Ultrasonographic vascular mechanics to assess arterial stiffness: a review

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In recent years, the role of arterial stiffness in the development of cardiovascular diseases has been explored more extensively. Local arterial stiffness may be gauged via ultrasound, measuring pulse transit time relative to changing vessel diameters and distending pressures. Recently, direct vessel-wall tracking systems have been devised based on new ultrasonographic methodologies, such as tissue Doppler imaging and speckle-tracking analysis—vascular mechanics. These advances have been evaluated in varying arterial distributions, are proved surrogates of pulse wave velocity, and are ascending in clinical importance. In the course of this review, we describe fundamental concepts and methodologies involved in ultrasound assessment of vascular mechanics. We also present relevant clinical studies and discuss the potential clinical utility of such diagnostic pursuits.

Keywords

arterial stiffness • speckle tracking • tissue Doppler imaging • vascular mechanics • strain • strain rate

Introduction

The development of accurate, non-invasive methods for early diagnosis of vascular degenerative changes is of significant clinical interest, given that cardiovascular disease remains the leading cause of death worldwide.¹

Arterial stiffness refers to arterial wall rigidity.² It increases with age, but it is also problematic in a number of systemic diseases. Moreover, changes in arterial stiffness are thought to occur in advance of clinically apparent cardiovascular disease.³ Consequently, appraisal of arterial stiffness in routine clinical practice may detect, predict, and eventually prevent cardiovascular diseases.⁴

The gold standard for study of arterial stiffness is carotid-femoral pulse wave velocity (PWV), which is usually obtained by tonometry or through mechanotransducers.⁵ Recently, a combination of echocardiography and pulse wave Doppler has been optimized for PWV testing, but it has not attained gold-standard status as yet.⁵

Ultrasound technology is capable of delivering dynamic images of the heart and central arteries. During the past decade, automated techniques for sophisticated analysis of cardiac mechanics have evolved,⁶ such as Doppler-based tissue velocity measurements [known as tissue Doppler imaging (TDI)] and speckle tracking (ST), based on displacement measurement.⁶ Regional and global parameters of myocardial mechanics, including displacement, velocity, strain (\(s\)), and strain rate (SR), are currently quantifiable.⁷ Early applications of these new methodologies involved the study of cardiac chambers,⁶ but their usages have been expanded and validated for the study of vascular wall mechanics.

This article is primarily intended to provide a critical review of TDI and ST, as emergent techniques for assessing vascular wall mechanics. Herein, fundamental concepts and methodologies are detailed. We also summarize key clinical studies, stratified by methods used and by vascular territories examined. Finally, the drawbacks and the growing importance of evaluating arterial stiffness are discussed.

Vascular stiffening

Arterial stiffening is one of the earliest manifestations of adverse structural and functional changes within vascular walls. Degenerative stiffening of arterial beds (i.e. arteriosclerosis) should be differentiated from atherosclerosis.⁸ Degenerative stiffness implies resistance to vascular deformation, and it is greatly influenced by radius, wall thickness, and vessels’ elastic modulus (E), the latter gauging stress/strain relationship is also known as Young’s modulus.⁹ In other words, vascular stiffening equates with a reduced capacity for
arterial expansion and recoil in response to pressure changes.\(^9\) In contrast, atherosclerosis represents the occlusive result of endovascular inflammatory disease, lipid oxidation, and plaque formation.\(^8\) Arteriosclerosis and atherosclerosis tend to co-exist, causing progressive, diffuse, and age-related deterioration in all vascular beds.\(^2\)

From a physiopathology perspective, vascular stiffening is essentially a degenerative state conferred by a string of biomolecular mishaps, including fragmentation of elastin, increased deposition of collagen, calcification, glycation of both elastin and collagen, and cross-linking of collagen by advanced glycation end products.\(^10\) In consequence, the increased arterial stiffness leads to elevated central arterial blood pressure, resulting in higher central pulse pressure\(^9\) and a subsequent increase in left ventricular (LV) load, which then promotes LV hypertrophy.\(^11\) Furthermore, diminished diastolic blood pressure reduces coronary perfusion, predisposing the heart to ischaemia.\(^12\) Apart from inherent cardiac damage, elevated arterial pulsatility also injures the microcirculation of various organs, especially those with high perfusion requirements, namely kidney and brain, contributing to decline in glomerular filtration rate\(^11\) and in cognitive function.\(^13\)

Vascular stiffness is a non-uniform disease process that preferentially affects proximal (vs. distal) arterial segments\(^14\) which increases with age.\(^15,16\) even in the absence of vascular disease or other risk factors.\(^15\) Arteries also stiffen in conditions such as hypertension,\(^17\) diabetes,\(^18\) and chronic renal disease.\(^19\) Some sources have thus suggested that arterial stiffness screening may be appropriate for patients predisposed to hypertension, aiming to prevent or delay the progression of subclinical arterial stiffening and the onset of hypertension.\(^20\) An array of medical conditions, such as connective tissue disorders,\(^21\) aortic valvular stenosis\(^22\) and regurgitation,\(^23\) hypertrophic cardiomyopathy,\(^24\) and heart failure with preserved\(^25,26\) or reduced\(^27\) left ventricular ejection fraction, commonly present vascular stiffening.

