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Measurement of arterial stiffness in subjects with vascular disease: Are vessel wall changes more sensitive than increase in intima–media thickness?

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ABSTRACT

Background and aims: It is widely accepted that subjects with vascular disease have increased arterial stiffness and intima–media thickness (IMT) when compared with healthy controls. The aim of this study was to investigate indices of arterial stiffness and IMT in the common carotid arteries (CCAs) of subjects with and without peripheral arterial disease (PAD), in order to look for evidence of change in wall quality and quantity to explain increased stiffness that has been found in the arteries of subjects with vascular disease.

Methods and results: The arterial distension waveform (ADW), IMT, diameter and brachial blood pressure were measured to calculate Young's Modulus (E) and elastic modulus (Ep) in the common carotid arteries of subjects with and without PAD. 38 subjects with confirmed PAD were compared with 43 normal controls matched for age, sex, smoking and hypertension. The mean diameter (8.35 mm [95% CI 7.93–8.77] *vs.* 6.93 mm [6.65–7.20] $P < 0.001$, increase 20%), IMT (0.99 mm [0.92–1.07] *vs.* 0.88 mm [0.82–0.93] $P = 0.020$, increase 12.5%), Ep (315 kPa [185–444] *vs.* 190 kPa [164–216] $P = 0.034$, increase 66%) and E (1383 kPa [836–1930] *vs.* 744 kPa [641–846] $P = 0.006$, increase 86%) were all significantly higher in subjects with PAD.

Conclusions: This study suggests that increased stiffness observed in subjects with peripheral vascular disease is a result of change in both quantity and quality of the arterial wall. Changes in indices of arterial stiffness were much higher than changes in IMT and diameter. These preliminary observations may be an indication that indices of arterial stiffness are a sensitive early marker of atherosclerosis.

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1. Introduction

An enlarging body of evidence suggests that increased arterial stiffness is associated with markers of cardiovascular risk and that this stiffness may herald the onset of cardiovascular disease before manifestation of symptoms or detection of frank atherosclerotic lesions [1,2]. Measurement of arterial stiffness could become a part of the process of both risk assessment and monitoring of therapy in patients with cardiovascular disease.

Research on arterial stiffness is based on elastic theory. Elastic theory attempts to explain and quantify the relationship between a force applied to an elastic body and its subsequent deformation and then return to original form. A force acting on a solid body at rest will cause deformation (parts of the body to move relative to each other). If the body regains its original form when the force is removed then it is termed elastic, as opposed to plastic if the body retains the deformation.

The general term arterial stiffness describes the rigidity of the arterial wall. Indices of arterial stiffness attempt to quantify the effect of stress on strain. Stress is defined as the intensity of the force (pulse pressure) acting on a given area of a body (the arterial wall). Strain is defined as the change in length of a body in response to stress. An increase in length is referred to as positive strain and decrease as negative strain.

Indices can be divided into two types: indices of 'structural stiffness' and indices of 'material stiffness' [3]. Indices of structural stiffness are descriptors of the overall stiffness of the wall of an artery, and describe the elastic behaviour of the whole arterial wall at the point of measurement. One commonly used index of structural stiffness is the 'pressure strain elastic modulus' Ep (Eq. (1)). It was first described by Peterson et al. [4], and requires measurement of the fractional arterial distension from diastole to systole, together with the corresponding blood pressures. Ep expresses the relationship between stress and strain as a ratio. It is therefore unit

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less, and has the additional advantage of not requiring information about wall thickness in order to be calculated:

$$Ep = \frac{\Delta p d}{\Delta d} \quad (1)$$

where d is the diameter, Δp is the systolic minus diastolic pressure and Δd is the difference in diameter at systole and diastole.

Indices of material stiffness describe the physical properties of the substance that makes up the subject body. Young's modulus E is the most common index of material stiffness. It is most simply described as the elastic modulus in the longitudinal direction of a material. E may be cast in a similar form to that for Ep, as shown in Eq. (2):

$$E = \frac{d}{2h} Ep \quad (2)$$

where h is the wall thickness.

