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EDITORIAL COMMENT

Imaging for Infected Cardiac Implantable Electronic Devices

A New Trick for Your Pet*

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Cardiac implantable electronic devices (CIEDs), having been shown capable of improving the quality as well as duration of life, are playing an increasingly important role in the management of patients with disorders of heart rhythm and/or function. Over the last decade there has been a remarkable increase in CIED utilization; in the United States alone 235,567 new and 101,042 replacement pacemakers and 133,262 new and 73,217 replacement implantable cardioverter-defibrillators (ICD) were implanted in 2009 (1). Much of this growth has been driven by the broadened utilization of the ICD, which now accounts for over a third of all CIEDs being placed. As the indications for CIEDs have expanded, the population in which they are being implanted has become older and afflicted with a higher prevalence of comorbidities (2). This would appear to underlie observations that the increased rate of device implantation has been accompanied by an even greater increase in the rate of CIED infection (3). Thus, from 2004 to 2008 the rate of CIED infection increased from 1.5% to 2.4% (4). Infection of these devices carries with it significant risk of death, considerable morbidity, and the certainty of expense.

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The CIED system most frequently consists of intravascular (leads) and subcutaneous (generator) components although sometimes leads are placed on the epicardial surface of the heart or, more rarely, subcutaneously, while the generators may be positioned below a muscle. Either of the components, placed at any location, may be the site of initiation and/or presentation of infection. Most often infection presents as a process localized to the generator pocket. It is thought to result from microbes introduced at the time of device placement or from a subsequent breach of the skin. This assumption is supported by the temporal relationship of pocket creation or revision with the onset of infection as well as the finding of typical skin flora in the pocket at the time of implant (5) and in asymptomatic patients receiving generator exchange (6). About 40% of infections present with systemic symptoms and bacteremia often due to seeding of leads from a source other than the pacemaker pocket (e.g., intravenous access line, hemodialysis fistula). Regardless of initial presentation, it is not unusual to find that both leads and generator culture are positive for the offending organism. While a wide variety of bacteria and fungi have been associated with CIED infections, those usually responsible are coagulase-negative *Staphylococcus* species, *S. aureus*, and *Enterococcus* (7). These organisms, in addition to exhibiting an increasing prevalence and spectra of antibiotic resistance, have surface components that facilitate attachments to tissue and foreign material. Once attached they may protect themselves from host defenses and antibiotics by producing biofilm and/or residing within or under endothelium (7,8). Thus, while CIED infections may be suppressible by antibiotics, they are generally considered incurable by such therapy alone. Thus, complete removal of all hardware (including prior abandoned devices) is considered necessary in almost all situations in which any part of the system is infected (8).

Removal of a recently implanted CIED is usually straightforward and safe; however, chronically implanted lead systems, whether infected or not, may be difficult to extract because of fibrous intravascular and intracardiac adhesions. Extraction in such cases is accompanied by major complication in up to 2% of procedures, including death in about 0.3%. The non–procedure-related in-hospital death rate of infected patients, influenced by the infection itself and/or comorbidity, may be as high as 5%, with a 1-year mortality of 17% (9). Death is more common in patients with endovascular infection and appears related to a delay in hardware removal despite antibiotic therapy (10). While as many as 40% of patients may not need a replacement CIED after extraction and infection control (11), most patients do eventually receive such. Device-dependent patients often remain in the hospital until this is accomplished, which may be in excess of 2 weeks in those having endovascular infection. Recurrent infection after removal and subsequent CIED replacement is not frequent but has been attributed to retained hardware, seeding from a persistent infection at another site, or premature replacement of a CEID. The in-hospital charges for a CIED infection are in excess of $140,000 (4).

Delay from presentation to hardware removal stems from failure to recognize the presence of an infection or mistaken attribution of an infection to another source is thought to increase the risk of adverse outcome for those with CIED

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infection. A high index of suspicion is essential for early diagnosis and should trigger blood culture, antibiotic therapy, and, in those with bacteremia or who have been on antibiotics prior to a negative culture, transesophageal echocardiography (TEE) (8). Unfortunately the diagnosis may still remain unclear because the results of such testing are neither absolutely specific nor sensitive for device infection. Physicians and surgeons with interest and expertise in the removal of chronically implanted CIEDs ("extractionists"), in consultation with infectious disease specialists, are the final arbiters of whether the system should be explanted. Their decision making would be facilitated by the availability of additional tools of demonstrably high diagnostic accuracy. The potential value of radionuclide imaging in the diagnosis of CIED infection has been suggested in a number of case reports and small series of patients. Agents such as ^{67}gallium (12), ^{111}indium-labeled leukocytes (13), and ^{99m}technetium-labeled leukocytes (14) have demonstrated uptake in both the device pocket and along the subcutaneous and intravascular course of leads in patients with infection.

