

REVIEW

Thoracic Aortic Aneurysm: Reading the Enemy's Playbook

John A. Elefteriades, MD

Section of Cardiothoracic Surgery,
Department of Surgery, Yale University
School of Medicine, New Haven, CT,
USA

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LIST OF ABBREVIATIONS:

MMPs = metalloproteinases
SNPs = single nucleotide polymorphisms
TIMPs = tissue inhibitors of
metalloproteinases

Correspondence to:

John A. Elefteriades, MD
Professor of Surgery
Yale University School of Medicine
Department of Surgery
Section of Cardiothoracic Surgery
New Haven, CT, USA
E-mail: john.elefteriades@yale.edu

ABSTRACT

Thoracic aortic aneurysm is a virulent disease which can rupture or dissect and thus hurt or kill our patients. Surgery can prevent rupture, but with inherent surgical risks, which include death, stroke, and paralysis. In order to know if operation is warranted, one must know how likely it is that rupture or dissection will occur for a given sized aorta. Based on scientific data, available to date, we recommend *pre-emptive surgery of the aneurysmal ascending aorta at a diameter of 5.5 cm* in order to avoid rupture or dissection in most patients, without exposing them unduly or prematurely to the dangers of aortic surgery. We recommend operating earlier, at an aortic dimension of about 5 cm, rather than the 5.5 cm, in patients with Marfan's disease or other family history of aortic diseases, as they can dissect unpredictably, at relatively smaller diameters. Aortic aneurysm is a genetic disease. As we clarify the genetics of this disease further, we hope to be able to test family member genomes to ascertain if they are afflicted. With genetic understanding will come, in the long term, the potential for specific genetic therapies to correct the underlying causative mutations.

INTRODUCTION

We all remember the playbook—that repository of all our team's secret strategies—which we guarded at all costs. Our opponent has one too, of course. What if we could read that playbook? What greater advantage in our struggle could we possibly imagine?

Mankind has a serious enemy, one that kills widely and silently. This opponent is the *aortic aneurysm*. Aneurysm refers to a swelling in an artery. Thoracic aortic aneurysm refers to a swelling located in the portion of the aorta that traverses the chest cavity. Albert Einstein, Olympic volleyball star Flo Hyman, Florida State University basketball star Rolanda Pierce, and actors Lucille Ball, George C. Scott, and most recently John Ritter, as well as thousands of others per year in the USA alone have been attacked and killed by thoracic aortic aneurysm.

Over the last ten years, our work at Yale University, as well as work at other major Aortic Centers, has permitted important glimpses into the playbook of aortic aneurysm. We are on the verge of reading the details of this playbook, spreading its pages wide-open, and taking advantage of the contained information. This article shares the

important glimpses we have already garnered and elucidates the future strides immediately at hand.

We now have computerized data on over 3000 patients with thoracic aortic aneurysm, including computerized information on some 9000 imaging studies and 9000 patient-years of follow-up. It is this clinical database that has permitted looking into the playbook of this virulent killer, thoracic aortic aneurysm.

The chronology of our investigations and findings over the last decade is indicated in **Table 1**. Each line item represents a revealing glimpse into the playbook of thoracic aortic aneurysm. These glimpses have shed light on the following topics:

- Size of the aorta at the time of rupture or dissection.
- Yearly likelihood of rupture or dissection based on size of the aorta.
- Family patterns of aortic aneurysm.
- Activation of metalloproteinase (MMP) enzymes in the aneurysmal aorta.
- Inciting events at the moment of dissection of the aorta, including the role of strenuous weightlifting.
- Mechanical properties of the aneurysmal aorta.
- Analysis of single nucleotide polymorphisms (SNPs), or mutations, underlying aneurysm disease.

This greater understanding of the ways and wiles of aneurysm disease has already enhanced treatment of this virulent opponent, and, as we shall see, even greater promise lies ahead.

NATURAL HISTORY OF THORACIC AORTIC ANEURYSM

We concentrated first on determining how the aneurysmal aorta behaves absent surgical therapy, “in the wild”, so to speak—what medicine calls *natural history*. We found that, while over 300 papers had been written on how to perform operations on the aorta, there was precious little information available on how the aorta affected by an aneurysm behaved naturally, or on when surgery should be performed. This, we

reasoned, was a good topic on which to begin our collaborative investigations.