A change in the elastic properties of a body may be due to a change in the quantity of that body, in this case a change in arterial wall thickness, or a change in the quality of that body. The principle elastic components in an arterial wall are collagen and elastin. A change in quality may reflect a change in the relative proportions of the components of an arterial wall or damage to these components. As E is thought to reflect true material stiffness, and is considered independent of wall thickness, a change in E measured in the arterial wall could therefore reflect changes in the composition of the wall, whereas a change in Ep (a measurement of structural stiffness) would suggest a change in the quantity of the arterial wall.

Patients with atherosclerosis have changes in the arterial wall, such as the formation of atherosclerotic plaques together with a varying degree of in situ thrombosis, and fibrosis and calcification of the tunic media. Increased wall thickness is also often demonstrated [5]. PAD is usually a reflection of a systemic atherosclerotic disease [6]. We hypothesise that material stiffness changes at a different rate from structural stiffness in patients with and without PAD.

The aim of this study was to investigate markers of material and structural arterial stiffness (E and Ep) and wall thickness (IMT) in the common carotid arteries (CCA) of human subjects with and without evidence of PAD in order to study which variable changes the most in affected subjects.

2. Methods

2.1. Study design

All subjects recruited into the study provided fully informed written consent. Ethical approval was granted by Birmingham East District Research and Ethics Committee. All subjects completed a questionnaire regarding past medical history and drug evidence.

2.2. Arterial distension waveform capture

This method has been described in detail previously [7], and is in agreement with the standardisation of subject conditions recommended by the Expert consensus document on arterial stiffness [8]. Briefly, all subjects were rested for 5 min prior to measurement, and were placed supine on an adjustable couch, with a pillow under their head to minimise movement. The artery was imaged longitudinally using the L12/5 linear array of an HDI 5000 ultrasound imaging system (Philips Medical Systems, Bothell, USA), and scan-plane alignment was performed using B-mode imaging to ensure that echoes from the intima–media layers were clearly visible. Tissue Doppler imaging (TDI) was enabled and real-time images collected over at least three cardiac cycles were saved to disc. The data was transferred off-line for analysis.

2.3. Arterial diameter and IMT measurement

Internal arterial diameter and far wall IMT were assessed separately for the distal left CCA. IMT and arterial diameter were calculated from the same segment of CCA in the same cineloop as arterial distension waveform (ADW) using an automated edge detection program examining the B-mode image (IMT plug-in, HDI-Lab, Philips Medical Systems, Bothell, WA, USA). This method is well recognised and has been used in previous published research with good reproducibility [9,10]. Mean IMT for the far wall in all frames across all cardiac cycles captured in the cineloop was used, in view of published advice that IMT changes across the cardiac cycle and that measurement of IMT in the far wall as opposed to the near wall is more accurate [5].

2.4. Blood pressure

Three blood pressure measurements in the right brachial artery using a Critikon automatic blood pressure manometer (GE Healthcare, Bucks, UK) were taken before, during and after the time the arterial distension waveform was captured, whilst the patient remained supine.

2.5. Arterial distension waveform analysis and calculation of indices

After transfer of the raw cineloop to the PC, a commercial software analysis package (HDI-Lab, Philips Medical Systems, Bothell, USA) was used to obtain wall distension waveforms from the TDI data. The core feature of this technique is that TDI data provide information on wall velocity as a function of time. Wall distension is then calculated by integration of velocity with respect to time. This is performed for each scan-line of the TDI image, providing some 40 measurements of the distension-time waveform over a 2 cm length of artery. The mean arterial diameter change (MADC) was calculated from all lines in all cardiac cycles in which the arterial diameter change was calculated by measuring the maximum excursion for each line and then taking the mean of all these values. E and Ep were calculated separately using MADC, arterial diameter, IMT and pulse pressure data for the respective carotid artery.

2.6. Subject selection

The elastic properties of CCAs in age- and sex-matched subjects with and without evidence of PAD were compared. Subjects with PAD were recruited from a dedicated nurse led outpatient clinic at the Heart of England NHS Foundation Trust for subjects with non-disabling lower limb claudication, who had opted to have conservative treatment for their symptoms. Their claudication symptoms were stable for at least 6 months. Prospective control

Table 1
Main characteristics of study populations.

