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EDITORIAL COMMENT

Improved Risk Assessment for Abdominal Aortic Aneurysm Rupture

Off-the-Wall Imaging*

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Vessel dimensions are currently the primary imaging parameter used to risk-stratify patients with abdominal aortic aneurysms (AAAs). Intervention is recommended for an AAA with a diameter >5.5 cm. But there is more to the story. Both the stresses experienced by the aortic wall and the intrinsic strength of the wall itself are crucial in predicting rupture. New developments in imaging enable the direct evaluation of these factors and allow a more complete, patient-specific assessment of risk for disease progression.

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Hemodynamic parameters derived from imaging are an attractive means of characterizing the status of the aortic wall. Abnormal wall shear stress, or the frictional force that blood flow exerts on the vessel wall, can be estimated from near wall velocity gradients captured by phase-contrast magnetic resonance imaging. Studies have shown that low wall shear stress causes endothelial dysfunction and the development of atherosclerosis (1). However, because significant intraluminal thrombus is often present, the importance of wall shear stress is confounded in later stages of aneurysm growth (2). Therefore, instead of measuring wall shear stress, the focus for the abdominal aorta is wall stress, the internal force within the vessel wall. Studies of wall stress have shown good predictive value for AAA rupture, but they are limited in practice because they require extensive and time-consuming computer modeling (3,4).

The 2 major components of the vessel wall are collagen and elastin, with decreased collagen thought to be associated with rupture whereas decreased elastin is associated with dilation (5). Pulse wave velocity, an easily measured imaging parameter, reflects the stiffness of the aorta (6) and likely measures atherosclerotic-related decreases in elastin (7). However, collagen is the critical component of the vessel wall that contributes to stability; its degradation and turnover lead to growth and rupture. In pathological specimens, increased levels of collagen breakdown products are seen in ruptured aneurysm (8), but collagen levels are higher in AAA tissue (9). The reason for this counterintuitive finding is that with increased collagen breakdown, there is also increased but dysfunctional cross-linking, which results in higher overall levels of collagen but a pathological unsound form of collagen. The breakdown of collagen depends on a complex balance between matrix metalloproteinases (MMPs) and the tissue inhibitors of the metalloproteinases, among other factors (10). Previous work has shown markedly abnormal MMP levels within AAAs (11).

Initial studies of the association between collagen breakdown products and AAA rupture focused on serum levels, which are easy to measure. To date, however, only weak correlations have been reported (12). Part of the problem may be that these circulating biomarkers are nonspecific and may be clouded by other processes, particularly atherosclerosis. Direct assessment of specific regions of the vessel wall is preferable. With recent developments in molecular imaging, wall-specific pathological processes can now be imaged.

Increased metabolic activity, as measured by using 18F-fluorodeoxyglucose positron emission tomography, has been associated with acute symptoms and with high wall stress in AAAs (13,14). Molecular agents that target specific pathological pathways have shown promise in animal models of AAAs. Quantification of macrophage content within the aneurysm wall has been performed (15); macrophages along with other inflammatory markers are known to secrete MMPs and alter collagen metabolism. In vivo imaging of MMP expression has been performed, although not applied in AAAs (16–18). Imaging MMPs alone is likely to be limited because it discounts other aspects of collagen breakdown, such as tissue inhibitors of the metalloproteinases and other interrelated proteins.

The study by Klink et al. (19) in this issue of the *Journal* measures collagen content in the wall of AAAs in mice using a collagen-specific gadolinium-labeled lipid micelle. The collagen specificity is provided by CNA-35, a protein borrowed from *Staphylococcus aureus* and thought to play a role in wound virulence. In their animal model, the investigators found an association between decreased collagen content and increased risk of rupture. This finding, if further validated, would make collagen imaging an important component of the clinical risk-stratification of AAAs. Collagen has been imaged previously using gadolinium-labeled and single-photon emission computed tomography agents (20,21), but these approaches used single moiety agents for collagen binding. One of the main benefits of using a micelle in the imaging of collagen, as done by

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Reulen et al. (22), is that having multiple moieties on the same molecule increases the binding strength to collagen. The main drawback is that due to its larger size, a healthy endothelium will prevent the micelle from entering the vessel media (23).

Imaging has advanced to the point where the old paradigm for risk-stratifying patients with AAAs using simple anatomic considerations is soon to be outdated. Molecular imaging not only allows direct imaging of vessel wall inflammation but also of specific matrix proteins and pathological pathways. Collagen imaging is one of many new developments that may allow better clinical management of patients with AAAs.

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