BACTERIAL ENDOCARDITIS

Imaging the Infected Heart

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This Focus discusses the merits of modern imaging techniques for the management of patients with suspected or proven infection and also addresses the challenges of detecting infective endocarditis early.

THE EVOLUTION OF IMAGING

The current generation of structural imaging techniques, including magnetic resonance imaging (MRI) and computed tomography (CT), provides anatomical scans with exquisite detail and high spatial resolution. However, many diseases start at the molecular and cellular levels, which may never translate to gross structural abnormalities. These technologies have proven to be insensitive for early detection of several diseases, including cancer, when therapeutic intervention would be desirable. In addition, because of the low sensitivity of structural imaging methods, the effects of systemic therapy cannot be adequately assessed, which is pivotal to clinical decision-making. In medicine, it is not uncommon to encounter suboptimal or no response to treatment, particularly for infectious diseases. As such, undue delays in using alternate therapies may result in further progression of the disease as well as undesirable side effects from the initial treatment. There is thus a dire need for imaging approaches that detect disease at the molecular and cellular levels during the early stages of pathogenesis.

In the 1970s, investigators noticed that the agent ^{18}F-fluorodeoxyglucose (FDG) was able to measure glucose metabolism in vivo quantitatively and in a dynamic manner, thus opening a new era in medical imaging at the molecular level (*1*). By that time, positron emission tomography (PET) had also emerged as a promising modality for imaging the biodistribution of labeled compounds in the clinic. Ever since, FDG–PET has been the workhorse for imaging glucose metabolism and has played a major role in examining disorders that are associated with altered glycolysis, such as central nervous system disorders, cancer, and inflammation.

We discuss in detail in this Focus recent efforts to image infection and inflammation, including recent papers on detecting acute infective endocarditis with advanced imaging methods, such as PET.

VISUALIZING INFECTION AND INFLAMMATION

In the 1930s, Warburg discovered increased glycolysis in cancer cells in vitro. It was noted thereafter that inflammatory cells also have high glycolytic activity that is similar to that of malignant cells (*2*–*4*). In recent years, the range of disorders with aberrant glycolysis that can be assessed by means of FDG-PET has increased and comprises common infections (such as an infected prosthesis, osteomyelitis, or a diabetic foot) and noninfectious inflammatory disorders, such as rheumatoid arthritis, regional ileitis, sarcoidosis, and atherosclerosis (*4*). FDG as a unique tracer has been used extensively for identification of infected sites in the human body and for monitoring response to treatment (*3*, *4*).

Two types of biological structures at the site of infection can be targeted with external imaging. One is microorganisms, such as bacteria; the other is inflammatory cells that home to the infected site. Although either of these could potentially serve as a reliable source for targeted imaging, there are major differences between the two with regard to modern imaging techniques. For example, the volume of microorganisms that reside at these sites is extremely small and provides limited options for detecting the infected areas (because few binding sites are available). Conversely, imaging inflammatory cells has proven to be relatively effective, as shown by a variety of approaches, in particular functional imaging techniques that use radiotracers. Nevertheless, detecting inflammatory cells is nonspecific and provides indirect evidence at best for local or diffuse infection. In other words, simply visualizing the presence of immune cells cannot differentiate between inflammation caused by microorganisms or by noninfectious diseases.

Efforts to radiolabel bacteria at the sites of infection have yielded minimal success, and most have not been translated into the clinic. This approach was adopted using single gamma-emitting radionuclides attached to bacteria-targeting compounds, including antibiotics (*5*). In recent years, efforts have been made to use positron-emitting radiotracers instead because of favorable physicochemical characteristics. With the radiolabled tracers, it is clear that positive results, which were reported by this approach, mostly reflected nonspecific leakage of the labeled agents at the sites of infection owing to the presence of a large number of leaky vessels. In other words, similar and positive results would be expected to be noted from inert preparations with no known attraction to the site, such as radiolabeled albumin. Therefore, there is some consensus that compounds that target bacteria and other microorganisms may not be promising enough to be pursued further at this time.

