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Plaque hemorrhage in carotid artery disease: Pathogenesis, clinical and biomechanical considerations

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ABSTRACT

Stroke remains the most prevalent disabling illness today, with internal carotid artery luminal stenosis due to atheroma formation responsible for the majority of ischemic cerebrovascular events. Severity of luminal stenosis continues to dictate both patient risk stratification and the likelihood of surgical intervention. But there is growing evidence to suggest that plaque morphology may help improve pre-existing risk stratification criteria. Plaque components such a fibrous tissue, lipid rich necrotic core and calcium have been well investigated but plaque hemorrhage (PH) has been somewhat overlooked. In this review we discuss the pathogenesis of PH, its role in dictating plaque vulnerability, PH imaging techniques, marterial properties of atherosclerotic tissues, in particular, those obtained based on in vivo measurements and effect of PH in modulating local biomechanics.

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1. Introduction

Carotid artery disease is responsible for about 30% of ischemic strokes (Levy et al., 2008), which is the third leading cause of mortality and the primary cause of disability in developed countries (Roger et al., 2011). Currently, carotid luminal stenosis is the only validated diagnostic criterion for clinical risk stratification. Large multicentre clinical trials have shown that carotid endarterectomy (CEA) provides maximum benefit to patients with a significant carotid stenosis ($\geq$70%) (Barnett et al., 1998). The overall risk-to-benefit ratio for CEA however becomes marginal in patients with moderate stenosis (50–69%). Since patients with moderate carotid stenosis constitute the majority of individuals suffering from clinical events (Barnett et al., 1998; Rothwell et al., 2003), there is therefore a need to identify better risk stratification tools besides luminal stenosis.

The primary mechanism for an ischemic stroke due to carotid atherosclerotic disease is believed to be an embolic event from a ruptured carotid plaque (Rothwell et al., 2000). As a multi-component structure, plaque stability is determined by both its structure and local haemodynamics, including arterial pressure and flow. A typical carotid atherosclerotic plaque is composed of lipid-rich necrotic core (LRNC), plaque hemorrhage (PH) and calcium, all covered by an overlying fibrous cap (FC). Large LRNC with or without PH and thin FC characterize a high-risk plaque. Although plaque components such as LRNC, FC and calcium have been extensively studied, PH has been much less investigated. There is growing evidence that PH is critical in dictating plaque vulnerability and is associated with subsequent ischemic events (Kolodgie et al., 2003; Michel et al., 2011; Sadat et al., 2010b). PH has been observed to be more prevalent in acutely symptomatic patients than in asymptomatic individuals (Imparato et al., 1983; Sadat et al., 2009), while prospective studies have confirmed that PH confers additional risk in both symptomatic and asymptomatic patients (Altaf et al., 2008, 2007; Eliasziw et al., 1994; Sadat et al., 2010b; Singh et al., 2009; Takaya et al., 2006).

Compositional features provide complementary information to luminal stenosis in carotid plaque vulnerability assessment. Indeed, about 60% symptomatic patients exhibit PH or FC rupture at baseline (Gao et al., 2007; Milei et al., 2003), yet only 10–20% will go on to experience a recurrent event at 1 year (Sadat et al., 2010b; U-King-Im et al., 2009). It is therefore clear that composition alone cannot serve

Abbreviations: ΔHU, density difference of Hounsfield (a quantitative scale for describing radiodensity); 2D, two dimensional; 3D, three dimensional; CEA, carotid endarterectomy; CT, computerized tomography; CTA, computerized tomography angiography; FC, fibrous cap; FSE, fast spin echo; FSI, fluid–structure interaction; FTIR, Fourier transform infrared; LRNC, lipid-rich necrotic core; MIP, maximum intensity projection; MRI,, magnetic resonance image; PH, plaque hemorrhage; SEDF, strain energy density functions; SHINE, Sequence for Hemorrhage assessment using INversion recovery and multiple Echoes; SNAP, Simultaneous Noncontrast Angiography and intraPlaque hemorrhage; SPI, slab-selective phase-sensitive inversion-recovery; TOF, time-of-flight

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as a marker for prospective cerebrovascular risk and there is a need to identify novel biomarkers. Under the physiological conditions, carotid plaques are subjected to mechanical loading driven by pulsatile blood pressure. FC rupture may occur when this loading exceeds its material strength. Therefore, a strategy integrating both high risk anatomical plaque features and mechanical conditions may improve patient risk stratification and ultimately guide clinical treatment. With this consideration, this review will focus on (1) the pathological features of PH and its clinical significance; (2) the non-invasive in vivo imaging techniques used to depict PH; (3) the material properties of atherosclerotic components, including PH; and (4) the critical mechanical conditions within a hemorrhagic plaque.

