Aortic Surgery for Ascending Aortic Aneurysms Under 5.0 cm in Diameter in the Presence of Bicuspid Aortic Valve

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ANEURYSM OF THE ASCENDING AORTA MAY CAUSE ACUTE TYPE A AORTIC DISSECTION, and the primary aim of a prophylactic operation is avoidance of this life-threatening complication. Current guidelines recommend prophylactic replacement of the aneurysmal ascending aorta at a diameter of $\geq 5.5$ cm. However, several reports have shown that nearly 50% of patients with an acute type A aortic dissection present with an aortic diameter $<5.5$ cm. It is controversial how to best respond to these observations. Because surgical advances have led to a reduction of early surgical mortality between 1% and 3%, many clinicians believe that surgery is warranted in smaller aortas. Given the frequency of a bicuspid aortic valve (BAV), such a strategy has health implications for this population.

Under 5.0 cm in Diameter

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Current guidelines. At first glance, it seems there is no doubt: the guidelines recommend prophylactic surgical replacement of the ascending aorta in non-Marfan patients at an aneurysm diameter of $\geq 5.5$ cm to avoid an acute type A aortic dissection (1). This is a class I quoted recommendation with general agreement of the writing committee, but the level of evidence is weak (grade C), based on expert opinion rather than randomized clinical trials or meta-analyses. On closer evaluation, it is apparent that the recommendation is based only on a 1997 study by Coady et al. (2), which defines an inflexion in the risk of dissection at an ascending aortic aneurysm diameter of 6.0 cm; an illustration of this is even displayed in the guidelines. Less widely known is that the resulting recommendation of surgery at 5.5 cm is based on the analysis of a heterogeneous cohort of only 54 patients with aneurysms of the ascending aorta or aortic arch, including both connective tissue disease and degenerative etiology. Analysis of the aneurysmal growth rate and aortic diameter at the time of dissection showed that the incidence of rupture or dissection was 45.2% at an aortic size of $>6.0$ cm. However, some additional information is pertinent. Acute dissections or ruptures occurred in this cohort at diameters $<6.0$ cm: in 7.1% of those with an aortic diameter $<4.0$ cm, 8.5% of those with a diameter of 4.0 to 4.9 cm, and 12.8% with a diameter of 5.0 to 5.9 cm (2). Thus, rupture or dissection occurred at an aortic diameter $<5.5$ cm in 22% of investigated patients. On the basis of this information, pursuit of the current recommendations of surgery at a diameter of $\geq 5.5$ cm would lead to nearly one-fourth of patients with an ascending aneurysm experiencing an acute type A aortic dissection or aortic rupture, which is a devastating disease with a poor outcome (3). This is surprising, because the primary aim of aortic aneurysm surgery is the avoidance of these complications!

There is further evidence that the recommended cutoff of 5.5 cm may be of harm for a number of patients with moderate-sized aneurysms of the ascending aorta. Neri et al. (4) measured the internal diameter of the ascending aorta by analyzing aortic samples from 220 patients who underwent surgery for an acute type A aortic dissection. They found that the median aortic diameter was only 41.3 mm for patients with an acute
type A aortic dissection without connective tissue disease. Thus, only 4.7% of patients with an acute type A aortic dissection had an aneurysm of the ascending aorta using the definition of a 50% increase in diameter compared with the expected normal aortic diameter. In the International Registry of Acute Aortic Dissection, 59% of 591 patients presenting with an acute type A aortic dissection had an ascending aortic diameter <5.5 cm and 40% had a diameter <5.0 cm (5). Independent predictors of the occurrence of an acute type A aortic dissection at a diameter <5.5 cm included history of hypertension, radiating pain, and increasing age. Aortic size at presentation was unrelated to mortality. Transesophageal echocardiography measurements of the aortic annulus, sinus segment, sinotubular junction, and ascending aorta in 177 non-Marfan patients with tricuspid aortic valves who presented with an acute type A aortic dissection showed that 62% had a maximal aortic diameter of <5.5 cm, 42% had a maximal aortic diameter <5.0 cm, and >20% had maximal aortic dimensions <4.5 cm (6).

