Presentation of a Non-Invasive Method for Detection of Initial Symptoms of Atherosclerosis using Estimation of Local Static Pressure by Ultrasound

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Abstract

Background- Non-invasive evaluation of vessel wall properties in humans is hampered by the absence of methods to directly assess local elasticity. Contemporary ultrasound methods are capable of assessing end diastolic artery diameter, the local change in artery diameter as a function of time and local wall thickness. However, to assess vessel wall properties of the carotid artery, for example, the pulse pressure in the brachial artery still must be used as a suitable example for local pulse pressure. The assessment of local static pressure as described in the present study provides a direct estimate of local vessel wall properties.

Methods- In 30 men, we estimated the static pressure-strain elastic modulus in the right common carotid artery (RCCA) under normal and atherosclerotic conditions. The detailed variation of the static pressure of RCCA throughout the carotid cycle was estimated by using the energy conservation law. The flow velocities during systole and diastole were measured using multi-frame image processing method of color Doppler ultrasonography. The static pressure-strain elastic modulus was defined as stress to strain.

Results- The results showed that: 1) the variation of the static pressure during the cardiac cycle was higher in the severe atherosclerotic group than that in both the mild atherosclerotic group and the normal artery group, respectively, 2) the relative increase in the vessel diameter during the cardiac cycle was lower in the atherosclerotic group than that in the normal, group and 3) the static pressure-strain elastic modulus in the atherosclerotic group was significantly different from that in normal individuals.

Conclusion- We concluded that by applying this method, we can detect the initial symptoms and disease process in atherosclerosis. This is an accurate and safe method suited to the screening of large populations of young and symptom-free individuals ***(Iranian Heart Journal 2004; 5(1):).***

Key words: ultrasonic tissue characterization ■ static pressure ■ elastic modulus■ carotid artery■ atherosclerosis

Deformation and stress induced in arterial walls by blood pressure are extremely important factors in the understanding of the physiology and pathology of the cardiovascular system. An increase in the arterial wall stiffness appears to be a common pathological pathway for the many factors that lead to the initiation and progression of the vascular changes associated with cardiovascular disease.[1-3] Functional disturbances of the vascular wall may

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occur early in the atherosclerotic process even before the anatomical changes of intima-media thickening become perceptible.[4-6] Therefore, the study of dynamic arterial wall properties in major arteries such as the carotid and femoral arteries is becoming more common.

The elastic properties of the carotid artery are affected by different physiological states and external stimuli.[7-10] Changes in the ratio of collagen to elastin may be one reason for the loss of arterial elasticity.[11,12] Furthermore, the proliferation of smooth muscle cells and deposition of lipids in the arterial wall may be additional factors.[13,14] An early non-invasive detection of atherosclerotic damage would be of great significance with regard to risk stratification and pre-symptomatic treatment of patients with atherosclerotic diseases, such as coronary artery disease (CAD).

Fundamental research on the assessment of arterial elasticity and on the effect of different physiological and pathological influences on arterial elasticity was done by Hoeks and coworkers.[15-19] They developed the phase-locked echo tracking technique[15,16] to quantify arterial elastic properties, used in several studies in this field.[20-22] Other non-invasive methods, such as applanation tonometry,[23,24] magnetic resonance imaging[25-27] and pulse wave velocitometry[28-30] were used to assess arterial elastic properties, as well. However, evidence for a causal relationship between arterial wall stiffening and atherosclerosis is still lacking.

An assessment of the local static pressure as described in the present article provides a direct estimate of the properties of the local vessel wall. The purpose of this study is to examine the differences in elasticity in the common carotid artery under normal and atherosclerotic conditions by directly estimating the static pressure using the energy conservation law.

