Pulse Wave Velocity Involving Proximal Portions of the Aorta Correlates with the Degree of Aortic Dilatation at the Sinuses of Valsalva in Ascending Thoracic Aortic Aneurysms

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Objective: To determine the relationship between arterial stiffness measured in different aortic segments and the presence and extent of ascending thoracic aortic aneurysm (ATAA).

Methods: Patients at a Thoracic Aortic Diseases clinic at a University teaching hospital were compared to patients attending a Cardiology outpatient Clinic at the same institution. A non-invasive measure of vascular stiffness was performed using pulse wave velocity (PWV) measurement of several vascular segments—carotid-femoral pulse wave velocity (cfPWV), heart-femoral pulse wave velocity (hfPWV) and brachial-ankle pulse wave velocity (baPWV). Aortic dimensions were measured on echocardiogram.

Results: Patients with ATAA (N = 32) were 66 years and the same age as those without ATAA (N = 46). There was no significant difference between those with or without aortic aneurysm with respect to cfPWV, hfPWV or baPWV. In ATAA, there was a significant (p < 0.05) inverse correlation between aortic diameter at the sinuses of Valsalva and cfPWV, as well as hfPWV, but not with baPWV. This relationship was not evident in persons without ATAA.

Conclusion: Reduced aortic stiffness (increased compliance), assessed by cfPWV or hfPWV, correlates with larger aortic size of ATAA at the level of the sinuses of Valsalva but not at the ascending aorta, suggesting cfPWV may be a useful method to assess the size of ATAA at the level of the sinuses of Valsalva. Overall aortic stiffness assessed by PWV did not differentiate persons with or without an ATAA, in individuals who do not have a genetic or inheritable cause of their ATAA.

Keywords: Thoracic aortic aneurysm, aortic compliance, aortic stiffness

Introduction

Thoracic aortic aneurysm (TAA), a condition with a potentially high mortality rate from sudden rupture of the aorta, has been increasing in prevalence.1,2 The thoracic aorta is comprised of several segments—sinus of Valsalva, ascending aorta and arch as well as the descending aorta. Each of which have some differences in embryologic development and composition.3 Ascending thoracic aortic aneurysm (ATAA) when it ruptures can be a challenging clinical problem.4 ATAA, which carries a greater mortality risk than descending TAA, can be due to a spectrum of genetic, degenerative, and traumatic conditions.5,6 The pathogenesis of this condition leading to aortic rupture involves changes in the composition of the aortic wall.7,8 Engineering calculations have estimated that as the aorta enlarges, distensibility of the aortic wall decreases, so that by approximately 6 cm, the aorta becomes rigid.9 Consistent with this suggestion is the data from cases with Marfan’s syndrome,10–13 the aortopathy associated with bicuspid aortic valves (BAV)14,15 and familial thoracic aortic aneurysms.16 The majority of ATAA cases, however, are not due to Marfan’s syndrome, aortopathy of BAV or familial/genetic factors, but rather are usually ascribed to degenerative factors and comprise 80% of all ATAA cases.17 There has, however, been little investigation as to whether changes in aortic stiffness occur in the usual cases of aortic aneurysms that are not due to a specific cause; are evident in smaller aneurysms and are manifest differently depending on the location of the expansion within the ascending thoracic aorta.
Aortic stiffness is an indicator of aortic structure and reflects its constituents, including the amount of elastin, collagen, and calcium.\textsuperscript{18} Quantification of vascular stiffness is readily accomplished by the measurement of the pulse wave velocity (PWV) or the speed of propagation of pressure through a defined portion of the arterial tree. As a measure of arterial stiffness, pulse wave velocity, in persons without ATAA, has been shown to be predictive of cardiovascular events and all-cause mortality.\textsuperscript{19-21} These findings highlight the robustness of the methodology and its value in cardiovascular risk assessment.

