Identifying Physical Causes of Failure in the Cerebral Aneurysm Wall

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1. Clinical Motivation

Cerebral aneurysms are abnormal enlargements of the walls of brain arteries that are typically saccular in shape and found largely at arterial bifurcations in the vicinity of an anatomic structure at the base of the brain called the Circle of Willis. Rupture of a cerebral aneurysm is a central cause of subarachnoid hemorrhage, a devastating type of stroke with high mortality and disability rates. As the majority of aneurysms do not rupture during a person's lifetime and treatments for unruptured aneurysms have serious medical risks, there is an urgent need to develop reliable methods for assessing the likelihood of rupture.

2. Approaches to Risk Assessment

It is well established that larger aneurysms are more likely to rupture, however, there is no size threshold that can be deemed safe and the majority of ruptured aneurysms are categorized as small. Presently, most efforts to improve risk assessment are directed at identifying correlations between rupture status at clinical presentation (ruptured versus unruptured) and data obtained from patient characteristics (e.g. hypertensive, smoker), aneurysm geometry, and flow inside the aneurysm. In parallel, research has been directed at developing new tools and approaches for evaluating the state of the aneurysm wall *in vivo*. For example, some regions of the aneurysm wall preferentially take up gadolinium-based contrast that can be seen during magnetic resonance imaging. Studies are under way to determine whether these regions of wall enhancement are possibly vulnerable to rupture.

3. Identifying Causes of Rupture

In parallel, our group is immersed in determining the physical causes of rupture of the aneurysm wall. We believe there are multiple causes of failure and that understanding these mechanisms will make it possible to stratify the data for correlative studies as well as guide efforts to develop new diagnostic approaches. To better understand the various failure processes, we have developed an *ex vivo* system for testing the aneurysm tissue that enables simultaneous mechanical testing and imaging of the collagen fibers using multi-photon microscopy [1,2]. More recently, we have expanded these methods to simultaneously image calcification and collagen fibers [3].

For these studies, cerebral aneurysm domes were harvested following clipping during open brain surgery. The harvested samples were analyzed using a combination of high resolution micro-CTimaging, multiphoton microscopy, electron microscopy, mechanical testing and histological assessment. Through mechanical testing of the aneurysm tissue, we identified a vulnerable subgroup within the unruptured population [2]. The multiphoton imaging also demonstrated a large heterogeneity in collagen fiber architecture, cellular content, calcifications, and lipid pools within these samples [2-4].

The calcifications in the aneurysm wall were found to range in size from microscopic to mesoscopic. They serve as mechanical inclusions in the wall and therefore have the potential to generate stress concentrations and to provide stress shielding to the fibers. Computational analysis was used to assess the stress distributions resulting from these inclusions. Briefly, using micro-CT data from the harvested tissue in conjunction with patient specific 3D clinical imaging data, 3D computational models of the aneurysm wall and surrounding vasculature were created. We used these models combined with multiphoton data to explore the impact of the inclusions and demonstrated their roles cannot be properly considered without the context of the surrounding collagen fiber matrix. The interface of between the fibers and the calcification can be a site of tear initiation. Another potential source of weakness is a daughter aneurysm, or bleb. Using multiphoton microscopy combined with computational biomechanics, we identified the capacity for effective remodeling even within these secondary aneurysms.

4. Bibliography

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