Implications of preoperative arterial stiffness for patients treated with endovascular repair of abdominal aortic aneurysms

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ABSTRACT

Arterial stiffening is associated with adverse cardiovascular patient outcomes; stiffness may also be associated with postsurgical events and has been suggested to be a fundamental mechanism in the pathogenesis of aortic aneurysms. Although open repair of aneurysms decreases aortic stiffness, implantation of a rigid endograft is associated with increased aortic stiffness after endovascular aneurysm repair (EVAR). This review provides an overview of aortic wall physiology and the contemporary understanding of aortic stiffness and its implications for patients undergoing abdominal aortic aneurysm repair. Recent data suggests that increased central arterial stiffness, estimated preoperatively using the pulse wave velocity (PWV), may predict aneurysm sac behavior after EVAR, with elevated preoperative PWV associated with less sac shrinkage, and even sac enlargement, after EVAR. With the development of several simple noninvasive methods to measure PWV, such as brachial-ankle PWV and single cuff brachial oscillometry, there may be a role for monitoring ambulatory PWV to predict outcomes after EVAR. Additionally, because aortic stiffness is associated with adverse cardiovascular outcomes, and EVAR increases aortic stiffness, assessment of aortic stiffness before aortic interventions may help to guide therapeutic decisions as well as surveillance protocols, leading to optimized patient outcomes. (JVS—Vascular Science 2024;5:100209.)

Keywords: Vascular stiffness; Pulse wave analysis; Endovascular aneurysm repair; Aortic aneurysm; Abdominal

Abdominal aortic aneurysms (AAA) are the localized, irreversible dilation of the aortic wall as a result of aberrant remodeling secondary to endothelial damage, loss of vascular smooth muscle cells (SMC), and degradation of the extracellular matrix (ECM), leading to focal areas of weakening.[1] The natural course of aneurysms is to expand progressively,[2] necessitating active surveillance once the aneurysm is identified anCopyright © 2024 The Author(s). Published by Elsevier Inc. on behalf of the Society for Vascular Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).d intervention to prevent rupture once the benefit-to-risk ratio is exceeded.[3] Definitive management of aneurysms is currently surgical intervention, either via open or endovascular approach.[4] With the improvement in durability of endovascular techniques, endovascular aneurysm repair (EVAR) has become the predominant method of management.[5,6] However, the factors that determine long-term durability are still not well-understood. Sac shrinkage is frequently used as a surrogate marker for procedural success, with a shrinkage of <10 mm serving as an independent risk factor for complications, including rupture.[7-10] Although several theories have been proposed regarding the mechanisms of sac regression, these mechanisms remain poorly understood.

The composition and regional heterogeneity of the aorta is associated with an increasing stiffness gradient along the length of the vessel under physiological conditions, and deviations of arterial wall composition and stiffness have important implications for cardiovascular disease. Increased stiffness is associated with adverse cardiovascular outcomes and overall mortality.[11] It is not well-understood how changes in stiffness contribute to the pathogenesis of aneurysmal disease, nor how

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A.D. is funded by the US National Institute of Health (NIH) grants R01-HL144476 and R01-HL162580. The NIH had no involvement in the study design, data collection, analysis or interpretation, manuscript writing or the decision to submit the manuscript for publication.

Presented at the 2023 European Symposium for Vascular Biomaterials, Strasbourg, France, April 21-22, 2023.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS-Vascular Science policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2666-3503

https://doi.org/10.1016/j.jvssci.2024.100209

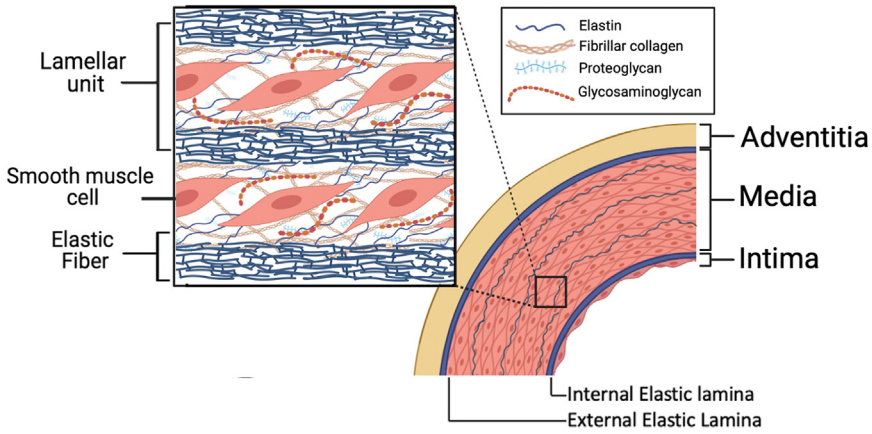

Fig 1. Aortic wall in cross-section. Magnified frame highlighting the microscopic structure of the media, which is arranged in lamellar units composed of thick elastic fibers with interposed smooth muscle cells (SMC) that are connected to the thick elastic bands via finer elastin fibers. The intervening space additionally contains cross-linked fibrillar collagen and other components of the extracellular matrix (ECM), including proteoglycans and glycosaminoglycans (GAG). Created with Biorender.

stiffness affects the risk of aneurysm rupture or sac regression after aneurysm repair. This review discusses the contemporary understanding of aortic stiffness and the clinical implications of stiffness as it relates to EVAR.