Serving as a reliable biomarker, increased arterial stiffness is one of the most important risk factors in cardiovascular mortality.\(^28\) Vascular stiffening is an independent predictor of coronary heart disease and stroke in otherwise healthy subjects and an independent predictor of community-wide mortality.\(^29\)

The latest European guidelines for managing arterial hypertension recommend vascular stiffness testing to evaluate target organ damage.\(^3\) Considering that aortic stiffness is a function of prevailing blood pressure, effective antihypertensive treatment is expected to encourage pliability. Nevertheless, such medications may differ in their effects on structure and function of arterial walls,\(^2\) and calcium channel blockers or angiotensin-converting enzyme inhibitors appear more beneficial than \(\beta\)-blockers and diuretics in this regard.\(^30\)

### Classic vascular stiffening assessment

Measurement of PWV is generally viewed as a simple, non-invasive, robust, and reproducible method of assessing arterial stiffness. Carotid-femoral PWV is measured directly, in accordance with the widely accepted propagative model of the arterial system.\(^10\) PWV and vascular compliance are inversely related, meaning that a rigid vessel will conduct pulse waves faster than a more distensible and compliant one. The relationship between PWV and arterial distensibility is embodied in the Bramwell and Hill equation as follows: $\text{PWV} = \sqrt{\frac{V^2}{D} \times \frac{D}{\Delta P}}$, where \(P\) is blood density, \(V\) is blood volume, and \(D\) is arterial blood pressure. PWV is determined by measuring pulse transit time of pressure waveforms at two points along a vascular segment (figure).\(^4\) Mechanotransducers or high-fidelity applanation tonometers are customary devices for obtaining carotid-femoral PWV measurements.\(^4\)

Ultrasound-based methods are also commonly used to assess local mechanical properties of arterial walls.\(^4\) In this way, arterial stiffness is directly determined from changes in pressure that dictate volume fluctuations, without need of a circulatory model.\(^4\) Derived from pressure and diameter measurements, vascular stiffness may be expressed as distensibility, compliance, Peterson’s elastic modulus, or Young’s elastic modulus—Table 1. Ultrasound also enables estimation of carotid intima-media thickening (CIMT), a standard marker of atherosclerosis.\(^31\) Furthermore, Dopplers studies permit calculation of PWV, using the difference between two recording sites in the line of pulse travel and the delay in flow wave between these corresponding points.\(^32\)

Echo-tracking systems are based on a radiofrequency tracking of the B-mode image of the vessel.\(^6\) The vessel diameter in end-diastole and its stroke change in diameter are obtained with a very high spatial and temporal resolution, achieving highly precise measurements of the vessel distension in real time.\(^33\)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Ultrasound-based classic arterial stiffness assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Formula</strong></td>
</tr>
<tr>
<td>Arterial compliance</td>
<td>(\frac{\Delta D}{\Delta P} (\text{cm/mm Hg})) or (\text{cm}^2/\text{mm Hg})</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>Distance/(\Delta t) (cm/s)</td>
</tr>
<tr>
<td>Pearson’s elastic modulus</td>
<td>(\Delta P \times D/\Delta D) (mm Hg)</td>
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<tr>
<td>Young’s modulus</td>
<td>(\Delta P \times D/(\Delta D \times h)) (mm Hg/cm)</td>
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<tr>
<td>Arterial distensibility</td>
<td>(\frac{\Delta D}{\Delta P} \times D) (mm Hg(^{-1}))</td>
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<tr>
<td>Stiffness index ((\beta_1))</td>
<td>(\text{Ln}(P_s/P_d)/(D_s - D_d)/D_d) (non-dimensional)</td>
</tr>
</tbody>
</table>

Adapted from O’Rourke et al.\(^5\)
Vascular mechanics and arterial stiffness

It is required the simultaneous measurement of the local blood pressure, usually obtained by applanation tonometry of the vessel. In this way, the stiffness index, arterial compliance, and the Young's elastic modulus are determined directly, and assumptions regarding models of the circulation are not required. The local PWV can be calculated from the time delay between the two adjacent distension waveforms, and some systems also provide the local PWV using on-line 'one-point' measurements. Since the 1970’s, many publications have addressed the indices above in terms of its normal reference values, clinical applications, and overall utility. However, none has proved superiority, and all present limitations in measurement and interpretation. The validity and reproducibility of these methods differ considerably; in consequence, none can be pointed as gold standard for evaluating local arterial stiffness at present time.

Vascular mechanics

In the past decade, a number of semi-automated techniques for sophisticated analysis of cardiac mechanics have emerged from two-dimensional B-mode ultrasound images: (i) Doppler-based tissue velocity measurements (TDI) and (ii) speckle tracking (ST) technology have dominated the field. Since the 1970's, many publications have addressed the indices above in terms of its normal reference values, clinical applications, and overall utility. However, none has proved superiority, and all present limitations in measurement and interpretation. The validity and reproducibility of these methods differ considerably; in consequence, none can be pointed as gold standard for evaluating local arterial stiffness at present time.

Methodology for vascular mechanics evaluation

The analysis of vascular walls is performed with short- and long-axis views of aorta or carotid arteries using conventional 2D grey-scale echocardiography, during breath-holding, along with a stable electrocardiographic (ECG) recording. A frame rate of 60–80 frames/s is set, and acoustic-tracking software is applied to process the recordings.

When using 2D-STE to study vascular mechanics, vascular circumference is usually divided into six equally sized regions. Numeric expressions of each regional ST variable represent mean values calculated from all points in respective arterial segments. These six regions contribute segmental determinants, from which a global value may be calculated, defined as the mean of peak values generated by the six aortic wall segments.