Thoracic aortic aneurysm is a virulent opponent with multiple means at its disposal to hurt or kill our patients.¹⁻⁷ This disease has two main “plays” on which it calls (**Fig. 1**). Rupture is indicated on the left, and dissection is indicated on the right. In **Figure 2**, the x-ray on the left and the CT scan on the right show a vivid example of rupture of a thoracic aortic aneurysm into the left chest, filling it with blood.

It was not conclusively known how fast the aneurysmal aorta grows or at what size the aneurysmal aorta ruptures or dissects. Exploring this topic was all the more important to

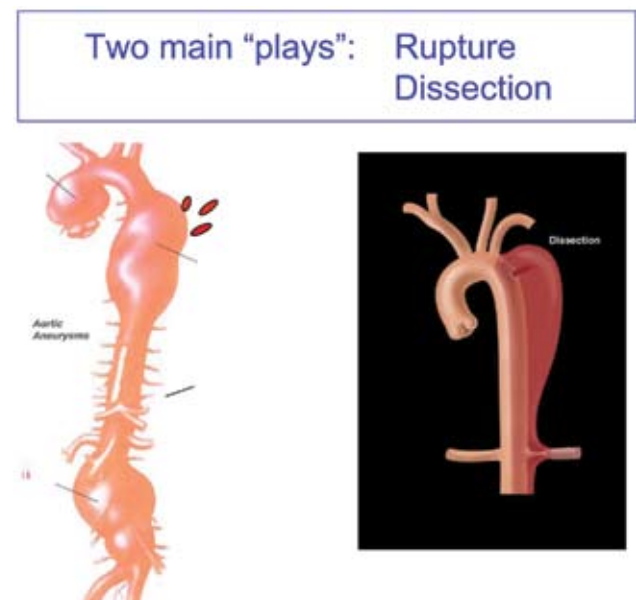


FIGURE 1. CT scan of our index patient, Carmella. Note the intimal flap in the aortic arch (arrow).

X-ray and CT scan in aortic rupture

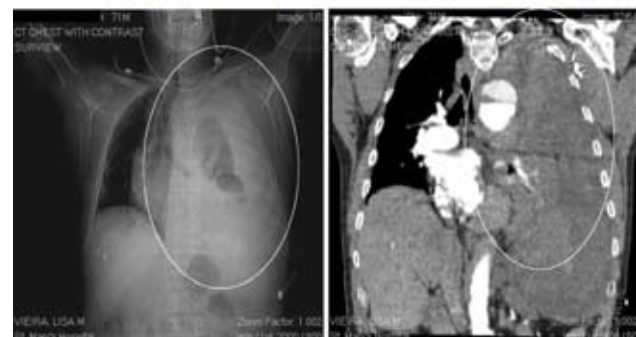


FIGURE 2. The two main “plays” of thoracic aortic aneurysm: Rupture on the left, and dissection on the right.

TABLE 1. Chronology in “Reading the Playbook” of Thoracic Aortic Aneurysm

1994	Center for thoracic aortic disease
1997	Size at time of rupture/dissection
1999	Family patterns
2001	Yearly rupture rates
2003	MMP activation in aortic wall Weight lifting as acute cause
2004	Mechanical properties Genome – SNP analysis 500 pts

our team because Dr. Rizzo's wife Carmella had dissected her aorta at the relatively modest size of 4.8 cm (Fig. 3). Dr. Rizzo developed sophisticated statistical techniques which allowed us to calculate growth rate accurately.⁸ This is much more complex than subtracting original size from current size and dividing by the time interval. For example, measurement error mandates that some later measurements will be smaller than earlier ones, although the aorta cannot really shrink. Earlier studies had truncated all smaller measures, leading to a spurious exaggeration of the growth rate. Careful statistical analysis using Dr. Rizzo's techniques indicates that the aneurysmal aorta grows inexorably, but only at a rate of 0.12 cm/year. Thus, the aorta will generally take a decade to grow one centimeter. Another implication of this is that these diseases probably begin in young adult life, or even earlier, in order to produce aortas the size of those seen in clinical practice.