AORTIC CELLULAR PHYSIOLOGY

The aortic wall is composed of three distinct layers: the intima, media, and adventitia (Fig 1). The intima is composed of a single layer of endothelial cells anchored to a basement membrane adjacent to a thick sheet of elastic fibers known as the internal elastic lamina. The media consists of alternating layers of SMC and structural ECM proteins (Fig 1). External to the media is the external elastic lamina, which serves as the boundary between the media and adventitia. The adventitia is largely composed of type I collagen fibrils, which form thick collagen fibers, and fibroblasts, providing strength and support.[12] In the media, collagen fibers are arranged circumferentially, whereas in the intima and adventitia, collagen fibers are arranged into helical structures with dispersion of individual fibers from their mean orientation.[13,14]

The ECM is the noncellular component of the aortic wall that not only provides structural support, but also regulates the availability of cytokines and growth factors, thereby influencing cell function and determining both physiological and pathological vascular functions, such as remodeling, in response to alterations in homeostasis. Elastic fibers and fibrillar collagen compose approximately one-half of the dry weight of the aorta and are the predominant matrix component of the aortic wall.[1] Elastic fibers confer distensibility and recoil, whereas fibrillar collagen confers tensile strength and structure. These proteins form lamellar units, the thick elastic bands with interposed fine elastin fibers, collagen, SMC, and other matrix components such as proteoglycans, glycoproteins, and glycosaminoglycans, that allow the aorta to distend with pressure without the risk of mechanical failure and rupture (Fig 1).[15]

The aortic wall varies in its composition and mechanical properties along its length from the aortic root to the bifurcation (Fig 2). The intima remains uniformly thin along the length of the aorta, whereas the adventitia increases in thickness distally where it ultimately contributes a significant portion of total wall thickness in the abdominal aorta. Differences in the SMC and ECM composition of the media are responsible for the variation in vessel function along the arterial tree. The aorta is considered an elastic or conducting artery based on its relatively high elastin content and is responsible for conducting blood from the heart to the tissues at a relatively constant pressure gradient throughout the cardiac cycle.[16] This phenomenon is termed the Windkessel effect, which is achieved through the conversion of kinetic energy applied to the vessel wall into stored elastic potential energy during systole, with conversion back to kinetic energy during diastole, thereby conducting blood through the arterial tree.[17,18] The Windkessel effect also limits the exposure of end organs to deleteriously high blood pressures, even with systolic hypertension; it also decreases left ventricular afterload and improves coronary blood flow.[17]

Muscular arteries, such as the brachial arteries, are resistance vessels and contain a higher proportion of SMC to elastin than the elastic arteries. Resistance vessels, along with arterioles, regulate blood flow to capillary beds, with the SMC constricting or dilating based on tissue requirements.[19] Along with a gradual decrease in lumen

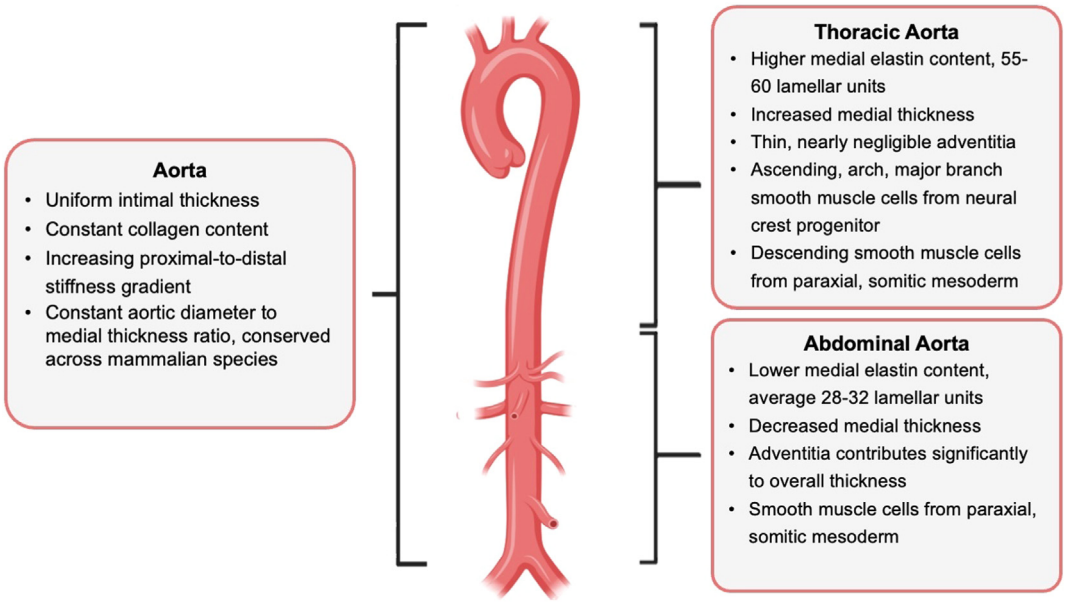

Fig 2. Comparison of regional differences in the thoracic and abdominal aorta. Created with Biorender.

diameter, the thickness of the media also decreases proximally to distally to maintain a constant thickness-to-lumen diameter ratio. Elastin comprises a higher proportion of the media in the thoracic aorta with significantly more lamellar units compared with the abdominal aorta (55-60 vs 28-32).[20] Collagen content remains constant along the aortic length, and thus the elastin-to-collagen ratio decreases proximally to distally. Together, these variations in aortic components create a gradient of stiffness that increases from the proximal ascending aorta to the distal abdominal aorta.

