¹⁸F-Fluorodeoxyglucose PET imaging in aortic graft infection: many more questions than answers

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Aortic graft infection (AGI) is an uncommon complication of this increasingly popular treatment for aortic diseases. Aortic grafts placed by open surgical or endovascular stent-graft approaches are utilized to treat aortic aneurysms, stenosis, dissection, or occlusive disease. Device-related infection occurs in approximately 0.5%–4% of cases.^{1,2} Nevertheless, AGI is associated with high morbidity and mortality, and its diagnosis and treatment remain challenging.^{1,2} Optimal management with device removal, revascularization, and antimicrobial therapy is associated with up to 30% mortality.^{3,4} If the device is left in place, the 2-year mortality can approach 100% despite prolonged antimicrobial treatment.^{3,4} An accurate and expedient diagnosis of AGI are essential for optimal management. Unfortunately, sampling perigraft collections for microbial confirmation of infection is difficult and frequently not feasible. Thus, diagnosis of AGI depends on a combination of clinical/surgical,

radiologic, and laboratory criteria. The overarching problems are: (1) determining that AGI is responsible for symptoms and signs of infection, (2) distinguishing sterile inflammation from infection at aortic graft site, and (3) identifying patients who would benefit from an initially conservative therapeutic strategy.

There is no “gold-standard” AGI diagnostic test and randomized controlled surgical trials are lacking.⁵ In 2013, the Management of Aortic Graft Infection Collaboration (MAGIC) between vascular surgeons, infectious disease physicians, and radiologists from the English National Health Service (NHS) was established and led to the publication of MAGIC criteria for AGI diagnosis in 2016.⁶ The MAGIC criteria components are classified as major or minor for 3 clinical/surgical, radiology, and laboratory categories. AGI should be suspected if 1 major criterion or ≥ 2 minor criteria from different categories are present. AGI is diagnosed when 1 major criterion and 1 major or minor criterion from another category are satisfied.

Molecular imaging with 99 m-Technetium (Tc) or 111-Indium (In) radiolabeled white blood cells (WBC) planar and single-photon emission computerized tomography/computed tomography (SPECT/CT) or Fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) allows evaluation of the whole body for the sites of infection. However, since the first approach detects accumulation of white blood cells and the second approach detects elevated cellular utilization of glucose, neither is specific for infection versus inflammation. Thus, the imaging readers have to utilize the intensity and pattern of activity to determine the likelihood of infection. Despite their inherently limited specificity, based on early studies by

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Liberatore et al.,⁷ and Fukushima et al.,⁸ WBC and ¹⁸F-FDG imaging perform well in detecting AGI. In the study by Fukushima et al.,⁸ ¹⁸F-FDG PET was more sensitive than CT (91% vs 64%), but less specific (64% vs 86%) for AGI. The specificity of PET improved with addition of CT, with a meta-analysis by Reinders Folmer et al.⁹ reporting a pooled 70% specificity and 94% sensitivity for ¹⁸F-FDG PET alone and 80% specificity and 95% sensitivity for ¹⁸F-FDG PET/CT. In the same meta-analysis, CT angiography had only 63% specificity and 67% sensitivity, while WBC scintigraphy was the most accurate test with 88% specificity and 90% sensitivity (planar imaging only) and 82% specificity and 99% sensitivity (planar imaging with SPECT/CT).⁹ However, there was considerably more heterogeneity in the data for WBC scintigraphy than for ¹⁸F-FDG PET/CT across the studies. Two other meta-analytic studies have confirmed the high sensitivity and moderate specificity of ¹⁸F-FDG PET/CT for AGI.^{10,11} Importantly, the ¹⁸F-FDG PET/CT performance in these studies has been evaluated against different standards of reference, most commonly combining graft site microbial culture and clinical follow-up, with some studies also including radiologic and surgical criteria.

In this issue of JNC, Dong et al., evaluated the concordance of ¹⁸F-FDG PET/CT and consensus MAGIC Graft Infection Criteria for detection of thoracic AGI.¹² Thirty-five consecutive patients with suspected thoracic AGI were prospectively imaged with arterial and portal venous phase contrast CT of graft site and ¹⁸F-FDG PET from the base of skull to mid thighs. The patients were prepared with high-fat and low-carbohydrate meal followed by 8 hours fasting prior to PET/CT scan. The patients' blood glucose was < 11.0 mmol/L prior to ¹⁸F-FDG injection and rapid-acting insulin was used as needed to reduce elevated blood glucose prior to injection. Non-contrast CT and PET (6-8 bed positions, 2 minutes per bed position) imaging were performed 60 minutes after ¹⁸F-FDG injection. Thus, aside from the specialized dietary preparation to suppress physiologic myocardial uptake, PET/CT image acquisition was consistent with the standard oncologic protocol rather than specialized vascular protocol which would typically involve scanning at 2-3 hours after injection with 8 minutes per bed position.¹³ Two experienced nuclear medicine physicians interpreted PET/CT images blinded to clinical information, using a combined visual and quantitative evaluation. The suspected AGI site activity was visually graded on a 5-point visual grading scale. The quantitative analysis included standardized uptake value (SUV) max and SUV max/SUV blood pool ratio (aka target-to-background (TBR) max). The PET/CT results were generally concordant with MAGIC criteria: MAGIC criteria and PET/CT (based on VGS) were