We know that surgery can prevent rupture, but the operation to replace the aorta is a very serious one, with inherent dangers, which include death, stroke, and paralysis.⁹ In order to know if operation is warranted, one must know how likely it is that rupture or dissection will occur for a given sized aorta.⁸⁻¹⁴ Dr. Rizzo developed exponential equations to permit such analysis upon our clinical data.⁸

We were amazed at the clarity of the demarcation when the data came out from the computer (Fig. 4). On the Y-axis is shown the lifetime risk of natural complications of the thoracic aortic aneurysm, including both rupture and dissection. On the X-axis, is shown the size of the aorta. Please note that by the time an aneurysm in the ascending aorta (upper part) reaches a diameter of 6 cm, 34% of the patients have already suffered the devastating complication of rupture or dissection. A similar "hinge point" was found for descending

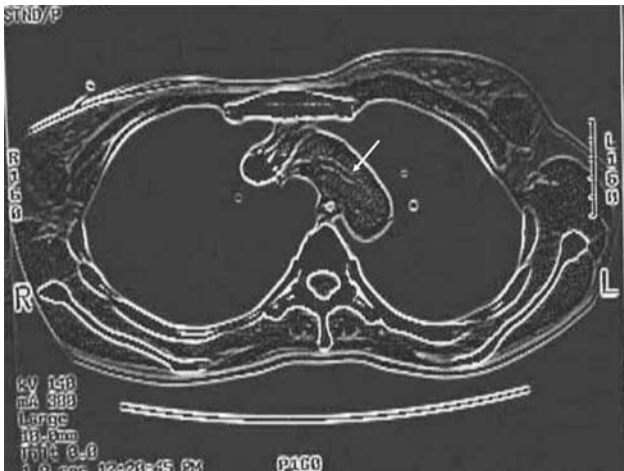


FIGURE 3. Example of ruptured thoracic aneurysm. Chest x-ray on left and CT scan on right show the left pleural space full of blood (circled).

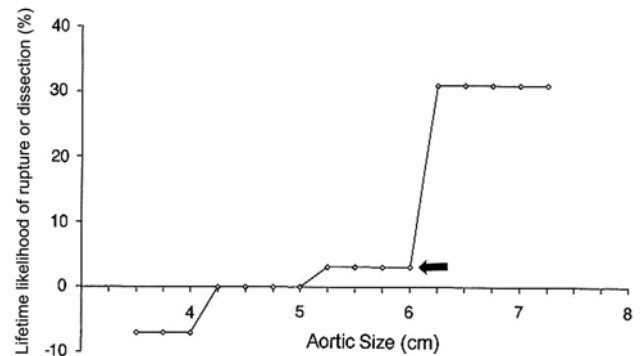


FIGURE 4. Cumulative lifetime likelihood of rupture or dissection (y-axis) plotted against aortic size (x-axis). Note the abrupt "hinge point" at 6 cm.

(lower) thoracic aorta.

These observations permitted our formulating scientifically-based following recommendations for surgical intervention in patients with thoracic aortic aneurysms. Based on these data, we recommend *pre-emptive surgical extirpation of the aneurysmal ascending aorta at a diameter of 5.5 cm* in order to avoid natural rupture or dissection. As one can see from the graph, using this criterion will prevent the vast majority of ruptures and dissections, without exposing patients unduly or prematurely to the dangers of aortic surgery. As will be seen later, we recommend operating earlier in patients with Marfan's disease or other family history of aortic diseases.

Now how big is this dimension of 6 cm for the ascending aorta? Our nurse coordinator gave me a sterilized soda can to illustrate this dimension in the patient depicted in Figure 5, with a large thoraco-abdominal aneurysm. The head is toward the left upper corner and the feet to the right lower corner. The soda can is 6.3 cm in diameter. So, the bottom line message here is that if the diameter of the aorta is approaching that of a soda can, the aorta should be extirpated.