The objectives of this study were three fold. First we sought to determine whether there were differences in PWV in persons with ATAA, of presumed degenerative etiology, compared to aged matched controls. Because PWV can be assessed in different vascular beds, we speculated that ATAA should preferentially affect PWV in segments that mainly consist of the thoracic aorta rather than measurements that include other segments. Third, we sought to determine whether the relationship of PWV to ATAA was influenced by the ATAA size in different segments of the thoracic aorta.

**Methods**

The patient population consisted of patients who attended the Aortic Diseases Outpatient Clinic at a University Hospital and the controls were patients concomitantly attending a Cardiology Clinic at the same institution during the same time period. The entry criteria for the study were individuals who had an echocardiogram and a CT angiogram that established the diagnosis of ATAA\textsuperscript{22} and the control group had an echocardiogram that did not show evidence of an ATAA. All individuals had consented to measurement of vascular stiffness. Exclusion criteria included clinical evidence or a family history of Marfan’s syndrome or a genetic disease known to be associated with aortic aneurysm. Patients were also excluded if they had a bicuspid aortic valve; significant aortic valve disease such as aortic stenosis or regurgitation, known aortitis, aortic dissection or previous aortic surgery.

**Assessment of arterial stiffness**

A non-invasive measure of vascular stiffness was performed as previous outlined.\textsuperscript{2,3,24} Briefly, patients were assessed in the supine position. Blood pressure cuffs were placed around both arms and ankles. Electrocardiographic electrodes were clipped on to both wrists. A phonocardiography sensor was placed on the left edge of the sternum. Tonometric sensors were placed at the right carotid and femoral arteries. The carotid-femoral length was measured from the surface landmarks of the patients’ carotid and femoral pulses using measuring tape. Measurements were made simultaneously on a vascular screening device (VP 2000; Colin Co. Ltd., Komaki, Aichi, Japan). This device permitted the calculation of PWV in three segments brachial to ankle pulse wave velocity (baPWV), heart to femoral pulse wave velocity (hfPWV), and carotid-femoral pulse wave velocity (cfPWV).

**Echocardiographic measurements**

All patients had undergone a transthoracic echocardiogram at our institution. Measurement of ascending aortic root dimensions and cardiac dimensions permitted the calculation of PWV in three segments: (Fig. 1). There was no attempt to define the shape of the ATAA.

**Results**

The characteristics of the study population show that both groups were 66 years of age and were not significantly different (Table 1). The degree of aortic dilatation was considerably and significantly larger in those with ATAA compared to those without ATAA (Fig. 1). There was no attempt to define the shape of the ATAA.

There was no significant difference between those with or without aortic aneurysm with respect to the cfPWV (p = 0.847), hfPWV (p = 0.405) or baPWV (p = 0.458) (Fig. 2).

The data were next examined for a correlation between aortic size at the sinuses of Valsalva and PWV for persons with ATAA using a linear least squares fit of the data (Fig. 3). There was an inverse relationship between PWV and aortic diameter at the sinuses of Valsalva. The relationship was significant (p < 0.05) between aortic diameter, at the sinuses of Valsalva and cfPWV, but not with hfPWV. In contrast there was no relationship between aortic diameter at the sinuses of Valsalva and PWV in persons without ATAA (Fig. 4).

To determine whether there might be a correlation between aortic size at the ascending aorta and PWV, a linear least squares fit of the data was performed. There were no significant correlations between aortic diameter in the ascending aorta and cfPWV, hfPWV, or baPWV in persons with ATAA (Fig. 5).

**Discussion**

The major contribution of this study is that it is the first, to our knowledge, to show discordanecs in the
Table 1 shows the subject characteristics of participants in the study.

<table>
<thead>
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<th></th>
<th>Control</th>
<th>SD</th>
<th>ATAA</th>
<th>SD</th>
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Fig. 1 shows the diameter of the aorta at the sinuses of Valsalva (top) and ascending aorta (bottom) for individuals with or without aortic aneurysm. *** p < 0.001

Fig. 2 shows the pulse wave velocity (PWV) for carotid-femoral pulse wave velocity (cfPWV, upper panel), heart-femoral pulse wave velocity (hfPWV, middle panel) and brachial-ankle pulse wave velocity (baPWV, lower panel) for persons with or without thoracic aortic aneurysm. The horizontal line indicates the mean for each group.

