

Predicting Aortic Aneurysm Expansion by PET

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An abdominal aortic aneurysm (AAA) is a permanent, localized aortic dilatation with a diameter of 3 cm or more. Aneurysms have a prevalence of around 5% in adults aged 65–74 y and are frequently asymptomatic until rupture (1). Historic series have shown that around 40% of aneurysms with diameters larger than 5 cm will rupture over a 5-y period (2). Rupture occurs when the mechanical wall stress exerted by the blood exceeds the tensile strength of the aneurysm wall. If this happens, even with prompt surgical intervention the mortality is high. The reduction of AAA mortality rates is the rationale behind screening programs, targeted at high-risk groups such as older men and smokers. Ultrasound is used to identify asymptomatic subjects with large aneurysms for repair (3). Repair can be undertaken either by surgical replacement of the abdominal aorta with a synthetic bypass graft (open repair) or by relining the aorta with a stent graft to direct blood flow away from the aneurysmal artery (known as an endovascular repair). Intervention

smooth muscle cell apoptosis and matrix degradation, which is in contrast to thoracic aneurysms, in which smooth muscle cell proliferation is particularly apparent (11). The result is a weakening of the structure of the wall, permitting expansion and ultimately aortic rupture. Our understanding of this late phase of the disease is greatly helped by the availability of specimens excised during aneurysm surgery; by contrast, the early phases of aneurysm development are less well understood. Preclinical studies in mouse models suggest that there is early infiltration of macrophages, lymphocytes, and mast cells into the medium and adventitia of the aortic wall (12). These cause cytokine and protease release that result in apoptosis and senescence of smooth muscle cells, eventually weakening the wall and allowing progressive dilatation. If the disease continues unchecked, the aneurysm wall becomes thinner and progressively less cellular. Finally, there is often substantial adherent luminal thrombus, variously described as either protective (13–15) or destabilizing (16) to the aneurysm.

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is indicated when the diameter exceeds 5.5 cm (4) or where serial measurements show rapid expansion rate (>10 mm per year (5)) as detailed in European (6) and American guidelines (7,8).

Management of those with AAAs below the surgical threshold comprises regular ultrasound surveillance, with a frequency dependent on aneurysm size. Aneurysms tend to expand in a non-linear fashion, making the prediction of growth with ultrasound an imperfect art. Imaging, or other biomarkers that improved risk stratification, would be of high clinical value.

There are currently no medical treatments that prevent aneurysm development or progression, although many are being tested in animal models and clinical trials. Only smoking cessation has been shown to slow AAA growth rate (9). At present, AAA size is the best predictor of rupture, but some patients have smaller AAAs that do rupture (10).

Pathologically, abdominal aneurysms are associated with inflammatory infiltration of all 3 layers of the aortic wall, along with

ROLE OF PET IMAGING IN ANEURYSM DISEASE

To improve risk stratification and to guide intervention and development of new disease-modifying drugs, a better understanding of the underlying pathology leading to expansion and rupture is warranted (10). This presents a role for noninvasive imaging, particularly where anatomy and pathophysiology can be assessed in a single test. There have been reports of targeted imaging being used to evaluate many aspects of the disease, including inflammation (17), structural protein turnover (18), and angiogenesis (19). Several imaging modalities have been tested, including PET, CT, SPECT, optical, and MR imaging. Despite some promising studies, imaging of aneurysms presents several significant challenges. There are few animal models that recapitulate the human disease. In humans, the thin, hypocellular aneurysm wall and the proximity of flowing blood and thrombus demand high spatial resolution and accurate tissue characterization.

¹⁸F-FDG PET/CT is commonly used to identify metabolically active cells for cancer diagnosis and risk stratification. The technique can be modified slightly (by increasing the ¹⁸F-FDG circulation time) for application in arterial disease, such as atherosclerosis (20–22) and vasculitis (23), as a surrogate marker of inflammation. It is believed that the arterial ¹⁸F-FDG signal reflects glucose accumulation, predominantly by macrophages (24) and other plaque inflammatory cells (25), which can be amplified by hypoxia (26). High levels of ¹⁸F-FDG accumulation in the carotid arteries and aorta are markers of high-risk, unstable disease and may predict future clinical events (27).

AAA and atherosclerosis both share inflammation as a pathologic hallmark, and this is the scientific basis for using ¹⁸F-FDG

Received Feb. 26, 2015; revision accepted Apr. 6, 2015.

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Published online Apr. 23, 2015.

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DOI: 10.2967/jnumed.115.154022

PET to determine who might be at risk of rapid aneurysm expansion and rupture. As highlighted by Morel et al. (28) in the current issue of *The Journal of Nuclear Medicine*, histologic reports have colocalized ^{18}F -FDG uptake with heavily inflamed regions of the aorta removed during surgery from subjects with large and symptomatic aneurysms. Other authors have additionally noted upregulated inflammatory gene expression, high wall stress levels, and a paucity of smooth muscle cells at sites of high ^{18}F -FDG uptake in aneurysm walls (29). In smaller, asymptomatic aneurysms, below the cutoff for surgery, there is no histologic validation of the ^{18}F -FDG signal, so its relevance can be extrapolated only from the studies mentioned above. Several authors (30–32) have noted low ^{18}F -FDG uptake in this group. This low uptake could reflect the true pathologic state—that is, inflammation is largely absent—or it might simply highlight the limitations of PET in this situation.