	No. of subjects	Age (range)	Male (%)	Systolic BP (95% CI)	Smoking (%)	Hypertension (%)	IHD (%)	CVD (%)	Diabetes (%)
PAD	38	69 (55–85)	32 (84)	154 (106–203)	25 (68)	20 (52)	3 (8)	2 (5)	6 (16)
Control	43	67 (55–82)	33 (77)	154 (110–203)	30 (69)	17 (40)	4 (9)	3 (7)	5 (12)

Key: PAD = peripheral arterial disease; BP = blood pressure; IHD = ischaemic heart disease; CVD = cerebrovascular disease.

Table 2
Concurrent drug therapy for study populations.

	No. of subjects	Statin	Diuretic	Ca antagonist	Nitrate	B-blocker	ACE-I
PAD	38	28 (74)	8 (21)	6 (16)	2 (5)	2 (5)	0 (0)
Control	43	6 (14)	10 (23)	6 (14)	4 (9)	5 (12)	6 (14)

Figure in parentheses is percentage.

population subjects were recruited from non-vascular outpatient clinics at the same hospital. These subjects were attending hospital with non-cardiovascular problems such as herniae, simple skin lesions and benign urological disease. All participants were subject to similar scrutiny in order to determine their vascular status. Subjects were deemed free from PAD if they had an unlimited walking distance and an ankle brachial pressure index (ABPI) greater than 0.9. Similarly all patients with PAD had a confirmed history of lower limb claudication and an ABPI of less than 0.9.

2.7. Statistical analysis

After extraction and collation of the raw data using Microsoft Excel, the data were analysed using Stata 8.1 for Windows (STATA Stata Corporation, College Station, TX, USA) in association with a statistician from the University of Birmingham. Mean values in the case population and the control population were compared using Student's *t*-test after log transformation.

3. Results

We assessed the left common carotid artery (LCCA) in 38 cases with evidence of PAD and 43 healthy controls. Both populations were well matched for age, sex and co-existing risk factors as demonstrated in Table 1. Co-existing medication is listed in Table 2. As can be seen, the PAD group had a higher incidence of statin use than the control group, but otherwise there is no other significant difference in cardiovascular medication between the two groups. Cases with PAD had a significantly increased *E* and *Ep*, diameter and IMT compared to subjects without PAD (Table 3). Interestingly, the increases in indices of stiffness, in particular material stiffness seen in subjects with PAD were higher compared to the increases seen in IMT and diameter. *E* was found to be 86% greater in the PAD group compared to the control group and *Ep* 66% greater. In comparison, diameter was only 20% greater and IMT 12.5% greater. All the results were statistically significant when analysed using Student's *t*-test after log transformation.

4. Discussion

We have shown that arterial diameter, IMT, *E* and *Ep* are significantly increased in subjects with PAD compared to controls without PAD. We are not aware of any study that has compared *E* and *Ep* in subjects with and without PAD. Differences in arterial stiffness between subjects with and without PAD have been shown before [11,12]. Increased carotid IMT has been shown to be a good indicator of generalised atherosclerosis [13], as well as a predictor of cardiovascular events [14–16]. This relationship is presumed to exist as increased carotid IMT represents mainly increased intimal thickening in the elastic carotid artery [13]. Similarly increased CCA diameter has been shown to be a marker of atherosclerotic change [17]. However, increased IMT and diameter may be late markers of atherosclerotic changes in the arterial wall. We demonstrated changes in the elastic properties of the arterial wall which are independent variables [3], and are thought to reflect material as well as structural change. The increase in *E* in the PAD group was mostly due to the increase in *Ep* as the increase in IMT and diameter in that group, as can be seen from Eq. (2), partly balance each other out. Our findings suggest that both *E* and *Ep* increase more than IMT and diameter in subjects with PAD. The change in *E* (86%) was nearly seven times greater than IMT (12.5%) and more than four times greater than diameter (20%) when compared to controls. Similarly, the change in *Ep* (66%) was more than five times greater than IMT (12.5%) and more than three times greater than diameter (20%). Based on this, we believe that markers of arterial stiffness, particularly those indicating material change in the arterial wall (such as *E*) could be a more sensitive index of developing atherosclerosis than structural measurements alone such as change in IMT and diameter, that may even change before IMT does. This is because these indices describe the relationship between stress and strain whereas IMT and diameter report the result of a change in this relationship. There is some evidence in the literature to support this hypothesis. Giannattasio et al. found that increased arterial stiffness, measured as reduced carotid artery distensibility, was present in normotensive mormoglycaemic offspring of type 2 diabetic parents, when compared to a control group [18]. However, there was no change in IMT between the two groups. Further research in this area is urgently required to confirm or refute our hypothesis.

