Ultrasonographic strain imaging is superior to conventional non-invasive measures of vascular stiffness in the detection of age-dependent differences in the mechanical properties of the common carotid artery

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Aims

Elastic properties of large arteries have been shown to deteriorate with age and in the presence of atherosclerotic vascular disease. In this study, the performance of ultrasonographic strain measurements was compared with conventional measures of vascular stiffness in the detection of age-dependent differences in the elastic properties of the common carotid artery (CCA).

Methods and results

In 10 younger (25–28 years, four women) and 10 older (50–59 years, four women) healthy individuals, global and regional circumferential, and radial strain variables were measured in the short-axis view of the right CCA using ultrasonographic two-dimensional (2D) strain imaging with recently introduced speckle tracking technique. Conventional elasticity variables, elastic modulus ($E_p$), and β stiffness index, were calculated using M-mode sonography and non-invasive blood pressure measurements. Global and regional circumferential systolic strain and strain rate values were significantly higher ($P < 0.01$ for regional late systolic strain rate, $P < 0.001$ otherwise) in the younger individuals, whereas the values of conventional stiffness variables in the same group were lower ($P < 0.05$). Among all strain and conventional stiffness variables, principal component analysis and its regression extension identified only circumferential systolic strain variables as contributing significantly to the observed discrimination between the younger and older age groups.

Conclusion

Ultrasonographic 2D-strain imaging is a sensitive method for the assessment of elastic properties in the CCA, being in this respect superior to the conventional measures of vascular stiffness. The method has potential to become a valuable non-invasive tool in the detection of early atherosclerotic vascular changes.

Keywords

Arterial stiffness • β stiffness index • Elastic modulus • Speckle tracking

Introduction

Cardiovascular disease is the leading cause of death worldwide and, as the population ages, its human and economic impact can be expected to become even more significant. The development of accurate, non-invasive methods for early diagnosis of atherosclerotic vascular changes in individuals without any symptoms of overt atherosclerotic diseases is therefore of considerable clinical interest. There are various techniques available for the detection of subclinical changes of mechanical properties in the arteries.1 2 In the daily clinical praxis, non-invasive methods, measuring surrogate markers for arterial stiffness are mainly...
based upon pulse transit time, analysis of arterial pressure pulse and its wave form or estimation of vascular stiffness from distending pressure and diameter measurements. The latter group of methods enables a local assessment of arterial stiffness, which can be expressed as distensibility, compliance, elastic modulus, or β stiffness index. The validity and reproducibility procedures of these methods show considerable differences and there is, in fact, no golden standard for evaluating arterial stiffness locally. Indeed, it should be remembered in this context, that arteries are not homogenous tubes and the compliance can vary in different parts of the artery.

Recent developments in ultrasonographic imaging created a technical basis for a new diagnostic approach to atherosclerotic disease by offering the possibility of two-dimensional (2D) strain imaging for estimation of vascular tissue motion and deformation (strain) during the cardiac cycle using speckle tracking. The technique identifies specific acoustic markers, speckles, in the grey-scale image and subsequently tracks these speckles frame by frame throughout the cardiac cycle. This enables angle-independent calculations of motion and deformation variables such as velocity, displacement, strain and strain rate. A number of speckle tracking algorithms have been developed and the technique has been successfully applied primarily in cardiac applications.

Several studies, using various assessment techniques, have verified an age-dependent increase of arterial stiffness in proximal, elastic arteries, and provided evidence that elastic properties fied an age-dependent increase of arterial stiffness in proximal, carotid segments. The validity and reproducibility procedures of these methods show considerable differences and there is, in fact, no golden standard for evaluating arterial stiffness locally. Indeed, it should be remembered in this context, that arteries are not homogenous tubes and the compliance can vary in different parts of the artery.