It is against this background that the paper by Morel et al. (28) should be set. The authors recruited 39 patients with small- to medium-size (mean diameter, 46 mm) aneurysms and imaged them with ^{18}F -FDG PET at baseline and again after 9 mo. There was no relationship between ^{18}F -FDG uptake and baseline aneurysm size, a finding noted previously by others. Morel's is, however, the first study to our knowledge, to obtain a second PET scan. Over the relatively short interval period, only 23% of patients experienced a significant increase in the diameter of their aneurysm (defined as >2.5 mm). The authors found that aneurysms with the lowest uptake of ^{18}F -FDG at baseline were the most likely to expand over 9 mo. Surprisingly, they also noted that the degree of ^{18}F -FDG uptake in the wall of the expansion group did catch up to the level of the nonexpansion group by 9 mo. As suggested in prior studies, they noted that the largest-volume aneurysms increased in size to the greatest extent during the surveillance period.

Morel et al. (28) concluded that low baseline ^{18}F -FDG accumulation (measured as standardized uptake value but not tissue-to-background ratio) was a significant predictor of subsequent aneurysm expansion. They suggested that the increase in ^{18}F -FDG uptake seen to accompany the expanded aneurysms might relate to the recruitment of inflammatory cells, a phenomenon that accompanies growth and wall instability. Kotze et al. also observed an inverse relationship between baseline aneurysm ^{18}F -FDG uptake and subsequent expansion in a study that used follow-up ultrasound (33). Barwick noted no association between baseline ^{18}F -FDG uptake and future expansion, although their retrospective study was not powered to be conclusive (34). Nchimi et al. found the opposite of Morel and Kotze; in their study of 47 subjects with aneurysm followed for nearly 3 y, the baseline level of ^{18}F -FDG accumulation was positively predictive of future complications (defined as a composite of aneurysm repair, rupture, rapid growth, or dissection), although few subjects actually experienced these events (35).

On the basis of their results, Morel et al. hypothesized that there is cyclical ^{18}F -FDG uptake (and, by implication, inflammation) within small aneurysms over time, a claim that fits with the known pathology of the disease, where periods of expansion are interspersed with more quiescent intervals (36). In atherosclerosis, although the short-term variability (2 wk (37) to 3 mo (38)) of ^{18}F -FDG uptake is low, a similar periodicity of ^{18}F -FDG accumulation has been noted in 2 studies over longer time periods (2 (39) and 5 (40) y, respectively).

Despite the data gathered from 2 PET scans obtained over 9 mo in well-characterized, asymptomatic patients with small aneurysms,

this study has several shortcomings. The subjects were followed for a short period of time relative to our current understanding of an aneurysm's life span (9). A longer study with more imaging visits (e.g., baseline, 3 and 5 y) alongside regular ultrasound surveillance would improve our understanding of the relationship (if any) between ^{18}F -FDG uptake and aneurysm expansion. It is not clear why the authors excluded the inferior and superior extremities of the aneurysm from analysis. Anecdotal experience suggests that the point of rupture is often within this shoulder region; this area is known to experience high mechanical stress and (presumably) inflammation (41). Additionally, the relationship between low ^{18}F -FDG uptake and subsequent expansion was not present when tissue-to-background ratio was used to quantify ^{18}F -FDG uptake instead of standardized uptake value, a fact also noted by Kotze et al. (33). The authors suggest this lack of relationship might be a result of the influence of metabolically inert thrombus on the aneurysm wall, negating the need for background blood ^{18}F -FDG correction of the wall signal.

UNANSWERED QUESTIONS AND SUGGESTED FURTHER WORK

^{18}F -FDG uptake is nonspecific for inflammation, being influenced by many factors, including hypoxia, endothelial cell activation, smooth muscle cell metabolism, and the efficiency of tracer delivery. It might be expected, therefore, that any relationship between ^{18}F -FDG uptake and these individual pathologic elements, as well as between ^{18}F -FDG uptake and clinical outcomes, would be weak. New PET tracers (or repurposing of old ones) specific for elements of the pathobiology of aneurysm disease may shed more light than ^{18}F -FDG, and such studies are under way.

The study by Morel et al. adds another piece to the jigsaw of imaging in aortic aneurysm but the puzzle is far from solved. Morel et al. provide useful data in helping to explain the pathology underlying expansion, but whether or not ^{18}F -FDG PET has a role in routine surveillance of small to medium aneurysms is still unproven.

Any new imaging biomarker will have to demonstrate some incremental benefit over current practice before finding acceptance into national guidelines for risk stratification. But if successful, the payoff of targeted imaging for early readout of efficacy of new drugs against aneurysm rupture would be high.

CONCLUSION

Morel et al. offer new insight into ^{18}F -FDG imaging of AAA expansion. The findings are interesting but inconclusive. Future prospective studies should concentrate on methodologic standardization to make comparisons between them more straightforward. Standardization would also open the possibility of meta-analyses to increase the number of clinical endpoints (such as expansion and rupture) by combining data from several studies. Other approaches, such as MR imaging with macrophage-avid nanoparticles, also show promise and should be considered as alternatives to nuclear imaging techniques (17).

DISCLOSURE

The work was supported in part by the NIHR Cambridge Biomedical Research Centre, the British Heart Foundation, the Wellcome Trust, the Academy of Medical Sciences, and the UK NIHR UCLH Biomedical Research Centre Funding. No other potential conflict of interest relevant to this article was reported.

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