Thus, these studies show that acute type A aortic dissection occurs in many patients at less than the recommended diameter of 5.5 cm for surgical intervention, so the current aortic diameter threshold excludes approximately 50% of patients with an acute type A aortic dissection from prophylactic replacement of the ascending aorta. Moreover, risk factors other than the diameter of the ascending aorta influence the development of an acute type A aortic dissection and must be identified. However, the law of Laplace cannot be ignored; aneurysmal diameter is definitively a risk factor for acute type A aortic dissection, and the incidence of dissection and rupture increases with increasing size of the ascending aortic aneurysm (7). The important question remains: is a diameter of 5.5 cm the right indication for prophylactic surgery, or must we readjust to a smaller diameter?

Outcome of prophylactic replacement of ascending aortic aneurysm. The primary aim of replacement of the dilated ascending aorta in asymptomatic patients is the avoidance of an acute type A aortic dissection; this is truly a prophylactic indication. In patients with chest pain, immediate surgery is indicated and may be warranted for significant valve disease. Various operative techniques are available for replacement of the ascending aorta; supracoronal tube graft replacement is a straightforward operation indicated for patients without aneurysmal involvement of the aortic root. Additional aortic valve replacement is possible. In cases with root dilation, the modified Bentall operation, in which a vascular tube graft incorporating a biological or mechanical aortic valve prosthesis is used to replace the root after reinsertion of the coronary ostia, has been the gold standard for 3 decades. Since the 1990s, valve-preserving techniques for root replacement have become the operation of choice when the native aortic valve is structurally intact.

In cardiac surgical centers experienced in aortic surgery, the results of these techniques are excellent. Today, the ascending aorta can be replaced with very low operative mortality and morbidity. Garrido-Olivares et al. (8) reported on combined aortic valve replacement and supracoronal ascending aortic replacement in 89 patients with an operative mortality rate of 2.3%. In a series of 597 patients reported from New York, the early mortality rate in elective patients undergoing the Bentall procedure was 1.4% for composite grafts with mechanical valves and 3.7% with biological valves (9). A group from South Korea reported an operative mortality rate of 2.6% in 195 patients, including 24 urgent patients with an acute type A aortic dissection (10). For the valve-sparing reimplantation technique, the Hannover group reported a 30-day mortality rate of 1.3% in 230 elective patients (11), and the Leipzig group reported a 0% mortality rate in 151 patients who underwent the David operation (12). Similar results have been achieved with the remodeling technique, with 1% to 3% early deaths in elective patients (13,14). At the University Hospital Heidelberg, an analysis of 548 consecutive patients who underwent surgery for an ascending aortic aneurysm over a period of 17 years had an average early mortality rate of 4.8%. However, during the last 5 years, the average mortality rate was 1.6% in 381 patients (including 0% mortality in the David group), reflecting technical advances in cardiac surgery and the effect of a large caseload (15). Encouraged by these results and in contrast to the current guidelines, we recommend surgery for an ascending aortic aneurysm in patients without connective tissue disease or a BAV at 5.0 cm and less in selected cases.

The balance between the risk of acute aortic dissection and operative risk. We must balance the reduced incidence of acute type A aortic dissection as a result of earlier surgery against the operative risk of prophylactic surgery in an asymptomatic patient. Because the occurrence of an acute type A aortic dissection is potentially life threatening but elective surgical replacement of the ascending aorta carries relatively low operative risk, the balance moves toward earlier surgery; the harm of an acute type A aortic dissection is greater than the risk of surgery. Consequently, patients should undergo surgery at a diameter of <5.0 cm because many patients experience dissection at a smaller diameter, as explained in the preceding text. The development of an acute type A aortic dissection is not only triggered by the size of the aneurysm; factors such as connective tissue disease (e.g., Marfan or Loey-Dietz syndrome), pregnancy, BAV, familial history of thoracic aortic aneurysm and dissection, hypertension, aortic stiffness (measured noninvasively), normative data instead of absolute aortic size (such as the Z-score), sex, and aortic growth may influence the timing of the operation, and several of these factors are already considered in the effective guidelines (16). Individual judgment of any patient is pivotal when calculating operative risk versus the likelihood of development of an acute
No, Not Under 5.0 cm in the Absence of Connective Tissue Disease
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No surgeon should approach the victim of his operation without a sacred dread and reluctance
—John Hunter (17)

