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Review article

A systematic literature review of the effect of carotid atherosclerosis on local vessel stiffness and elasticity

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ABSTRACT

Objective: This systematic literature review sought to determine the effects of carotid atherosclerotic plaque on local arterial stiffness.
Methods: MedLine, EMBASE, and grey literature were searched with the following term: ("atherosclerosis" or "carotid atherosclerosis" or "carotid artery disease" or "carotid plaque") AND ("distensibility" or "elasticity" or "stiffness" or "compliance") NOT ("pulse wave velocity" or "PWV" or "carotid-ankle" or "ankle-brachial" or "augmentation index" or "cardio-ankle" or "CAVI" or "flow mediated dilation" or "FMD"). Results were restricted to English language articles reporting local arterial stiffness in human subjects with carotid atherosclerosis.
Results: Of the 1466 search results, 1085 abstracts were screened and 191 full-text articles were reviewed for relevance. The results of the 50 studies that assessed some measure of carotid arterial elasticity or stiffness in patients with carotid plaque were synthesized and reviewed.
Discussion: A number of different measures of carotid elasticity were found in the literature. Regardless of which metric was used, the majority of studies found increased carotid stiffness (or decreased distensibility) to be associated with carotid plaque presence, the degree of atherosclerosis, and incident stroke.
Conclusion: Carotid artery mechanics are influenced by the presence of atherosclerotic plaque. The clinical applicability of carotid elasticity measures may be limited by the lack of reference values and standardized techniques.

1. Introduction

The elastic nature of large- and medium-sized arteries is a critical factor in determining overall cardiovascular health [1–4]. These arteries dampen flow pulsatility and generate a steady flow of blood at the capillary level by reflecting the pulsed waves of blood from the heart [5,6]. Diminished arterial elasticity results in reduced pulse wave reflection and can have adverse effects on cardiovascular health, such as increased pulse pressure and left ventricular hypertrophy [6,7]. Arteries are known to stiffen in healthy aging [8,9] and with atherosclerosis, diabetes, hypertension and obesity [10–13]. In addition, decreases in arterial distensibility near the carotid bifurcation, are associated with carotid atherosclerosis [14] and increased incidence of cerebrovascular events [15]. Atherosclerosis, characterized by the accumulation of plaque within vessel wall, alters both the structure and function of arteries, increasing vessel wall stiffness. It has also been proposed that changes in carotid elasticity further promote both plaque development and rupture [16]. While some imaging studies have employed carotid elasticity as a primary outcome [17], their clinical applicability is limited by a lack of standardized techniques and reference values in atherosclerotic arteries. We undertook a systematic literature review to determine the reported effects of carotid atherosclerosis on local vessel wall elasticity and stiffness measures derived from ultrasound (US) and magnetic resonance (MR) imaging.

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1.1. Structure and mechanics of blood vessels

Larger blood vessels are made up of three concentric layers: the intima, media, and adventitia (Fig. 1 inset). The innermost layer of a vessel wall, the intima, is comprised of a single layer of endothelial cells and is bounded on the outside by a layer of elastic tissue called the internal elastic lamina. The medial layer of an artery is made up of smooth muscle cells, collagen, small elastic fibers, and is bounded on the outside by the outer elastic lamina. The intima-media connection provides both stretch and strength to the artery through the presence of elastin and collagen. A fatty streak, the first visible manifestation of an atherosclerotic lesion (Fig. 1), consists of isolated macrophage foam cells containing lipid droplets. As extracellular lipids accumulate, they form lipid pools within the intima, disrupting the cellular structure of the artery, breaking elastic fibers and causing thickening of the vessel wall. In response to this intimal disorganization, some lesions develop new connective fibrous tissue – the so-called 'fibrous cap' of an atherosclerotic plaque. Local wall thickening has been associated with altered hemodynamic and mechanical conditions of the artery, in that intimal thickening may represent an adaptive response to maintain normal values of both shear and tensile stresses [18]. The most common locations for such adaptive thickening are regions of disrupted blood flow and/or decreasing vessel diameter [19]. As such, the carotid bifurcation is a common site of atherosclerosis and poses a significant risk for incident cerebrovascular events.

Though the degree of stenosis has long been regarded as defining plaque severity, the notion of a vulnerable plaque based on its composition has recently gained clinical traction. Lesions with large lipid pools and thin fibrous caps are regarded as likely to rupture, resulting in clot-promoting materials being exposed to the lumen [20]. In addition to the morphological evaluation of plaques, the effects of arterial wall mechanics have also been studied with respect to lesion vulnerability and stroke risk [16]. Computational models of plaque within an elastic artery emphasize that stress concentrations occur in regions of mismatched elasticity, for example, where the fibrous cap meets a normal vessel wall [21]. Histological [21,22] and MR-based 3D fluid–structure interaction models [23] confirm that the majority of plaques rupture in these regions of high structural stresses.

