Aortic Organ Disease Epidemic, and Why Do Balloons Pop?

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As children, we learned that a balloon blown up to its limit of elasticity would pop. For similar aortic ballooning, we hardly know more. Furthermore, in the 21st century, with a nascent epidemic of aortic-related deaths, there have been no consequential advances in preventing the loss of aortic elasticity or in describing the etiology or injury that causes aortic disease. Nor is there an explanation as to why, in some people the aorta “pops” and in others, the aorta dissects.

In the United States between 1999 and 2001, at least 129,533 people died from diseases of the aorta and its branches, excluding carotid and coronary disease—an average of 43,199/year, according to the Centers for Disease Control and Prevention ICD-10 codes (Table). The upper limit could potentially exceed 46,817 per year. This number is greater than the ~40,000 people who die annually from breast cancer, homicides, pancreatic cancer, colon cancer, prostate cancer, or motor vehicle accidents. Despite this, little research and even less funding have been allocated to aortic disease research, possibly because disease of a supposedly utilitarian pipe that conveys blood to a pantheon of organs engenders less interest or sympathy in comparison with, for example, cancer. Furthermore, the dismal prognosis of aortic disease, a marker of systemic problems despite successful surgery, has not roused much concern, with a 5-year average survival rate of only 60% in most patients. Concurrently with the increasing diagnosis of aeurysms before death, successful management of cardio-aortic and aortic disease has increased, with some 80,000 to 100,000 patients having surgery each year. Operative mortality rates are now <1% for aortic root repairs, aortic valve replacements, ascending aortic surgery, bicuspid valve plus ascending aorta repairs, Marfan syndrome surgery, and a 2% mortality rate for complex aortic arch surgery, including “elephant trunk” procedures. Likewise, for descending aortic repairs, including endovascular stent grafting, a <2% to 3% mortality rate can be expected, and the dreaded complication of leg paralysis for descending or thoracoabdominal aneurysm has been reduced to 3.1% in our most recent analysis of 285 such repairs. Similar results have been achieved in our series of 480 thoracic endovascular grafts. Despite these major clinical management advances, little has advanced with regard to either the etiology or the pathology of aortic disease.

Most classifications of aortic disease have only described aortic pathology depending on the layers of the aorta involved, loss of either elastic tissue or smooth muscle cells, and whether inflammatory cells are present and their arrangement. Thus, based on light microscopic studies, the findings have been classified as a loss of medial elastic tissue (medial degeneration), loss of smooth muscle cells (medial necrosis), increase of extracellular components (ground substance or mucopolysaccharides), the presence of white blood cells (inflammatory), fat deposition (atherosclerosis), and intimal thickening (intimal hyperplasia).

In the fine study by Tang and colleagues from Yale University in this issue of Circulation, they have taken the investigation of aortic disease and pathology to a new level of sophistication. Indeed, the most striking finding is that the aorta behaves like any other organ subjected to increasing functional loads by hypertrophying as an organ, just like the heart or liver, and not only dilating as a utilitarian pipe. In trying to understand this process several questions come to mind: (1) How does this aortic organ sense the need to increase its mass? (2) How does it actually grow? (3) Is the function of the organ preserved? (4) Does uncontrolled adaptation lead to an aberrant pathological repair?
Deaths Related to Aortic Disease

<table>
<thead>
<tr>
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<th>Yearly</th>
<th>Average</th>
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<tbody>
<tr>
<td>Minimum</td>
<td>129 533</td>
<td>43 177</td>
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<tr>
<td>Assuming 10% of deaths from</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis unspecified (ICD10-I70.9)</td>
<td>4139</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest (ICD10-I46.9)</td>
<td>4801</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease unspecified (ICD10-I51.6)</td>
<td>1162</td>
<td></td>
</tr>
<tr>
<td>Sudden cardiac (ICD10-I46.1)</td>
<td>818</td>
<td></td>
</tr>
<tr>
<td>Potential total</td>
<td>140 453</td>
<td>46 817</td>
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Not included are deaths related to mycotic aneurysms, deaths from aortic valve pathology associated with potential aneurysms, congestive heart failure, or other promising causes with potential aortic disease.