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Several studies, using various assessment techniques, have verified an age-dependent increase of arterial stiffness in proximal, elastic arteries, and provided evidence that elastic properties of large arteries are impaired in the presence of atherosclerotic cardiovascular disease and several risk factors. We believe that the speckle tracking technique has potential to be a useful tool for separating groups of individuals with differences in arterial stiffness. Therefore, the aim of the present study was to test if speckle tracking derived strain information can detect age-dependent differences in mechanical properties of the common carotid artery (CCA), and to compare the discriminating performance of 2D strain with that of conventional measures such as elastic modulus ($E_p$) and the β stiffness index.

**Methods**

**Studied population**

The studied population consisted of 10 younger (<30 years, range 25–28 years) and 10 older (>50 years, range 50–59 years) healthy individuals, four women in each group. No participant had any history of cardiovascular disease or underwent any medical treatment, and all had normal resting echocardiographic data. The study was approved by the local ethics committee and all participants gave their informed consent to participate.

**Echocardiography**

Echocardiographic baseline data were acquired using a Vivid i system (GE Vingmed Ultrasound, Horten, Norway) with a standard 2D transducer (M3S). Cine loops of at least three consecutive heartbeats were obtained from parasternal long-axis and short-axis images and from apical two and four chamber projections. A workstation with preinstalled Echopac software (EchoPac 7.0.0, GE Vingmed Ultrasound, Horten, Norway) was used for offline analysis. Tissue velocity imaging was performed with temporal resolution of >98 frames/s and the longitudinal atrioventricular (AV)-plane displacement during ventricular contraction was calculated as an average of displacements in the basal segments in the lateral and septal left ventricular (LV) walls. LV ejection-fraction (LVEF) was measured with the biplane Simpson’s method and LV stroke volume (LVSV) by subtracting the end-systolic volume from the end-diastolic volume. The E/A ratio was obtained by dividing mitral flow peak early diastolic velocity (E) with mitral flow peak late diastolic velocity (A).

**Carotid ultrasonography and strain imaging**

Two-dimensional long- and short-axis grey-scale cine loops of the right CCA were acquired using a Vivid i equipment (GE Vingmed Ultrasound) with a 14 MHz linear transducer. At least three consecutive heartbeats were stored with an average frame rate of 78 (SD 2) frames/s. Offline analysis was performed using a workstation equipped with 2D-strain software (EchoPac 7.0.0, GE Vingmed Ultrasound). The software enables automatic identification of speckles in the vessel wall and subsequent tracking of their movements during the cardiac cycle.

For measurements of circumferential and radial strain variables, a region of interest (ROI) was placed to cover the cross-sectional area of the CCA wall (Figure 1A). Adequate tracking of the vessel wall was verified and, if necessary, adjusted. The ROI had an initial width of ≈1.6 mm, but since the speckle tracking algorithm follows the movement of the speckles throughout the cardiac cycle, there were small variations of the ROI width along with the changes of vascular wall dimension. Circumferential peak systolic strain (%) as well as early and late systolic strain rate (strain per time unit, 1/s) variables were measured as an average of the whole, circular ROI giving respective ‘global’ strain and strain rate values. ‘Global’ values for radial variables could not be calculated due to limitations of the Echopac software and consequently, radial peak systolic strain and early and late systolic strain rates were only obtained ‘regionally’ from a discrete point (20 x 20 pixels) located in the far wall of the vessel (Figure 1A, large yellow dot), where also corresponding ‘regional’ circumferential variables were determined. The early systolic strain rate value was defined as the first peak in the strain rate curve that occurred after the QRS-complex in the ECG curve whereas the late systolic strain rate value was the first peak in the strain rate curve that occurred after the T-wave in the ECG curve and was sign-reversed compared with early systolic strain rate. The early systolic strain rate is a result of the blood pressure rise associated with ventricular ejection and late systolic strain rate occurs during the pressure decrease associated with ventricular relaxation. During systole, circumferential strain assumes positive values due to stretching, or expansion of the vessel wall whereas radial strain becomes negative as a result of the compression of the vessel wall. All measurements were averaged over three heartbeats. Figure 1B and C shows typical circumferential strain and strain rate curves.

