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Nanomechanics and ultrastructure of the internal mammary artery adventitia in patients with low and high pulse wave velocity

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ABSTRACT

The collagen-rich adventitia is the outermost arterial layer and plays an important biomechanical and physiological role in normal vessel function. While there has been a lot of effort to understand the role of the medial layer on arterial biomechanics, the adventitia has received less attention. In this study, we hypothesized that different ultrastructural and nanomechanical properties would be exhibited in the adventitia of the internal mammary artery (IMA) in patients with a low degree of arterial stiffening as compared to those with a high degree of arterial stiffening. Human IMA biopsies were obtained from a cohort of patients with arterial stiffening assessed via carotid-femoral PWV. Patients were grouped as low PWV (8.5 ± 0.7 ms^{-1}, n = 8) and high PWV (13.4 ± 3.0 ms^{-1}, n = 9). Peakforce QNM atomic force microscopy (AFM) was used to determine the nanomechanical and morphological properties of the IMA. The nano-scale elastic modulus was found to correlate with PWV. We show for the first time that nano-scale alterations in adventitial collagen fibrils in the IMA are evident in patients with high PWV, even though the IMA is not involved in the carotid-femoral pathway. Our approach provides new insight into systemic structure-property changes in the vasculature, and also provides a method of characterizing small biopsy samples to predict the development of arterial stiffening.

Statement of Significance

Arterial stiffening occurs as part of the natural aging process and is strongly linked to cardiovascular risk. Although arterial stiffening is routinely measured *in vivo*, little is known about how localised changes in artery structure and biomechanics contributes to *in vivo* arterial stiffening. This study focusses on the role of the outermost layer of arteries, the adventitia, in arterial stiffening. The study provides data on nano-scale changes in collagen fibril structure and mechanical properties in the adventitia and shows how it relates to *in vivo* stiffness measurements in the vascular system. This is the first study to link *in vivo* arterial stiffening with nanomechanical changes in artery biopsy samples. Hence, this approach could be used to develop new diagnostic methods for vascular disease.
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1. Introduction

Arteries are composite structures composed of three distinct layers, an inner intimal layer composed of endothelial cells, an elastin-rich medial layer and a collagen-rich external adventitial layer. Arteries stiffen as part of the natural aging process and *in vivo* assessment of the arterial stiffening is important for clinical diagnosis. The most commonly used technique is pulse wave velocity (PWV). PWV is based on recording the transit time of blood across two points in the vascular system and is considered a reliable method to determine arterial stiffness in routine clinical assessment [1]. Although PWV is a powerful predictor of risk of morbidity and mortality in a general population [2], it does not capture the intricate and complex structural and biomechanical processes that occur in the aging artery. Stiffness measurements derived from PWV assume that arteries are homogenous conduits,

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due to the inherent assumptions in the Moens-Korteweg equation on which the concept of PWV is based, although they are highly heterogeneous [3].

Arterial stiffening is associated with distinct changes across the individual layers. For example, age-related arterial stiffening is largely attributed to changes in the intima due to atherosclerosis, and degeneration of the media [4]. Furthermore, within these layers, alterations can be localized to individual components at the nano- and micro- scale [5,6]. Hence, to understand the mechanisms driving arterial stiffening, the nano-structure and mechanical properties of individual layers within the artery need to be considered.

Most studies which are concerned with vascular pathology or aging have focused on the intima and medial layers of the artery whilst the adventitia has received less attention [7]. The medial layer has an important biomechanical role because during circumferential tension it bears approximately 60% of the load [8]. However, the mechanical role of the adventitia in normal arterial function cannot be ignored. The adventitia is dominated by circumferentially arranged, wavy collagen fibrils [8]. Due to its high collagen content, the adventitia is the stiffest layer of the artery and is thought to bear around 75% of the load during longitudinal tension [8,9]. It becomes the mechanically dominant layer during high pressure loading [7]. The adventitia has also been found to exhibit differing nanomechanical and viscoelastic responses in different arteries, which is related to their *in vivo* physiological environment [10]. The adventitia is not only an important structural and load-bearing layer of arteries, it also plays an important physiological role in several vascular processes including atherosclerosis [11] and pulmonary hypertension [12]. The adventitia also has properties of a stem/progenitor cell niche [13]. It has been hypothesised that the adventitia may have an important role in the aging process due to a loss of function of niche-dependent signalling [13].