The physical characteristics of the aortic wall affect its compliance and distensibility. Aortic stiffness may vary owing to modifications in the makeup of the wall that lead to changes in the elastic structure.[21] Competent elastic fibers are important to aortic function and decrease the ventricular workload, as well as augmenting blood flow throughout the cardiac cycle, whereas collagen limits overdistension. Under normal conditions, elastin is synthesized, organized, and cross-linked by SMC before adulthood.[22] Elastic fibers have a very long half-life in adults, approximately 25 to 70 years, and are not effectively repaired or replaced after injury.[23] There is a decrease in messenger RNA transcript levels of elastin precursors with age[24] and an age-associated decrease in lysyl oxidase leading to insufficient elastin cross-linking.[25] These changes leave elastic fibers uniquely susceptible to mechanical fatigue, in addition to degradation by proteolysis; thus, damage to elastin fibers over time causes irreversible changes to the aortic wall structure[22] and contributes to the arterial stiffening associated with aging. The loss of elastin leads to decreased elastic recoil and diminished distensibility and may influence resident SMC to assume a secretory phenotype. This phenotypic change, from contractile to secretory, likely serves a mechanoadaptive role to maintain or restore the physiological state of the aortic wall. Unlike elastin, collagen fibers have a much shorter half-life and are less susceptible to mechanical fatigue; collagen fibers undergo routine turnover during physiological remodeling, via increased secretion by synthetic SMC.[26,27] However, abnormal covalent cross-linking of adjacent collagen fibers in response to injury may contribute to stiffening.[26]

In AAA, the reorientation of adventitial fibers in the circumferential direction, rather than the normal longitudinal orientation, alters the anisotropic properties of the vessel and likely contributes to diminished compliance. Patients with AAA have decreased aortic wall distensibility as estimated by the pulse wave velocity (PWV) compared with age- and sex-matched patients without AAA.[28] This factor suggests an increased stiffness of the arterial tree, with the majority contribution coming from the aorta, which may additionally contribute to the overall greater cardiovascular risk that has been observed in patients with AAA.[28]

AORTIC PWV AS A MEASURE OF STIFFNESS

With increased wall stiffness, there is increased velocity of the forward pulse wave, and peripherally reflected arterial waves reach the heart in early systole, rather than diastole, causing increased systolic blood pressure, lower diastolic blood pressure, augmentation of the cardiac workload, and decreased coronary perfusion pressure. Calculation of the pulse pressure, or the difference between the systolic and diastolic pressures, has been used traditionally as an indirect measure of arterial stiffness that has been used to predict worse outcomes

with hypertension; however, when adjusted for known cardiovascular risk factors, the pulse pressure loses its prognostic value.[29] Propagation of the pulse wave through the arterial tree depends on the physical properties of the blood, which are relatively invariable, and the characteristics of the arterial wall, including its stiffness and geometry. The term stiffness can be used to refer to the structural stiffness of the aorta, largely driven by the change in geometric effects accompanying changes in compliance, as well as the material stiffness, which describes the intrinsic properties of the arterial wall. Measurement of the propagation speed of the arterial pulse wave along the arterial wall, termed the PWV, is used to estimate the structural stiffness of the wall. Using the Bramwell-Hill equation, the PWV can be calculated in a uniform elastic tube with cross-sectional area (A) filled with a uniform liquid of density ρ:

$$PWV = \sqrt{\frac{A}{\rho}\frac{\Delta P}{\Delta A}}.$$

where ΔA is the change in luminal cross-sectional area in response to a change in pressure, ΔP. Distensibility (D), is often used synonymously with compliance and is calculated as:

$$D = \frac{\Delta A}{A\Delta \mathrm{P}}.$$

Therefore, the PWV varies inversely with the distensibility or compliance of the vessel[27]:

$$PWV = \sqrt{\frac{1}{\rho D}}.$$

Although compliance and distensibility are frequently used interchangeably, they are technically different. Compliance, which is related to the buffering function of the vessel, is defined as the change in volume per pressure unit, whereas distensibility, related to the determinant stress of the vessel wall, is the relative change in volume per unit of pressure. Arterial compliance is the product of the arterial distensibility and volume.[30] This equation is limited by the assumptions that the artery is a long, straight tube that is uniformly elastic and uniform in diameter throughout its length. This supposition neglects the effect of surface area differences owing to large aneurysmal dilations, stenoses, branch points, and vessel tortuosity.

Alternatively, the PWV can be calculated based on the material stiffness of the vessel using the Moens-Korteweg equation:

$$PWV = \sqrt{\frac{Eh}{2R\rho}}$$

where E is the Young's modulus, or the resistance of a material to elastic deformation, h is the wall thickness, R is the internal vessel radius, and ρ is the density of blood.[31,32] This equation neglects reflected pulse waves, initial fluid pressure, and vessel wall density. Although this equation can be used to calculate the PWV, the variables are not constant, depend on the artery itself, and are more challenging to evaluate clinically.[33] Additionally, the PWV may be incorrectly calculated using this equation in patients with hypertension.[33]

Direct measurement of distensibility proves to be technically challenging, as precise measurement requires invasive intraluminal pressure measurement within the aorta with simultaneous measurement of the change in luminal area at the same level as the pressure measurement. In the clinical setting, PWV can be estimated as the time difference (ΔT) between detection of the arterial pulse wave between two points in the line of pulse travel (ΔL)[27]:

$$\mathrm{PWV} = \frac{\Delta \mathrm{L}}{\Delta \mathrm{T}}.$$

The original measurements of PWV used invasive pressure catheters positioned within the aorta, with one catheter placed immediately distal to the aortic valve and the other placed just above the aortic bifurcation (Fig 3, *A*). Although this method directly measures the aortic PWV, it is an invasive procedure that must be performed in an endovascular suite by highly skilled technicians, which limits its routine use.[34]