Methods

Cardiovascular diseases present differently in men and women. Men have more than twice the total incidence of cardiovascular morbidity and mortality than women between the ages of 35 and 84. Women, on the other hand, have a more favorable risk profile in some respects: higher HDL cholesterol levels, lower triglyceride levels, and less upper-body obesity than men. But women also have a less favorable risk profile in other respects: more obesity, higher blood pressure, higher plasma cholesterol levels, higher fibrinogen levels, and more diabetes. The simplest explanation for the sex differential in cardiovascular disease is the "cardio-protective" effect of estrogen, due to the improvement of the lipid profile, a direct vasodilatory effect, and perhaps other factors.[31] this study was performed from between Nov. 2000 and March 2002. The method of research was cross-sectional and sampling was random. In light of previous studies,[32,33] sample size were estimated at 10 samples with confidence level of 95% and power of test of 90% in each group. Therefore, 30 men (mean age 65 ± 5 years) entered this study, including 10 healthy subjects with no history of cardiovascular disease, cerebrovascular disease, hypertension and diabetes and 20 patients with angiographically documented CAD. All the subjects underwent color Doppler ultrasonography. A complete examination including common external and internal carotids was performed on every subject. More than 40% diameter narrowing in the carotid arteries was evaluated as severe carotid stenosis. The subjects were divided into 3 groups based on the presence of diameter narrowing as follows: 1) normal: no diameter narrowing, 2) mild stenosis:

less than 40% diameter narrowing (30±7 percent of stenosis) and 3) severe stenosis: more than 40% diameter narrowing (65±10 percent of stenosis).

Arterial remodeling during atheroma formation represents a frequently over-looked but clinically important feature of lesion evolution. During the initial phases of atheroma development, the plaque usually grows in the direction away from the lumen (abluminally). Vessels affected by atherogenesis tend to increase in diameter, a type of vascular remodeling known as compensatory enlargement. Not until the plauque covers more than about 40% of the circumference of the internal elastic lamina does it begin to encroach on the arterial lumen. Thus during much of its history, an atheroma will not cause stenosis that can limit the blood flow.[31]

Ultrasonic examination of the right common carotid artery (RCCA) was performed after at least 15 minutes' rest in a supine position, when the heart rate and blood pressure had reached a steady state. All the subjects were examined using a color Doppler ultrasound machine (GE logic 500 MD version 4 with 7.5 MHz linear array transducer). With the subject supine and the neck in partial extension, the transducer was oriented perpendicularly to the longitudinal axis of the vessel based on the acoustic Doppler signal and on the B-mode echo image. The transducer was placed with the least possible pressure so as not to compress the overlying jugular vein and allowing expansion of the carotid artery in all directions. A data acquisition system consisting of a personal computer and video-blaster board was used for monitoring and grabbing the changes of the blood flow velocities and cross sectional area of the right common carotid artery over two cardiac cycles. Peak systolic and end-diastolic velocities were determined in the RCCA at a point approximately 2 cm proximal to the bifurcation. The angle of insonation was maintained below 60ºC, and all the velocity measurements were taken at the mid-lumen. For the measurement of cross sectional area, matching longitudinal views of the RCCA were located and frames, representing a minimum of two cardiac cycles, were grabbed throughout two cardiac cycles. The maximum and minimum cross-sectional areas were determined over each cardiac cycle with processing of sequence frames. Then systolic-diastolic changes (ΔD) and the diastolic diameter (D_d) of RCCA were calculated from cross-sectional areas. The arterial strain was defined as $\Delta D/D_d$.

