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The perivascular environment along the vertebral artery governs segment-specific structural and mechanical properties

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ABSTRACT

The vertebral arteries (VAs) are anatomically divided into four segments (V_1-V_4), which cumulatively transport blood flow through neck and ultimately form the posterior circulation of the brain. The vital physiological function of these conduit vessels depends on their geometry, composition and mechanical properties, all of which may vary among the defined arterial segments. Despite their significant role in blood circulation and susceptibility to injury, few studies have focused on characterizing the mechanical properties of VAs, and none have investigated the potential for segmental variation that could arise due to distinct perivascular environments. In this study, we compare the passive mechanical response of the central, juxtaposed arterial segments of porcine VAs (V_2 and V_3) via inflation-extension mechanical testing. Obtained experimental data and histological measures of arterial wall composition were used to adjust parameters of structure-motivated constitutive models that quantify the passive mechanical properties of each arterial segment and enable prediction of wall stress distributions under physiologic loads and boundary conditions. Our findings reveal significant segmental differences in the arterial wall geometry and structure. Nevertheless, similar wall stress distributions are predicted in these neighboring arterial segments if calculations account for their specific perivascular environments. These findings allow speculation that segmental differences in wall structure and geometry are a consequence of a previously introduced principle of optimal operation of arteries, which ensures effective bearing of physiological load and a favorable mechanical environment for mechanosensitive vascular smooth muscle cells.

Statement of Significance

Among the numerous biomechanical investigations devoted to conduit blood vessels, only a few deal with vertebral arteries. While these studies provide useful information that describes the vessel mechanical response, they do not enable identification of a constitutive formulation of the mechanical properties of the vessel wall. This is an important distinction, as a constitutive material model is required to calculate the local stress environment of mechanosensitive vascular cells and fully understand the mechanical implications of both vascular injury and clinical intervention. Moreover, segmental differences in the mechanical properties of the vertebral arteries could be used to discriminate among distinct modes of injury and disease etiologies.

1. Introduction

The vertebral artery (VA) is a conduit vessel that directs blood flow cranially through the neck, and is anatomically divided into four arterial segments along its course (V_1-V_4). The first arterial segment (V_1) extends from its origin at the subclavian artery to

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the C6 transverse process. The second arterial segment (V_2) comprises the intraosseous course from the C6 to C2 vertebrae through the transverse foramina. The third arterial segment (V_3) takes an extraosseous course from the C2 transverse process until entry into the dura mater at the foramen magnum. And finally, the fourth arterial segment (V_4) is the intradural portion from the foramen magnum until the two VAs merge to form the basilar artery. Essentially, V_1 is at the transition from the thorax to the neck, V_2 and V_3 course through the neck (and are therefore the most vulnerable to trauma) and V_4 is the final portion of the artery within the skull before it merges to form the basilar artery [1,2].

In the event of a blunt cervical spine trauma, arterial injury occurs in 30% of patients, with the most injury sustained by the vertebral and carotid arteries. Injuries to the VA present as dissections, pseudoaneurysms, and arterial occlusions [3,4]. Studies show that 18% of injuries involve the V_1 arterial segment, 67% involve the V_2 (intraosseous) arterial segment, 31% involve V_3 arterial segment, and 6% the V_4 arterial segment [5]. All VA injuries can lead to a delayed onset of vascular occlusion, with potentially devastating consequences that include posterior cerebral bleeding or irreversible ischemic tissue damage [6]. For example, in the cases where delayed presentation of vertebrobasilar ischemia from posterior circulation occurs, reported mortality rates range from 75% to 86% [7].

Treatment modalities for VA injuries include antiplatelet and anticoagulation therapies, open surgical repair, and endovascular approaches [5]. In the cases of enlarging pseudoaneurysms or symptomatic dissections, endovascular stent therapy is the most common intervention with consistent and acceptable clinical outcomes [8]. Additional endovascular interventions including microcatheters, balloons, glues, and coils have shown utility and promise in a subset of injuries and disease states [9–11]. Given the rates and varied clinical outcomes of these injuries and the established interplay between most interventional modalities and the mechanical behavior of the compromised vessels, there is a clear need to characterize the mechanical properties of VAs [8,10,12].