With recent data supporting the measurement of central arterial stiffness for cardiovascular prognostication and risk stratification, less invasive methods to measure the PWV have been developed (Fig 3, *A*, Table I). Although additional blood vessels besides the aorta contribute to each of these measurements, the peripheral muscular arteries are generally considered stiff and the contribution of peripheral arterial disease can be largely neglected in favor of the assumption that the aorta contributes most significantly to this measured value.[27] Direct measures of the PWV (carotid-femoral applanation tonometry, brachial-ankle pressure, and finger-toe photoplethysmography) measure two points along a relatively straight line, and indirect measures (single cuff brachial oscillometry) use a proprietary transfer function to calculate the PWV from a single measurement point. The most ideal noninvasive measure to estimate aortic PWV, while minimizing contribution of the aortic branches would be the heart-femoral PWV in which the start of ventricular ejection, either determined by electrocardiogram or phonocardiogram, would be time point A with propagation of the pulse wave to a device measuring the femoral pulse as point B; this measurement is not routinely performed clinically.[27,35,36,41]

Consensus guidelines for PWV measurements cite carotid-femoral applanation tonometry as the standard for ambulatory stiffness measurement.[37] This method uses tonometry devices placed at the common carotid and common femoral arteries; the time delay between pulse arrival at the respective sites and the distance

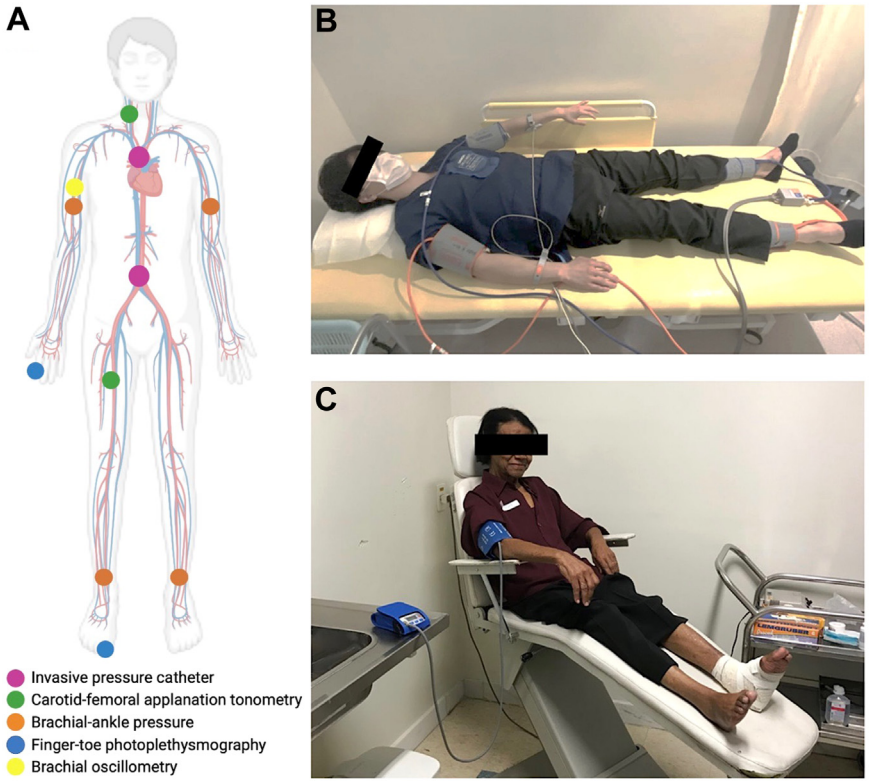

Fig 3. Methods for measuring pulse wave velocity (PWV). **(A)** Comparison of anatomical sites for PWV measurement. Examples of patient setup for PWV determination by **(B)** brachial-ankle oscillometry or **(C)** single-cuff brachial oscillometry. Created with Biorender.

between them is calculated from a normalized curve based on height and weight. This method has the benefit of being noninvasive, but it is limited by the need for technical expertise as well as anatomical limitations in accessing the carotid and femoral arteries; in addition, calculations neglect the impact of the aortic arch.[37]

The brachial-ankle pressure (Fig 3*A* and *B*, Table I) is measured using automated modified pressure cuffs placed on bilateral upper and lower extremities in the supine position. Pulse volume waveforms are measured in the upper arm and ankle using a pressure sensor in the modified cuffs, and the PWV is calculated based on the timing of the front of the waveforms and the calculated distance between the arm and the ankle.[38,42] This method has the benefit of being noninvasive, automated, and relatively inexpensive and has been validated against invasive measures of PWV; it may be confounded by significantly elevated blood pressures or severe peripheral arterial disease.[27,39]

Finger-toe photoplethysmography (Table I) is a noninvasive, direct measurement of the PWV. Sensors (similar to a pulse oximeter) are placed on an ipsilateral finger and toe and infrared light measures the change in blood volume in the finger and toe with each pulse wave; the distance between the finger and toe are estimated based on normalized curves of height and weight.[40] This method has been validated against the carotid-femoral PWV,[40] but has not been validated in the presence of advanced atherosclerotic or metabolic diseases. Finger-toe photoplethysmography is inexpensive, noninvasive, and easy to perform. A major pitfall is the neglect of the intervening lengths of the arterial tree, which introduces error in the presence of advanced atherosclerotic disease.[39]

Single cuff brachial oscillometry (Fig 3*A* and *C*, Table I) is an indirect method of calculating the PWV featuring a single high-fidelity brachial sensor cuff capable of capturing brachial artery pulse waves and brachial arterial blood pressure; the PWV is estimated using a device-dependent mathematical transfer function. This method is noninferior compared with other noninvasive methods and is relatively easy to use with a low cost. A major pitfall of this method is the indirect method by which it is calculated; the proprietary transfer functions are not available widely, which makes independent validation of results challenging.[43]

Validation studies have shown good agreement between tonometric and oscillometric methods of measuring PWV with invasive measures.[44,45] In addition, studies that have compared tomometric and oscillometric methods with each other suggest agreement

Table I. Modalities to measure pulse wave velocity (PWV)