consistent with infection in 25/35 (71%) and 27/35 (77%) of patients, respectively. The highest concordance between MAGIC criteria and PET/CT was for VGS ≥ 3 (88.6%), SUV max ≥ 7.3 (85.7%), and TBR max ≥ 4.2 (88.6%). Requiring 2/3 or 3/3 PET parameters positivity slightly increased concordance with MAGIC criteria to 91.4%. A small subset of patients had repeated PET/CT during antibiotic treatment, with 4/6 patients showing improvement in quantitative PET parameters and laboratory markers of inflammation.

The study by Dong et al.¹² meets nicely the quality standard measures as defined by the American College of Radiology (ACR) Definitions of Quality Components. These include utilization of statistical analysis, prospective design, consecutive patients to minimize selection bias, utilization of MAGIC criteria as reference standard, and blinded interpretation by 2 independent readers. Inter-observer and intra-observer agreements were excellent for VGS, SUV max, and TBR max (ICC > 0.9). In the absence of a "gold standard", which is a limitation of this and many other diagnostic studies in the field of AGI, Dong et al. compared the performance of PET/CT with MAGIC criteria. These include evidence from ¹⁸F-FDG PET/CT as a minor radiologic criterion. It is not clear whether the results of ¹⁸F-FDG PET were included as a minor radiologic criterion in classifying the patients or utilized to guide patient management. In this series of the patients, all subjects with at least one major criterion were ultimately classified as positive for AGI. So, inclusion of ¹⁸F-FDG PET as a minor criterion might not have affected the ultimate classification of the patients. However, this may be considered a fundamental problem if the tested methodology is also a part of the reference standard. Ultimately, in this small study of 35 subjects, 10 were considered negative for AGI. It is not clear how these patients were treated. Of the 4 patients with discordant PET/CT and MAGIC criteria, 1 was positive for AGI by MAGIC criteria, but had negative FDG PET/CT results. All four patients were treated with antibiotics with apparently no adverse outcome after 3 months. Unfortunately, no information is provided on the long-term management of the patients and whether the FDG PET/CT results played a role in selecting a conservative strategy, as in the 4 patients with discordant FDG PET-MAGIC criteria. As it is, we don't know if PET/CT and MAGIC criteria without PET/CT as a minor criterion had a similar accuracy or indeed were complementary in diagnosing AGI. In addition, it is not clear to what extent the diagnostic yield of FDG/PET may have been affected by antibiotic therapy.

The results of the study by Dong et al.¹² are generally in line with the results of another study recently published in JNC by Einspieler et al.¹⁴ This study, which

included a control group, utilized an almost identical approach in terms of PET analysis (with slightly more in-depth quantitative analysis) and reference standard (MAGIC), but it was retrospective and analyzed both thoracic and abdominal grafts. Einspieler et al.¹⁴ also demonstrated very high agreement between ¹⁸F-FDG PET/CT and MAGIC criteria. Yet, these studies leave us without the answer how to best utilize ¹⁸F-FDG PET/CT in the setting of suspected thoracic AGI. The high concordance of ¹⁸F-FDG PET/CT with MAGIC criteria would suggest that it can serve as an excellent alternative for contrast-enhanced CT in patients with renal failure or contrast allergy. However, in patients who can undergo contrast-enhanced CT, the impact of ¹⁸F-FDG PET/CT requires further investigation.

In the absence of a “gold-standard” of reference for AGI, longitudinal outcome studies are needed to assess the impact of different diagnostic tests on management decision, morbidity, mortality, and quality of life. In patients without contraindications to CT contrast, the added value of ¹⁸F-FDG PET/CT to contrast-enhanced CT or MAGIC criteria in driving the management or improving clinical outcomes, will have to be demonstrated to justify its routine utilization. Unfortunately, this study provides a little insight in this regard. Given the small number of patients at any single center, multi-institutional research (to allow enrollment of a large number of patients) and long follow-up periods are necessary to truly understand the impact of ¹⁸F-FDG PET/CT in AGI.

