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The influence of composition and location on the toughness of human atherosclerotic femoral plaque tissue

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ABSTRACT

The toughness of femoral atherosclerotic tissue is of pivotal importance to understanding the mechanism of luminal expansion during cutting balloon angioplasty (CBA) in the peripheral vessels. Furthermore, the ability to relate this parameter to plaque composition, pathological inclusions and location within the femoral vessels would allow for the improvement of existing CBA technology and for the stratification of patient treatment based on the predicted fracture response of the plaque tissue to CBA. Such information may lead to a reduction in clinically observed complications, an improvement in trial results and an increased adoption of the CBA technique to reduce vessel trauma and further endovascular treatment uptake.

This study characterises the toughness of atherosclerotic plaque extracted from the femoral arteries of ten patients using a lubricated guillotine cutting test to determine the critical energy release rate. This information is related to the location that the plaque section was removed from within the femoral vessels and the composition of the plaque tissue, determined using Fourier Transform InfraRed spectroscopy, to establish the influence of location and composition on the toughness of the plaque tissue. Scanning electron microscopy (SEM) is employed to examine the fracture surfaces of the sections to determine the contribution of tissue morphology to toughness.

Toughness results exhibit large inter and intra patient and location variance with values ranging far above and below the toughness of healthy porcine arterial tissue (Range: 1330–3035 for location and 140–4560 J/m^2 for patients). No significant difference in mean toughness is observed between patients or location. However, the composition parameter representing the calcified tissue content of the plaque correlates significantly with sample toughness ($r = 0.949$, $p < 0.001$). SEM reveals the presence of large calcified regions in the toughest sections that are absent from the least tough sections. Regression analysis highlights the potential of employing the calcified tissue content of the plaque as a preoperative tool for predicting the fracture response of a target lesion to CBA ($R^2 = 0.885$, $p < 0.001$).

Statement of Significance

This study addresses a gap in current knowledge regarding the influence of plaque location, composition and morphology on the toughness of human femoral plaque tissue. Such information is of great importance to the continued improvement of endovascular treatments, particularly cutting balloon angioplasty (CBA), which require experimentally derived data as a framework for assessing clinical cases and advancing medical devices. This study identifies that femoral plaque tissue exhibits large inter and intra patient and location variance regarding tissue toughness. Increasing calcified plaque content is demonstrated to correlate significantly with increasing toughness. This highlights the potential for predicting target lesion

Abbreviations: PTA, Percutaneous Transluminal Angioplasty; BR, bifurcation region; CBA, cutting balloon angioplasty; CFA, common femoral artery; DFA, deep femoral artery; FTIR, Fourier transform infrared; SEM, scanning electron microscopy; SFA, superficial femoral artery; Ca:Tot, ratio of calcification to total measurable plaque content; Col:Tot, ratio of collagen to total measurable plaque content; Lip:Tot, ratio of lipid to total measurable plaque content; EDX, energy-dispersive X-ray; Ca:P, calcium to phosphorus ratio.

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toughness which may lead to an increased adoption of the CBA technique and also further the uptake of endovascular treatment.

1. Introduction

The femoral arteries are one of the most susceptible vascular locations for the development of atherosclerosis. The occurrence of this disease process in these vessels is the leading cause of lifestyle-limiting claudication and ischemic rest pain [1]. Common femoral endarterectomy has been the standard treatment for focal occlusive disease of the femoral arteries for over 50 years [2]. Numerous studies have examined the 5 year patency rates of this procedure and found them to range between 68% and 94% [3–5]. Further data examining the effectiveness of this procedure have suggested that it should remain the standard of care for atherosclerosis of the femoral arteries due to its safety and efficacy. However, despite the proven efficacy of this treatment modality, morbidity rates remain high (10–20%) due to its invasive nature and certain groups of patients are considered high risk for surgery [6,7].

The use of percutaneous transluminal angioplasty (PTA) has been advocated as a treatment alternative for patients at higher risk of surgical morbidity and mortality [7]. Despite this, the long term results for PTA in the femoral arteries are disappointing due to uncontrolled dissections in complex lesions, inadequate luminal expansion in rigid strictures and recurrent stenosis in the dilated segment [8–11]. PTA has also been shown to cause significant trauma to the plaque tissue [12] and stretching to the vessel wall [13]. This has been suggested as a major contributor to constrictive vascular remodelling and neointimal hyperplasia which are directly associated with restenosis [14]. Stent implantation for the treatment of femoral arterial lesions does address the issues of elastic recoil, residual stenosis, and flow-limiting dissection that are typically associated with PTA. This is achieved by the stent acting as a permanent implant therefore supporting the tissue. However, it does not substantially improve primary patency [15–17] due to exaggerated neointimal hyperplasia that leads to in-stent restenosis in 20–40% of patients at 2 years [18,19].