Now, a "Holy Grail" in aneurysm diseases has been to predict the *yearly* rupture rates for aneurysms.¹³ The data presented above represented cumulative *lifetime* rates. The calculation of yearly rates requires extremely robust clinical data, with enough hard endpoints per year for each size of aorta to permit meaningful statistical analysis. We have only recently amassed data robust enough permit our attacking this problem of yearly rates of rupture and dissection. In Figure 6, please note the stepwise increase in the yearly risk of rupture as the aorta grows up to 6 cm. By the 6 cm point, the yearly risk of rupture is 3.6%. Yearly risk of dissection increases in a similar pattern as the aorta grows, and the yearly risk of death increases dramatically when the aneurysm reaches 6 cm. Many of these deaths are aortic related. If we put all of these devastating adverse events together, we find that the risk of having rupture, dissection, or death on a yearly basis is a staggering



FIGURE 5. Intra-operative photograph of a large thoraco-abdominal aneurysm (patient's head is to left upper corner, and patient's feet to the right lower corner). A soda can is used to illustrate the criterion dimension of 6 cm, at which the aorta tends to rupture or dissect. The can was sterilized before being placed in this provocative juxtaposition.

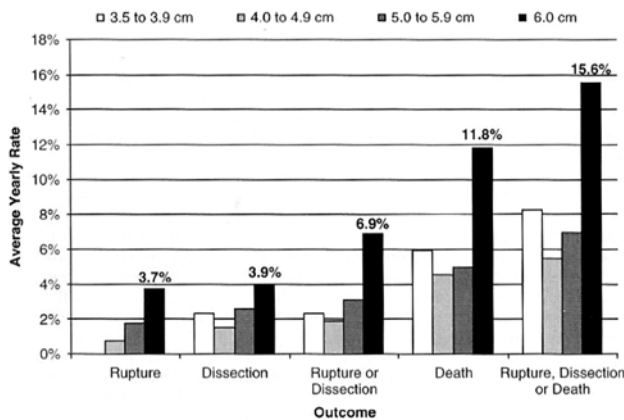


FIGURE 6. Yearly rates of rupture, dissection, death, and combined events, plotted by aortic size. Note again the critical criterion dimension of 6 cm.

14.1% if the patient harbors an aneurysm of dimension 6.0 or greater. These recent data strengthened the resolve behind our clinical recommendation that the aneurysmal thoracic aorta be removed surgically, in a pre-emptive strike, well before it reaches 6 cm diameter.

FAMILY PATTERNS

We will look now at family patterns. As many people are aware, controversy surrounds the possibility that President Lincoln may have suffered from Marfan's disease. Historians have expended a tremendous amount of effort looking into this

issue. Lincoln certainly did have the extreme height and lanky build characteristic of Marfan's disease. It is an indication of the intensity of the historical interest that one paper focuses on a photograph of Lincoln with an open-toed shoe. The whole picture is in focus except the great toe. The toe is out of focus, the historian argues, because it was throbbing from its "Quinkie's pulse". Patients with aneurysms often develop leakage of the aortic valve, leading to an exaggerated, throbbing pulsation called by that eponym. The historical analysis is pertinent because if Lincoln did indeed have Marfan's disease, he likely would have died naturally even if he had not been shot at the Ford Theater. Few Marfan's patients survive (without surgical intervention, impossible in Lincoln's time) into or beyond middle age. Thus, if Lincoln did have Marfan's disease, he would have died soon anyway, even if he had not been assassinated.

The genetic characteristics of Marfan's disease have been fully elucidated. A variety of mutations in the fibrillin gene cause the Marfan phenotype. However, Marfan's disease accounts for only 5% of all aneurysms and dissections.