	Method of measurement	Benefits	Pitfalls
Pressure catheter[35]	• Direct measurement of aortic pulse wave with catheters placed immediately distal to the aortic valve and proximal to bifurcation	• High resolution • The most direct method of PWV measurement	• Requires endovascular suite and highly specialized equipment and personnel • Expensive • Invasive
Carotid-femoral applanation tonometry[36]	• Direct measurement using applanation tonometry at the common carotid and common femoral arteries	• Gold standard for noninvasive measurement • Inexpensive	• Requires greater degree of technical expertise • Anatomical limitations in accessing carotid and femoral arteries owing to body habitus
Brachial-ankle pressure[37,38]	• Direct measurement using pressure-sensing cuffs on all four extremities with patient in supine position	• Noninvasive • Inexpensive • Relative ease of use, automated device	• May be confounded by significant elevations in blood pressure • May be unreliable with severe peripheral arterial disease
Finger-toe photoplethysmography[39]	• Direct measurement using infrared sensing photodiode devices on ipsilateral finger/toe, similar to pulse oximetry	• Noninvasive • Inexpensive • Relative ease of use	• May be unreliable in patients with severe peripheral vascular disease or metabolic diseases
Single cuff brachial oscillometry[40]	• Indirect method of calculating PWV using a single brachial cuff and proprietary transfer function informed by several anthropomorphic variables	• Noninvasive • Inexpensive • Relative ease of use	• Indirect • Proprietary transfer functions are not published for validation •Potential for significant error if device calibration is flawed

PWV, Pulse wave velocity.

between these methods, although oscillometric methods may underestimate the PWV in younger patients with accelerated vascular aging.[43,46-49]

Another method to evaluate arterial stiffness is to measure arterial wall motion directly or indirectly. As arterial wall stiffness increases, wall movement diminishes; this observation has important implications for surveillance (Table II).[54] Gold standard imaging modalities for aneurysm surveillance, both preoperatively and postoperatively, include computed tomography angiograms and conventional duplex ultrasound examination; however, these modalities do not specifically image aortic wall motion or compliance. Dynamic magnetic resonance angiography can determine wall stiffness and the elastic modulus based on wall motion and electrocardiogram gating techniques, and thus is a potentially useful imaging modality for surveillance because it is noninvasive and can image the entirety of the aorta without anatomical barriers of ultrasound examination; however, magnetic resonance angiography is limited by expense, accessibility, and device incompatibility with ferromagnetic stent grafts.[50]

Several techniques to measure aortic compliance, and thereby stiffness, have been adapted from conventional duplex ultrasound examination. Tissue Doppler imaging measures direct changes in the displacement of the aortic wall with each pulse wave that is propagated through the aorta on the order of tens of micrometers; this modality can measure and compare the segmental difference in vessel compliance along the length of the accessible aorta.[51,52] Similarly, pulse wave imaging measures the propagation of pulse waves along the aorta to calculate the PWV. In a murine AAA model, pulse wave imaging distinguished between normal aorta and the stages of progressive disease, including aneurysmal dilation, ulceration, and ruptured aneurysms.[53] Additional investigation is warranted, especially in terms of applicability to surveillance of human patients. Ultrasound-based techniques have the advantage of lower overall costs, but are limited by anatomical considerations of body habitus, intrathoracic air, and overlying bowel gas. These modalities have largely not been compared with each other, and before being incorporated into routine clinical practice, should be studied in comparison with gold standard invasive and noninvasive modalities.

As imaging techniques become increasingly advanced, there are several modalities that show promise for potential clinical assessment of aortic stiffness with improved reliability (Table III). Speckle tracking imaging (STI) is another ultrasonographic technique that uses imaging

Table II. Aortic imaging modalities

	Measures of stiffness	Benefits	Pitfalls
CT angiography[51]	• Not applicable	• Traditional gold standard • Cross-sectional imaging, allows for detection of endoleak, changes in sac size • Minimal anatomical limitations • Can evaluate endograft position and displacement	• Radiation exposure with cumulative 0.42%-1.03% risk of malignancy • Requires intravenous contrast, risk of contrast-induced nephropathy • Higher cost
Conventional duplex ultrasound examination	• Not applicable	• Accurately determines sac size, detects presence of some endoleaks • Reduced cost • Avoids ionizing radiation • Generally well-tolerated • No requirement for contrast administration	• Operator dependent • Anatomical limitations owing to body habitus, intrathoracic locations, overlying bowel gas • No information regarding stent graft integrity, migration or aneurysm neck and proximal seal zone • Limited characterization of endoleak
Conventional MRA	• Not applicable	• Avoids ionizing radiation • Comparable with CTA in assessing aneurysm size • Increased sensitivity for type II endoleak compared with CTA • Few anatomical limitations	• Higher cost • Lower availability • Decreased patient tolerance • Incompatibility of ferromagnetic grafts
Dynamic MRA[50]	• Using ECG gating, can characterize stiffness and elastic modulus based on wall motion	• Minimal anatomical limitations • Compliance determination in axis perpendicular to blood flow	• Higher cost • Lower availability • Decreased patient tolerance • Incompatibility of ferromagnetic grafts
Tissue Doppler imaging[51,52]	• Ultrasound measurement of wall displacement with each pulse wave • Allows for measurement of wall displacement with accuracy of a few micrometers • Ability to obtain segmental compliance	• Reduced cost compared with invasive or cross-sectional studies • Avoids ionizing radiation • Generally well-tolerated • No requirement for contrast administration	• Operator dependent • Anatomical limitations owing to body habitus, intrathoracic locations, overlying bowel gas • Less availability
Pulse wave imaging[53]	• Visualization of pulse wave propagation patterns, vessel structure and wall motion via ultrasound examination • Measures regional stiffness based on PWV estimation	• Avoids ionizing radiation • No requirement for contrast administration • Can obtain multiple wave forms per cardiac cycle, increasing number of temporal and spatial samples for PWV with improved accuracy	• Operator dependent • Anatomical limitations owing to body habitus, intrathoracic locations, overlying bowel gas

