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Controlled peel testing of a model tissue for diseased aorta

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ABSTRACT

In this study, we examine the effect of collagenase, elastase and glutaraldehyde treatments on the response of porcine aorta to controlled peel testing. Specifically, the effects on the tissue's resistance to dissection, as quantified by critical energy release rate, are investigated. We further explore the utility of these treatments in creating model tissues whose properties emulate those of certain diseased tissues. Such model tissues would find application in, for example, development and physical testing of new endovascular devices. Controlled peel testing of fresh and treated aortic specimens was performed with a tensile testing apparatus. The resulting reaction force profiles and critical energy release rates were compared across sample classes. It was found that collagenase digestion significantly decreases resistance to peeling, elastase digestion has almost no effect, and glutaraldehyde significantly increases resistance. The implications of these findings for understanding mechanisms of disease-associated biomechanical changes, and for the creation of model tissues that emulate these changes are explored.

1. Introduction

Arterial dissection refers to separation of the inner layers of the arterial wall. This is almost always initiated by trauma, either directly to the vessel wall, e.g. a catheter piercing or tearing the intimal layer of the vessel during an endovascular procedure (Mamas et al., 2008), or indirectly via external trauma, for instance from motor vehicle crashes (Srivastava et al., 2008). Depending on the direction of blood flow, the circulatory pressure will either press the tissue flap to the wall or act to propagate the dissection (Fig. 1). The former often results in the dissection remaining benign, whereas the latter can eventually progress to create a large tissue flap that blocks downstream blood flow in the true lumen and encourages flow into the newly formed false lumen between the flap and remaining artery wall. In large arteries this is often fatal: mortality rates for aortic dissections are reported to be 50% (Anagnostopoulos et al., 1972).

The increasing use of endovascular treatment methods renders desirable the development of new medical devices such as endovascular catheters. Research in this area requires access to large supplies of arterial tissue - preferably diseased, to reflect the state of real patient tissues - for physical testing of designs. But, accessing human diseased tissue is costly and has numerous ethical and legal implications. Recently, we proposed porcine arterial tissue, processed with a suitable combination of enzyme solutions, as a model of diseased human tissues for use in such developments (Noble et al., 2016). Various enzymatic treatments were explored as a means of emulating the effects of diseases on the mechanical properties. Correspondingly, the effects of collagenase, elastase and glutaraldehyde treatments on the uniaxial elastic and failure behaviour of arterial tissues were investigated. In the present work, we expand on those results by investigating the effects of these treatments on dissection resistance. More specifically, we compare the mode 1 critical energy release rate (G_c), as a measure of the strength of the tissues, before and after treatment with each of the mentioned solutions. The cheapness and ready availability of porcine arterial tissue (often considered a waste product in meat preparation), and avoidance of aforementioned ethical issues, suggests tissue models produced in this way can ameliorate the cost and complexity of medical device design.

The media of the arterial wall is most prone to dissection, as a result of its organisation into lamella units, stacked on top of one another (Wolinsky and Glagov, 1967). These lamellae are primarily composed of fibres of rubber-like elastin and stiffer collagen, and smooth muscle cells. These constituents, moreover, are oriented predominantly within planes tangential to the vessel axis, and with a bias towards circumferential directions over axial (Clark and Glagov,

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1985). This organisation in turn imparts the highest mechanical strength in circumferential directions, somewhat lower strength in axial directions, and significantly lower strength in radial directions (Schriefl et al., 2012; MacLean et al., 1999). This can be seen in Fig. 2.

Various diseases are associated with higher susceptibility to arterial dissection. For individuals with Marfan's syndrome the most common cardiovascular complication is enlargement of the ascending aorta, often leading to aortic dissection (Milewicz et al., 2005). This is caused by a mutation to the fibrillin-1 glycoprotein which in turn affects elastin protein structure in the thoracic aorta, resulting in a weakened arterial wall (Wityk et al., 2002). A further disease linked to increased dissection incidence is Ehlers-Danlos syndrome, which is associated with a mutation in the gene coding for collagen III. This again leads to weakened arterial walls, with rupture or dissection the most common form of death (Ulbricht et al., 2004; Goldfinger et al., 2014). It was also speculated that low collagen content related to post-partum hormonal imbalance is associated with instances of arterial dissection (Bonnet et al., 1986). Additionally many cases of dissection accompany aneurysm formation and this is again linked to a change in the structure of both elastin and collagen (Adams et al., 1982; He and Roach, 1994; de Figueiredo Borges et al., 2008). Finally, there is also experimental evidence for diminution of vessel strength (specifically, aorta) associated with these diseases, which could explain this higher susceptibility (Sommer et al., 2016, 2008).