Total fluid energy (E) per unit volume of blood equals the sum of the pressure, plus a factor related to the influence of gravity, plus the kinetic energy:

$$E= P+ \rho g h + \tfrac{1}{2} \rho v^2 \qquad (1)$$

where P is static pressure, ρ is blood density, g is the earth's gravity acceleration constant, h is the height of the fluid above or below a reference level and v is flow velocity. If all parts of the fluid system are at the same level, the gravitational factor can be ignored (this is the case in the supine but not the erect position). When the left ventricle contracts, all the energy imparted to the blood does not appear immediately as kinetic energy. Some is used to stretch the elastic fibers in the arterial walls and is stored there as potential energy. During systole, when the diameter of the vessel widens and velocity slows, the kinetic energy term is decreased and the static pressure tends to rise due to lower velocity. At diastole, the recoil of the elastic tissue returns the energy stored in the arterial wall to the blood, so the velocity of flow increases again and the static pressure decreases; this is because in

a blood vessel, total energy (E) is constant (energy conservation law).[34]

The variation of the static pressure in arteries is associated with variation in the blood flow velocities throughout the cardiac cycle. We estimated the detailed variation of the static pressure (ΔP_s) in the RCCA by the equation:

$$\Delta P_s = ½ \times \rho(V_1^2 \_ V_2^2) \qquad (2)$$

Where V_1 and V_2 are the peak systolic velocity (PSV) and end diastolic velocity (EDV) in the RCCA. Blood density is 1060 kg/m^3. On the other hand, blood pressure was recorded in the right brachial artery with the patient in a supine position using a semiautomatic device (Riester 0124, Germany). The pulse pressure (ΔP) was defined as systolic minus diastolic blood pressure.

From the diameter and pulse pressure measurements, pressure-strain elastic modulus (E_p) was defined based on Peterson et al.[35] as:

$$Ep = \frac{\Delta P}{\Delta D / Dd} \qquad (3)$$

where ΔP is the pulse pressure and $\Delta D/D_d$ is arterial strain.

We also estimated the static pressure-strain elastic modulus (E_{ps}) in the RCCA using static pressure change (ΔP_s). It was defined as:

$$Eps = \frac{DPs}{DD / Dd} \qquad (4)$$

All the observations were performed by the same investigator under the same standard conditions.

Results from individual subjects were averaged and are shown as mean±1 standard deviation (SD).

The statistical significance of the differences in mean values was assessed with one-way ANOVA. The p-value less than 0.05 were taken as the level of statistical significance.

Linear discriminate analysis is a conventional statistical procedure for testing the extent to which groups such as various classes of lesions can be discriminated on the basis of their quantitative specifications. Therefore, the discriminant functions of types of lesions based on static pressure-strain modulus are formulated.

Results

The data obtained from the examination of 30 subjects are given in Table I.

Table I. Mean and standard deviation of peak systolic velocity (PSV), end diastolic velocity (EDV), carotid cross-sectional area, strain and arterial pulse pressure and static pressure changes.

Group	Normal	Mild stenosis (<40%)	Severe stenosis (≥40%)
Peak systolic velocity (cm/s)	51.3 ± 1.8	74.1± 3.3	104.0 ± 17.0
End diastolic velocity (cm/s)	15.6 ± 2.3	27.1 ± 5.3	55.4 ± 2.6
Diastolic cross section area (cm^2)	0.56 ± 0.03	0.53 ± 0.03	0.48 ± 0.04
Strain	0.075 ± 0.004	0.064 ± 0.005	0.057 ± 0.007
Pulse pressure (Pa)	1026.4 ±40.0	799.8 ±106.6	1038.7 ± 239.9

The diameter of the RCCA decreased from 8.4 ± 0.2mm in the normal subjects to 8.2 ± 0.2mm in the mild stenosis group and 7.8 ± 0.3mm in the severe stenosis group, as shown in Table I. The arterial strain was highest in the normal group and lowest in the group of patients with severe stenosis.

Fig. 1 shows an increase in the blood flow velocities in relation to the progression of atherosclerosis. The group of patients with severe stenosis had higher blood flow

velocities than those with mild stenosis and the normal group.

