The aortic wall: Four questions and insights

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Video clip is available online.

The aortic wall is a complex structure, and “much more than a tube.”¹ Ranging normally in dimension to as large as 3.2 cm in women and 3.6 cm in men,² the aorta has a complex physiologic function, which capitalizes on its normal elastic properties to participate actively with the left ventricle in a “game of catch” with the stroke volume.¹ We will look at 4 specific insights—new, emerging, and largely unpublished—from 4 teams of the Aortic Institute at Yale: clinical, surgical pathology, engineering, and molecular genetics.

CLINICAL: CAN THE AORTIC WALL COMMUNICATE WITH US?

It is well known that most patients with thoracic aortic aneurysms (as many as 95%³) have no symptoms until dissection or rupture occurs. Some patients, however, indeed do have symptoms, usually including chest pain. We wished to explore the significance of these symptoms. Specifically, we looked at gross findings in the operating room in patients with symptoms. Of 120 consecutive patients brought to the operating room in a 22-month period for elective ascending aortic replacement, 46 had symptoms. Although the incidence of symptoms among our patients was greater than expected, our patients had all sought care in some way and were not culled from the general population, where many asymptomatic aneurysms are to be found. For these 46 patients with symptoms, we reviewed the operative and pathologic reports to look for findings that could be expected to produce clinical pain. We looked specifically for aortic adventitial injection, periaortic adhesions, focal

thinning or bulging of the aortic wall, intimal disruption, and focal wall necrosis or degeneration.

Such gross anatomic findings were indeed found frequently among patients with symptoms. (Table 1 and Figure 1). The frequency of abnormal gross anatomic findings in patients with symptoms was, in fact, quite high. On microscopy of the symptomatic aortas, inflammatory findings abounded (details omitted in this overview). We believe that these findings “explain” the chest pain reported by these patients. Many symptom-free patients also had such anatomic findings, although at a much larger aortic size and later stage of disease.

Because these gross anatomic findings indicate inflammation (injection, adhesions) or focal wall deterioration (thinning or bulging, intimal disruption, wall necrosis, or degeneration), we consider them to be indicators of aortic “activity” that likely portend impending rupture or dissection. We therefore believe that these data lend support to the long-standing surgical dictum that symptomatic aneurysms merit resection regardless of size.

The anatomic neural pathways by which signals from the distressed aortic wall can be relayed to higher brain centers for processing have been elegantly described and illustrated by Boudoulas and Stefanidis.⁴

SURGICAL PATHOLOGY: WHAT HAPPENS ANATOMICALLY WHEN THE AORTIC WALL THINS?

One often finds very impressive and frightening focal wall thinning (“bubbles”) in patients undergoing elective surgical resection (Figure 2). We have wondered what anatomic changes underlie such “bubbles” in the aortic wall. Accordingly, we have looked with our pathologists specifically at such areas under the light microscope.

What we have found is that the medial lamellae are lost in such regions of extreme thinning or bubble formation. Elastic fibers and smooth muscle cells are lost, giving way to myxoid degeneration of the aortic wall. This process leaves only intima and adventitia.

We believe that loss of the elastic media, which normally buffers the force of aortic expansion in systole, reinforces the obviously dangerous appearance of such lesions.

ENGINEERING: DO THE MECHANICS OF THE AORTIC WALL CORRELATE WITH CLINICAL BEHAVIOR?

Our group and others have studied the aortic wall via application of engineering analytic principles.⁵ Most analyses of

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TABLE 1. Frequency of positive gross anatomic findings among patients with symptoms undergoing elective aortic ascending aortic resection

Finding	n	%
Injection	1	2
Adhesions	12	23
Wall thinning or bulging	22	47
Intimal disruption	3	6
Wall necrosis or disruption	3	6

this type have relied on in vitro uniaxial deformation of pieces of the aortic wall. Of course, in real life the aortic wall deforms in both longitudinal and in circumferential directions.

One of us (S.W.) recently performed advanced engineering analysis of specimens of ascending aortic wall removed at surgery. These specimens were processed immediately on harvest to preserve full mechanical function. Furthermore, this investigator has tested our specimens in biaxial deformation. This has permitted novel advanced engineering analysis and permitted expression of the behavior of the aortic wall through exponential equations.