Our investigations at Yale University reveal that it is very common for patients without Marfan's disease to have a positive family history. It is literally astounding how often one obtains affirmative answers to hereditary inquiries: Do any of your family members have an aneurysm? Has anyone in your family died suddenly or unexpectedly, at a young age or of an apparent cardiac cause? Please note in the pedigree displayed (**Figure 7**) that the father, our proband, passed on the aneurysm disease to every one of his natural offspring. We look for evidence of long bones and excessively mobile joints in our family patients. One can see that the young woman in **Figure 8** can cross her thumb all the way over her palm, indicating that she harbors connective tissue abnormalities. **Figure 9** presents the family pedigrees in our first 100 fam-

Family Pedigree—Aortic Dissection

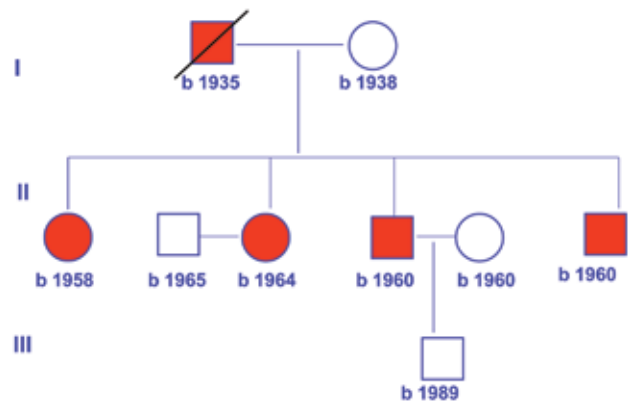


FIGURE 7. Family pedigree showing that the proband has passed on the aneurysm diathesis to every one of his natural offspring.



FIGURE 8. The positive thumb/palm sign. Note that this young woman with a family pattern of aortic aneurysm disease can cross her thumb all the way over her palm. This unusual ability is a manifestation of connective tissue disease, signifying long bones and lax joints, which go along with aortic disease.

ily pedigree analyses. Please note that of those 100 families analyzed, 21% of them had a positive genetic pattern. Those 21 patterns are depicted in the figure. Autosomal dominant is the predominant mode of inheritance, with other patterns noted as well.

We treat these patients with a positive family history with great clinical respect. Like patients with Marfan's disease, they can dissect unpredictably, at relatively small diameters. We operate electively at an aortic dimension of about 5 cm, rather than the 5.5 cm that we use for non-Marfan's, non-familial patients.¹⁵

METALLOPROTEINASES—THE “HATCHET MEN”

So, thoracic aneurysms are genetic. How does the genetic proclivity actually lead to aneurysm formation or to aortic dissection? Very recently, we have begun looking at the events in the aortic wall that may lead to aneurysm formation. The enzymes known as metalloproteinases, or MMPs, lyse important proteins in the aortic wall. The TIMPs, or tissue inhibi-