CT, computed tomography; *CTA*, computed tomography angiography; *ECG*, electrocardiogram; *MRA*, magnetic resonance angiography; *PWV*, pulse wave velocity.

pixels or speckles within the aortic wall that are tracked from frame to frame and are used to calculate the strain based on wall deformation.[55] Compared with TDI, STI is angle independent and is not limited by translational motion of the vessel itself; however, this is not used routinely in human patients with AAA and is limited by time or the availability of STI-based software, among other limitations associated with ultrasound examination.[55] Phase-contrast magnetic resonance imaging (MRI) uses information from moving protons to provide blood velocity data in one, two, or three dimensions and can be used to noninvasively calculate the regional PWV of a portion of the aorta, as well as map regional stiffness throughout the aorta.[50] These measures have good correlation with invasive PWV measures in both human and tissue-mimicking phantoms.[56,57] Deformable registration algorithms, which align two-dimensional and three-dimensional images to quantify changes in shape, size, and position, can be applied to cine-MRI to calculate wall strain and estimate aortic stiffness.[58,59] Displacement encoding with

Table III. Advanced imaging modalities

	Measures of stiffness	Benefits	Pitfalls
US with speckle tracking[55]	• Uses aortic wall deformation to provide velocity and wall strain data with high spatial resolution	• Angle independent • Not influenced by translational motion of the vessel • Avoidance of ionizing radiation, contrast	•Time consuming, technically challenging study •Anatomical limitations •Need for specialized software
Phase-contrast MRI[50,56]	• Measures blood velocity based on phase change of moving protons in one to three dimensions	• Noninvasive measure of regional PWV • Interobserver and intraobserver reproducibility • Correlates well with invasive measures[56,57] • Can be used to map spatial stiffness of the aorta in "elastograms"[56]	• High cost • Limited availability • Decreased patient tolerance • Incompatibility of ferromagnetic grafts • One- and two-dimensional techniques associated with error from influence of temporal resolution
Cine-MRI with deformable registration[58,59]	• Uses a deformable registration algorithm to track displacement of image voxels to calculate wall strain	• Noninvasive measure of regional wall strain • Avoidance of ionizing radiation, contrast • Shown to have good reproducibility in other applications	• High cost • Limited availability • Decreased patient tolerance • Incompatibility of ferromagnetic grafts
DENSE MRI[60,61]	• Spatially encoded displacement of moving tissues tracked by encoding each image voxel in each MR phase in up to three directions	• Noninvasive measure of regional wall strain • Avoidance of ionizing radiation, contrast • High spatial and temporal resolution • Validated in humans for myocardial assessment	• Time consuming analysis, need for specialized software • High cost • Limited availability • Decreased patient tolerance • Incompatibility of ferromagnetic grafts

DENSE, displacement encoding with stimulated echoes; *MRI*, magnetic resonance imaging; *PWV*, pulse wave velocity; *US*, ultrasound.

stimulated echoes MRI is a modality in which tissue displacement is encoded by the MR signal phase with high spatial and temporal resolution that is then used to calculate tissue strain. Although there is a potential application for measurement of tissue stiffness of the aorta, it has been limited largely to myocardial assessments in the clinical setting.[60,61]

AORTIC STIFFNESS AFFECTS SURVIVAL AND PREDICTS CARDIOVASCULAR OUTCOMES

Aortic stiffness adversely impacts cardiovascular function, including coronary blood flow and myocardial perfusion with subsequent myocardial dysfunction, and contributes to multiple systemic adverse effects.[11] With increasing stiffness, the Windkessel effect is diminished, leading to transmission of the undampened cardiac pulse wave to end-organs. This process is especially deleterious in low-resistance organs, such as the brain and kidney. Additionally, there is abnormal reflection of the pulse wave proximally that leads to increased left ventricular afterload and impairs coronary perfusion in diastole, exacerbating coronary artery disease and potentiating myocardial ischemia.[62]

Stiffness independently predicts coronary heart disease and stroke in otherwise healthy individuals and has an additive predictive value for cardiovascular disease in the presence of risk factors such as smoking, hypertension, obesity, hypercholesterolemia, diabetes, and prior myocardial infarction or stroke.[63] Increased stiffness strongly predicts both cardiovascular and all-cause mortality in patients with end-stage renal disease, hypertension, and patients with type 2 diabetes or impaired glucose tolerance.[64-66] In a prospective cohort study, each PWV increase of 1 m/s was associated with an all-

cause mortality relative risk of 1.39 (95% confidence interval [CI], 1.19-1.62) with patients in the upper tercile (PWV >12.0 m/s) having a 5.4-fold adjusted risk of all-cause mortality (95% CI, 2.4-11.9) compared with patients in the lower tercile (PWV <9.4 m/s). A large prospective cohort study showed that an increased brachial-ankle PWV is associated with a higher risk of new-onset heart failure in a dose-dependent manner.[67]

SURGICAL INTERVENTION ALTERS AORTIC COMPLIANCE

Aortic compliance changes after surgical intervention, the magnitude of which depends on surgical technique.[15,68] In open aortic surgery the fluid-filled aneurysm sac is opened and thus no longer pressurized, although the sac is closed over the implanted graft. Open repairs are performed with compliant knitted grafts that lack the rigid, circumferential nitinol skeleton of endografts, and the repaired aorta shows increased circumferential wall movement at a given pressure.[15] In cases of endoleak, compliance can be decreased significantly compared with preoperative measurements. In these cases, failure to exclude the aneurysm sac from the systemic circulation leads to pressurization of the aneurysm sac.[69] A recent meta-analysis showed that endovascular aortic repair is associated with increased aortic stiffness, as measured via the PWV, with no statistically significant change in baseline aortic stiffness after open repair.[21] Several studies have shown increased PWV after endograft implantation; these data suggest that the endograft itself is largely responsible for the change in stiffness.[70-73] A comprehensive study of the mechanical properties of the entire length of the aorta before and after implantation has yet to be performed owing in part to the invasive nature of the testing needed to interrogate segmental regions of the aorta in isolation.