We have been astounded by the close correlation of the engineering findings with the clinical behavior of the aorta in patients (Figure 3). Inputting the precise ultimate tensile strength from uniaxial testing into the equations modeled from biaxial deformation permits exact “prediction” of when dissection or rupture would have occurred in a specific patient. Figure 3, A, shows that a particular patient would have had dissection occur at a diameter of 5.29 cm and a pressure of 168 mm Hg. Rupture would have occurred at a diameter of 5.47 cm and a pressure of 263 mm Hg. These parameters correlate well with our recommendations, which are based on serial monitoring of large cohorts of thoracic aortic aneurysm patients, that prophylactic operation should be performed before a diameter of 5.5 cm is attained.⁶ These parameters also correlate nicely with our clinical findings that blood pressure rises accompanying extreme exercise or emotion can indeed precipitate aortic dissection.⁷⁻⁹ These experiments were done with incorporation of aortic size into the equations but without consideration of body size or the aortic size index, which we have used clinically to “adjust” for extremely small or large patients.¹⁰ We have made initial comparisons of aortas from patients with bicuspid aortic valves and those from patients with tricuspid aortic valves; no major differences in engineering properties have come to light.

This close correlation between engineering modeling and clinical behavior of thoracic aortic aneurysms promises to enhance our understanding of the pathophysiology of acute aortic events and to refine our criteria for surgical intervention.

FIGURE 1. A, Note this localized disruption (arrow) of the ascending aortic wall just above the aortic valve in a 38 year-old woman with persistent chest pain despite imaging studies showing no evidence of dissection. This disruption would likely have progressed to typical ascending aortic dissection had surgery not been performed. B, Anatomic pathways by which distress signals from the aortic wall can be relayed to higher centers to produce pain. Signals travel along sensory nerves originating in the aortic wall to the sympathetic chain and from there, through the rami communicantes, to the spinal cord, through which they ascend to the brain. CNS, Central nervous system. Reprinted with permission from: Elefteriades JA. Controversies in diseases of the aorta: preface. *Cardiol Clin*. 2010;28:xvii. Boudoulas H, Stefanadis C. *The aorta: structure, function, dysfunction, and diseases*. New York: Informa; 2009.

FIGURE 2. A, Area of extreme thinning (“bubble”) in aortic wall. B, Histologic slide of area of severe thinning in aortic wall. Note degeneration of the aortic media with loss of smooth muscle cells and elastic lamella, as well as myxoid degeneration in the center of the section. Normal aorta, not thinned and with preserved media, is seen to the periphery of the section on the right and left.

MOLECULAR GENETICS: CAN WE MONITOR THE SURGICAL PATHOLOGY OF THE AORTIC WALL?

To know the ongoing biology of the aortic wall would be exceptionally helpful. The search for biomarkers of thoracic aortic disease, although hopeful, has not yet yielded fruit.¹¹ Markers of matrix metalloproteinases, of elastin and collagen metabolism, of muscle proteins, and of cytokines have not yet led to clinical fruition. Unfortunately, of course, the aorta is not amenable to periodic biopsy.

Initial efforts are underway to use positron emission tomography to assess the aortic wall, with some early limited success in the abdominal region.^{12,13} The hope is that the finding of increased metabolic uptake, signifying inflammation, can validate a decision for prophylactic surgery.

With colleagues at Applied Biosystems (Life Technologies Corporation, Carlsbad, Calif), we recently published results of an “RNA Signature” blood test that we hope may ultimately come to represent a “virtual biopsy”

indicative of ongoing molecular biology in the aortic wall.¹⁴ Such monitoring of disease state by assessment of RNA expression profiles in peripheral blood is being applied to various systemic diseases in addition to aneurysms.¹⁴ It is becoming apparent that for these systemic diseases, molecular activity in the blood reflects the underlying disease process.

If the DNA is the body’s blueprint, determining how the “house” will be built, then the RNA profiles reflect current work activity in different “rooms” (eg, kitchen, den, garage). Some parts of the DNA are actively being transcribed into specific RNA molecules for protein fabrication, whereas others may be dormant.