Here, we have employed an atomic force microscopy (AFM) method, PeakForce Quantitative Nanomechanical Property Mapping (PFQNM) [14] to investigate nano-scale properties of the adventitia in the human internal mammary artery (IMA). PFQNM enables the co-localisation of ultrastructural and mechanical properties with a high resolution. We have previously shown that this technique allows detection of regional variations in the nanomechanical properties of collagen-rich tissue [15]. In this study, we present both nanomechanical and ultrastructural data from the adventitia in a group of patients with known low or high PWV. The IMA can be collected during coronary by-pass operations and has already been established as a suitable model artery for generalized nonatherosclerotic arterial investigations because its matrix composition and biochemistry reflect alterations that occur in both the coronary and carotid arteries [16–18]. We also relate our data to the expression of small leucine-rich proteoglycans (SLRPs) which are involved in collagen fibril formation and have recently been found to be molecular targets for arterial stiffening [19]. Our fundamental study offers new insight into how nano-scale changes in the adventitia are manifested in patients with a high degree of arterial stiffening. A number of studies have previously examined the specific contribution of the adventitia to the overall biomechanical properties of arteries [7,20,21]. However, to the best of our knowledge, there have been no previous studies which have studied the contribution of the adventitia in relation to high PWV in humans. Furthermore, there are still very limited studies on the mechanical properties of the adventitia at the nano-level [10].

2. Materials and methods

2.1. Clinical characterization

The left internal mammary artery (IMA) was collected from 17 patients during coronary artery bypass grafting (CABG) operations and provided by the Centre of Individualized Medicine in Arterial Diseases (CIMA) (Odense University Hospital, Odense, Denmark), as part of a project approved by the Local Ethical Committee in Region Southern Denmark (S-2010044). The IMA is the repair artery for CABG operations. This study has made use of non-utilised IMA after the surgical procedure.

Prior to CABG, patients were assessed by carotid-femoral pulse wave velocity (PWV) by using the Sphygmocor system under standardized conditions as previously described in [19]. Clinical data, including age, gender, BMI, diabetes and hypertension were recorded before the surgery. The included patients were taken from a larger cohort [19] to form two groups; low PWV ($8.5 \pm 0.7\ ms^{-1}$, n = 8 patients) and high PWV ($13.4 \pm 3.0\ ms^{-1}$, n = 9 patients), as summarized in Table 1. The categorization of these patients as having 'low' and 'high' PWV are based on accepted reference and normal values for carotid-femoral PWV [22].

2.2. Peakforce Quantitative nanomechanical Mapping (PFQNM) Atomic force microscopy (AFM)

Immediately after surgery the IMA vessels were embedded in optimal cutting temperature (OCT) compound (Tissue-Tek Sakura

Table 1
Clinical parameters for IMA biopsy donors for the low (n = 8) and high PWV groups (n = 9). Mean and standard deviation (SD) or percentages are provided for each parameter. Student's *T*-test was conducted for statistical analysis of the data. Abbreviations: BMI, body mass index; PWV, pulse wave velocity; HDL, high-density lipoprotein; LDL, low-density lipoprotein;. NS, not significant. Additional data on smoking history is provided in the Supplementary Material, Fig. S3.

Clinical parameters	Low PWV		High PWV		*P* Value
	Mean	SD	Mean	SD	
Age, y	67.9	10.7	69.9	7	NS
BMI	26.5	4.7	28.4	4.6	NS
PWV, ms^{-1}	8.5	0.7	13.4	3	<0.001
Systolic blood pressure, mm Hg	131.3	18.7	154.1	28.6	NS
Diastolic blood pressure, mm Hg	77	10.7	79.4	12.3	NS
Male, sex, %	87.5		100		NS
Diabetes, %	12.5		0		NS
Hypertension, %	50		66.7		NS
Smoking, %	62.5		88.9		NS
Total cholesterol, $mmolL^{-1}$	4.1	0.5	4.9	1.5	NS
P-Cholesterol LDL, $mmolL^{-1}$	2.1	0.5	3.1	1.3	NS
P-Cholesterol HDL, $mmolL^{-1}$	1.2	0.1	1.1	0.3	NS
P-Triglyceride, $mmolL^{-1}$	1.6	0.6	1.6	0.5	NS
P-creatinin, $mmolL^{-1}$	89.8	19.9	91.6	20.4	NS
HbA1c (glycated haemoglobin (A1c)	0.06	0.007	0.06	0.002	NS

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