Various ST software packages are available that differ primarily by tracking and filtering algorithms. Two-Dimensional Speckle Tracking (GE Medical Systems, Horten, Norway) and Vector Velocity Imaging (VVI: Siemens Medical Solutions, Mountain View, CA, USA) are the two most commonly used applications, and respective studies have generated comparable values for cardiac mechanics. Vascular deformation patterns may be analysed by longitudinal, radial, and circumferential directions. Nevertheless, circumferential analysis is the one typically performed, including ε and SR determinations. During systole, circumferential vascular ε assumes a positive value, due to vessel-wall expansion. Similarly, vascular SR in systole is identified as the value of the first upward peak, termed early circumferential vascular SR. Upon vessel recoil, circumferential ε returns to a normal value, but SR assumes a negative value (late vascular SR). The ε determinant is expressed as % and SR as s⁻¹—Figure 1. Validation studies in vitro and in vivo have demonstrated the potential to analyse both radial and longitudinal mechanics. Radial ε assumes a negative value, based on thinning of the vascular wall during systole, whereas lengthening of arterial wall during systole confers a positive value to the longitudinal ε curve.

From the global circumferential ε value, it is possible to calculate a corrected ε as (circumferential ε)/(pulse pressure); and the β₂ index is then calculated as Ln (systolic blood pressure/diastolic blood pressure)/circumferential ε. Time to peak ε is also considered a promising variable. Segmental time to peak circumferential ε analysis of the six vascular wall regions has served as a means of assessing vascular dyssynchrony.

A sampling of anterior (superficial) or posterior (deeper) segments of vessel circumference is generally selected for TDI diagnostics. Gain settings, filters, pulse repetition frequency, sector size, and depth should also be adjusted to optimize colour saturation. Motion in the test segment is automatically tracked through the cardiac cycle, from which velocity in radial direction is determined. Mechanical indices (i.e., ε and SR) are then calculated from TDI data by integrating velocity over time.

Validation studies of vascular mechanics

The validation of ST technology for determining circumferential, radial, and longitudinal ε values of common carotid artery (CCA) has been attempted experimentally via sonomicrometry. This was accomplished by connecting polyvinyl gel phantoms to a pump capable of simulating carotid flow profiles. Grey-scale ultrasound images of the phantoms were then obtained in long- and short-axis views, using both standard clinical and high-frequency ultrasound systems equipped with linear array transducers. Sonomicrometry crystals additionally were glued to the phantom surfaces. Ultimately, there was good agreement between systems, confirming the feasibility of carotid ε estimation using ultrasound ST—Figure 2. The investigators further noted that high-frequency ultrasound use increased spatial...
resolution and thus improved arterial ST diagnostic performance, particularly in circumferential mode. Importantly, these results were aligned with those of previous studies examining the feasibility of estimating carotid arterial ε values in silico and in vitro.

The in vivo feasibility of ultrasound-based assessment of carotid arterial wall strain by ultrasound ST was similarly proved recently through sonomicrometry use in a sheep model. The results showed acceptable agreement and strong correlation between ST and sonomicrometric ε assessment, especially circumferential and longitudinal testing. Critical histological validation of vascular mechanics has been demonstrated by Kim et al., who divided a group of 14 female dogs into young (1–2 years) or senescent (8–9 years) animals for VVI of thoracic descending aorta. Subsequent histological analysis revealed significant negative correlation in terms of radial velocity, circumferential ε, and SR of aortic wall collagen content. However, vascular mechanics and aortic wall elastin did not correlate significantly.

As summarized in Supplementary data online, Table S1, these validation studies support the clinical use of ultrasonographic vascular...
Clinical studies of speckle tracking circumferential mechanics at aortic level

Clinical investigation of vascular mechanics was first conceived by Oishi et al.\textsuperscript{42} in 2008, who studied 39 subjects at the level of abdominal aorta, showing feasibility of the ST analysis, with satisfactory inter- and intra-observer variability—Figure 3A and B. Moreover, significant negative correlation was identified for vascular $e$ ($r = -0.79; P < 0.01$), vascular SR ($r = -0.87; P < 0.01$), and time to peak $e$ ($r = -0.36; P < 0.01$) with respect to age. The $e$-derived $\beta_2$ index showed a positive association with age ($r = 0.69; P < 0.01$), as did classic $\beta_1$ index. This was the first indication that aortic imaging, using this newly developed technology, could serve as a surrogate marker of the degenerative ageing process. Afterwards, an independent association between age and
Figure 3 (A and B) Examples of the global circumferential strain (A) and strain rate (B) assessed at the abdominal aorta. Reprinted from Oishi et al., with permission from John Wiley and Sons. (C and D) Examples of the global circumferential strain (C) and strain rate (D) assessed at the right common carotid artery. Reprinted from Podgórska et al., with permission from Termedia & Banach Publishing.

circumferential $\varepsilon$ was shown in normal subjects, in contrast with a group of hypertensive patients. The latter demonstrated an important non-linear association between age and circumferential $\varepsilon$, as well as $\beta_2$ index. In a 2013 study, Oishi et al. investigated the vascular mechanics of both abdominal aorta and common carotid artery, observing that circumferential $\varepsilon$ of abdominal aorta was significantly greater than that of the carotid arteries.

