JOURNAL OF THE MECHANICAL BEHAVIOR OF BIOMEDICAL MATERIALS 55 (2016) 12–20

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jmbbm

Research Paper

A microstructurally inspired damage model for early venous thrombus

Manuel K. Rausch*, Jay D. Humphrey

Department of Biomedical Engineering, Yale University, New Haven, CT, United States

ARTICLE INFO

Article history:
Received 23 June 2015
Received in revised form
8 October 2015
Accepted 12 October 2015
Available online 17 October 2015

Keywords:
Continuum damage mechanics
Intraluminal thrombus
Material modeling
Uniaxial tensile properties

ABSTRACT

Accumulative damage may be an important contributor to many cases of thrombotic disease progression. Thus, a complete understanding of the pathological role of thrombus requires an understanding of its mechanics and in particular mechanical consequences of damage. In the current study, we introduce a novel microstructurally inspired constitutive model for thrombus that considers a non-uniform distribution of microstructural fibers at various crimp levels and employs one of the distribution parameters to incorporate stretch-driven damage on the microscopic level. To demonstrate its ability to represent the mechanical behavior of thrombus, including a recently reported Mullins type damage phenomenon, we fit our model to uniaxial tensile test data of early venous thrombus. Our model shows an agreement with these data comparable to previous models for damage in elastomers with the added advantages of a microstructural basis and fewer model parameters. We submit that our novel approach marks another important step toward modeling the evolving mechanics of intraluminal thrombus, specifically its damage, and hope it will aid in the study of physiological and pathological thrombotic events.

1. Motivation

Thrombus plays crucial roles in physiology and pathology. It involves a complex interplay between platelet activity and coagulation, the latter of which depends on the conversion of fibrinogen to fibrin, which in turn is cross-linked to form a complex, three dimensional mesh. As the fibrin mesh forms, it traps cellular and non-cellular components of the blood that affect the structural integrity and biological activity of the thrombus (Undas and Ariëns, 2011). If the thrombus is not proteolytically dissolved, it can be remodeled from a fibrin-dominated mesh to a collagen-dominated matrix (Schriefl et al., 2012).

Physiologically, formation of thrombus can be an essential step in the well-orchestrated healing response to internal and external insults; it is thus vital to reestablishing hemostasis after injury. Pathologically, thrombus plays a significant role in diseases of the arterial and venous circulation. On the arterial side, thrombus contributes to heart attacks and strokes, and it can be found in most abdominal aortic aneurysms (Sakalihasan et al., 2005; Silvain et al., 2011). Of particular note on the venous side, thrombus contributes to deep vein thrombosis (DVT) (Kyrle and Eichinger, 2005). In

*Corresponding author.
E-mail address: manuel.rausch@yale.edu (M.K. Rausch).

http://dx.doi.org/10.1016/j.jmbbm.2015.10.006
1751-6161/

DVT, thrombus forms in the deep veins, usually of the legs, where it may embolize and lead to pulmonary embolism (López et al., 2004). Embolization, the detachment of whole or partial thrombus, occurs when mechanical forces exceed the strength of the thrombus that in turn depends on its spatially and temporally varying histomechanical properties. Thus, pulmonary embolism, which is responsible for an estimated 60,000 to 100,000 deaths per year in the US alone (Beckman et al., 2010), is at least in part a mechanical phenomenon. Therefore, we suggest that thrombus mechanics, specifically damage mechanics, has a critical role in understanding and possibly predicting the outcome of DVT and its clinical sequelae.

Despite the important role of thrombus, both as an isolated pathological event and in conjunction with pathologic processes, thrombus mechanics has not received the attention one would expect (see Section 2.1). Even more concerning is the lack of data on the failure mechanics of thrombus. Among the few data available, Gasser et al. (2008) studied failure properties of intraluminal thrombus retrieved from human abdominal aortic aneurysms and subjected to static and cyclic mechanical loading. They found intraluminal thrombus to be susceptible to damage following repeated loading. They suggested a crucial role of intraluminal thrombus failure in aortic aneurysm rupture, hence emphasizing the broad roles played by thrombus in diverse pathologies.