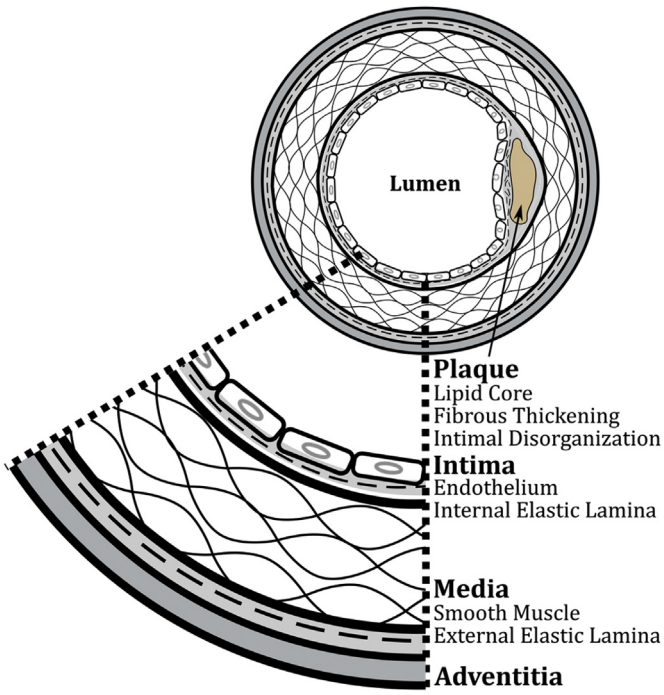

Fig. 1. Cross-sectional schematic of a vessel wall showing the three concentric layers of a healthy artery: the intima (containing the endothelium and internal elastic lamina), the media (containing smooth muscle and external elastic lamina), and the adventitia. An atherosclerotic plaque with lipid core and fibrous thickening in the intimal layer is also shown.

While global measures of arterial resistance, such as pulse wave velocity and ankle-brachial index, are popular methods for determining vessel stiffness, there are a number of measures to indicate the local elasticity of an artery [24,25]. Specifically, the local elasticity of the carotid artery, particularly in association with cardiovascular risk factors, has been investigated using a variety of modalities and measurements.

1.2. Measures of local carotid elasticity

The elasticity, distensibility or stiffness of the carotid artery can be quantified using many different parameters, all employing some measure of the systolic-diastolic diameter or area change (by either US or MR). The most common measures found in the literature are summarized in Table 1, with an indication of their interrelation [26]. Fig. 2 defines the key relevant carotid measurements employed in the calculation of the stiffness and elasticity parameters listed in Table 1. The most basic of these measures is absolute distension – simply systolic minus diastolic diameter. Normalizing this value to the diastolic diameter produces the oft-reported strain (typically reported as a percentage of diastolic diameter). One factor affecting vessel compliance that this normalized value does not account for, is the blood pressure exerted on the artery. Peterson's pressure-strain elastic modulus (E_p), Young's elastic modulus (YEM), distensibility (D) and distensibility coefficient (DC) all normalize the change in carotid cross-sectional area or diameter by pulse pressure ($\Delta P = P_s - P_d$, where P_s and P_d are systolic and diastolic blood pressure, respectively). The unit-less beta stiffness index, for which increasing values indicate stiffer arteries, accounts for the effect of blood pressure by taking the natural logarithm of the systolic to diastolic blood pressure ratio and dividing by the strain.

All of the parameters summarized in Table 1 have been used to report carotid elasticity or stiffness in healthy, aging and diseased populations. This range of modalities, parameters and units used to express carotid elasticity or stiffness makes it challenging, if not impossible, to compare results between these studies. If any of these parameters are to be truly useful in a clinical environment for the evaluation of cardiovascular and stroke risk, a standardization of methods and measures is needed. We undertook a systematic literature review to (a) explore the effect of carotid plaque on local vessel stiffness and elasticity, and (b) describe the reported values for each elastic index. Given the wide range of indices used to report vessel elasticity, we did not attempt to synthesize the data or perform a meta-analysis of the literature.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was adopted for this literature review [27]. Two databases (MedLine and EMBASE) were searched with the following search term: ("atherosclerosis" or "carotid atherosclerosis" or "carotid artery disease" or "carotid plaque") AND ("distensibility" or "elasticity" or "stiffness" or "compliance") NOT ("pulse wave velocity" or "PWV" or "carotid-ankle" or "ankle-brachial" or "augmentation index" or "cardio-ankle" or "CAVI (cardio-ankle vascular index)" or "flow mediated dilation" or "FMD"). This search term returned studies of atherosclerosis and carotid plaques that mention vessel wall stiffness or