A study of thoracic descending aortic mechanics was first reported by Kim et al. in 2009. The authors enrolled 137 patients who were referred transoesophageal echocardiography (TEE). A majority of the referrals were due to stroke (46.7%) and valvular heart disease (33.6%). The authors found a significant negative correlation between vascular $\varepsilon$ and ageing identified, but also discovered a negative correlation between $\varepsilon$ and aortic intima-media thickness and with heart-femoral and brachial-ankle PWV. This was the first publication supporting the use of vascular $\varepsilon$ to estimate global vascular stiffness. Subsequently, Petrini et al. studied descending aortic mechanics in patients with aortic stenosis (AS) and aortic regurgitation (AR), and shown that patients with AS had lower vascular $\varepsilon$ values than those with AR. Vascular stiffness and distensibility were similar, whether an M-mode or a VVI assessment was done. Patients with pure AS displayed both higher vascular stiffness and lower distensibility, relative to those with pure AR. Although reproducibility of vascular $\varepsilon$ was excellent, the authors noted an important bias and variability in assessing vascular rotational displacement. As well, our group has previously reported a cohort of 45 elderly patients with moderate-to-severe degenerative AS, where stroke volume index was the most important determinant of circumferential ascending aortic $\varepsilon$. Moreover, we identified an independent association between $\beta_1$ index and SR of ascending aorta, thus concluding that the aortic $\varepsilon$ was linked to changes in vascular flow, whereas aortic SR was influenced by local arterial rigidity.

The impact of systolic flow on vascular mechanics was again demonstrated by Petrini et al. in a study of 140 patients with isolated
AS and 52 patients with isolated AR. Here, the authors demonstrated that age, systolic flow, and aortic diameters independently influenced circumferential aortic $\varepsilon$ at the level of thoracic descending aorta. It was also demonstrated that patients with AS had lower values of aortic $\varepsilon$, lower aortic distensibility, and higher aortic stiffness (both accessed via VVI methodology) than those with AR. In both groups with valvular heart disease, VVI-tested stiffness was greater in patients with tricuspid (vs. bicuspid) aortic valves.63

Our research group has recently confirmed the feasibility of measuring aortic arch mechanics. We have established normal reference levels64 and have shown lower age-matched values of both $\varepsilon$ and SR in a group of hypertensive patients, compared with a control group.65 Associations between aortic arch mechanics and PAV, as well as estimated central blood pressure, have also been demonstrated.56 We subsequently proved that hypertensive patients with lower values of aortic arch mechanics had lower early LV relaxation velocities ($\varepsilon'$) and higher left atrial volumes.67 ST studies at aortic level are summarized in Supplementary data online, Table S2.

Three-dimensional aortic mechanics

The methods previously described, conveying information on aortic wall motion, used one cross-section image for assessment. However, it is now possible to study the change in aortic wall motion in every direction. The first study in this regard used a 3D-volume data set of abdominal aorta. A computed offline analysis was performed, assessing longitudinal $\varepsilon$, circumferential $\varepsilon$, and temporal wall dyssynchrony. Custom commercial ST software (Advanced Cardiac Package; Toshiba Medical Systems Corporation, Otawara, Japan) was engaged, with a finite element analysis to improve spatial resolution. Although the number of subjects was limited, patients with abdominal aortic aneurysms exhibited reduced mean $\varepsilon$ values and more pronounced temporal dyssynchrony than a control group—Figure 4.68

Another group of investigators have validated 3D abdominal aortic mechanics in vitro, using a silicone aneurysm model (perfused by a pulsatile artificial circulatory system), a high-speed laser scan (for radial displacement), and video photogrammetry (for longitudinal and circumferential displacement).69 An in vivo study of five patients with aorto-abdominal aneurysm was also conducted, demonstrating a marked difference between mean and maximum values of longitudinal and circumferential $\varepsilon$ within aneurysm wall. These results suggest a strong local heterogeneity of biochemical properties in abdominal aortic aneurysms. It was thus speculated that this novel technology may hold promise in estimating the risk of aortic aneurysm rupture.69

TDI of ascending aorta

Considerable research has been done on segmental ascending aortic anterior wall velocity assessment using TDI, usually at a level 3 cm above the aortic valve and in either short-axis50 or long-axis parasternal view,70 and it is possible to estimate aortic systolic radial $\varepsilon$ from aortic wall velocities using TDI software.

Vitarelli et al. have demonstrated that ascending aorta velocities (systolic and diastolic) were significantly lower for hypertensive patients, compared with a group of normal controls. As a marker of vascular stiffening, aortic radial $\varepsilon$ correlated significantly with LV mass index and with LV diastolic function.56 In another study, the authors found significantly elevated aortic wall velocities and radial $\varepsilon$ in endurance and martial arts athletes, compared with a control group, whereas these values were significantly lower in power athletes. It was hypothesized that aortic velocities in conjunction with LV parameters, as an assessment of ventricular–vascular coupling, may be appropriate to study the cardiac remodelling in various types of athletes.71

Clinical studies of circumferential mechanics at carotid arterial level

In 2010, Bjallmark et al. reported outcomes of a 2D-ST study of right CCA circumferential mechanics involving 20 normal subjects. This proved to be a particularly sensitive method for assessing age-dependent elastic properties of CCA, outperforming conventional echo determinations of vascular stiffness.35

Catalano et al.81 subsequently studied carotid mechanics in a cohort of 47 patients with no known vascular disease, stratified by cardiovascular risk (low, intermediate, and high) according to an Italian scoring system. Circumferential $\varepsilon$ correlated significantly with CIMT ($r = -0.52; P < 0.01$), $\beta$ index ($r = -0.54; P < 0.01$), and Ep ($r = -0.56; P < 0.01$). Unlike circumferential $\varepsilon$, CIMT, $\beta$ index, vascular distensibility, and Pearson’s elastic modulus, corrected circumferential $\varepsilon$ (for pulse pressure) was the only parameter showing a significant between-group difference.81