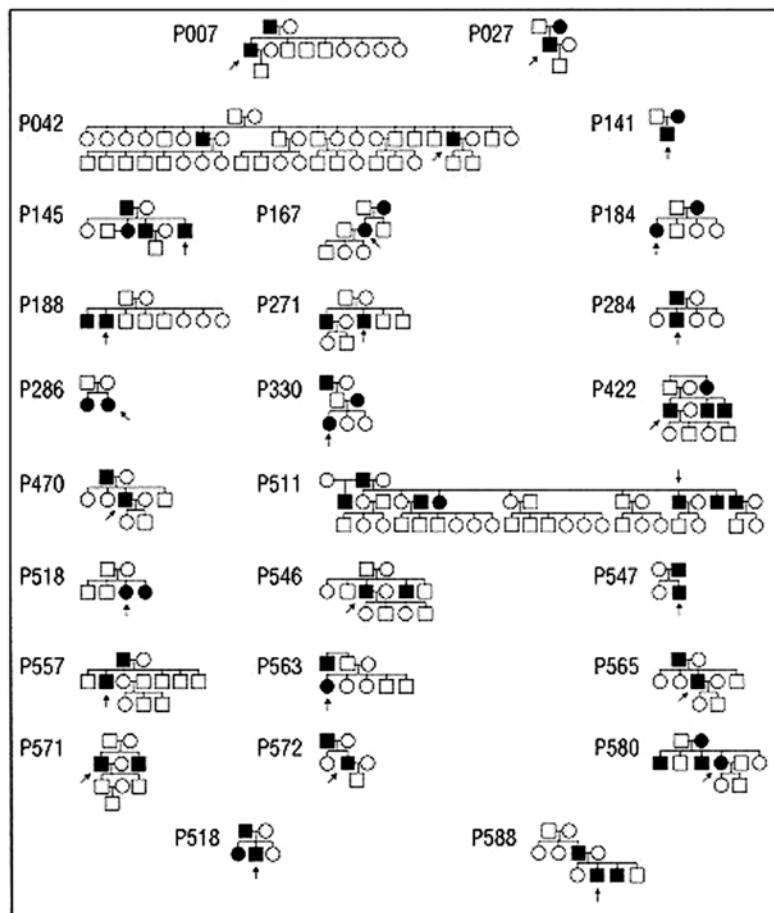


FIGURE 9. The 21 positive family pedigrees among the first 100 families that we investigated. Autosomal dominant inheritance predominates.

tors of metalloproteinases, subdue the MMPs. Thus, in the normal aorta a balance between synthesis and lysis of aortic wall constituent proteins maintains a healthy aortic wall. In our aneurysm patients, however, the levels of the important MMPs 1 and 9 are dramatically elevated above normal. This leads to a state of increased proteolysis, which we believe underlies the development of thoracic aortic aneurysms. You can see in the photograph (Figure 10) that this patient's aorta has become so thin through these processes that the markings of the ruler can be read right through the aortic wall.

INCITING EVENTS: STRESS AND STRAIN

Aortic dissection, the splitting apart of the aortic wall into two layers, is an instantaneous phenomenon. One moment, the aorta is normal; the next instant, it is split into two layers. We actually create iatrogenic dissections in the laboratory,

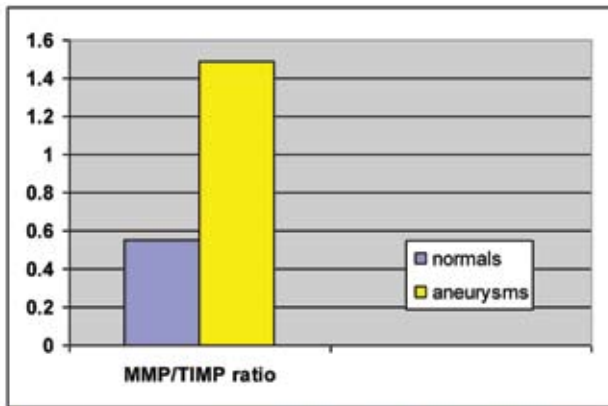


FIGURE 10. We have found that matrix metalloproteinases are upregulated in thoracic aortic aneurysm tissue. These enzymes degrade the structural proteins of the aortic wall. Please note the extreme thinning of the aortic wall that can be produced by destruction of the protein components of the aorta. One can read the markings on the ruler through the wall of the opened aorta. Before opening the aorta, we could see the blood swirling immediately beneath the surface of this dramatically thinned aorta. The inset shows that the ratio of lytic MMPs to lysis inhibiting TIMPs is elevated in the aortic wall of our aneurysm patients.

watching this instantaneous process.

Recently, we have begun looking at what are the particular inciting events that cause dissection to occur at one particular moment in time in a susceptible individual. We find that in the vast majority of cases, a specific *extreme emotion or physical exertion* occurs immediately preceding the dissection.¹⁶⁻¹⁸ The presumption is that the emotion or dissection raise the blood pressure and split the aorta. In late 2003, we reported in JAMA the tragic occurrence of aortic dissection in a series of otherwise healthy young athletes during the process of weight training.¹⁸ This particular young man in Figure 11 sports a median sternotomy scar on his chest. He presented to us with a ruptured ascending aortic dissection. He underwent successful urgent surgical repair. As can be seen, he has returned to his strenuous weight lifting activities, at very high levels, despite our best recommendations.

We have confirmed that blood pressure rises to extremely high levels during weightlifting. We actually studied ourselves in this activity. Figure 12 shows the response to weightlifting in our team. Please note levels exceeding 300 ml of mercury in one individual. For this reason, we have recommended that athletes with a history of aortic aneurysm or any known aortic enlargement use great discretion in pursuing weightlifting activities. We believe very strongly in the benefits of this activity but recommend caution or echocardiographic evaluation in susceptible individuals. We believe that an echocardiographic examination will soon become commonplace before inception of weight training programs.