There are two possible options for visualizing inflammatory cells at the infected sites. One method is to label a patient's white cells ex vivo, reinfuse them intravenously, and monitor cell migration to the infected lesions by using conventional scintillation cameras. Unfortunately, there are serious shortcomings to this approach. The procedure is very time-consuming (3 to 5 hours for labeling, 24 hours for imaging), which results in many nonfunctional cells. In addition, the image quality is very poor (nontomographic), and the radiation dose to the sensitive organs is unacceptably high. The other option is to label white cells with positron-emitting compounds, such as FDG, and to image with PET. This method has also experienced minimal success. Because of these limitations to ex vivo labeling and positron-emitting labels, others have explored radiolabeled nanoparticles and FDG for visualizing immune response and inflammation. Further research is needed to determine the viability of this nanoparticle-based technique for routine use in humans.

FOCUSING IN ON ENDOCARDITIS

In spite of the successes made by modern imaging techniques in detecting infections in many organs, their role in visualizing

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endocarditis has been limited. Acute endocarditis is classically defined as inflammation of the endocardium (inner layer of the heart) and is a major clinical problem that progresses rapidly. Vegetations, the hallmark lesions of endocarditis, are composed of platelets, fibrin, microorganisms, and inflammatory cells. Endocarditis occurs as a result of implantation of circulating bacteria on the cardiac or aortic valves that have entered the bloodstream from the mouth cavity or the gastrointestinal tracts. Moreover, preexisting damage to the valve is considered a predisposing factor for infection. Of all of the modern structural imaging techniques, echocardiography (particularly the transesophageal approach) has been the most successful in identifying vegetative lesions present in the valves of the heart and the aorta in patients with endocarditis. Unfortunately, because of the small size of the lesions (several millimeters), a large number of lesions go undetected. In addition, structural imaging is nonspecific, cannot differentiate between active and inactive infection, and is unable to assess response to systemic therapy. Therefore, there is an unmet need for methodologies that allow timely detection of endocarditis and its complications, such as embolic lesions at distant locations, and also monitor response to treatment.

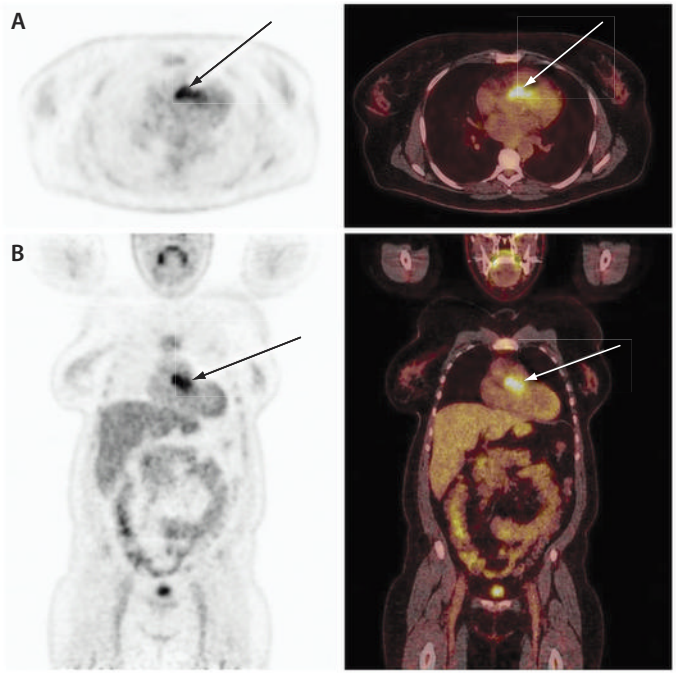

Fig. 1. The role of PET-CT in imaging infection. (**A**) Transaxial and (**B**) coronal FDG-PET-CT in a 47-year-old woman with infective endocarditis. PET images are on the left; the fused PET-CT images are on the right. Focal FDG uptake in the heart is noted by arrows in the region of the aortic valve. Reproduced with permission from (*7*).