Normal reference values for CCA circumferential $\varepsilon$ were recently reported by Yuda et al. in 2011. They tested 51 normal subjects (mean age, 29 ± 11 years), with a mean global circumferential $\varepsilon$ of 6.7 ± 2.1%. Similar values were reported for segmental analyses, and there were no significant differences between right- and left-sided CCA assessments. Execution was simple and quick, with a mean time for $\varepsilon$ analysis of 128 ± 12 s per subject, conferring high feasibility and excellent reproducibility ratings.41 It was also shown that diabetic patients had lower values of segmental (farwall) and global carotid mechanics, compared with controls. This disparity persisted after adjustments for age, gender, race, and blood pressure, underscoring the already known association of diabetes
with vascular stiffening. Contrary to the study above, arterial \( \varepsilon \) was significantly higher in the right (vs. left) CCA, with similar differences reported for CIMT. Such discrepancies are possibly explained by differences in blood pressure, shear force, and vascular anatomy. The same group later demonstrated the utility of time-interval analysis of the CCA curve, whereby slopes of carotid arterial area curve were used to discriminate between patients with hypertension and diabetes, relative to controls.

In another study, Saito et al. demonstrated greater vascular stiffening in patients with hypertension, compared with an age- and gender-matched control group, based on the \( \beta_2 \) index. Age, heart rate, and the presence of hypertension were independently associated with this index.

Yang et al. showed the importance of a uniform arterial expansion during systole. In a group of 100 healthy controls, the authors demonstrated an increase in the time to peak plus standard deviation (SD) of both \( \varepsilon \) and SR of left CCA, across different age groups. They also found a negative correlation of \( \varepsilon \) (\( r = -0.48; P < 0.01 \)) and SR (\( r = -0.53; P < 0.01 \)) with PWV (assessed via radial tonometry). On the other hand, there was a positive association between SD and PWV, suggesting that asynchronous arterial expansion and arterial stiffening are linked.

A pivotal study by Kim et al. revealed a correlation between carotid arteriosclerosis and coronary artery atherosclerosis in 104 patients referred for coronary angiography, of whom 49 had CAD. In contrast with CIMT, both carotid circumferential \( \varepsilon \) and SR values

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**Figure 4** 3D circumferential vascular strain. Spatially resolved circumferential strain of abdominal aortic segment in (A) healthy volunteer and (B) patient with abdominal aortic aneurysm during one cardiac cycle. Higher circumferential strain curve in healthy volunteer shows synchronous systolic peak, whereas peak circumferential strain is reduced and shows temporal delay in patient with abdominal aneurysm. Reprinted from Karatolios et al., with permission from Elsevier.
showed significant associations with CAD in a model adjusted for age, gender, hypertension, diabetes, hyperlipidaemia, and smoking. This study also disclosed an association between vascular mechanics and severity of CAD.

The largest study on vascular mechanics reported to date was the one conducted by Park et al. involving 1057 patients, with documented atherosclerosis in 216. The high feasibility and excellent reliability of circumferential CCA $e$ was established. Patients with a history of vascular disease had lower values of global $e$ (3.3 ± 1.3 vs. 4.2 ± 1.9%; $P < 0.01$). Vascular mechanics and a number of risk factors for vascular disease correlated significantly. When added to CIMT, the utility of vascular $e$ (vs. $\beta_1$ index) was proved as an estimate of elevated cardiovascular risk, corresponding with Framingham risk score.

Vascular mechanics of CCA were also recently shown to correlate with coronary artery calcium score. In a group of 58 patients referred for cardiac tomography, investigators reported a significant negative correlation between calcium score and circumferential $e$ ($r = -0.4; P < 0.01$), as well as SR ($r = -0.39; P < 0.01$). This was in contrast with the classic $\beta_1$ stiffness index and carotid distensibility.

Assessments of vascular mechanics have been done in a variety of clinical settings, serving as surrogate markers for vascular stiffening in pregnancy-induced hypertension, Takayasu arteritis, rheumatoid arthritis. CCA circumferential $e$ and late SR in particular have been used to demonstrate that children with Kawasaki disease develop sclerotic changes during early stages of the disease.

In addition, assessment of vascular mechanics was performed in patients with Marfan syndrome. These patients displayed times to peak $e$ and SR values (including standard deviations) that exceeded those of age-matched controls. All related studies are summarized in Table 2. An example is showed in Figure 3C and D.

Another clinical aspect of carotid vascular mechanics has been addressed by Tsai et al., showing that $e$ and SR values were associated with a past history of stroke in older subjects with existing vascular stiffening, after adjustment for age, heart rate, systolic blood pressure, and cholesterol levels.

The concept of vascular mechanics as a surrogate of atherosclerosis and a marker of target organ damage has also been successfully tested in animal studies of aortic abdominal aneurysm, intimal hyperplasia, and vascular remodelling.

### Longitudinal vascular mechanics

Longitudinal motion of the arterial wall is more difficult to assess in ultrasound imaging, due to low-amplitude signals and inherently lower spatial resolution in azimuthal plane. Nevertheless, variations in ultrasound ST approach have shown that longitudinal determinations are feasible and are of the same magnitude as measured radial movement.

In both animal experimentation and clinical studies, low longitudinal vascular displacement has shown important associations with high cholesterol levels, atherosclerotic plaque burden, and CIMT. Zahnd et al. observed lower longitudinal carotid (proximal and far-wall) displacement in patients with diabetes, compared with a control population. Kawasaki et al. also demonstrated that CCA far-wall longitudinal mechanics correlated significantly with CIMT and distensibility index. In the same study, patients with CAD displayed significantly lower determinants of longitudinal vascular mechanics than a control group. Likewise, TDI vascular mechanics showed a significant negative correlation with Framingham risk scores, resulting in similar predictive accuracies. However, no significant difference was evident in comparing inspiratory and expiratory vascular mechanics.