**Elastic modulus and β stiffness index**

$E_p$ and β stiffness index are conventional measures of arterial stiffness that relates changes in arterial pressure to changes in arterial diameter. Increases in $E_p$ and β stiffness index correspond to increased arterial stiffness. For calculation of $E_p$ and the β stiffness index, the lumen diameter was measured in the long-axis view of the CCA, 5–10 mm proximal to carotid bulb, as the distance between the leading edge of the lumen-intima echo of the near wall and the leading edge of the intima-lumen echo of the far wall. Blood pressure was measured after the vascular examination using an automatic blood pressure device (Riester, Germany). $E_p$ and the β stiffness index were calculated...
according to the following formulas using M-mode sonography:

\[ E_p = \frac{(P_{\text{sys}} - P_{\text{dias}})}{(D_{\text{sys}} - D_{\text{dias}})/D_{\text{dias}}} \]

\[ \beta = \frac{\ln(P_{\text{sys}}/P_{\text{dias}})}{(D_{\text{sys}} - D_{\text{dias}})/D_{\text{dias}}} \]

where \( D_{\text{dias}} \) and \( D_{\text{sys}} \) were the minimal diastolic and maximal systolic lumen diameters, and \( P_{\text{sys}} \) and \( P_{\text{dias}} \) were the systolic and diastolic pressures. \( E_p \) was presented in kilopascals (kPa).

**Statistical analysis**

The statistical analysis was performed using SPSS, version 16. The data were expressed as mean (SD) unless otherwise stated, and a \( P \)-value of \(<0.05\) was considered significant. Differences in clinical and echocardiographic data, strain variables, \( E_p \) and \( \beta \) stiffness index between the two age groups were tested using unpaired \( t \)-tests. The reproducibility of the arterial stiffness measurements was tested in the younger subjects and the intra- and inter-observer variability was assessed by calculating coefficients of variation (CV).

The discriminating capacity of the vascular stiffness variables was evaluated using principal component analysis (PCA), which allows extraction of relevant information from larger data sets containing dependant as well as independent variables. The method enables a dimensional reduction of a data set by retaining the characteristics of the data that mostly contribute to its variance, and has the benefit of being data driven implicating that the algorithm finds mathematically relationships within and between the subjects and the variables. PCA and the regression extension partial least squares or projection to latent structures (PLS) was used to create a patient distribution plot (score plot) and a variable distribution plot (loading plot) from which a ranking list of the stiffness variables separating between the younger group and the older group was obtained. The ranking list was based on variable influence of importance (VIP), which gives information about the relevance of variables pooled over all dimensions. VIP > 1 corresponds to significant contribution to the separation of the groups.\(^16\) The results of the ranking were used to create refined models in order to optimize the separation between the groups by reducing the amount of variables.

**Results**

Clinical and conventional echocardiographic characteristics of the studied population are summarized in Table 1. The two age groups did not differ in BMI and arterial blood pressure, and had normal cardiac function with the exception of slightly reduced \( E/A \) ratio reflecting age-dependent diastolic disturbance in the older group.

In the strain measurements, no segment was excluded because of insufficient tracking quality according to the EchoPac software quality assurance tool. Circumferential measurements (global and regional) could be performed in all ROIs, compared with radial measurements of which 18% (32/180) were excluded due to high signal to noise ratio in the strain and strain rate curves. Calculation of \( E_p \) and \( \beta \) stiffness index was feasible in all images.

Table 2 displays the intra- and inter-observer variability of the arterial stiffness variables. Global strain and strain rate measured in the circumferential direction showed generally lower variability.
than regional strain and strain rate in the same direction, with global circumferential early systolic strain rate having the lowest variability. The variability of the radial measurements was consistently considerably higher than that of circumferential measurements, the variability of late systolic strain rate being especially striking. The variability of the conventional stiffness variables agreed with previously reported values, and was higher than that of circumferential strain variables.