There is increasing evidence that fluorodeoxyglucose marked by fluorine-18 (^{18}F-FDG) positron emission tomography (PET) coregistered with computed tomography (CT) is useful for the detection and localization of infection (15–17) including infective endocarditis (18). A number of case reports confirm the potential applicability for this technique in suspected CIED infection (19–21) with the ability to localize infection on the device as well as its spread to near (heart valves) and distant metastatic sites, which can be of great practical value. The high diagnostic accuracy and cost effectiveness of ^{18}F-FDG-PET in the evaluation of fever of unknown etiology (22) and blood stream infections (23) suggest that this modality may be helpful early in the workup of these disorders. Ploux et al. (24) explored the utility of ^{18}F-FDG-PET in 10 CIED patients presenting with fever of unknown origin despite evaluation that included TEE. Six had tracer uptake on a lead and had hardware removal while 4 had no uptake and were treated conservatively. Infection was confirmed by culture of extracted leads in all 6 of the former while none of the latter had recurrence during a 13-month follow-up. Forty additional CIED patients undergoing ^{18}F-FDG-PET/CT for suspected malignancy formed a control group in which 3 had a false positive scan for CIED infection. Similarly, Bensimhon et al. (25) evaluated 21 patients suspected of having device infection and 14 "control" CIED patients being evaluated by ^{18}F-FDG-PET for oncologic purposes. Of the former the sensitivity and specificity for detecting pocket infection were both 100%; for lead infection, specificity was also 100%, however, the sensitivity was only 60%. Overall, ^{18}F-FDG-PET/CT performed well in the detection of CIED infection per se, with a sensitivity of 80% and specificity of 100%. In 4 patients having device infection ^{18}F-FDG-PET/CT also demonstrated 2 lung infections, infection of a right ventricular to pulmonary artery conduit, and an infection of the tarsal bone. None of the control patients were positive for CIED uptake. The authors suggest that these results might have changed management in 28% of patients suspected of having CIED infections.

In this issue of the *Journal*, Sarrazin et al. (26) make additional important contributions regarding the utility of ^{18}F-FDG-PET/CT for suspected CIED infection. They provide evidence that inflammation accompanying acute pocket surgery does not result in false positive imaging, thus extending the applicability of this technique to suspected early device infection. The authors also demonstrate the ability to distinguish deep pocket infection, which implies device infection and the necessity for device removal, from superficial infection, which can be treated with antibiotics alone. Interestingly they identified 4 patients (3 of whom were bacteremic) with negative scans, despite TEE-defined lead and/or valve "vegetations," who were treated with antibiotics only and remained free of recurrence over extended follow-up. The authors conclude that incorporation of ^{18}F-FDG-PET findings in the clinical decision making prevented the need for device removal in 6 of the 42 patients without late sequelae.

Like other imaging options including TEE, ^{18}F-FDG-PET does not identify infection per se; rather, it localizes in metabolically active cells be they malignant growths or leukocytes responding to inflammation or infection. It is not clear, then, whether this modality can be relied upon in the presence of marked leukopenia, although some recent data suggests that it might (27). Similarly, suppression of infection by a prolonged course of antibiotics prior to ^{18}F-FDG-PET scanning may result in false negative imaging. Because imaging depends on the uptake of tagged glucose, the presence of hyperglycemia may interfere with this process and also be a cause of a false negative study. False positive scans may occur as well; Sarrazin et al. (26) attributed false positive pocket uptake in one patient to a Dacron pouch used to contain the generator. Further study is necessary to determine whether other additions to the pocket, such as an antimicrobial envelope used preferentially in patients at increased risk of pocket infection, would produce a similar situation. Clot may also exhibit ^{18}F-FDG-PET uptake (28) and, as thrombus in the central venous system is not uncommon after lead placement, it may be difficult to differentiate infection on the lead traversing the vein from clot.

Should ^{18}F-FDG-PET be part of the routine evaluation of CIED infection? The evidence thus far is encouraging, but wider experience is needed before such a recommendation can be made. The scan is relatively expensive (at least 3 times that of a TEE at my institution) and it exposes the patient to radiation, which admittedly is modest considering the importance of establishing a diagnosis. While its use at this time is justified in diagnostic dilemmas, a better appreciation of the incidence of false-negative and false-positive scans as well as the possible causes of such would be necessary before it is widely embraced. Additionally, while

^{18}F-FDG-PET/CT is generally available, it is not clear whether additional interpretive skills to appreciate subtleties of CIED infection are required for optimal diagnostic accuracy. Favorable experience derived from prospective employment of the diagnostic algorithms proposed by Sarrazin et al. (26) would go far in determining whether this PET will indeed become the extractionists' best friend.

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