In the context of CAD, Svedlund et al. studied a group of 441 patients with suspected CAD referred for myocardial perfusion scintigraphy. Those with lower carotid longitudinal displacement suffered more severe myocardial ischaemia, leading to worse medium-term outcomes.

It has also been shown an association between periodontal disease and lower longitudinal vascular displacement, independent of cardiovascular risk factors, cross-sectional distensibility, and CIMT. Hence, it seems likely that longitudinal vascular mechanics will emerge as a marker of cardiovascular disease. The same group credited with these findings has further demonstrated progressive attenuation of longitudinal vascular displacement along CCA in a group of healthy subjects.

### Limitations and future directions

ST analysis is a new and complementary imaging technology allowing segmental and global assessment of vascular circumference without angle dependency. In spite of the thinness of the vascular walls, this method has been validated by histological and sono-micrometric studies of circumferential vascular mechanics. Nevertheless, the study of vascular mechanics relies heavily upon image quality. Out-of-plane motion due to patient and transducer movement and tissue compression must be minimized to limit speckle decorrelation.

As noted in this review, a number of indices may be examined in the course of studying vascular mechanics. In our experience, vascular circumferential $e$ and SR are the more reliable parameters, being radial and longitudinal motion of arterial walls more difficult to assess. From a mechanistic standpoint, vascular wall systolic expansion and diastolic recoil best fit the concept of circumferential mechanics. Moreover, it is also apparent that circumferential vascular mechanics provide a reliable means of assessing arterial stiffness, surpassing conventional ultrasound-based methods in its performance.