2. Pathology of plaque hemorrhage and clinical significance

2.1. Plaque hemorrhage and associated neovascularization

The involvement of hemoglobin-rich plaque hemorrhage in the transformation of a stable to unstable atherosclerotic lesion was proposed as early as 1936 (Paterson, 1936). At the same time it was suggested that rupture of neovessels could be the initiating event for PH (Paterson, 1938; Wartman, 1938). After this initial period, the clinical and biological significance of PH became rather overlooked. The majority of biological studies focussed on either lipid metabolism or the inflammatory response within the plaque. Imparato et al. (1979) reported the relationship between PH observed in CEA samples and neurological symptoms. Since then various studies have assessed this relationship which are summarized by Gao et al. (2007). Others have investigated the relationship between PH and plaque neovessels (Fryer et al., 1987; McCarthy et al., 1999). Observations that erythrocyte extravasation and PH are related to high density of plaque neovessels, in the absence of plaque fissuring, support the common viewpoint that PH is related to neovessels leakage (Virmani et al., 2005), due to leaky endothelial junctions (Jeziorska and Woolley, 1999) (Fig. 1). An alternate viewpoint is that repeated plaque fissuring and associated formation of non-occlusive luminal thrombus gets incorporated into the plaque (Davies and Thomas, 1985). Either way, the extracorpuscular hemoglobin released following the phagocytosis of red blood cells in PH acts as a pro-inflammatory agent, promoting local inflammation (Fig. 2) and plaque progression (Moreno et al., 2012). PH also carries proteolytic enzymes, causing thinning of the FC and making the plaque liable to rupture (Michel et al., 2012). Readers are directed to other excellent articles (Levy and Moreno, 2006; Michel et al., 2011) for further relevant pathological details, as they are beyond the scope of this review.

2.2. Prevalence of plaque hemorrhage (PH) in patients with carotid artery disease

The prevalence of PH in symptomatic and asymptomatic patients has been mostly obtained from ex vivo histological examination of CEA or cadaveric tissue. In the 29 histological studies (Table 1) including both symptomatic and asymptomatic

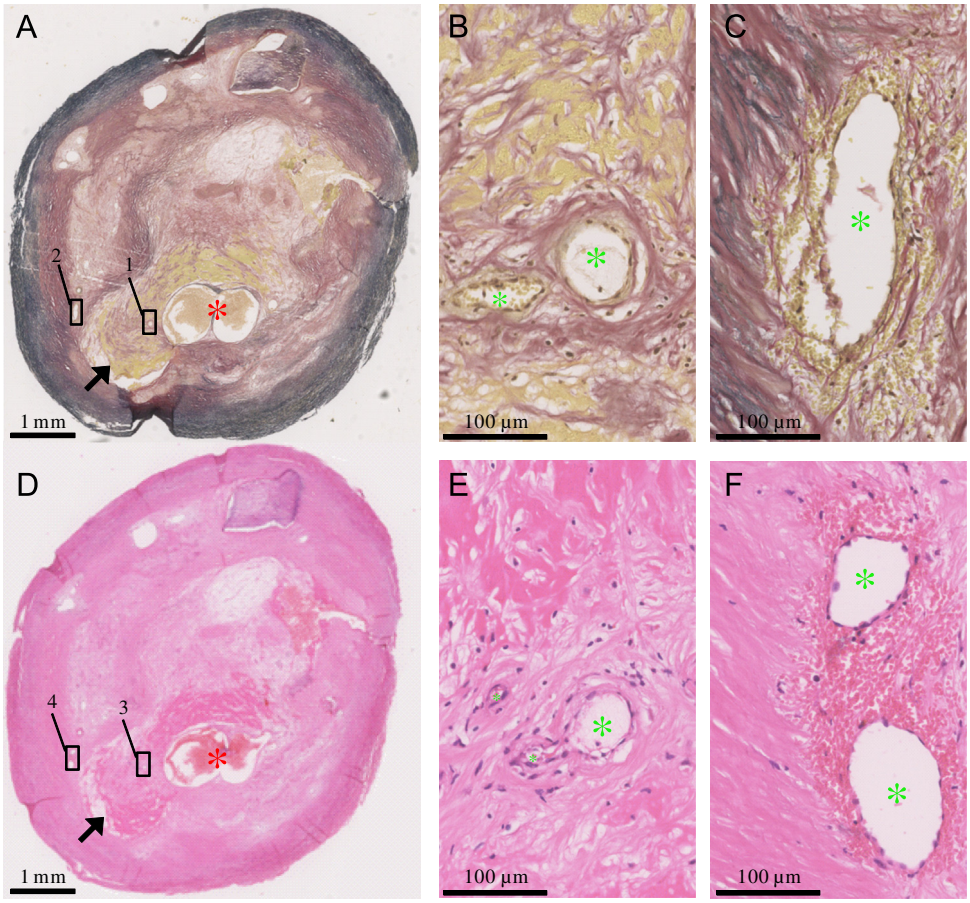

Fig. 1. Atherosclerotic plaque sample collected from carotid endarterectomy of a 72-year old symptomatic patient (male) showing both old thrombus and plaque hemorrhage around neovessels: (A and D) Van Gieson's (EVG) and Hematoxylin and eosin (HE) stains showing elastin (black in EVG), collagen (pink in HE) and erythrocyte and its debris (brown in EVG and red in HE); (B and E) local views of 1 in (A) and 3 in (B) showing neovessels in a old thrombus resulted from previous rupture (marked by arrow in A and D); (C and F) local views of 2 in (A) and 4 in (B) showing erythrocytes (fresh plaque hemorrhage) around neovessels; red asterisk: arterial lumen; green asterisk: the lumen of neovessels. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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