The quantification of real-time polymerase chain reaction methods, they showed that transcripts of cellular proteins such as smooth muscle α-actin were preserved in aneurysms, although the total expression of transcripts of extracellular matrix proteins in media were decreased, possibly leading to increased matrix protein breakdown. This was likely caused by metalloproteinasises (MMPs) such as MMP-9 rather than to decreased production. The association of MMP-9 with ascending aortic aneurysms has, however, differed between studies. Indeed, the complex biochemical relationship among the metalloproteinasises, tissue inhibitor, plasmin, cytokine, interleukin, prostaglandin E2, transforming growth factors, tumor necrosis factor, vascular endothelial growth factor, integrin, tenoscin, endothelial nitric oxide synthetase, cysteine proteases, undiscovered molecules, macrophages, other inflammatory endothelial cells, fibroblasts, and smooth muscle cells has yet to be definitively unraveled. Part of the authors observed differences, in comparison with previous reports about the abdominal aorta, is that the ascending aorta has more elastic tissue content as compared with the abdominal aorta; in the abdominal aorta, collagen fibers predominate. Although there are some structural differences between the thoracic and abdominal portions of this aortic organ, these are not well characterized at the cell and molecular biology level. Little is known about whether there are changes over time in the component layers of the aorta such as the vasa vasorum or the innervation of the aorta. Besides baroreceptors, what other functions do the nerves play in the biology of this organ? Interactions among smooth muscle, endothelium (of the aortic lumen, and vasa vasorum), and the nervous system that may give clues to the normal and abnormal maintenance and turnover of cellular and extracellular components of this organ are not known. Are changes in the expression of MMP-9 regulated by these interactions? Or perhaps, as we know now about the heart, could these changes be secondary to gene polymorphisms in the MMP-9 genes, the genes that regulate them, or other extracellular matrix proteins such as elastin, fibrillins, fibulins, or collagen?

The authors have shown that despite the commonly noted thinning of the aortic wall associated with aneurysmal dilatation, there is in fact a total increase in the bulk of the aortic wall because the diameter of the aorta has increased. The reason for this is that as an aneurysm dilates and because of the increased wall stress, hypertrophy seems to compensate for increased wall stress, as predicted by Laplace’s law. They did, however, note that the elastic tissue matrix increasingly degenerates, degrades, and fragments. Previous studies have suggested that the elastic fibers are replaced by inelastic collagen scar tissue; thus, limits of elasticity are reached and the aortic aneurysm bursts. Of additional interest, there is evidence that elastases are associated with the progressive degeneration of elastic tissue matrix, although increasing levels of collagenases (MMP-1) particularly associated with chronic pulmonary disease are more often associated with aortic rupture. In this article, using the expression of these metalloproteinasises as measured by real time-polymerase chain reaction, Tang et al found diminished synthetic capacity of the smooth muscle cells for these proteins, despite their demonstrated ability to proliferate and increase their mass. This raises other questions: When do smooth muscle cells begin to proliferate? Do we see the aneurysm years after these cells proliferated, when the number of smooth muscle cells has already increased but perhaps other synthetic capacity has diminished?

What Tang and colleagues do not address are the potentially more complex processes that occur with aortic dissection and aortic diseases associated with inflammatory cell infiltrates. They also excluded patients with known elastic tissue structural problems such as Marfan syndrome. Acute aortic dissection, particularly in patients with Marfan syndrome, may be associated with greater degrees of loss of smooth muscle cells or increases in proteoglycan material (ground substance). The initial inducing injury that causes inflammation in the aorta, namely aortitis, is similarly unknown. Interesting developments include the association with chlamydia in thoracic aneurysms but not in dissections, tuberculosis bacteria surface antigens, cytomegalovirus, other microbial DNA fragments, and Staphylococcus aureus toxic shock–associated bacteria sharing antigens with the aorta in patients displaying aneurysms and Kawasaki disease. The underlying pathways of aortic wall degeneration and inflammation are also better understood for diseases such as Takayasu disease (nonspecific aortic arteritis), giant cell arteritis (Horton disease) and other autoimmune and vascular diseases that may also affect the aorta. The authors indicate that they will address the inflammatory process in the aorta in a future study.

In summary, there is an epidemic of unrecognized aortic disease that is poorly understood and investigated. The article by Wang and colleagues has shown the aorta hypertrophies under stress like other organs but eventually reaches a limit of compensation, and in the case of the aorta, because of degeneration and degradation of its elasticity, like a balloon, it bursts or dissects. What inducing injury causes this chain of events needs to be determined. Nevertheless, the aorta should be considered as important an organ as other organs in the human body that for the long-term survival of humans should be more thoroughly investigated. The tools of molecular biology and genetics are providing us with the opportunity to answer many of these questions in humans, but funding agencies that claim to be interested in translational research
may not be giving priority to funding this kind of investigation. Indeed, institutions with large populations of this type of patient struggle for research funding only to learn that mainly mechanistic approaches studying animal models (which sometimes do not really reproduce a human disease) are the funding priority. Thus, the study by Wang et al in humans is a good example of what can be achieved by an excellent, descriptive, well-designed study that takes a translational bench-to-bedside approach to research. Clearly, the cost of not learning how to effectively diagnose, prevent, or cure this health problem, which causes a level of morbidity and mortality that is higher than cancers and homicides, will continue to grow. A relatively small investment in research will likely have an important impact on the cost of diseases of the aortic organ to our society.

References


Key Words Editorsials ▪ aorta ▪ pathology ▪ metalloproteinases ▪ aneurysm
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