Fig. 3 shows the correlation between aortic dimension at the sinuses of Valsalva and pulse wave velocity (PWV) for carotid-femoral pulse wave velocity (cfPWV, upper panel), heart-femoral pulse wave velocity (hfPWV, middle panel) and brachial-ankle pulse wave velocity (baPWV, lower panel) for persons with thoracic aortic aneurysm.

Fig. 4 shows the correlation between aortic dimension at the sinuses of Valsalva and pulse wave velocity (PWV) for carotid-femoral pulse wave velocity (cfPWV, upper panel), heart-femoral pulse wave velocity (hfPWV, middle panel) and brachial-ankle pulse wave velocity (baPWV, lower panel) for persons without a thoracic aortic aneurysm.
intriguing to speculate that a larger aorta at the sinuses of Valsalva is more compliant, leading to lower PWV. A similar reduction in aortic stiffness has been shown in abdominal aortic aneurysm, and is associated with an increase after aneurysm repair.26,27 The inverse relationship between cPWV or hPWV and sinus of Valsalva size may negate a potential positive relationship between PWV and ATAA that affects other segments of the thoracic aorta. Most ATAA are a composite of aneurysms affecting all of segments of the thoracic aorta. The sinuses of Valsalva have physiologic functions and can play specific roles in valvular function such as the ability to minimize stress in the aortic leaflets.28 The unique feature of the sinuses of Valsalva is that they server to rapidly accommodate the initial blood ejected from the left ventricle so that it is reasonable to conclude that dilated sinuses of Valsalva will more readily accommodate ejected blood and lead to a change in aortic compliance in this segment of the aorta.

We found a significant association between aortic diameter and measurements of PWV in segments closest to the thoracic aorta, such as cPWV and hPWV, rather than the more generalized assessment of aortic stiffness provided by baPWV. This is consistent with the concept that different components of the arterial tree are measured by baPWV compared to cPWV, as we and others have pointed out. cPWV is more of an indicator of central arterial stiffness, while baPWV is an indicator of the combination of central and peripheral arterial stiffness.29–33 Measurement of PWV was not able to identify individuals with ATAA. There are a number of potential explanations. First, the ascending aorta defines the presence of an ascending aortic aneurysm. There was no correlation between PWV and the diameter of the ascending aorta. The sinuses of Valsalva are a relatively small part of the ascending aorta. We speculate that the presence of concomitant factors that increase arterial stiffness and alter PWV in older individuals, preclude that ability of PWV to identify ATAA or restating our suggestion is that PWV is not specific enough to be an indicator of the presence of ATAA. Our study excluded persons with Marfan’s syndrome, BAV, and familial thoracic aneurysm. Increased aortic stiffness has been reported from several studies of patients with Marfan’s syndrome.13,16 However the persons in those studies were young–most were younger than 30 years.12,13,16 Detailed analysis provides some supporting evidence for our conclusion. De Wit et al. found that patients with Marfan’s syndrome aged 40 years or younger had stiffer aortas than controls, but those over 40 years were similar to controls.16 Nistri et al. found that aortic stiffness was increased in BAV compared to age-matched controls, but the mean age of the subjects with BAV was 23 years.15

Fig. 5 shows the correlation between aortic dimension in the ascending aorta and pulse wave velocity (PWV) for carotid-femoral pulse wave velocity (cPWV, upper panel), heart-femoral pulse wave velocity (hPWV, middle panel) and brachial-ankle pulse wave velocity (baPWV, lower panel) for persons with thoracic aortic aneurysm.
In another study of patients with BAV but without aortic dilatation, the mean age was 46.5 years and aortic stiffness was similar in persons with BAV and controls.\(^3\)\(^4\) In contrast to these studies, the mean age of the patients in our study was 66 years. Age is not the only factor, and the nature of the inherited aortopathy likely also plays a role as another study of persons with BAV with a mean age of 52 years, still younger than the mean age in our study, reported a greater aortic stiffness compared to controls.\(^3\)\(^5\)

