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Development of a quantitative mechanical test of atherosclerotic plaque stability

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ABSTRACT

Atherosclerotic plaque rupture is the main cause of myocardial infarction and stroke. Both clinical and computational studies indicate that the shoulder region, where a plaque joins the vessel wall, is rupture-prone. Previous mechanistic studies focused on mechanical properties of the fibrous cap and tensile stresses, which could lead to tearing of the cap. Based on clinical observations of "mobile floating plaques," we postulate that de-adhesion between the fibrous cap and the underlying vessel wall may also play a role in plaque failure. Thus, measuring adhesive strength of the bond between plaque and vascular wall may provide useful new insights into plaque stability. Delamination experiments, widely used in examining inter-laminar adhesive strength of biological materials, were used to measure adhesive strength of advanced plaques in apolipoprotein E-knockout (apoE-KO) mice after 8 months on Western diet. We measured adhesive strength in terms of local energy release rate, $\mathcal{G}$, during controlled plaque delamination. As a measure of the fracture energy required to delaminate a unit area of plaque from the underlying internal elastic lamina (IEL), $\mathcal{G}$ provides a quantitative measure of local adhesive strength of the plaque–IEL interface. The values for $\mathcal{G}$ acquired from 16 plaques from nine apoE-KO mouse aortas formed a positively skewed distribution with a mean of 24.5 J/m^2, median of 19.3 J/m^2, first quartile of 10.8 J/m^2, and third quartile of 34.1 J/m^2. These measurements are in the lower range of values reported for soft tissues. Histological studies confirmed delamination occurred at the interface between plaque and IEL.

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1. Introduction

Atherosclerotic plaque rupture is the main cause of myocardial infarction, coronary thrombosis and stroke. Since plaque rupture has taken more lives than any other disease in the Western world over the past century, a better understanding of this pathology is needed to develop effective approaches for treatment or intervention.

A normal elastic artery is composed of concentric layers of intima, which is a layer of endothelial cells on a basement membrane, media, which consists of multiple smooth muscle cell layers separated by elastin lamellae, and adventitia. Atherosclerotic disease progression results in a dramatically thickened intima. Clinical observations indicate that a vulnerable plaque features a thin, collagen-rich fibrous cap overlying a large necrotic core (Libby et al., 1996). Clinically, plaque rupture is defined as failure of the plaque resulting in exposure of the necrotic core. Plaque rupture and plaque vulnerability (susceptibility to rupture) were initially defined based on pathological features seen in autopsy specimens; namely, an apparent break in the fibrous cap, often with superimposed thrombus (Virmani et al., 2000). Pathological observations reveal two classes of rupture sites: 63% of ruptures occur in the shoulder region, where the plaque joins the more normal intima, while the remainder (37%) occur in the center of the fibrous cap (Richardson et al., 1989; Maehara et al., 2002). Pathological studies of ruptured plaques reveal little of the actual failure mechanism, since they focus on the endpoint rather than the event itself. Previous mechanistic studies of plaque rupture have focused on mechanical properties of the fibrous cap (Lendon et al., 1991; Holzapfel et al., 2004) and local tensile stresses which could lead to tearing of the cap (Loree et al., 1992; Cheng et al., 1993; Vengrenyuk et al., 2006).

Autopsy studies have confirmed that the shoulder region, where a plaque joins the surrounding vascular wall, is rupture-prone (Richardson et al., 1989; Cheng et al., 1993). Rupture in the shoulder region may be due to tearing of the fibrous cap adjacent to the vessel wall, physical separation of the plaque from the artery along their interface in a manner similar to delamination processes in bonded materials, or a combination of both mechanisms. Thus, shoulder rupture may involve propagation of the separation in a direction that is parallel to one surface of the plaque (Richardson, 2002). Support for this mechanism comes from clinical observations of "mobile floating plaques" (Ferrero et al., 2009; Cho et al., 2002),

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