Table 3 summarizes the measurements of arterial stiffness. The younger group showed significantly higher circumferential global and regional peak systolic strain indicating greater systolic diameter change when compared with the older individuals (P < 0.001). Similarly, the absolute values of circumferential global and regional early and late systolic strain rate were also significantly higher in the younger group (P < 0.01 for regional late systolic strain rate, P < 0.001 otherwise). Among the corresponding radial variables, only early systolic strain rate differed significantly between the groups (P < 0.05), reflecting the high intra- and inter-observer variability of the radial measurements. $E_p$ and $\beta$ stiffness index were significantly lower (P < 0.05) in the younger group, thus expressing higher vascular elasticity in the younger individuals.

The ranking list generated by the PLS analysis showed that all circumferential variables, except the regional late systolic strain rate displayed a VIP-value > 1 and, hence, contributed significantly to the discrimination of the two age groups (Table 3). The remaining variables (VIP < 1) did not provide any significant contribution. On the basis of the circumferential variables, two refined models were created, one containing the three global variables, and one with the three regional variables. Figure 2 illustrates the distribution of the subjects according to the refined models, where subjects with similar characteristics cluster more closely. The model containing the global variables (left) showed a clear separation between the younger group (squares) and the older group (diamonds). This was not as clearly seen in the model containing regional variables (right) where the subject groups overlapped. Further evaluation of the global model identified global peak systolic strain as the most important variable for separating the younger from the older individuals, followed by global early systolic strain rate and late systolic strain rate.

**Discussion**

In this study, the performance of ultrasonographic speckle tracking-based strain measurements was compared with the performance of conventional measures of vascular stiffness, elastic modulus, and the $\beta$ stiffness index, in the detection of age-dependent differences in the elastic properties of the CCA. The addressed issue is of clinical importance since several studies conducted in recent years have identified arterial stiffness as an early manifestation of atherosclerotic cardiovascular disease, and also showed that decreased elasticity of the arterial wall may be present even before the occurrence of any clinical symptoms or atherosclerotic plaques. Furthermore, it has been demonstrated that arterial stiffness increases gradually along with advancing age, which process may predispose to the development of atherosclerotic vascular lesions. There is therefore a growing need for new, sensitive, and accurate non-invasive methods for the evaluation of elastic properties of the arterial wall that would provide an efficient identification of individuals at the early stage of atherosclerotic disease.
Hitherto, $E_p$ and $\beta$ stiffness index have been commonly used for the determination of arterial stiffness. However, the value of these variables is somewhat limited. $E_p$ expresses the relationship between stress (change in transluminal pressure) and strain (fractional change in lumen diameter) as a ratio and describes the overall stiffness of the arterial wall, but is blood pressure dependent. $\beta$ stiffness index was constructed to attenuate the effect of blood pressure on vascular stiffness measurements, but the blood pressure independency of this variable has been questioned since an effect of blood pressure has, nevertheless, been observed in a cohort of patients with stroke.\textsuperscript{22} The two groups of subjects in the present study did not differ in terms of arterial blood pressure or LV function. The older group showed signs of age-dependent diastolic relaxation disturbances, and the existence of age-dependent decrease in carotid vascular elasticity could accordingly also be anticipated in these individuals. The obtained results show that both $E_p$ and $\beta$ stiffness index indeed separated the two age groups, implying that both these variables possess the capacity to disclose age-dependent changes in the elastic properties of the carotid artery. However, the current PLS discrimination analysis
demonstrates at the same time that circumferential strain variables, even if they most likely are blood pressure dependent as well, are at the same blood pressure level more sensitive than $E_p$ and $\beta$ stiffness index in the detection of age-dependent differences in the elastic properties of CCA. The high variability of $E_p$ and $\beta$ stiffness index may provide at least one probable explanation of the difference in the discriminating capacity of 2D-strain and the two conventional variables. The fact that blood pressure and lumen diameter for calculation of $E_p$ and $\beta$ stiffness index are measured at different locations imposes certainly further limitations on the accuracy of these variables.