A weakness of our study is that carotid IMT is not a measurement of entire arterial wall thickness and represents the intima and the tunica media of the carotid artery [13]. Both Pignoli and Wong have demonstrated that ultrasonic estimation of IMT was accurate when compared to histological verification, as long as the far wall of the insonated artery was examined, a practice that we have followed. Wong suggest that the adventitial layer contributes 25% of the thickness of carotid arterial walls by histological analysis, but that the adventitial layer is not recognised by ultrasound consistently or accurately [19,20]. Clearly the adventitial layer of an artery has important mechanical properties. In a study of human femoral arteries, Schulze-Bauer et al. estimated that the adventitial layer carried approximately 25% of the arterial wall load [21]. In line with previous studies of this nature we have not attempted to correct for the lack of measurement of the adventitial layer in our estimation of wall thickness [22]. A change in wall thickness of 25% or less would not alter the statistical significance of our results, and it is widely accepted that most structural change in the

Table 3
Wall properties of study populations. Mean values and 95% confidence intervals in brackets. *P* values are calculated with the Student's *t*-test after log transformation.

	No. of subjects	IMT (mm)	Diameter (mm)	*Ep* (kPa)	*E* (kPa)
PAD	38	0.99 (0.92–1.07)	8.35(7.93–8.77)	315 (185–444)	1383 (836–1930)
Control	43	0.88 (0.82–0.93)	6.93(6.65–7.20)	190 (164–216)	744 (641–846)
Increase		12.5%	20%	66%	86%
		$P = 0.020$	$P < 0.001$	$P = 0.034$	$P = 0.006$

IMT = intima–media thickness; *Ep* = elastic modulus; *E* = Young's modulus.

arterial wall in response to ageing and development of atherosclerotic disease are believed to be in the intima and media [23,24]. As demonstrated in Table 2, the PAD group had a higher incidence of statin use than the control group as a result of best medical therapy intended to limit progression of known cardiovascular disease and prevent secondary cardiovascular events. We do not believe that this discrepancy affects the result, as published literature suggests that statin use decreases rather than increases arterial stiffness [25].

In line with other studies of this nature we have used data from the left CCA only. This artery demonstrated superior reproducibility to the right in our reproducibility study [7]. The left CCA is anatomically the most closely related to the aorta arising directly from the aortic arch as opposed to the right CCA which arises indirectly from the aorta via the brachiocephalic trunk. Thus the left CCA is thought to be most likely to reflect the qualities of the central aorta.

5. Conclusion

This study has shown a significant difference in *E* and *Ep*, diameter and IMT in the CCAs of subjects with and without PAD, which suggests that the increased stiffness in subjects with PAD is not just a function of increased wall thickness or diameter, but a change in arterial wall structure as well. The change in indices of arterial stiffness was much greater than the changes in IMT or diameter. We believe that this is because changes in arterial stiffness are an indication of a change in the relationship between strain and stress on the arterial wall, rather than changes in diameter or IMT which are a result of this change. It is possible therefore that atherosclerotic change may be herald at an earlier point by noting a change in arterial stiffness rather than a change in the structure of the arterial wall, and we recommend that prospective research is carried out in this area to confirm or refute this.

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