Graft composition impacts compliance after EVAR; the best engineered endografts are four times less compliant, and thus much stiffer, than the native aorta.[74,75] Polyester grafts showed greater increase in PWV than PTFE, and exoskeleton-based stent grafts did not show significant changes in PWV compared with endoskeleton-based stent grafts.[21] Excluder endografts (W. L. Gore & Associates, Flagstaff, AZ) showed increased stiffness compared with Talent endografts (Medtronic, Minneapolis, MN), suggesting stiffness variances between devices may affect long-term durability.[31] Thus, EVAR immediately and drastically increases aortic stiffness as measured by noninvasive PWV, leading to deleterious changes in cardiovascular hemodynamics. This change in compliance seems to stabilize on follow-up evaluation,[51] but studies listing these long-term outcomes are limited.

In a case series of four patients treated with thoracic EVAR (TEVAR) and subsequent EVAR, each of four patients developed symptomatic left ventricular hypertrophy and diastolic dysfunction within 2 years, and three of the four patients died secondary to cardiovascular causes.[76] Another study of 40 patients treated with EVAR for AAA showed increases in postoperative arterial stiffness, left ventricular hypertrophy with associated diastolic dysfunction, and subsequently impaired exercise tolerance.[73] A case series of 45 patients undergoing EVAR or TEVAR showed that evidence of cardiac remodeling can be detected as early as one 1 postoperatively.[77] Although a larger prospective study would help to further elucidate the relationship between increased stiffness after EVAR and clinical outcomes, these data suggest a role for post-EVAR cardiac surveillance.

INCREASED PREOPERATIVE AORTIC STIFFNESS IS ASSOCIATED WITH LESS SAC REGRESSION AFTER EVAR

Aneurysm sac shrinkage is a phenomenon unique to EVAR; the sac is not opened as is done during open repair. Although much remains to be elucidated regarding the biomechanics of sac regression, stability, and enlargement, several biologic, anatomical, and perioperative factors are influential. For example, a genetic polymorphism causing low expression of matrix metalloproteinase (MMP) 1, an MMP associated with elastin and collagen remodeling, was associated with aneurysm sac shrinkage.[78] Similarly, genetic mutations involving increased expression of MMP9 were associated with increased endoleak, which was postulated to be the result of remodeling at the aortic neck.[78] Both calcification and thrombus at the level of the iliac arteries and aneurysm neck negatively impact sac shrinkage, although the role of thrombus in the sac is controversial. In the perioperative setting, the absence of endoleak, particularly type I and/or II endoleak, is associated with an increased likelihood of sac regression, although the contribution of type II endoleak is an ongoing topic of debate.[79] These factors, among countless others, have been variably implicated as factors influencing sac behavior; however, their usefulness in predicting sac behavior after intervention remains to be proven.

Sac behavior after EVAR is an important prognostic factor after intervention; sac regression is associated with a lower risk of mortality, rupture, and reintervention, whereas expansion of the sac is associated with increased mortality, risk of rupture, and, per the Society for Vascular Surgery best practice guidelines, is a determinant for reintervention.[4,80,81] Because EVAR is associated with decreased aortic wall compliance, the role of preoperative measurements of compliance and stiffness to predict sac behavior postoperatively has been examined in two retrospective studies (Table IV). Nishibe et al[38,82] showed that preoperative PWV predicted sac shrinkage with optimal shrinkage occurring with a PWV

Table IV. Studies measuring pulse wave velocity (*PWV*) and sac behavior after endovascular aneurysm repair (*EVAR*)

	Nishibe 2021[82]	Ugajin 2022[83]
Study type	Retrospective cohort	Retrospective cohort
No. of patients	119	175
Exclusion criteria	• ABI <0.9 • Lack of PWV measurement • Requirement of intervention beyond EVAR • Lack of follow-up CT	• ABI <0.9 • Prior arterial bypass • Saccular or mycotic aneurysm • Persistent type I or III endoleak
Method used to measure PWV	Brachial-ankle PWV	Brachial-ankle PWV
Follow-up	2 years	3 years
Threshold for elevated PWV	17.79 m/s[a]	18.50 m/s[b]
Outcomes	Elevated preoperative PWV is associated with decreased sac regression (OR, 0.87; P =.045)	Elevated preoperative PWV is associated with increased sac enlargement (OR, 3.059; P =.005)

ABI, Ankle-brachial index; *CT*, computed tomography; *OR*, odds ratio.
[a]PWV threshold determined by ROC curve analysis.
[b]PWV threshold determined by classification and regression tree methodology.

of <17.79 m/s (odds ratio, 0.25; 95% CI, 0.11-0.57; $P < .001$); for every 1 m/s decrease in PWV there was a 1.15-fold higher odds of sac shrinkage following repair. Similarly, Ugajin et al[83] showed that age-adjusted increases in PWV of >18.50 m/s not only decreases sac regression, but also increases the risk of significant (>5 mm) sac growth (odds ratio, 3.059; 95% CI, 1.41-6.64; $P = .005$). These data suggest that preoperative measurement of arterial stiffness may be useful to predict sac behavior after EVAR. Although direct measure of the material stiffness of the aorta may be a promising variable for sac prognostication, this measurement is not practical clinically and PWV is likely to be a reasonable surrogate marker to approximate stiffness. Larger studies, ideally prospective cohort studies investigating the outcomes of patients with increased stiffness after endovascular vs open repair as well as comparing outcomes in patients with variable PWV after endovascular repair, are needed to determine the role of preoperative measurements of stiffness in operative planning and prognostication.