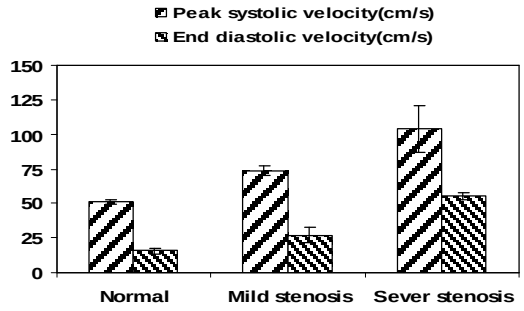


Fig.1. The blood flow velocities, peak systolic velocity and end diastolic velocity in RCCA.

In Fig. 2, the values of static pressure changes are presented. The static pressure change in RCCA is markedly increased with progression of atherosclerosis.

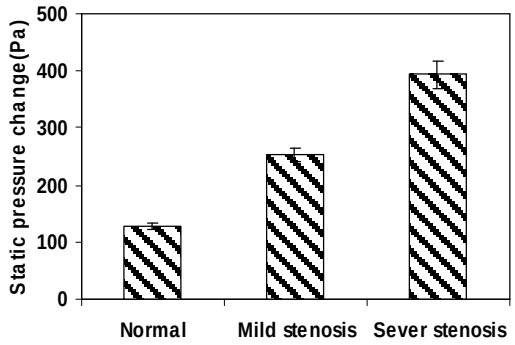
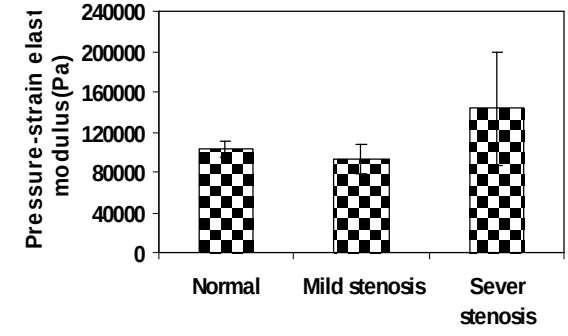
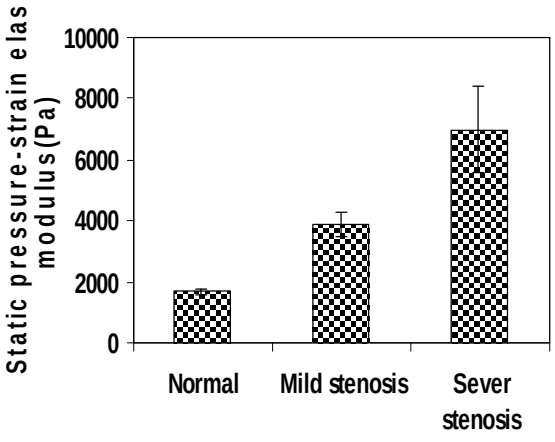


Fig.2. Static pressure changes (Pa) in RCCA throughout the carotid cycle in each group

Fig. 3 (a) and (b)[33] present the static pressure-strain elastic modulus (E_{ps}) and pressure-strain elastic modulus (E_p) of the RCCA under normal and atherosclerotic conditions. The static pressure-strain elastic modulus is significantly (p-value≤0.05) greater in: 1) the group of patients with severe stenosis compared to those with mild stenosis, and 2) the group of patients with mild stenosis compared to the normal group, whereas there is no significant difference in pressure-strain elastic modulus between the group of patients with mild stenosis and the normal group. Regarding the influence of atherosclerosis on elastic modulus of the RCCA, it was found that the static pressure-strain elastic modulus was influenced by atherosclerosis, whereas pressure-strain elastic modulus increased only at advanced stages of atherosclerosis. The discriminant function of types of lesions based on static pressure-strain elastic modulus (E_{ps}) in the three groups is formulated by discriminant analysis.

Fig.3. Static pressure-strain elastic modulus (a) and pressure-strain elastic modulus (b)[33] in RCCA.





In Table II, the discriminant functions, group centroids and canonical correlation were calculated in the three groups.