The apparent lack of data on thrombus mechanics, especially thrombus damage, may be due in part to a lack of sample availability. Most studies have been reported on human thrombus which, for obvious reasons, is not readily available for mechanical testing (Tong et al., 2011; O'Leary et al., 2014; Geest et al., 2006; Ashton et al., 2009; Di Martino et al., 1998). Furthermore, human samples necessarily are from mature thrombus. Hence, past reports are limited in their mechanical and histological diversity, which makes the formulation of general models difficult. To overcome these shortcomings, we developed a mouse model to form suitably sized and shaped thrombus samples in vivo (Lee et al., 2015). By ligating the inferior vena cava, we successfully created cylindrical samples of thrombus that lend themselves well for mechanical testing. During our first experiments, we explanted thrombi after 2 weeks and studied their mechanical and structural properties. We found that young venous thrombus exhibits distinctly different mechanical behavior from previous reports on mature thrombus, often retrieved from the arterial side (Tong et al., 2011; O'Leary et al., 2014; Geest et al., 2006; Di Martino et al., 1998). For example, our samples demonstrated a stretch driven failure behavior that has not been reported before.

The goal of this work is to develop a microstructurally inspired constitutive model that provides a flexible framework for the study of thrombus mechanics. We will employ our novel model to describe the mechanical behavior observed in our recent experimental study of early venous thrombus. Furthermore, due to the highlighted importance of thrombus damage mechanics, we will extend our material model to incorporate damage effects observed in the same experiments. Last, we will show that our novel model compares favorably to standard models of material damage developed by Simo and Ogden (Simo, 1987; Ogden and Roxburgh, 1999), with the added advantage of fewer material parameters to estimate.

2. Thrombus material modeling

2.1. Previous models of thrombus mechanics

One of the first studies on thrombus mechanics dates back to Di Martino and colleagues who performed uniaxial tensile tests on intraluminal thrombus from human abdominal aortic aneurysms (Di Martino et al., 1998). They assumed that thrombus exhibits an isotropic linearly elastic behavior and identified Young's modulus and Poisson's ratio. Since at least the study by Vorp et al. (1996), however, we know that thrombus may exhibit a mildly nonlinear response over finite strains in vivo. To overcome limitations of Di Martino's model, Wang et al. (2001) and Di Martino and Vorp (2003) extended the description of thrombus to finite elasticity. Based again on uniaxial tensile data, they proposed a hyperelastic model for both the luminal and medial regions of human intraluminal thrombus retrieved from aortic aneurysms. Their isotropic strain energy is written as a linear function of the second invariant of the left Cauchy–Green tensor. Vande Geest et al. (2006) further tested similar thrombus samples under biaxial extension. Based on their data, a hyperelastic constitutive relation was written as a second order polynomial, also of the first invariant of the left Cauchy–Green tensor. This model has since been used in finite element analyses of aneurysm mechanics (Polzer et al., 2011). One of the most comprehensive studies to date is that of Tong et al. (2011); they fit an anisotropic Fung-type hyperelastic model to biaxial data from the different layers of aneurysmal thrombus and suggested that such layers exhibit "aging" characteristics (Pierce et al., 2015).

Thrombus has also been modeled using approaches other than linear and nonlinear elasticity. For example, van Dam et al. (2006, 2008) modeled thrombus as viscoelastic based on shear experiments performed on samples from human aortic aneurysms. Thrombus has also been modeled as poroelastic; Polzer et al. (2012) employed a poroelastic model to study the influence of intraluminal thrombus on wall stress in abdominal aortic aneurysms.

Whether modeled as elastic, viscoelastic, and poroelastic, of particular importance here is the need to account for the apparent cycle-dependent damage that could compromise the structural integrity of thrombus and lead to adverse mechanical and biological effects on the underlying vascular wall and downstream organs. Moreover, our review of the literature revealed that all prior models of thrombus have been phenomenological and, with the exception of Karšaj and Humphrey (2009), no attempts have been made to model thrombus at times prior to advanced maturity or during its "development". Thus, there is a clear need for models that consider the microstructure and account for the evolving mechanical properties with age and damage; ultimately, there is also a need to characterize differences in thrombus mechanics depending on its source, arterial versus venous and intraluminal versus intramural or extravascular.