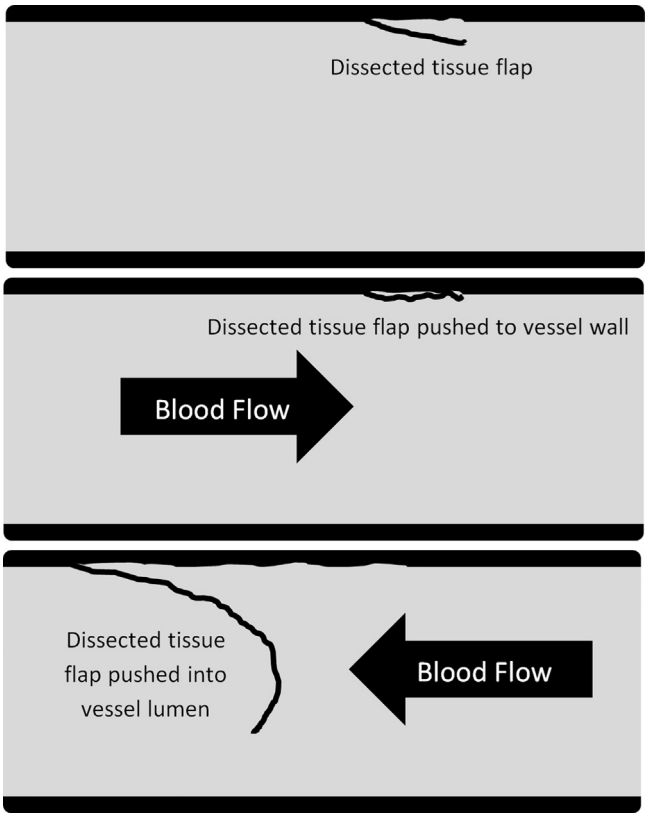

Fig. 1. Schematic detailing dissection becoming benign or propagating depending on blood flow direction. Top, initial dissection with tissue flap extending in to vessel lumen. Middle, tissue flap pushed back onto vessel wall by blood flow. Bottom, further tissue peeled from vessel wall by blood pressure, with the tissue flap now obscuring a large portion of the vessel lumen.

Enzyme digestion has been utilised previously to alter arterial mechanical properties. Treatment with collagenase or elastase was applied to reduce or remove the respective proteins, and the resulting changes in mechanical response were investigated via uniaxial, biaxial or inflation testing (Kochová et al., 2012; Weisbecker et al., 2013; Gundiah et al., 2013). However, little investigation of the effects on failure behaviour of the tissues, such as during dissection, has been performed. Those studies that have been performed were concerned with tensile failure modes (Dadgar et al., 1997; Noble et al., 2016). In contrast, characterisation of dissection properties in *untreated* tissue has been well investigated. Dissection propagation was first investigated by infusing liquid into the media to mimic the process of blood flow initiating and propagating a dissection (Hirst and Johns, 1962; Roach and Song, 1994; Carson and Roach, 1990). Later, Sommer et al. performed controlled peeling of the aortic media and recorded the force displacement behaviour (Sommer et al., 2008). This method has been used with tissue from complex sites like bifurcations (Tong et al., 2011), and with diseased human thoracic aortic and abdominal aortic aneurysms (Tong et al., 2014; Pasta et al., 2012).

Controlled peeling in this way clearly represents a simplification of in vivo loading regimes, and it could be argued that liquid infusion experiments more closely resemble blood flow-driven dissection, at least. In the latter configuration, while the separation of vessel layers would remain predominantly mode 1 (Fig. 3), there is likely an ambiguous mixture of rupture modes involved in any particular experiment. It is correspondingly difficult to extract meaningful and repeatable measures of tissue strength by this means. Peeling, by contrast, involves pure mode 1 rupture, and the physical meaning of the derived energy release rate G_c is correspondingly clear. The rupture process, being driven by displacements of opposing tissue flaps, is also easier to control, further improving repeatability. Therefore, as a means of quantifying resistance to dissection (i.e. separation of tissue layers), and of reliably assessing the effect on this of the different treatments, peeling tests were adopted in this work.

The remainder of the paper is structured as follows: in Section 2, the preparation of tissue samples, and the mechanical testing procedures are described; in Section 3, experimental results are summarised; and

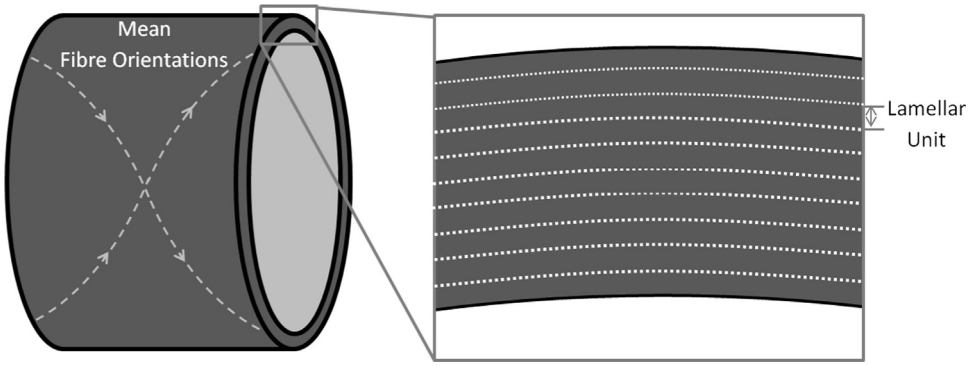

Fig. 2. Idealised representation of the organisation of the aortic media. Families of fibres are oriented predominately into helices around the vessel wall, as shown on the left, with mean orientations closer to circumferential, rather than axial direction. The lamellae are stacked upon one another with interconnecting fibres providing some radial resistance.