FIGURE 11. This young man had presented to us in extremis with an acute ascending aortic dissection. This had been induced by extreme weight lifting. He underwent urgent surgery to replace his aorta. Note the midline sternotomy scar (arrow). He has done well. Despite medical advice, as can be seen in this photograph, he has returned to very heavy exercise.

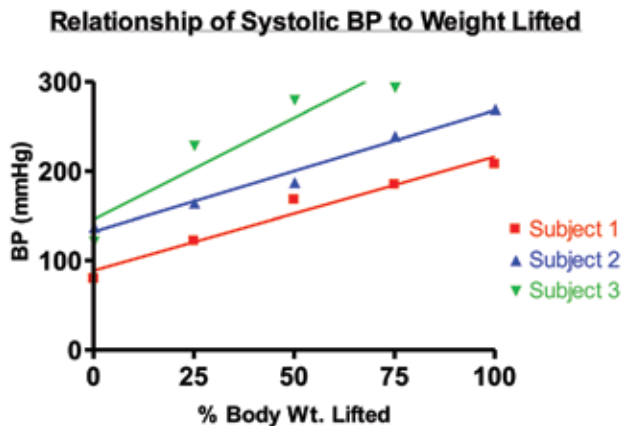


FIGURE 12. Blood pressure response to weight lifting among our team members. Note that even in these healthy individuals, blood pressure rises to astronomical values exceeding 300 mm Hg. We believe it is this type of hypertension that leads to aortic dissection in otherwise healthy athletes. Subject 1 is the author's 16 year-old athlete son. Subject 2 is the author, who lifts weights regularly and did not approach 300 mm Hg until lifting his full body weight. Subject 3 is a colleague, a former athlete who is now sedentary; he exceeded 300 mm Hg blood pressure lifting only one-half his body weight.

MECHANICAL PROPERTIES OF THE ANEURYSMAL AORTA

Very recently, in a program designed by our colleague Dr. George Koullias, we have begun looking at the mechanical properties of the dilated aorta. We use a direct epi-aortic probe through a water-filled interface. We measure the diameter of the aorta, the thickness of the aortic wall, and the blood

pressure in systole and diastole. These six parameters allow complete calculation of important mechanical properties. This type of evaluation has recently permitted the following insights: As the aorta enlarges, the distensibility falls. That is the aneurysmal aorta develops a very stiff wall. Please note in Figure 13 that by 6 cm, that same critical parameter that we identified in our natural history studies, the aorta becomes essentially a rigid tube. This has major consequences because in the non-distensile aorta, the force of systole all becomes a shearing force adversely affecting the aortic wall.

SINGLE NUCLEOTIDE POLYMORPHISM ANALYSIS

Our most exciting glimpse into the playbook of thoracic aortic aneurysm concerns analysis of the genetic mutations that allow susceptibility to this disease.^{19,20} We have been working with our scientific colleagues at Celera Diagnostics to identify the particular mutations which underlie the aneurysm diathesis. Celera has an incredible technological array of equipment. We are looking at 16,000 particular genetic loci in 500 of our aneurysm patients and 500 matched controls. We are aiming to identify the particular mutations that permit aneurysms to develop. Our analysis to date has identified six particular mutations that distinguish our aneurysm patients from the normal controls.²⁰ Extremely high P-values characterize the discriminatory power of these mutations; that is, these are very powerful predictors that the patient can develop an aneurysm. These are preliminary findings that await confirmation in our entire cohort as well as in a replication population from a different environment. Our replication study is underway in Europe. We hope that in the future we will be able to determine from a simple blood test whether a family member is susceptible to this devastating disease.