In order for prospective, multi-institutional longitudinal outcome trials to incorporate ¹⁸F-FDG PET/CT, the imaging approach will have to be standardized from acquisition, processing, and interpretation standpoints.¹⁵ Due to relatively favorable target-to-background ratio for ¹⁸F-FDG uptake in AGI, a major departure from standard oncologic PET/CT is not necessary,¹³ and EANM/SNMMI Guideline for ¹⁸F-FDG use in infection and inflammation can serve as an excellent starting point.¹⁶ Although studies investigating the use of ¹⁸F-FDG PET/CT in AGI, including this study, have recognized the value of both semi-quantitative scaling of visual findings (in particular, the importance of focality and high intensity of uptake for positive predictive value), as well as quantification with SUV max and TBR, the optimum approach to signal quantification remains to be determined. For instance, determining SUV max in the presence of metallic objects is fraught with inaccuracies. Accordingly, a more stringent approach will be necessary to standardize image interpretation across institutions.

The study by Dong et al.¹² also adds another layer of complexity by demonstrating better concordance between ¹⁸F-FDG PET/CT and MAGIC criteria in 14

patients with endovascular graft placement than in 21 patients with open surgical graft insertion. All 3 patients with positive PET and only minor MAGIC criteria were treated with open surgery. The authors speculated that open surgery may induce more sterile inflammation than endovascular approach, which may mimic infection on ¹⁸F-FDG PET/CT. ¹⁸F-FDG uptake at the suture sites may also complicate the interpretation of the images.¹⁷ However, with the small number of subjects in this study, it is premature to draw any firm conclusions on the effects of graft placement approach, except that this factor should be considered when planning and analyzing future studies.

With the myriad of imaging approaches for AGI that can potentially be taken, including contrast-enhanced CT, non-contrast CT, and MRI, each of which can be combined with PET, the most optimal imaging approach may remain elusive for a foreseeable future. Although at present, contrast-enhanced CT is considered the test of choice, the added value of CT contrast is not entirely certain. For example, major MAGIC radiologic criteria (perigraft air and fluid) can be assessed without the use of intravenous contrast. On the other hand, CT contrast will certainly improve assessment of minor radiologic criteria such as soft tissue inflammation/abscess or pseudoaneurysm formation. Although modern PET/CT scanners are perfectly capable of obtaining high-quality, diagnostic contrast-enhanced CT and PET images, the logistic and billing/reimbursement issues remain, and many institutions may be reluctant to take this approach. The EANM/SNMMI guidelines suggest that the use of contrast is probably indicated for vascular prostheses such as aortic graft and post-operative fever/fever of unknown origin, but not for vasculitis or orthopedic infection.¹⁶ Nevertheless, even a low dose non-contrast CT and PET combination, provides the opportunity to assess the structural criteria for AGI on CT images in addition to the biological information from PET. In fact, in the study by Dong et al., the highest VGS score of 5 was assigned based on combined focal intense uptake on PET and fluid collection on CT.¹² Emerging PET/MRI may also eventually impact the optimal approach toward AGI diagnosis. The potential advantages of PET/CT are not limited to AGI site itself. PET/CT protocols provide more complete body coverage than standard diagnostic CT protocols and may be superior to CT for detection of metastatic (from AGI), additional (in addition to AGI), or alternative (instead of AGI) sites of infection. In the settings of fever of unknown origin, FDG PET/CT is considered the test of choice capable detecting and often distinguishing (with limited specificity) between infectious, inflammatory, and neoplastic causes.¹⁶

Based on our experience with oncologic imaging, the true value ¹⁸F-FDG PET/CT in AGI management, may ultimately be in treatment response assessment rather than in the initial diagnosis. Instead of immediately deciding on surgical versus nonsurgical management, ¹⁸F-FDG PET/CT may allow the decision to be tailored based on the initial antimicrobial treatment response. In responding patients on ¹⁸F-FDG PET/CT, it may be possible to avoid morbid surgery and manage AGI conservatively in select cases. On the other hand, non-responding patients would undergo surgery. Such approach has been successfully utilized in oncology for many cancers. For example, a recent head and neck cancer prospective controlled randomized trial showed similar survival with lower morbidity and cost in patients who underwent PET/CT-guided surveillance than in patients who underwent planned neck dissection following the initial chemoradiation.¹⁸

In summary, the study by Dong et al.¹² adds to the considerable body of evidence supporting the value of ¹⁸F-FDG PET/CT in the evaluation and management of AGI. However, several issues regarding optimal ¹⁸F-FDG PET/CT utilization remain unclear. In particular, the added value of ¹⁸F-FDG PET/CT to clinical, laboratory, and contrast-enhanced CT evaluation has to be defined, for which carefully designed prospective multi-institutional longitudinal outcome studies will be required. In addition, a standardized approach for ¹⁸F-FDG PET/CT acquisition, procession, and interpretation, including formal FDG PET/CT interpretation criteria for AGI will need to be adopted. In the meantime, alternative, more specific molecular imaging approaches to imaging infection are under development and if introduced in the clinic may transform the diagnosis and management of AGI and other infectious processes.¹⁹

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