A recent technical report by Panizzi *et al*. (*6*) describes in vivo detection of endocarditis caused by coagulase-positive *Staphylococcus aureus*, which is the most dangerous and virulent type that might not respond readily to treatment. The authors introduce an interesting method that incorporates both noninvasive fluorescence and PET imaging to visualize growing bacterial vegetations. First, a mouse model of *S. aureus* endocarditis was developed that recapitulates the bacterial lesions seen in the human condition. Because *S. aureus* is able to induce blood coagulation via staphylocoagulase, Panizzi *et al*. created a fluorescent prothrombin-based probe that could be activated in vivo by the enzyme. When injected into mice with endocarditis, the probe deposited at the sites of vegetation (damaged endothelium) and fluoresced brightly in ex vivo sections of the mouse aortas (*6*). A faint response was also noticeable in mice infected with coagulase-negative *Staphylococcus epidermidis*, but none at all was seen in uninfected control mice.

The goal is to use this noninvasive imaging method for diagnosis of endocarditis in humans. To this end, the authors used their prothrombin probe with fluorescence molecular tomography combined with x-ray computed tomography (FMT-CT) to image bacterial growths in vivo in living mice. They were able to confirm the presence of such vegetations 24 hours after injection with high specificity and high signal over background when compared with various control animals. Furthermore, Panizzi and colleagues were able to visualize in vivo the response to treatment with the antibiotic vancomycin, which resulted in a decrease in signal over the course of 48 hours. Lastly, a new prothrombin-based probe was generated for PET-CT imaging, which allowed for radiological imaging with standard instrumentation widely available in clinics. This radiolabeled prothrombin probe was similarly able to confirm the presence of vegetations in damaged aortas in living mice.

The observations made in mice with experimental endocarditis using both FMT-CT and PET-CT imaging are intriguing and innovative and may provide a powerful means for assessing this potentially life-threatening infectious disease in humans. It is important moving forward that this approach be tested in larger animals in order to determine the merit of optical imaging in detecting lesions that are distant from the imaging devices. Translation of this approach would also entail further clarifying the specificity of this tracer for *S. aureus* and no other bacteria. Panizzi *et al*. tested their agent in coagulase-negative *S. epidermidis*–infected mice, which argues for the specificity of the agent. However, the fact that the *S. epidermidis* vegetations accumulated a small amount of tracer (albeit much less than *S. aureus*) would be one reason to examine this in larger vegetation to ensure that the partial-volume effect common to imaging is not playing a role in the minimal visualization of vegetation.

TRANSLATIONAL CHALLENGES AND PROSPECTS

FDG in combination with PET-CT has also been used to identify vegetative lesions in the human heart, as well as at distant sites, owing to embolization of detached lesions (*7*–*10*). FDG binds to both clots and inflammatory cells and has therefore been used with great interest. Early clinical trial observations using FDG-PET show promise for the routine, noninvasive detection of endocarditis (*7*–*10*). As shown in Fig. 1, FDG-PET-CT was used to detect suspected infective endocarditis in a 47-year-old woman (*7*). One hour after injection, there was substantial uptake of FDG in the infected areas of the aortic valve, which was confirmed with separate blood cultures to be coagulase-negative *Staphylococci*. Other single-case studies have described the applicability of FDG-PET for diagnosing infection in the heart (*8*–*10*), especially when echocardiography presents unclear results, such as in the case of patients with prosthetic vales or indwelling pacemakers (*7*).

The method described by Panizzi *et al*. allows for concurrent imaging to detect

vegetative lesions and confirmation of the type of bacteria present by use of the prothrombin dye. This multifaceted approach is promising for early detection and treatment in humans; however, further validation will be needed to assess its utility in routine diagnosis. The major concern is that a very small fraction of the vegetations might be stained superficially with the compounds described, which may not be resolved by existing PET imaging instruments. Therefore, there is a need for novel imaging efforts that overcome some of the deficiencies associated with PET and CT. The major challenges of visualizing relatively small lesions, such as vegetations due to endocarditis in the heart and aortic valves, are twofold: the size of the abnormalities to be detected and the constant rhythmic motion of the heart. Although modern structural imaging modalities, such as CT and ultrasound, have high spatial resolution and can generate scans quickly, they lack high-contrast resolution and therefore suffer from low sensitivity in detecting these lesions.

