and, ultimately, improved treatment in mind, we have begun to collaborate with scientists at Celera Diagnostics in Alameda, Calif., to search for genetic markers called SNPs—single nucleotide polymorphisms—that correlate with aortic disease. SNPs are DNA sequences that differ by a single nucleotide, or code letter, between one part of a population and another. James Devlin, Olga Iakoubova and their Celera team are comparing DNA samples obtained from 500 of our patients with thoracic aneurysms and from 500 healthy individuals, in this case the patients' spouses. Then, using automated equipment, they will scan some 16,000 genetic regions for SNPs that appear more often in patients than in the healthy controls.

Our preliminary work has revealed a number of SNPs that might signify increased risk, and we are pursuing these leads in our large patient group. In addition, we are conducting a similar

THE AUTHOR

JOHNA. ELEFTERIADES attended Yale University as an undergraduate and never left. He graduated magna cum laude with a triple major in physics, French and psychology before completing his medical degree and clinical training in general and cardiothoracic surgery. Elefteriades is currently professor and chief of cardiothoracic surgery at Yale and the Yale–New Haven Hospital. He began a weight-training program while on his seventh-grade wrestling team and has been lifting ever since; he benches 75 percent of his weight and has confirmed, by echocardiogram, that he does not harbor an aneurysm.

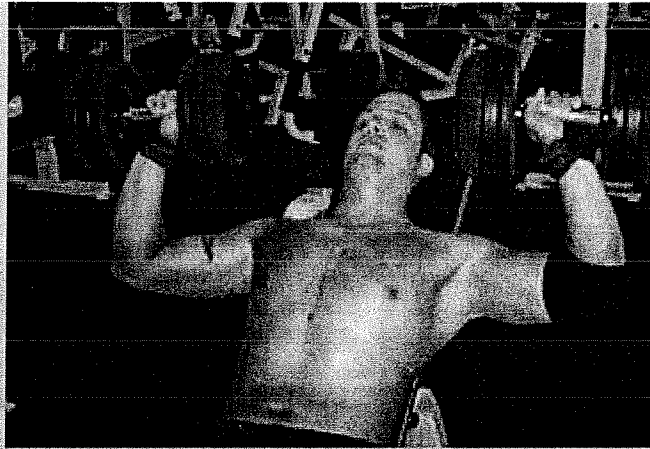
A Warning for Weight Lifters

In late 2003 my colleagues and I described in the *Journal of the American Medical Association* the tragic occurrence of a dissection of the aorta in five seemingly healthy individuals who were engaged in strenuous strength training. Each unknowingly harbored a bulge in the part of the aorta emerging from the heart, and the inner half of the distended wall suddenly, and life-threateningly, separated from the outer part. At the time of dissection, two were lifting weights, two were doing push-ups, and the fifth was attempting to lift a heavy piece of granite. Three were saved by surgical intervention. We have since become aware of dozens of additional cases of aortic dissection during weight lifting, suggesting that the phenomenon is not a medical rarity.

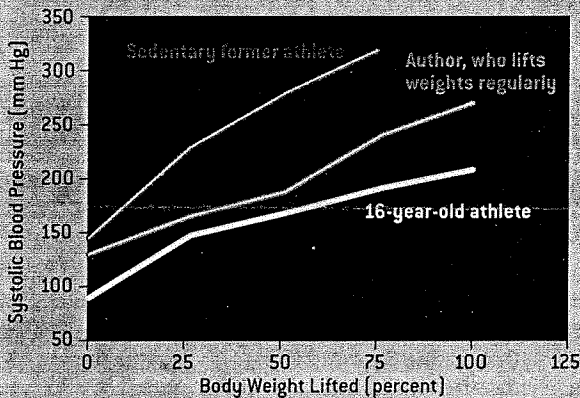
What might account for this link? Part of the explanation seems to be that exercise that involves straining against a fixed resistance, as weight lifting does, can push the blood pressure to dangerously high levels. Some studies have recorded a systolic pressure [that in the arteries when the heart contracts] of 380 millimeters of mercury (mm Hg) in competitive weight lifters, as compared with a normal value of 120 or below. We have confirmed such soaring pressures in a small, three-volunteer study of our own. One of our volunteers hit 319 mm Hg when lifting just three quarters of his body weight (*graph*).

Such pressure can be too much for an already stretched artery to bear. From separate studies of the mechanical properties of the distended aorta, we find that at 200 mm Hg, a six-centimeter aneurysm experiences 800 kilopascals of pressure—a value that equals the ultimate tensile strength of the tissue. So it should come as no surprise that an aortic aneurysm subject to a blood pressure that approaches or exceeds 300 mm Hg will not hold.

Because of this pressure elevation, we tell athletes with a personal or family history of aortic aneurysm or any known aortic enlargement to use great discretion in pursuing weight-lifting activities, perhaps limiting bench presses to half their



YOUNG MAN who suffered an aortic dissection induced by lifting extremely heavy weights bears the scar of the surgery that saved his life. Chances are good that a sharp rise in blood pressure during a workout precipitated the dissection. Even in healthy individuals, blood pressure can soar to astronomical values, exceeding 300 mm Hg, during weight lifting (*graph*).



body weight or less. Weight lifting can be highly beneficial for preserving muscle mass and bone strength, but we strongly advise that individuals who intend to embark on heavy weight-training programs get an echocardiogram to check for potential aneurysms before they begin. —J.A.E.

study on aneurysm patients in Europe, to be sure that the findings will hold up in a different population.

