Macrophage Detection in Aortic Aneurysm
The Heat Is On

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Aortie aneurysm is a common condition that is associated with a risk of rupture and sudden death. Clinical screening and surveillance are based largely on noninvasive assessment of aneurysm diameter and rate of change of diameter, often with serial ultrasound examination. An ability to identify vessel characteristics or processes that are associated with aneurysm enlargement or predictive of rupture would be valuable in guiding the selection of patients for repair and for optimizing the timing of intervention. Current approaches, focused on the detection of these anatomic changes, reflect relatively late stage pathology, in which dilatation and structural changes have already occurred. Overlooked in gross anatomic imaging are the pathological processes relating to aneurysm enlargement, including cellular infiltration and secretion of proteolytic enzymes that degrade structural components of the arterial wall.

To focus on these critical processes will require development of molecular, cellular, and functional imaging techniques with the potential to accelerate and to refine diagnosis, determine prognosis, and guide and monitor specific treatments.

In this issue, Nahrendorf et al report using a particle-based positron emission tomography (PET) approach to characterize experimental abdominal aortic aneurysm in apolipoprotein E−/− mice treated with angiotensin II. Aneurysm size was determined by computed tomography, whereas macrophage content was assessed using 18fluorine-labeled cross-linked iron oxide particles (18F-CLIO).

Using PET, aneurysmal segments of aorta showed significantly higher standard uptake values than normal aorta and were also higher than atherosclerotic (but noneurysmal) segments of aorta. Significantly, there was only a modest correlation between vessel diameter determined by computed tomography and PET activity in the same segment, reinforcing the additional information provided by functional characterization of the aortic wall, over and above anatomic definition (Fig.).

The plasma half-life of the particle was 192 minutes, ie, 3 to 4 half-lives before the imaging time point at 10 to 12 hours providing an optimal target to blood ratio. For clinical translation, an equivalent delay from contrast agent administration to image acquisition may be potentially limiting. In keeping with observations made of iron oxide nanoparticles used for magnetic resonance imaging in atherosclerosis, the 18F-CLIO were taken up by macrophages in the vessel wall and were present in all layers—intima, media, and adventitia. The precise mode of delivery of particles is uncertain, for instance, the extent to which CLIO are passively extravasated from leaky blood vessels and taken up by cells in situ versus being transported into the wall following uptake by monocytes elsewhere. Flow cytometry was used to coregister CLIO and monocytes, and yet, as Nahrendorf et al recognize, this would not detect free CLIO that were not cell associated within the wall. Furthermore, it seems likely that the precise localization of macrophages in the wall of the artery may be important in determining the behavior of an aneurysm. Degradation of medial and adventitial structural elements may be more important than intimal macrophage content. Accordingly, the relatively low spatial resolution of PET may be limiting, and macrophage detection using computed tomography or magnetic resonance imaging may offer additional, or complementary, insights.

Accelerated Diagnosis, Determination of Prognosis, and Response to Treatment

The approach laid out in the article of Nahrendorf et al addresses 3 important aspirations of molecular/cellular imaging techniques. First, there is the idea that diagnosis can be accelerated. In mice treated with angiotensin II, inflammation was identified early (7 days) and before vessel enlargement could be seen by computed tomography. Second, the more refined functional data from PET provided prognostic information, with early increases in PET signal anticipating disease progression to aneurysm rupture. Third, response to therapeutic intervention can be quantified; in this case, splenectomy resulted in a reduction in monocytes that was detectable using noninvasive PET.

The study also highlights but does not yet solve another emerging issue. The population of monocytes and macrophages in the vessel wall is heterogeneous. Optimal lesion characterization may require positive identification of leukocyte subsets. Current markers (eg, of nanoparticle uptake or glycolytic activity) may be insufficiently precise to detect the subtleties of progression and regression of atherosclerosis and aneurysm inflammation. The disposal of particles taken up by plaque monocytes/macrophages will also be of interest. For instance, in atherosclerosis, egress to local lymph node may occur and may potentially represent a target for imaging and quantification.
The study of Nahrendorf and colleagues elegantly demonstrates how molecular and cellular imaging can be harnessed to provide nuanced diagnostic and prognostic information that complements and extends existing anatomic imaging approaches.

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References

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Figure. Schematic of aortic aneurysm in cross section. Asymmetrical enlargement of the vessel lumen is associated with disruption of medial smooth muscle cells and proteolytic degradation of connective tissue elements by monocytes/macrophages, predominantly found in the adventitia and media (less so on the luminal aspect). Macrophages contain 18F-CLIO, which are identified by PET.
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