Circumferential vascular mechanics may thus serve as a surrogate of local vascular stiffening, having a significant association with PWV, the gold-standard marker of arterial rigidity. Its utility as an imaging vascular risk marker has been demonstrated in a number of disease states and its clinical importance has been globally highlighted. Nevertheless, we must note that the normal variability across the aorta and in the more peripheral arteries has not been fully explored to establish reference ranges. More studies should also be performed with a large number of subjects in relation to age and gender to establish consistent references for vascular mechanics. We have reported in this review adequate values for vascular mechanics feasibility and reproducibility, but we note that most of the studies excluded patients with inadequate image quality or poor tracking. This means that the reported values should not expect to be obtained in unselected subjects. Finally, and in agreement with our experience, we recognize it is still a time-consuming methodology.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Number</th>
<th>Methodology</th>
<th>Main findings</th>
<th>Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjallmark et al.</td>
<td>2010</td>
<td>10 younger (25–28 years) + 10 older (50–59 years) healthy individuals</td>
<td>Right CCA 2D-ST</td>
<td>Circumferential mechanics were feasible, unlike radial mechanics (18% segments excluded due to high signal-to-noise ratio). Similarly, reproducibility was excellent for circumferential e and SR, but not for radial mechanics. Younger patients displayed higher global circumferential e (8.3 ± 0.8 vs. 4.5 ± 1.0%; P &lt; 0.01), higher global circumferential early SR (1.2 ± 0.2 vs. 0.6 ± 0.1 s⁻¹; P &lt; 0.01), and higher global circumferential late SR (−0.43 ± 0.08 vs. −0.26 ± 0.06 s⁻¹; P &lt; 0.01), compared with older patients. Regional circumferential mechanics was also higher in the younger age group. Among all mechanical and conventional stiffness variables, principal component analysis with regression identified only circumferential systolic strain variables as significant contributors to observed differences between younger and older age groups.</td>
<td>R. Teixeira et al.</td>
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<tr>
<td>C. Cho et al.</td>
<td>2010</td>
<td>12 patients with Takayasu’s arteritis + 12 healthy age- and sex-matched controls</td>
<td>CCA VVI</td>
<td>Patients with Takayasu’s arteritis exhibited lower values of vascular mechanics (velocity, e, SR, and displacement), compared with controls. Higher standard deviation of vascular mechanics in patients (vs. controls) suggested disturbed arterial expansion symmetry.</td>
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<td>N. Catalano et al.</td>
<td>2011</td>
<td>47 patients with CV risk factors, stratified by risk (low, 16; intermediate, 15; high, 15)</td>
<td>Bilateral CCA 2D-ST</td>
<td>Marfan syndrome was independently associated with the SD of time to peak e and SR in a model adjusted for age. Circumferential e and adjusted e (ε/pulse pressure) showed a significant negative correlation with CIMT (r = −0.52; P &lt; 0.01; r = −0.60; P &lt; 0.01), β1 index (r = −0.54; P &lt; 0.01; r = −0.61; P &lt; 0.01), and Ep (r = −0.56; P &lt; 0.01; r = 0.72; P &lt; 0.01). A positive correlation between circumferential mechanics and vascular distensibility was also noted. Circumferential adjusted e (0.11 ± 0.03 vs. 0.07 ± 0.03 vs. 0.04 ± 0.01%/mmHg) decreased significantly as CV risk increased. No such differences were noted for circumferential ε (5.5 ± 2.2 vs. 2.9 ± 1.2 vs. 2.4 ± 0.5%), CIMT, β1 index, vascular distensibility, and Ep.</td>
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<td>N. Yang et al.</td>
<td>2011</td>
<td>20 controls + 20 diabetic patients</td>
<td>Bilateral CCA VVI</td>
<td>Far-wall (4.3 ± 0.4 vs. 5.6 ± 0.3%; P &lt; 0.01) and global (4.3 ± 0.3 vs. 5.5 ± 0.3%; P &lt; 0.01) circumferential ε values were lower for diabetics, compared with controls. The differences remained significant when adjusted for age, gender, race, smoking, heart rate, and blood pressure (and after appropriate exclusions). Global and segmental ε values were significantly higher in right (vs. left) CCA. Assessment of carotid mechanics were feasible and modestly reliable. Speckle-tracking derived ε was more sensitive than luminal-based distension assessment as a measure of vascular stiffness.</td>
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<td>S. Yuda et al.</td>
<td>2011</td>
<td>51 controls</td>
<td>Bilateral CCA 2D-ST</td>
<td>Of 612 carotid wall segments tested, waveforms were adequate for analysis in 94%. Mean global circumferential ε was 6.7 ± 2.1%. Right- and left-sided CCA vascular mechanics did not differ. Age and pulse pressure were independently associated with global circumferential ε. Corrected ε (ε/pulse pressure) was independently associated with systolic blood pressure, age, and β1 stiffness index. Studies of vascular mechanics simply and quick, requiring only 128 ± 12 s per subject for ε analysis. The methodology showed high feasibility and excellent reproducibility. Mean absolute difference and coefficient of variation in intra- and inter-observer determinations of mean CAS were 0.7 ± 0.6% (CoV: 8.8%) and 0.5 ± 0.4% (CoV: 5.9%), respectively.</td>
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<tr>
<td>Authors</td>
<td>Year</td>
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<td>Methodology</td>
<td>Main findings</td>
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<td>Yang et al.</td>
<td>2011</td>
<td>100 healthy volunteers</td>
<td>Left CCA VVI</td>
<td>Circumferential $\varepsilon$ and SR decreased significantly across five age groups: 20–29 years: $\varepsilon$ 8.5%; Ts 275 ± 25 ms; SR 0.73 s$^{-1}$; Tsr 161 ± 6 ms 30–39 years: $\varepsilon$ 7.1%; Ts 293 ± 61 ms; SR 0.63 s$^{-1}$; Tsr 157 ± 13 ms 40–49 years: $\varepsilon$ 5.1%; Ts 321 ± 73 ms; SR 0.40 s$^{-1}$; Tsr 165 ± 21 ms 50–59 years: $\varepsilon$ 4.7%; Ts 343 ± 97 ms; SR 0.35 s$^{-1}$; Tsr 163 ± 32 ms 60–69 years: $\varepsilon$ 3.1%; Ts 361 ± 122 ms; SR 0.26 s$^{-1}$; Tsr 159 ± 46 ms Negative correlations of $\varepsilon$ ($r = -0.48$, $P &lt; 0.01$; $r = -0.54$, $P &lt; 0.01$) and SR ($r = -0.53$, $P &lt; 0.01$) with PWV and with AIx were demonstrated. Positive correlation of the Ts and Tsr with PWV and with AIx were also documented. Age was independently associated with variability in carotid mechanics, when adjusted for gender, body mass index, and heart rate, similar to PWV and AIx. Unlike PWV and AIx, a linear association between vascular mechanics (including Ts and Tsr) and age was evident.</td>
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<td>Kim et al.</td>
<td>2012</td>
<td>104 patients referred for a coronary angiogram (CAD, 49)</td>
<td>Left CCA 2D-ST</td>
<td>CIMT correlated negatively with circumferential $\varepsilon$ ($r = -0.19$, $P = 0.046$) and SR ($r = -0.22$, $P = 0.022$). Patients with CAD had lower circumferential $\varepsilon$ (2.3 ± 0.8 vs. 2.8 ± 0.9%; $P &lt; 0.01$) and SR (0.3 ± 0.1 vs. 0.5 ± 0.2 s$^{-1}$; $P &lt; 0.01$) values. Carotid mechanics were significantly associated with CAD in a model adjusted for age, gender, hypertension, diabetes, hyperlipidaemia, and smoking, in contrast to CIMT. Severity of CAD (i.e. number of diseased vessels) and carotid mechanics correlated significantly.</td>
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<td>Saito et al.</td>
<td>2012</td>
<td>90 healthy subjects + 40 age- and sex-matched hypertensive patients</td>
<td>Right CCA 2D-ST (posterior wall)</td>
<td>The $\beta_3$ index correlated positively with age ($r = 0.37$, $P &lt; 0.01$), with classic $\beta_1$ index ($r = 0.31$, $P &lt; 0.01$), and with brachial-ankle PWV ($r = 0.26$, $P &lt; 0.01$). The $\beta_3$ index was significantly higher in hypertensive patients than in controls. Age, heart rate, and the presence of hypertension correlated significantly with $\beta_3$ index. Inter- and intra-observer variability was superior in assessing $\beta_2$ (vs. $\beta_1$) index.</td>
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<td>Park et al.</td>
<td>2012</td>
<td>1057 patients; 216 with documented atherosclerosis</td>
<td>Bilateral CCA 2D-ST</td>
<td>Vascular mechanics showed high feasibility, with excellent inter- and intra-observer reliability. Circumferential $\varepsilon$ values were lower in patients with documented (vs. undocumented) without atherosclerosis (3.3 ± 1.3 vs. 4.2 ± 1.9%; $P &lt; 0.01$). Circumferential $\varepsilon$ decreased stepwise from low- to high-risk Framingham scored risk groups. As risk factors for atherosclerosis increased (0–4), carotid $\varepsilon$ decreased accordingly. Addition of vascular $\varepsilon$ to CIMT significantly improved the accuracy of detecting patients at high risk of vascular disease (according to Framingham score), unlike the $\beta_1$ stiffness index.</td>
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<td>Lee et al.</td>
<td>2012</td>
<td>120 patients with rheumatoid arthritis + 50 healthy controls</td>
<td>CCA 2D-ST</td>
<td>Patients with rheumatoid arthritis showed lower values of global circumferential $\varepsilon$ and of posterior radial $\varepsilon$, compared with controls. Vascular mechanics were associated as well with hs-CRP, with disease duration, and with disease activity score.</td>
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<td>MA et al.</td>
<td>2012</td>
<td>24 pregnant women with pre-eclampsia + 34 normotensive pregnant women</td>
<td>Right CCA VVI</td>
<td>Longitudinal velocity, strain, and strain rate of anterior and posterior walls of CCA were significantly lower in women with pregnancy-induced hypertension, compared with normotensive pregnant women. Similar results were also found for circumferential velocity, strain, and strain rate of anterior and posterior walls and for interior and exterior lateral walls of CCA.</td>
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Table 2 Continued

