Fluorine-18-fluorodeoxyglucose (FDG) is an indicator of vascular macrophage or leukocyte burden that has been reported in atherosclerosis, infection, large-artery vasculitis, chemotherapy- or radiation-induced vascular inflammation, and foreign-body reaction (1). FDG positron emission tomographic (PET) imaging may detect early phases of large-artery vasculitis before progression to arterial narrowing ensues. However, once the diagnosis of large-artery vasculitis, such as Takayasu’s arteritis, is established and patients are treated with arterial bypass graft surgery, the reliability of FDG PET metabolic signal for differentiating recurring or partially treated disease activity from foreign-body reaction at the graft surgery site remains challenging. Unrecognized vasculitis or graft infections that are treated late carry high mortality rates. Identifying early phases of vasculitis is critical for timely initiation of immunosuppressive therapy and prevention of arterial stenosis, perianastomotic dilatation, and aneurysm. Identifying infection early can facilitate antibiotic therapy or graft revision and thus forestall suppurrative complications. In contrast, mistaking infection for disease recurrence and instituting immunosuppressive therapy might be disastrous, or making a mistake the other way around also may result in additional imaging studies, delayed therapy, or unnecessary surgery. As such, high specificity for vasculitis and infection imaging is equally important as high sensitivity.

Similar to vasculitis and infection, the sterile inflammatory process triggered by synthetic grafts (foreign-body reaction) includes the recruitment of neutrophils and macrophages and the production of proinflammatory cytokines and chemokines. Thus, in patients with clinically inactive disease and without arterial involvement, FDG uptake can be seen within synthetic arterial prosthetic grafts. The intensity of the FDG signal can be quantified using the maximum standardized uptake value (2), which has been reported to be higher in infected grafts and correlates with subsequent risk for thoracic artery aneurysms in patients with giant cell arteritis. However, it is not the mere presence of metabolic activity but rather the pattern of FDG uptake that more reliably distinguishes infected from noninfected grafts. Infected grafts tend to have a heterogeneous pattern, with areas of more focal and intense FDG uptake, often accompanied by computed tomography (CT) abnormalities on anatomic colocalized PET/CT imaging. In contrast, noninfected grafts tend to exhibit a more homogeneous pattern of FDG uptake, which is diffuse and circumferential, encompassing the entire length of the graft without focal areas of intense signals.

To address this clinically relevant issue, Youngstein et al. (3) identified 26 patients with Takayasu’s arteritis who had undergone open vascular synthetic graft bypass of the aorta or branches of the aorta and underwent FDG PET/CT imaging at least 6 months...
after graft surgery. These patients, who were afebrile with negative blood cultures, were followed prospectively with baseline and mean of 24-month follow-up magnetic resonance angiography, along with clinical assessment for signs and symptoms of disease progression and immunosuppressive therapy. Nine patients underwent repeat FDG PET/CT studies. Despite the high prevalence of graft-associated FDG uptake post-operatively that persisted on follow-up FDG PET/CT imaging in the subset of patients with follow-up FDG imaging, sequential magnetic resonance angiography did not demonstrate arterial progression in 96% of the patients. The investigators conclude that in patients with large vessel vasculitis and graft surgery; FDG uptake confined to arterial graft sites is a nonspecific finding and does not reflect clinically relevant disease activity or progression. Therefore, this work calls for a more specific imaging technique that may target a specific bacterium, macrophage population, unique signaling pathway, or cytokine expression depending on the clinical setting. Accordingly, the investigators recommended that in patients with Takayasu’s arteritis with vascular synthetic graft bypass, as long as the disease is clinically quiescent and there are no signs of infection, with negative blood cultures and circulating biomarkers, such as C-reactive protein, it is best to follow them with magnetic resonance angiography.

The challenge of distinguishing inflammation from infection in clinical practice extends beyond vascular grafts to prosthetic joints, valves (4), and cardiac implantable electronic devices such as automated implantable cardioverter-defibrillators and left ventricular assist devices (5). Ongoing antibiotic therapy may decrease the sensitivity of the FDG signal for identifying infected grafts. An alternative to FDG imaging for infection is radiolabeled leukocytes, which are also nonspecific for distinguishing vascular graft inflammation from infection, and sensitivity can vary depending on factors such as the viability of radiolabeled white blood cells. Unlike the in vivo FDG targeting of the pre-existing inflammatory cells at the infectious site, where the inflammatory cells (macrophages, neutrophils, and lymphocytes) overexpress glucose transporter 1 (because of the stimulation of cytokines) and accumulate FDG in high concentration, radiolabeled leukocytes imaging is based on the in vitro labeling process of white blood cells and the migration rate of the cells to the infection site. The latter becomes particularly problematic among patients who are on antibiotic therapy, in whom cell chemotaxis is decreased. Given the nonspecific nature of both FDG and radiolabeled leukocyte signal for differentiating infection from inflammation, the pursuit of noninvasive molecular imaging probes that target imaging bacteria or chemotactic peptides is a commendable goal. Such new radiotracers may target similarities across bacterial species, such as sugars (e.g., maltohexaose) and antibiotics, while others target bacteria-specific monoclonal antibodies or chemotactic peptides. For example, maltodextrins are taken up as a major energy source through the maltodextrin transporter in bacteria but not in mammalian cells. Thus, maltohexaose-targeted imaging probes can take advantage of this unique difference in maltodextrin transporter expression between mammalian cells and bacteria. Bacterial-specific probes that have been published include: 1) bacterial-specific maltodextrin transporter: 18F-maltohexaose; 2) bacterial-specific nucleoside analogs (TK): 18F-arabinofuranosyl-5-ethyluracil; and 3) 89Zr-labeled bacterial-specific F(ab)’2 PET/CT scan.

Is it possible that metabolic activity at the graft site represents low-grade, clinically undetectable but histologically evident disease activity that precedes arterial remodeling and subsequent morphologic changes? The absence of clinical symptoms and signs of systemic or local disease recurrence or vascular infection, although reassuring, may miss smoldering pathology that may take a longer time to reveal itself. It is thus important to keep looking for other circulating biomarkers and various imaging modalities to improve the early diagnoses of active, vascular disease and differentiate it from infection or a simple foreign-body reaction. Such differentiation requires not only retooling with an ideal radiotracer that targets the biology of the disease process with high specificity but also improving the technology and the measurement system to be both accurate and precise. Improved spatial and contrast resolution of hybrid PET/CT systems, high counts and signal-to-noise ratios of molecular targeting agents, and accurate and reliable correction for the effects of tissue attenuation and scatter may bring the field closer to that realization. In the meantime, there should be a cautious approach to interpreting FDG uptake within synthetic arterial prosthetic grafts as indicative of vasculitis or vascular graft infection in the clinical setting.

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REFERENCES