Remarkable technological advances in recent decades have made high-resolution imaging widely available. With their broader application, physicians are increasingly confronted with management of the asymptomatic, and often incidentally discovered, anatomic “abnormality.” Gratifying advances in surgical care have also reduced the mortality and morbidity of many elective operative interventions, and surgeons are, in turn, increasingly asked to consider “prophylactic” procedures. Because the risks associated with both the natural history of these incidentally discovered abnormalities and the interventions to “fix them” lie at the low extreme of the bell-shaped curve, decision making on the basis of risk/benefit analysis is increasingly challenging. Nowhere is this dilemma more apparent than in the debate over management of moderate nonsyndromic aortic dilation.

The drivers to early aortic intervention are strong. Aortic dissection is the most common fatal aortic complication by a factor of 2 or 3, with abdominal aneurysms more frequent but less often lethal. Of those with dissection involving the ascending aorta who make it to the hospital, one-fourth will die before discharge; an unknown number die before diagnosis (18). On long-term follow up, 10% to 30% of patients with involvement of the entire aorta (DeBakey type I) will require late operation on the distal segments (19) and late survival falls far below expected (20). Perhaps a contributing factor to the operative risk is the likelihood, at least in the United States, that the emergent repair will be conducted by a surgeon performing fewer than 2 operations for acute dissection each year (21). Add to this the emotional strain associated with the risk of a catastrophic event occurring at an uncertain time, and it is clear why the trend to recommend elective surgery for aortic enlargement in a “center of excellence” has grown over time.

Are we asking the right questions? How solid are the data? How rational are our recommendations?

There is no question that aortic dissection is a dreaded disease for all of the reasons stated in the preceding text, but this alone is not an argument for indiscriminant aortic replacement. Diseases of other organs, such as cancer of the pancreas, have a dismal prognosis but are not themselves arguments for prophylactic extirpation of the susceptible site. This is true regardless of the skill of the surgeon and how close his or her rate of operative complications is believed to approach zero. Of course, with regard to this estimate of operative outcomes, surgeons (like all other humans) are subject to illusory superiority or “the Lake Wobegon effect” and the literature is flawed by publication bias, but that is another discussion (22). Suffice it to note that, according to the Society of Thoracic Surgeons database, the operative risk associated with replacement of the proximal aorta under elective circumstances is 3.4% (23).

The question at hand is “What is the risk that any individual, specifically the one sitting across from me in my office, will get the dreaded disease?” and not merely the risk of death should the patient develop the condition. To determine this risk, accurate assessment of both the numerator and the denominator is needed for the given clinical parameter (risk factor) of interest. Unfortunately, in most cases, we have only a global picture of the condition with very imprecise information on specific subsets of patients at risk, derived in most instances from study of those experiencing the complication (the numerator) rather than from the total population (the denominator). Specifically with regard to aortic dissection, we have a growing understanding of the spectrum of aortic diameter before dissection among those experiencing dissection. What we need to inform our discussion of prophylactic surgery with our patient in the office, however, is knowledge of the risk of dissection among those with a given aortic diameter. The 2 questions yield dramatically different results; for example, the likelihood of female sex with breast cancer is approximately 99%, but the likelihood of breast cancer with female sex is one-fifth that number. Fortunately, Bayesian analysis can suggest answers to these questions; unfortunately, it is not always intuitive.