The age group of patients with ATAA in our study was not preselected, but instead was representative of the age of patients referred to our center with ATAA who have this condition from a degenerative etiology often with concomitant hypertension, rather than from specific genetic conditions that are identified at a young age.

There are several limitations of this study that warrant discussion. First, a relatively small number of patients were studied. However, the exclusion criteria eliminated patients who have ATAA, namely Marfan’s syndrome, BAV, and familial ATAA, as well as persons who have had aortic surgery. Second, case control studies are subject to issues related to the composition of the control group. However, we did not apply any selection criteria to the control group other than age, in order to obtain age matched controls. Third, ATAA is associated with changes in the aortic wall mechanical properties that may produce altered arterial pulse wave transmission in a manner that is not readily detected by the traditional measurement of PWV which considers the pulse wave contour rise between different sites (foot-to-foot method). Fourth, patients in this study were receiving antihypertensive drugs, with about 40% were being treated with a beta-blocker and 30% with an ACE inhibitor. Different antihypertensive drug treatments can differentially affect aortic stiffness.\(^3\)\(^6\) Whether the nature of the antihypertensive drugs used in this patient population affected aortic stiffness measures is unknown. However, in patients with Marfan’s syndrome, a randomized cross-over trial of the ACE inhibitor, perindopril, the calcium channel blocker, verapamil, and the beta-blocker, atenolol, found that these drugs all produced a similar reduction in central systolic blood pressure.\(^3\)\(^7\) Fifth, some might argue that the correlation is modest between PWV and the dilatation of the sinuses of Valsalva and the echocardiogram would be a more accurate non-invasive method to assess aortic root. However, echocardiography requires a more skilled technician and interpreter and is not universally available in a timely manner, in many centers. In contrast, the measurement of PWV can be readily performed with less expensive equipment and repeated more readily than echocardiography. Importantly PWV measures aortic stiffness and provides another element of aortic vascular assessment in addition to aortic size. Lastly, PWV is an indicator of aortic stiffness but is not synonymous with aortic stiffness as the precision of the estimate of aortic stiffness by PWV needs to be considered. PWV, however, has a strong theoretic basis to be considered as marker of aortic stiffness, since it is related to the square root of the elasticity modulus and to the arterial thickness/radius ratio.\(^3\)\(^8\) Furthermore, PWV is a reliable indicator of aortic stiffness\(^3\)\(^9\) and can be considered a reliable noninvasive evaluation of regional aortic stiffness.

In summary, central aortic stiffness by measured by cfPWV or hfPWV is inversely related to aortic size at the level of the sinuses of Valsalva in the most common form of ATAA namely ATAA not due to an inherited aortopathy.\(^3\)\(^7\) The measurement of PWV does not distinguish individuals with ATAA from individuals of the same age with various other cardiovascular conditions without ATAA. These data suggest that the unique features of the sinuses of Valsalva result in an increased aortic compliance that may provide an easy indirect method to evaluate the sinuses of Valsalva in ATAA.

**Disclosure Statement**

There are no conflicts of interest with respect to this manuscript.

**References**


23) Rabkin SW, Chan SH. Correlation of pulse wave velocity with left ventricular mass in patients with hypertension once blood pressure has been normalized. Heart Int 2012; 7: e5.


25) Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-63.


33) Chow B, Rabkin SW. Brachial-ankle pulse wave velocity is the only index of arterial stiffness that correlates with a mitral valve indices of diastolic dysfunction, but no index correlates with left atrial size. Cardiol Res Pract 2013; 2013: 986847.