CAVEATS TO THE INTERPRETATION OF AORTIC STIFFNESS MEASUREMENTS

Although a few smaller studies have described the association between increases in PWV and outcomes such as sac regression or cardiovascular function, there have been no large trials that directly compare outcomes after intervention in patients with elevated PWV compared with normal PWV, or that compare outcomes after open vs endovascular repair in patients with an increased PWV. Further clinical studies may be undertaken to evaluate PWV as a prognostic factor for technical success, operative timing, and long-term outcomes.

Global measurements of central arterial pressure and stiffness may ignore some important variables that are comprehensively more comprehensively assessed by local methods of estimating stiffness. The stress patterns along the aortic wall are complex, with localized variations in mechanical properties that are not easily identified by global measurements.[84] Additionally, global stiffness measurements do not assess the particular contribution of intramural thrombus within aneurysms with an estimated 50% to 82% underestimation of distensibility if intraluminal thrombus is neglected.[85] Based on the equation for PWV, underestimation of distensibility, D, would falsely elevate the PWV and thus it is important to consider the contributions of thrombus. Although the role of thrombus remains controversial,[54,86,87] thrombus may assist the arterial wall in bearing the pulse pressure load, with less peak wall stress in the presence of thrombus, although these conclusions are largely based on in silico models as opposed to in vivo measures.[88] Intraluminal thrombus is associated with increased activity of certain MMP (ie, MMP9) and inflammatory infiltrate that may accelerate aneurysm sac degeneration and promote rupture.[84,89] Alternatively, the presence of other types of metalloproteinases and other associated factors may be beneficial to sac remodeling and potentially shrinkage. Thus, thrombus introduces a source of error that needs to be considered when using PWV to predict AAA and sac behavior.

Inflammation may also play a role in potentiating arterial stiffness. Increased arterial stiffness predicts an increased risk of cardiovascular events, and inflammation is associated with large artery stiffening via endothelial dysfunction, SMC migration, and increased activity of proteolytic MMP that lead to matrix degradation. Both markers of inflammation and arterial stiffness are associated with adverse cardiovascular outcomes. Inflammatory markers have been related to endoleak and sac behavior,[7,8] and these markers may be useful clinically to identify reversible causes of arterial stiffening; future

destiffening therapies may target components of the immune system.[90]

CONSIDERATIONS FOR CLINICAL PRACTICE

There are several potential considerations that may be useful in clinical decision making in patients with aneurysms. Preoperative considerations include the decision for open vs endovascular repair and device selection; the association with potentially increased cardiovascular dysfunction in the long term after endovascular implantation of a more rigid endograft should be used to guide the discussion of open vs endovascular repair in an otherwise medically fit patient.[73,75,77] In patients undergoing endovascular repair with an anticipated long survival, augmented cardiovascular surveillance may need to be considered to identify early indications of cardiac dysfunction. In cases of elevated PWV in the preoperative setting, the surgeon may consider opting for open repair or repair with a less rigid device, as well as more frequent or alternative imaging surveillance studies to monitor graft and aneurysm sac behavior. In addition, for patients identified as having an elevated PWV concerning for increased stiffness, medical strategies such as lifestyle modification, management of hypertension, or perhaps in the future, medical therapy for destiffening of the arterial wall may be considered to curtail worsening disease.

SUMMARY AND CONCLUSIONS

The shift to the endovascular treatment of AAA has brought a need to determine long-term outcomes after EVAR. Sac regression is frequently used to measure success, but the factors influencing sac regression remain poorly understood. Studies suggest that increased arterial stiffness detected preoperatively predicts less sac regression, perhaps owing to underlying medial dysfunction that prevents sac remodeling in the absence of transmitted pressure. The development of automated methods to measure PWV in the ambulatory setting suggest a promising modality for the rapid, noninvasive estimation of aortic stiffness, which may prove useful to predict outcomes after EVAR, and possibly even optimize therapeutic decision-making. Further studies could be undertaken to further evaluate the usefulness of PWV in managing aortic aneurysmal disease.

Aortic aneurysmal disease is associated with changes in the wall dynamics of the aorta that lead to the dysregulation of biomechanical homeostasis. These changes may be exacerbated by the sudden and significant increase in central stiffness that occurs immediately after endovascular stent graft placement with unintended negative cardiovascular outcomes. Increased arterial stiffness can be associated with unintended side effects and may contribute to major cardiovascular events and increased all-cause mortality. With several case reports implicating endovascular stent grafts as a factor in the development of new left ventricular hypertrophy with subsequent heart failure, it seems imperative to monitor patients routinely for the development of cardiovascular dysfunction after TEVAR or EVAR.

The authors to sincerely acknowledge the reviewers of this manuscript as their comments have greatly improved the quality of this work.

AUTHOR CONTRIBUTIONS

Conception and design: CT, MK, DMP, TPN, TN, AD
Analysis and interpretation: Not applicable
Data collection: Not applicable
Writing the article: CT, AD
Critical revision of the article: CT, MK, DMP, TPN, TN, AD
Final approval of the article: CT, MK, DMP, TPN, TN, AD
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: AD

DISCLOSURES

None.

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Submitted Apr 25, 2023; accepted May 9, 2024.