What of the quality of the data that we do have at hand? One of the first studies concerning the natural history of thoracic aortic aneurysmal disease was performed in the early 1960s by Dr. John Joyce at the Mayo Clinic. In that study, which was inspired by surgical progress that made intervention on the dilated aorta a realistic therapeutic option, he identified the 6.0-cm mark as a particularly important risk factor for significant aortic complications (24). Subsequent studies, particularly those performed by Dr. John Elefteriades and his collaborators at Yale University, have confirmed that, for the ascending aorta, the incidence of complications rises dramatically at a diameter of 6.0 cm (25). It is largely on the basis of these studies that it is reasonable and prudent to replace the
ascending aorta at 5.5 cm in the interest of providing a bit of a safety margin.

Although it is comforting that a number of studies by different investigators point roughly to the same critical diameter, it should also be noted that these studies are subject to entry bias. Far from a population-based dataset, surgical databases at any large academic center located in a dense population and surrounded by multiple community providers are likely to be enriched for those patients who experience complications. I would argue that the implication is that the risks will be overestimated even for dilation to 5.5 or 6.0 cm, but what about the mounting evidence that dissection can occur at aortic diameters <5.0 cm? Data on aortic diameter from 591 patients with type A dissection were reported from the International Registry of Acute Dissection in 2007 (5). The average ascending aortic diameter was 5.3 cm, and 40% of patients had an aortic diameter <5 cm! Surely this argues for aggressive intervention at lower and lower diameters.

There are at least 2 problems with this line of thinking. Given the aforementioned “numerator/denominator problem,” we cannot make a statement about the risk of dissection among patients with aortic diameters <5.0 cm without considering the denominator, which in this case is enormous because most humans have aortas <5.0 cm in diameter. The second problem is that the dataset itself includes only those patients who made it to the hospital. An unknown number likely died before entry into the dataset, and their aortic diameters are unknowable.

I would argue that it is not a surprise that aortic size alone is a poor predictor of the risk of aortic complications. Aortic dissection represents a mechanical failure of the aortic wall. That failure can be expected when wall stress exceeds wall strength. The law of Laplace certainly predicts higher wall tension with greater aortic radius, but there is more to the equation than radius; intraluminal pressure is equally important (law of Laplace: \( T = PR \)). We have no direct assessment of material strength in clinical practice today. The presence of a known connective tissue disorder characterized by medial degeneration suggests reduced wall strength, as does the dilation itself in most instances. Incidentally, in the special case of the BAV, it could be argued that moderate aortic dilation is “normal” and not evidence of medial degeneration. I am not aware of any data that support greater susceptibility to dissection or rupture at any given diameter compared with patients with a tricuspid valve.

Where does that leave the concerned clinician anxious to prevent aortic catastrophe? Surely the ideal solution to the problem is a patient-specific assessment of the risk of aortic complications on the basis of noninvasive imaging assessments of material properties of the aortic wall and calculation of wall stress. A similarly patient-specific determination of the risks associated with prophylactic surgery of this type can now be calculated for coronary bypass or aortic valve replacement on the Society of Thoracic Surgeons website (http://sts.org/quality-research-patient-safety/quality/risk-calculator-and-models). In the meantime, our clinical decision making is likely to be as much anecdote driven as evidence based. Both the physician and the patient will be subject to the decision-making biases that form the basis for the entire field of behavioral economics (26). The valence effect will influence our thinking in favor of a greater likelihood of a positive than negative outcome of the surgical procedure, while the impact of vividly framing the risk associated with aortic enlargement as a “time-bomb in my chest” will push us toward intervention. Additionally, the certainty effect will favor a decision to take definitive action to eliminate even a small risk of an event occurring at an unknown time. This all adds up to a busy operative schedule, particularly when considering that 30% to 50% of the approximately 3 million patients in the United States with a BAV will have some aortic enlargement, as noted in the preceding text. Still, it is worth remembering John Hunter’s admonition and recognizing that at some point the lines describing risk and benefit will cross; with an overly aggressive approach, we will surely hurt more people than we help. We don’t know where that point is, but it exists.