We looked at RNA expressions in peripheral white blood cells to assess the relative expression levels of more than 29,000 genes in patients with thoracic aortic aneurysm relative to healthy control subjects. Of those 29,000 genes, some were upregulated compared to control levels, and some were downregulated. We sifted out the 41 most

FIGURE 3. A, Engineering analysis combining ultimate tensile strength from uniaxial testing with mathematic modeling from biaxial testing permits “prediction” of exact sizes at which rupture and dissection would have occurred (Video 1). B, Note that the predicted dissection and rupture points for the patient illustrated in panel A fall exactly in the size range for adverse events (arrow) found in our previous clinical studies. Reprinted with permission from: Elefteriades JA, Rizzo JA. Epidemiology: incidence, prevalence, and trends. In: Elefteriades JA, editor. *Acute aortic disease*. New York: Informa; 2007.

FIGURE 4. A, Note the high sensitivity, specificity, and overall accuracy of the RNA Signature test in correctly discriminating between blood samples from patients with thoracic aortic aneurysms and those from healthy control subjects. These values are certainly within or exceed the parameters of other clinical screening tests in wide use. In the 3-dimensional plot on the right, if all the red patient dots and all the blue control dots were contained in their respective 3-dimensional ovals, the test would have been 100% accurate. B, Explanation of hierarchic cluster diagrams, now entering the literature in our specialty with some frequency. C, If all the *red dots* representing aneurysm patients (TAA) and all the *blue dots* representing control subjects had been grouped together, the test would have been 100% accurate; almost all the assignments were correct. *Red* represents overexpressed and *green* represents underexpressed. Reprinted with permission from Wang Y, Barbacioru CC, Shiffman D, Balasubramanian S, Iakoubouva O, Tranquilli M, et al. Gene expression signature in peripheral blood detects thoracic aortic aneurysm. *PLoS One*. 2007;2:e1050.

upregulated or downregulated RNAs. We were able to measure this characteristic pattern of gene expression on automated testing arrays, and we used the expression pattern as a predictive test. Remarkably, sensitivity, specificity, and overall accuracy were about 80% in distinguishing patients with thoracic aneurysms from healthy control subjects. In essence, this novel RNA Signature appeared to have significant potential as a general screening test for thoracic aortic aneurysm. We published these results a few years ago.¹⁴ A lethal, asymptomatic disease such as thoracic aortic aneurysm cries out for a biomarker suitable for screening of the general population. In Figure 4, one can see visually displayed the considerable discriminative power of the RNA Signature test.

We have not yet made the transition to clinical application of this RNA Signature test, preferring rather to revalidate our findings in a fresh cohort of patients before proposing clinical use of this novel screening method. At the time of the 2012 Aortic Symposium, we can report

that our first batch of replication samples confirms our earlier findings; namely, that sensitivity, specificity, and overall accuracy of the RNA Signature appear to be satisfactory to justify clinical application. The remaining batches of samples will be analyzed soon and, if confirmatory, will justify transitioning this research finding into a clinical tool.

Most importantly, the metabolic pathways in which our 41 discriminatory genes reside subtend processes known to be involved in the pathophysiology and genesis of thoracic aortic aneurysm—including inflammatory, apoptotic, and proteolytic pathways. We are hopeful that, by sampling peripheral blood, we may be able in the future to obtain a virtual biopsy of molecular pathways in the aortic wall. It is distinctly possible that specific alterations in expression of key genes may precede and predict rupture and dissection. If this concept is borne out, such a virtual biopsy may be able to augment and personalize our current anatomic (size) criteria for surgical intervention.

CONCLUSIONS

In summary, regarding these 4 questions about the aortic wall, we may state the following:

1. Can the aorta communicate with us? Yes. Symptoms are often accompanied by serious gross irregularities in the appearance and structure of the aortic wall.
2. What happens anatomically when the aortic wall thins? The elastic lamellar units of the media are lost, being replaced by myxoid material and leaving a vulnerable aorta composed only of intima and adventitia.
3. Do the mechanics of the aortic wall correlate with clinical behavior? Yes, emphatically so. Mathematic modeling derived from uniaxial and biaxial tensile testing confirms that rupture and dissection can be expected in the same size range, from 5 to 5.5 cm, as seen in our previous clinical studies.
4. Can we monitor the surgical pathology of the aortic wall? The RNA Signature blood test promises to detect aneurysms and possibly to permit a virtual biopsy of molecular events reflective of the aortic wall.

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