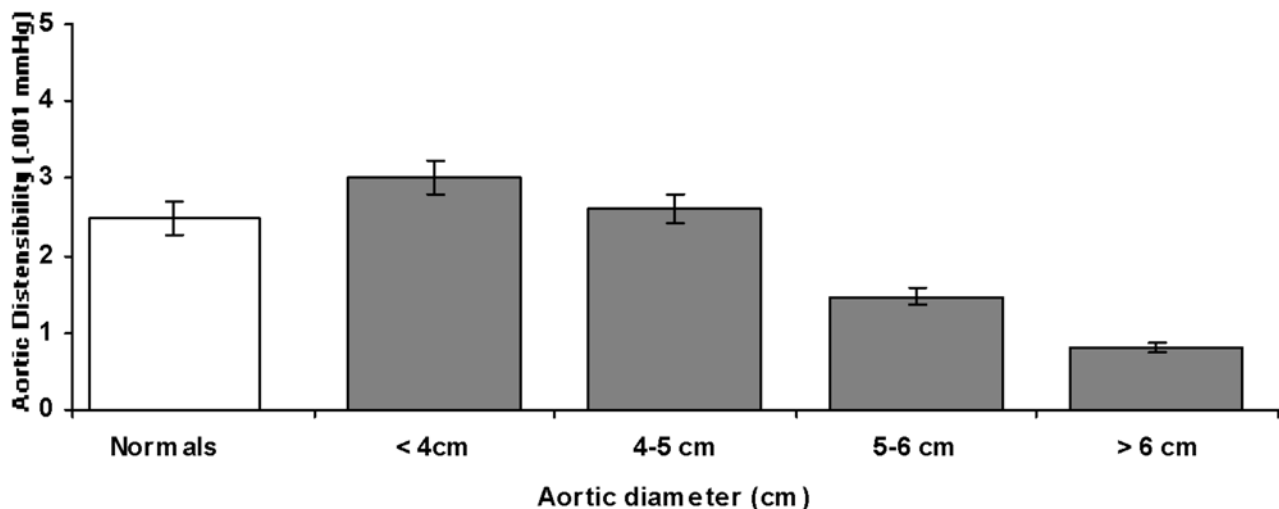


FIGURE 13. Deterioration of mechanical properties in the aneurysmal aorta. Please note that by the critical dimension of 6 cm, the aorta has become essentially a non-distensile, rigid tube.

SYNTHESIS

The renowned nineteenth century physician Sir William Osler stated that “there is no disease more conducive to clinical humility than aneurysm of the aorta.”* In this article, we have discussed the following insights into the Playbook of thoracic aortic aneurysm. We have examined the size of the aorta at the time of rupture or dissection. We have discussed our observations regarding family patterns of these diseases. We have described a pattern of excessive activation of the lytic metalloproteinase enzymes. We have looked at the particular inciting factors for occurrence of dissection at a particular time. We have shown interesting information indicating a deterioration in mechanical properties that accompanies dilatation of the aorta. The deterioration of mechanical properties at 6 cm dovetails perfectly with the clinical observation that rupture and dissection occur at precisely this same critical diameter. These findings help us to understand the pathophysiology of thoracic aortic aneurysm. The clinical observations have permitted us to time surgery effectively, so as preemptively to prevent the devastating complications of rupture and dissection.

And finally we have had a glimpse into the mutations that permit the thoracic aortic aneurysm to occur. As we clarify the genetics of this disease further, we hope to be able to test family member genomes to ascertain if they are afflicted. If not, they can rest easy. If so, then they can be followed closely with imaging studies to permit optimally timed preemptive surgery. Once we understand the genetics more fully, we can determine which proteins are coded by the affected mutations. Such understanding will permit the targeted development of conventional drugs aimed at strengthening the defective proteins, with an eye toward preventing aneurysms from developing or from growing. And, of course, with genetic understanding will come, in the long term, the potential for specific genetic therapies to correct the underlying causative mutations.

We are hopeful that as these insights into the Playbook of thoracic aortic aneurysm progress, Sir William Osler's assessment will no longer be true. We hope that reading the Playbook of thoracic aortic aneurysm will change the balance of power in favor of the patients as well as the physicians and surgeons striving on their behalf.

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*Quotation courtesy of Drs. Vincent Gott and Duke Cameron of Johns Hopkins University.