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<tr>
<td>Yang et al.⁸³</td>
<td>2013</td>
<td>20 controls + 20 patients with hypertension + 21 patients with diabetes</td>
<td>CCA 2D-ST + Time-interval analysis of the ε curve + slope analysis of the carotid artery area curve</td>
<td>Four time intervals of the ε curve were set as follows: (i) pre-distension period, (ii) peak ε time, (iii) distension period, and (iv) diastolic time. Hypertensive and diabetic patients showed greater delays in pre-distension peak and in peak ε time than did controls. The distension period was prolonged and the diastolic time was shortened for both hypertensive and diabetic patients, relative to controls. Adding four time intervals to ε non-significantly increased the C-statistic to better distinguish between patients and controls. The carotid artery area curve allowed estimation of four slopes (S1–S4), relating to arterial distension and contraction periods. S2 and S4 slopes were markedly steeper in the group of patients with hypertension and diabetes, compared with healthy controls. Adding slopes S2 and S4 and the four time intervals to ε achieved the largest improvement in accuracy to differentiate patients from controls.</td>
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<td>Tsai et al.⁴⁸</td>
<td>2013</td>
<td>89 patients (&gt;60 years) from community health survey program; past history of stroke in 11%</td>
<td>Left CCA 2D-ST</td>
<td>Carotid circumferential ε and SR were significantly lower in stroke subjects. The association remained significant after adjustments for age, heart rate, systolic blood pressure, and cholesterol levels. This was in contrast to the classic echo-derived stiffness indices (CIMT, β1 index, and distensibility), as well as PWV. Vascular mechanics did not correlate significantly with PWV or with CIMT.</td>
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<td>Oguri et al.⁹²</td>
<td>2014</td>
<td>75 children with a history of Kawasaki disease (mean age: 8 ± 3 years) + 50 healthy controls (mean age 8 ± 4 years)</td>
<td>CCA 2D-ST</td>
<td>Carotid circumferential ε (6.7 ± 4.0 vs. 8.6 ± 4.1%; P &lt; 0.01) and late SR (−0.28 ± 0.26 vs. −0.51 ± 0.31 s⁻¹; P &lt; 0.01) were significantly lower for children with a history of Kawasaki disease. No differences were noted in terms of time to peak ε, early SR, CIMT, β1 index, and Ep. Values of ε in girls with a history of Kawasaki disease were lower than those of male counterparts. Both β1 index and Ep correlated negatively with ε and late SR. Clinical and laboratory variables such as fever, Gunma score, CRP, and peripheral neutrophil count during acute phase did not influence variability of vascular mechanics.</td>
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<td>Podgórski et al.⁸⁸</td>
<td>2015</td>
<td>58 patients referred for cardiac tomography</td>
<td>Left CCA 2D-ST + Multi-slice CT</td>
<td>Calcium score correlated significantly with circumferential ε (r = −0.4; P &lt; 0.01) and with SR (r = −0.39; P &lt; 0.01). No significant correlation was identified between β1 stiffness index or Ep and calcium score. Patients with calcium scores &gt;0 had lower circumferential ε (3.2 ± 1.4 vs. 4.1 ± 1.5%; P &lt; 0.01) and SR (0.4 ± 0.2 vs. 0.5 ± 0.2 s; P &lt; 0.01) values than patients with calcium scores of 0.</td>
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2D-ST, two-dimensional speckle tracking; Aix, augmentation index; AS, aortic stenosis; AR, aortic regurgitation; CAD, coronary artery disease; CCA, common carotid artery; CIMT, carotid intima-media thickness; CV, cardiovascular risk; CoV, coefficient of variation; Ep, Peterson’s elastic modulus; ICC, intraclass correlation coefficient; CHD, congenital heart disease; hs-CRP, high-sensitivity C-reactive protein; PWV, pulse wave velocity; SR, strain rate; TDI, tissue Doppler imaging; TEE, transoesophageal echocardiogram; Ts, time to peak strain; VHD, valvular heart disease; VVI, vector velocity imaging.

At the present time, the use of this technology is still investigational, but continued advances in ultrasound technology, as well as its use and analysis in large epidemiologic studies, will clarify the part of ultrasonographic assessments of vascular mechanics in clinical diagnosis and prediction of outcomes.

Supplementary data

Supplementary data are available at European Heart Journal—Cardiovascular Imaging online.

Conflict of interest: none declared.

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