Comprehensive mechanical characterization of the VAs likely requires arterial segment-specific characterization of vessel wall geometry, composition, and mechanical properties. The V_2 and V_3 arterial segments are of particularly high clinical relevance, as they are implicated in an overwhelming majority of VA injuries (over 90%) following blunt cervical trauma [5]. Moreover, the transition from the V_2 to V_3 arterial segment is anatomically coupled with a distinct change in the perivascular environment. That is, the V_2 arterial segment is embedded within the bone (intraosseous) and thus possibly subjected to restricted deformation while the V_3 arterial segment exists outside the bone (extraosseous). We posit that understanding and differentiating the arterial segmental mechanical behavior of the VA can provide guidelines to evaluate predisposing factors for delayed and sudden occurrence of complications in high grade injuries and design site-specific protocols for endovascular interventions.

Among the numerous biomechanical investigations devoted to conduit blood vessels, only a few deal with VAs [12–16]. While these studies provide useful information that describes the vessel mechanical response, they do not enable development of a constitutive formulation of the mechanical properties of the vessel wall. This is an important distinction, as a constitutive material model is required to calculate the local stress environment of mechanosensitive vascular cells and fully understand the mechanical implications of both vascular injury and clinical intervention. Moreover, segmental differences in the mechanical properties of the VA could be used to discriminate among distinct modes of injury and disease etiologies. The objectives of this study are two-fold. First, an integrated experimental-theoretical approach was applied to quantify the passive mechanical response of the porcine V_2 and V_3 arterial segments. Obtained data were then processed to yield a structure-motivated constitutive model of the arterial tissue and enable segmental comparisons in wall geometry, composition, and mechanical properties. Second, a comparative analysis of the stress distribution across the arterial wall was performed between these arterial segments, and the results obtained were interpreted in the framework of a previously elaborated principle of optimal mechanical operation [17].

2. Materials and methods

2.1. Vessel isolation

Whole porcine spines were purchased from a local slaughterhouse immediately after sacrifice of adult animals (8–12 month old, 75–125 lbs, male American Yorkshire Pigs), cooled on ice, and transported immediately to the laboratory. The transverse canal was approached both ventrolaterally and from the vertebral canal using an autopsy saw (Stryker Model 810) to cut within 3–5 mm of the canal. The transverse canal was fully accessed using chisels, bone cutters, and rongeurs. The vessels were then removed using scissors and scalpels to dissect minor arteries and connective tissue. Care was taken to neither nick the VA nor stretch it beyond its anatomical length. The experimental sample set includes 5 caudal VAs embedded in the bone from C2–C6 (V_2 arterial segment) and 5 cranial VAs (V_3 arterial segment) (Fig. 1). Excised vessels were rinsed and submerged in phosphate buffer solution and cooled in ice until the initiation of mechanical testing. No more than three hours passed from the time of animal sacrifice to the initiation of mechanical testing.

2.2. Zero-stress configuration

The zero-stress configuration of each vessel was obtained by introducing a radial cut into a ring-shape sample (1 mm thick), and was considered to be a circular sector. The zero-stress configuration was quantified by measuring the inner and outer arc lengths (L_i and L_o) and the thickness (H) of the idealized sector via analytical microscopy (Image-Pro 6.0).

The opening angle (Φ) and cross-sectional area (A) of the sector were then calculated as [18]:

$$\Phi = \pi - \frac{L_o - L_i}{2H}, \quad A = \frac{(L_o + L_i)H}{2} \tag{1}$$

2.3. Mechanical testing

The sample was cannulated via sterile suture and mounted within a chambered mechanical testing system (Bose BioDynamic 5270, Eden Prairie, MN) configured for an inflation-extension test. The sample was submerged in and perfused with continuously aerated (95% O_2 + 5% CO_2) Krebs-Henseleit solution at 37 °C and pH of 7.4. The passive mechanical response was assessed under a fully relaxed smooth muscle cell state, which was induced by flushing the circulating medium with a 10^{-5} M sodium nitroprusside solution and allowing 15 min for acclimation [19]. To initiate mechanical testing, each sample was mechanically preconditioned via repeated inflation (internal pressure of 20–200 mmHg) at an intermediate degree of axial stretch (axial stretch ratio of 1.3). The in vivo axial stretch ratio of each vessel was estimated using a series of inflation-extension tests in which the sample was inflated (internal pressure of 20–200 mmHg) at constant axial stretch ratios between 1.1 and 1.5. The in vivo axial stretch ratio was taken to be the axial stretch ratio under which the axial force remained approximately constant during the inflation-deflation process [20,21]. Samples were then maintained at the identified in vivo