PET-CT has the greatest potential for overcoming these deficiencies and should be pursued as a viable option for managing patients with this serious heart infection. Newly developed PET compounds should label the entire lesion and not bind superficially to the surface. At present, the suboptimal spatial resolution of PET (around several millimeters under ideal conditions) in detecting small lesions will prevent the accurate diagnosis of endocarditis. To overcome further deterioration of image quality owing to cardiac motion, gated imaging based on cardiac cycle by using ECG may improve image resolution and, in turn, the sensitivity of the PET-based approach. Assessing global disease activity in the entire heart may prove to be a possibility in this setting.

As described in this Focus, there are several emerging and novel approaches to diagnosing and treating infective endocarditis early (*6*–*10*). Large-scale, prospective multicenter trials should be carried out to define the merits of these novel imaging methodologies in the near future. Until more human trials are undertaken, the potential role and benefit of such approaches in the clinic will remain unclear.

REFERENCES AND NOTES

1. J. B. Alavi, A. Alavi, J. Chawluk, M. Kushner, J. Powe, W. Hickey, M. Reivich, Positron emission tomography in patients with glioma: A predictor of prognosis. *Cancer* **62**, 1074–1078 (1988).
2. H. Zhuang, M. Pourdehnad, E. S. Lambright, A. J. Yamamoto, M. Lanuti, P. Li, P. D. Mozley, M. D. Rossman, S. M. Albelda, A. Alavi, Dual time point 18F-FDG PET imaging for differentiating malignant from inflammatory processes. *J. Nucl. Med.* **42**, 1412–1417 (2001).
3. S. Basu, A. Alavi, Unparalleled contribution of 18F-FDG PET to medicine over 3 decades. *J. Nucl. Med.* **49**, 17N–21N, 37N (2008).
4. S. Basu, T. Chryssikos, S. Moghadam-Kia, H. Zhuang, D. A. Torigian, A. Alavi, Positron emission tomography as a diagnostic tool in infection: Present role and future possibilities. *Semin. Nucl. Med.* **39**, 36–51 (2009).
5. K. E. Britton, D. W. Wareham, S. S. Das, K. K. Solanki, H. Amaral, A. Bhatnagar, A. H. Katamihardja, J. Malamitsi, H. M. Moustafa, V. E. Soroa, F. X. Sundram, A. K. Padhy, Imaging bacterial infection with (99m)Tc-ciprofloxacin (Infecton). *J. Clin. Pathol.* **55**, 817–823 (2002).
6. P. Panizzi, M. Nahrendorf, J. L. Figueiredo, J. Panizzi, B. Marinelli, Y. Iwamoto, E. Keliher, A. A. Maddur, P. Waterman, H. K. Kroh, F. Leuschner, E. Aikawa, F. K. Swirski, M. J. Pittet, T. M. Hackeng, P. Fuentes-Prior, O. Schneewind, P. E. Bock, R. Weissleder, In vivo detection of *Staphylococcus aureus* endocarditis by targeting pathogen-specific prothrombin activation. *Nat. Med.* (2011). 10.1038/nm.2423
7. S. H. Vind, S. Hess, Possible role of PET/CT in infective endocarditis. *J. Nucl. Cardiol.* **17**, 516–519 (2010).
8. S. Moghadam-Kia, A. Nawaz, B. C. Millar, J. E. Moore, S. E. Wiegers, D. A. Torigian, S. Basu, A. Alavi, Imaging with (18)F-FDG-PET in infective endocarditis: Promising role in difficult diagnosis and treatment monitoring. *Hell. J. Nucl. Med.* **12**, 165–167 (2009).
9. R. F. Yen, Y. C. Chen, Y. W. Wu, M. H. Pan, S. C. Chang, Using 18-fluoro-2-deoxyglucose positron emission tomography in detecting infectious endocarditis/endoarteritis: A preliminary report. *Acad. Radiol.* **11**, 316–321 (2004).
10. J. Van Riet, E. E. Hill, O. Gheysens, S. Dymarkowski, M. C. Herregods, P. Herijgers, W. E. Peetermans, L. Mortelmans, (18)F-FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. *Eur. J. Nucl. Med. Mol. Imaging* **37**, 1189–1197 (2010).

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