Moving Imaging From Part of the Problem to Part of the Solution

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Current surgical decision making regarding aortopathy is almost completely based on the aortic dimension and surgical plans for the aortic valve. However, as discussed in the preceding text, aortic dissections are quite commonly reported in vessels that are smaller than the recommended threshold. Controversy about the appropriate threshold will be informed by clinical trials or decision models, but imaging may be able to inform this better than simply by provision of aortic diameters. Indeed, there is nascent evidence that a number of other observations may be of value.

In patients with a BAV, leaflet morphology may be an important consideration. In a study of 581 patients with a BAV, a “type 1” morphology (fusion of the right and left cusps with opening in an anterior-posterior direction) was present in 71% of bicuspid valves and was associated with annulus and sinus enlargement (27). In a separate study, this morphology was associated with aortic regurgitation, whereas fusion of the right or left cusp with the noncoronary cusp was associated with aortic stenosis and enlargement extending into the aortic arch (28). Indeed, aortic stenosis has an important association with aortopathy, with aortic dilation rates increased similarly in stenotic...
bicuspide and tricuspid valves (29). Although the previous teleologic explanation of aortopathy on the basis of post-stenotic dilation has fallen into disfavor, there is evidence to show increased aortic wall stress in the setting of a right-left fusion of the bicuspid valve, independent of the severity of stenosis (30). In this setting, the stenotic jet is directed anteriorly and to the right, and this is associated with asymmetric enlargement of the aortic root, most commonly on the convexity of the vessel (31). The resulting inhomogeneity of circumferential aortic strain has been associated with the degree of reduced cusp motion (32). The measurement of flow direction may be helpful in understanding the risk of dissection, given that most patients with a BAV have neither symmetrical nor markedly asymmetrical valves (33). In this issue of JACC, Della Corte et al. (34) describe the importance of aortic morphology to disease progression. In a study of 133 adult outpatients with a BAV at baseline, 69% showed fusion on the right and left aortic cusps, ascending aortic dilation was present in 57%, and root dilation was present in 13.5%. Over an average follow-up of 4 years, the mean growth rate was 0.3 mm/year at the sinuses and 0.6 mm/year at the ascending level. Root phenotype at presentation, rather than absolute baseline diameter, was an independent predictor of rapid progression (>0.9 mm/year) for the ascending aorta. In contrast, the more common ascending phenotype proved a more stable disease entity, generally with slower progression. Aortic morphology might therefore warrant closer surveillance and earlier treatment of aortopathy, and indeed a variety of other factors might also be helpful for decision making.

The nature of the aortic tissue is another aspect that may be important in understanding the risk of events. Measurements of stiffness index and pulse-wave velocity in patients with a BAV and hereditary thoracic aneurysms have shown a relationship between stiffness and progression, but unfortunately the negative predictive value of abnormal stiffness and pulse-wave velocity has been only modest, with a large overlap between patients with Marfan syndrome, BAV, and familial aeurysm (35). Thus, current techniques for measurement of aortic tissue appear insufficiently sensitive to play a role in surgical decision making. However, evidence of activation of molecular pathways by hemodynamic and jet-related stimuli may control extracellular matrix regulation and thereby link to aortic thinning and dilation (36–38). Therefore, tissue measurements may not provide substantial incremental information to that provided by jet characteristics. Nonetheless, although aortic thickness does not differ between patients undergoing aortic surgery with bicuspid and tricuspid valves, patients with BAV are reported to have thinner elastic lamellae and a greater distance between lamellae (39).

The current guidelines for surgery in aortopathy are heavily dependent on measurement of aortic dimension. However, these measurements have a number of limitations, not the least of which is how best (or whether at all) to index the measurement for size. A more sophisticated risk evaluation approach should be considered, incorporating the morphology of the aorta, the severity of aortic stenosis, the morphology of the aortic valve, and perhaps also the characteristics of the aortic wall tissue.

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