Drug eluting stents have been employed in the femoral arteries to address the issue of in-stent restenosis by delivering an anti-restenotic drug to the treated area. This approach has been shown to offer improved patency rates compared to PTA in the Zilver PTX trial [20]. However, drug eluting stents have failed to demonstrate a significant reduction in restenosis when compared to traditional stents in the SIROCCO I and II trials [19]. Furthermore, microfriction due to stent movement remains an issue after complete elution of the loaded drug. This can lead to vessel irritation, inflammation and ultimately restenosis [21].

Cutting balloon angioplasty (CBA) has been developed to alleviate the injury response observed following endovascular treatment using existing minimally invasive devices. The cutting balloon is a non-compliant balloon with 3–4 radially positioned microblades that incise the plaque and propagate a controlled fracture thereby reducing elastic recoil, vessel dilation, vessel injury, and subsequent restenosis compared with PTA [22–24]. Relatively low balloon pressures are recommended for use with CBA (4–8 atmospheres) that dilate the target vessel with reduced force to potentially decrease the risk of a neoproliferative response and restenosis. Numerous studies have demonstrated the safety and efficacy of CBA [24–29] and several reports highlight the possibility of CBA application in the peripheral arteries due to the relatively low restenosis rates observed during short-term follow-up [30–34] with one randomised controlled trial recently demonstrating the superiority of CBA over PTA [35]. The potential of CBA is based on a decrease in inflammatory response [36], a decrease in proliferative response [37], and an increase in plaque reduction with accompanying decrease in vessel stretch following CBA compared with PTA [13].

Despite these promising findings, a number of studies have observed low effectiveness of this method [38,39] and two randomised controlled trials failed to demonstrate the superiority of CBA over PTA in both coronary and peripheral arteries [38,40]. Various complications related to CBA have also been reported including arterial rupture, delayed perforation, and fracture of microsurgical blades [41–43]. Arterial injury response to endovascular treatment varies significantly with plaque composition [44–46] and it has been previously stated that the mechanisms of CBA affected by plaque composition need to be clarified [47]. While the mechanical response of femoral plaque tissue to circumferential stretch has recently been characterised [48,49], the toughness of this tissue remains unknown. Toughness measures the ability of a material to absorb energy prior to fracturing. This parameter is of pivotal importance to understanding the mechanism of luminal expansion during CBA. Furthermore, the ability to relate this parameter to plaque composition and pathological inclusions would allow for the improvement of existing CBA technology and for the stratification of patient treatment based on the predicted fracture response of the plaque tissue to CBA. Such information may lead to a reduction in clinically observed complications, an improvement in trial results and an increased adoption of the CBA technique to reduce vessel trauma and further endovascular treatment uptake.

This study therefore characterises the toughness of atherosclerotic human tissue extracted from the femoral arteries using a lubricated guillotine cutting test to determine the critical energy release rate, a measure of toughness. This information is then related to the location that the plaque section was removed from within the femoral vessels, the composition of the plaque tissue as determined using Fourier Transform InfraRed (FTIR) spectroscopy, and the pathological inclusions identified using scanning electron microscopy (SEM).

2. Materials and methods

2.1. Patient characteristics

Following hospital ethical research committee approval, femoral plaque samples were gathered from 10 consecutive consenting patients undergoing common femoral endarterectomy to treat high grade arterial stenosis. Plaque samples were endarterectomised *in toto* with preservation of plaque structural integrity when cutting along the longitudinal length of the specimen. Samples were taken from the hospital and frozen in phosphate buffer solution (Fisher Scientific, Product code: 12821680) at −20 °C as this method of storage has been shown to have no significant effects on arterial tissue mechanical properties [50–52]. Prior to testing, samples were equilibrated to 37 °C in fresh phosphate buffer solution and divided into 7 mm wide sections for testing. Plaque sections are grouped based on their location within the femoral vessels i.e. common femoral artery (CFA), bifurcation