Table II. The discriminant functions of types of groups based on Static-pressure-strain elastic modulus

Elastic modulus	Discriminant functions	Group centroids			Canonical correlation
		Normal	Mild stenosis	Severe tenosis	
Static pressure strain elastic modulus	110.38Eps*-4.67	-2.80	-0.33	3.14	0.9319

The statistical power of discriminant analysis can be tested by canonical corelation that must be close to 1. The classification results of the groups with measurement of static pressure-strain elastic modulus were shown in Table III.

Table III. The percentage of classified results

Actual group	No. of Cases	Predictive group membership		
		Normal	Mold stenosis	Severe stenosis
Normal (1)	10	100.0%	0.0%	0.0%
Mild stenosis (2)	10	0.0%	100.0%	0.0%
Severe stenosis (3)	10	0.0%	0.0%	100.0%

It is observed that the correctly classified means for the discrimination of all cases is 100%. The percentage of correctly classified groups, and the sensitivity and specificity of the normal, mild stenosis and severe stenosis groups by *static* pressure-strain elastic modulus and pressure-strain elastic modulus is shown in Fig. 4. It is considerable that the evaluation of elastic parameter with arterial pulse pressure has 60% correct classification, whereas the percentage rises to 100% with static pressure-strain elastic modulus.

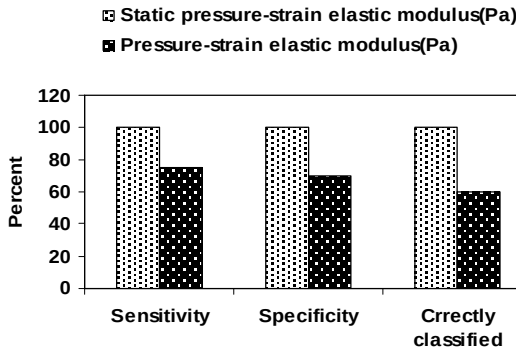


Fig.4. The percentage of the sensitivity, specificity and correctly classified groups with static pressure-strain elastic modulus and pressure-strain elastic modulus.

Discussion

Although many studies have been done on the elastic properties of atherosclerotic walls, the results obtained are conflicting and inconclusive. Some of them indicate that the arterial wall stiffens with the development of atherosclerosis. For example, Band et al. and Pynadath and Mokherjee showed that the dynamic Young's modulus of the rabbit aorta was markedly increased by feeding cholesterol diet.[36,37] Ritcher and Mittermayer reported that the modulus of volume elasticity of the human aorta was higher in more advanced stages of atherosclerosis.[38] On the other hand, several investigators have reported contrary data. Mark et al. and Hudetz et al. reported that the incremental elastic module of human cerebral arteries was lower in the fibrosclerotic walls than in the normal ones, although there were no differences in the structural stiffness

between them.[39,40] Nakashima and Tanikavat showed that the structural stiffness of the human aorta increased gradually with age, regardless of the stage of atherosclerosis.[41] Hayashi et al. showed that even if atherosclerosis was greatly advanced, there were essentially no changes in the material stiffness, unless there was considerable calcification in the wall. At the most severe stages of atherosclerosis, the arterial wall has high structural and material stiffness due to calcification and wall hypertrophy.[42]

Young modulus is essentially a measure of the intrinsic elastic properties of a given material independent of the amount of thickness of that material. However, pressure-strain elastic modulus, which has been used to describe the relationship between the pulse pressure and arterial diameter change is a measure of Young modulus and the amount and configuration of the material, and it essentially represents overall arterial stiffness limiting the pulsatile expansion of the artery.

There is no consensus on the methodology of obtaining the pulse pressure used in the calculation of elastic modulus. Various ultrasonic methods proposed for the non-invasive assessment of the local pulse pressure are not reliable. Moreover, most of the methods designed for direct evaluation of arterial elasticity use the pulse pressure in the brachial artery instead of the local pulse pressure in the actual explored artery. Different approaches in blood pressure measurements affect the precision of elastic modulus estimation.