A decrease in arterial elasticity is considered to be largely a result of progressive degeneration of elastin fibres in the arterial media layer, a process that can be expected to influence the arterial deformation pattern, but not necessarily in a homogenous way. A possible heterogeneity of the deformation pattern and compliance may be further accentuated by the presence of atherosclerotic plaques. Both $E_p$ and $\beta$ stiffness index are based on a 1D approach that does not take into account any local variations in arterial compliance. In contrast, the speckle tracking method provides 2D data that are obtained directly in the arterial wall itself. This creates the possibility for the detection of heterogeneous motion pattern and local variations in compliance in different sectors of vascular wall, and paves the way for an entirely new approach to the diagnostic characterization of atherosclerotic plaques in carotid arteries. Characterization of carotid plaques is an important step in the evaluation of the atherosclerotic vascular involvement and the prediction of risk for cerebral vascular events. The commonly used plaque classification is based on evaluation of their echolucency in grey-scale images and their possible vulnerability is then determined. In contrast, the 2D-strain approach offers the possibility of a direct measurement of vascular elastic properties in different parts of the plaque area and in the adjacent vascular sectors. A considerably improved assessment of plaque vulnerability can thus be expected which, in turn, would result in a more efficient and adequate anti-atherosclerotic treatment and thereby also the prevention of cerebral vascular events.

The results of the present study indicate that the measurement of circumferential global strain has a potential to be a reliable tool for the assessment of arterial stiffness and also circumferential global strain rates appear to perform well in this context. This is in keeping with and extends the observations made in the recent study of Oishi et al. who reported a good capacity of 2D-strain imaging in the detection of age-dependent differences in the aortic stiffness. In the above-mentioned study, that was the first to focus on the feasibility of vascular strain measurements, the peak circumferential strain and $\beta$ stiffness index variables obtained from the 2D-images of the abdominal aorta were found to correlate significantly with age. In addition, the circumferential strain variables appeared to discriminate better than $\beta$ stiffness index between different age groups. However, in contrast to the present study, no direct comparison of the discriminating capacities of the performed strain and conventional stiffness measurements was made and the performance of only one vascular strain component, i.e. that of circumferential strain, was evaluated. Furthermore, the suggested approach involved ultrasonography of the abdominal aorta below the level of the renal arteries and it is known that the acquisition of the optimal, noise-free images from this particular vascular location may be technically difficult in some individuals. The currently proposed image acquisition from the CCA is much more convenient in the routine clinical setting. It is technically easy to perform and can be time-efficiently obtained during routine ultrasonographic evaluation of the structural atherosclerotic changes in extracranial carotid arteries.

Compared with circumferential strain variables, the radial strain variables evaluated in the present study do not appear to be sufficiently sensitive in the assessment of CCA stiffness. In fact, only the measurement of radial early systolic strain rate provided a significant discrimination of the two studied age groups. The high variability of the radial strain variables contributes to their poor performance. Indeed, whereas the intra- and inter-observer variability of circumferential strain measurements was comparable to generally reported values, the corresponding variability of radial strain measurements was considerably higher. The different way to calculate strain and strain rate in circumferential and radial direction can, at least partly, explain this difference. The calculation of circumferential strain variables is based on the displacement estimates, in contrast to the calculation of radial strain variables, which is based on measurements in the derived domain, i.e. the velocity estimates. Furthermore, the circumferential strain estimation is averaged over a larger number of tracking points, which reduces the amount of noise in the obtained data and may explain why the circumferential variables demonstrate lower variability and overall better performance.

Summing up, ultrasonographic 2D-strain imaging is a sensitive and reliable method for the assessment of the arterial stiffness in the CCA and its performance in this respect appears to be superior to the conventional measures such as elastic modulus or $\beta$ stiffness index. The procedure is non-invasive, fast and easy to perform, and may offer a valuable tool for the detection of increased arterial stiffness and hence, early identification of patients with atherosclerotic disease.

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**References**