What Goes Wrong

ONCE WE IDENTIFY the genes in which aneurysm-related SNPs occur, we can discern which proteins those genes encode and learn how they contribute to aortic malfunction. But already researchers have a sense of some of the proteins that might be involved. For instance, we know that in most patients with aortic aneurysms, the stretched part of the vessel wall shows a loss of

elastic fibers and collagen as compared with healthy tissue. Together these proteins give the artery its strength and flexibility. The defects that contribute to this problem could occur in the genes that code for those proteins or in other genes that regulate the manufacture or maintenance of elastin and collagen.

In Marfan's, the genetic defects that are at fault usually hobble the gene for fibrillin, a protein that combines with elastin to form elastic fibers. As a consequence, the synthesis and deposition of fibrillin are disrupted, a problem that presumably weakens the aortic wall and

renders it vulnerable to the formation of an aneurysm. No one yet knows, though, whether mutations in the fibrillin gene are common in patients who do not have Marfan's.

We have recently found evidence that an overabundance of certain enzymes in the aortic wall probably contributes to the formation and growth of aneurysms in many victims. All blood vessels harbor enzymes called metalloproteinases (MMPs) that chew up old proteins to make way for new. The same vessels also possess inhibitory proteins that help hold MMPs at bay. In a healthy

aortic wall the activity of these proteins is balanced, so that protein turnover remains constant. In segments of aorta removed from our aneurysm patients, in contrast, we find an excess of two types of MMP and decreased amounts of one of the inhibitory proteins.

This imbalance could lead to an enhanced degradation of proteins, including elastin and fibrillin, in the aortic wall—a situation that might pave the way for thoracic aortic aneurysms by weakening the vessel wall. In one patient, the aorta had become so thin that the markings of a ruler could be read through its wall. Other scientists have also found evidence of a role for overzealous MMPs. These findings suggest that drugs able to block MMP activity might help retard growth or forestall rupture of aortic aneurysms, but study of this concept is just beginning.

With our Yale colleague George Koullias, we have recently begun to assess the mechanical properties of the dilated aorta to better understand why it becomes **more** dangerous as it enlarges. Before surgically removing an aneurysm, we measure its diameter, the thickness of its wall, and the blood pressure as the heart contracts and relaxes. From these parameters we can calculate the vessel's mechanical properties.

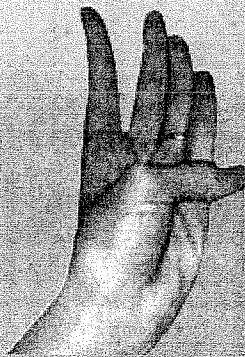
We have shown that as the aorta grows larger its distensibility, or ability to stretch, falls. We have also demonstrated that by the time an aneurysm in the ascending aorta reaches six centimeters—the same critical value we encountered in our previous studies of aneurysm behavior—the vessel behaves as a rigid tube. This stiffening maximizes the stress that gets absorbed by the wall of the aorta as blood pounds against it with every heartbeat and helps to explain why trouble often ensues when an aneurysm hits the crucial dimension of six centimeters.

Inflexibility sets an aortic aneurysm up for disaster. But what sends it over the edge? We have begun to categorize the specific events that cause dissection to occur at one particular moment in time in a susceptible individual. After interviewing patients in our database, we find

Who Should Worry

In some ways, an aortic aneurysm is like a time bomb in the chest. It can sit silently until one day it ruptures or dissects. But certain conditions often signal a susceptibility to aortic aneurysms:

- A family history of aneurysms
- Having someone in the family collapse and die suddenly or unexpectedly
- Marfan's syndrome or its hallmarks. These include long limbs, a tall, thin frame and loose joints (such as are evident in the ability, shown at right, to cross the thumb all the way over the palm while keeping the hand flat)



My colleagues and I tell patients who meet any of these criteria—or who plan on engaging in serious weight training—to have regular CT scans or echocardiograms to check for aneurysms. Weight training does not elevate risk for having an aneurysm, but, as noted in the box on the opposite page, it can increase the likelihood that an existing aneurysm will suddenly become lethal. —J.A.E.

that nearly three out of four recall experiencing an intense episode of extreme emotion or physical exertion immediately preceding the dissection. What these activities have in common is that both presumably cause a spike in blood pressure that splits the vulnerable aorta. For one class of athletic activity—weight lifting—we have specific evidence that this is the case; indeed, this activity can put so much stress on an aneurysm that it prompts a crisis even when the swelling has not crossed the six-centimeter mark [see box on opposite page]. It seems logical to surmise that pressure spikes from other events could also induce rupture, although we have not looked at that possibility directly yet.

The renowned 19th-century physician Sir William Osler once observed

that “there is no disease more conducive to clinical humility than aneurysm of the aorta.” Today investigations into the biology and behavior of thoracic aortic aneurysms—from the genetic susceptibility that drives their formation to the physical or emotional events that cause them to blow out or tear—are helping to render the condition a little less humbling.

As for Carmela, she continues to be in good health and has returned to her work as an artist. “I know it sounds clichéd,” she says, “but I feel I’ve been given a second chance to live my life”—a chance her father did not have when he died from an aortic dissection at the age of 34. We hope that our research, inspired by Carmela’s crisis that terrifying spring day, will provide many others with the same opportunity. ■

MORE TO EXPLORE

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Yearly Rupture or Dissection Rates for Thoracic Aortic Aneurysms: Simple Prediction Based on Size. R. R. Davies, L. J. Goldstein, M. A. Coady, S. L. Tittle, J. A. Rizzo, G. S. Kopf and J. A. Elefteriades in *Annals of Thoracic Surgery*, Vol. 73, No. 1, pages 17–27; January 2002.

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Perspectives on Diseases of the Thoracic Aorta. John A. Elefteriades in *Advances in Cardiology*, Vol. 41, pages 75–86; 2004.

Kevin Helliker and Thomas M. Burton's *Wall Street Journal* series on aortic aneurysms: www.pulitzer.org/year/2004/explanatory-reporting/works/