In the present study, we estimated local static pressure changes in the common carotid artery under normal and atherosclerotic conditions using energy conservation law. It is worth noting that the pressure drop in any segment of the arterial system is due both to the resistance and to the conversion of potential into kinetic energy. The pressure drop due to energy lost in overcoming resistance is irreversible, since the energy is dissipated as heat, but the pressure drop due to conversion of potential to kinetic energy as a vessel stretches during systole is reversed when it recoils during diastole. Furthermore, vessel resistance is directly proportional to the length of the vessel and the viscosity of the blood, and inversely proportional to the radius to the fourth power. Vessel length does not change appreciably *in vivo* and therefore can generally be considered as a constant. Blood viscosity normally does not change very much; however, it can be significantly altered by changes in hematocrit, temperature and by low-flow states. In contrast, the change in the radius will alter resistance to the fourth power. Therefore, in large vessels, for example the carotid artery, vessel resistance is negligible because the vessel radius is large.

In our subjects, a significant increase in blood flow velocities and the static pressure changes were observed with the progression of atherosclerosis. Bernoulli principle[43,44] has significant application in pathophysiology; according to this principle, the greater the velocity of the flow in a vessel, the lower the static pressure distending its walls. Atherosclerotic changes in the arteries include thickening of the intimal layer, lipid deposits, a decrease in elastin and an increase in collagen contents. Because the elastic modulus of collagen is greater than that of elastin, the arterial wall becomes stiffer with the progression of atherosclerosis.[43] The static pressure throughout the cardiac cycle rises and falls extraordinarily when a vessel becomes stiffer by a pathologic process such as atherosclerosis. Therefore, the static pressure change correspondingly increases during the disease process. The decrease in diameter and systolic-diastolic diameter change in pathological groups compared

with that in normal state is associated with an increase in the wall thickness. The decrease in strain is due to the change of collagen/elastin ratio associated with atherosclerosis; an increase of this ratio decreases the arterial strain.

We also estimated the pressure-strain elastic modulus by using the pulse pressure obtained from the brachial artery (ie. where pulse pressure magnitude and waveform are different from those within the carotid artery). The pressure-strain elastic modulus in the RCCA was significantly higher in the group of patients with severe stenosis than that in the normal subjects, whereas no significant difference was seen in the group of patients with mild stenosis compared to the normal group.

It is known that arterial pressure waves undergo transformation, with more prominent peaks the further the waves travel from the heart, the peak pressure in the brachial artery being higher than in the CCA.[44] This results in an overestimation of the systolic blood pressure and pulse pressure, and thus in pressure-strain elastic modulus when the brachial pressure is used in the estimation of pressure-strain elastic modulus. This might yield inconclusive results.

This method is based on measuring the static pressure change using the energy conservation law. There is an important relationship between the atherosclerosis disease and the characteristics of the blood flow in the arteries. In this study, Doppler ultrasonographic velocity measurements were used to predict the static pressure change caused by atherosclerosis.

We measured the systolic and diastolic blood flow velocities in the right common carotid artery by color Doppler imaging. The energy conservation law having been applied, detailed static stress-strain elastic modulus was estimated by the equation:

$$Eps = \frac{\frac{1}{2} r (V_S^2 - V_d^2)}{DD / Dd} \qquad (5)$$

Where V_s and V_d are the peak systolic velocity (PSV) and end diastolic velocity (EDV) in the RCCA, and r is the blood density. The static stress-strain elastic modulus used to quantify arterial elasticity in the RCCA under normal and atherosclerotic conditions. The results showed that the variation of static pressure and static pressure-strain elastic modulus in atherosclerotic groups was significantly greater than that in the normal groups (sensitivity and specificity of 100%).

We concluded that by estimating the local static pressure and static pressure-strain elastic modulus, we can detect atherosclerosis early in the disease process, and that it was an accurate and safe method suited to not only the screening of large populations of young and symptom free individuals, but also the detection of high risk cardiovascular patients.

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