A Foregone Conclusion?
Risk Stratification in Pacemaker-Associated Endocarditis*

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Recent European guidelines have emphasized the association of vegetation size with embolic risk in endocarditis (1). On these grounds, left-sided vegetations >1 cm, and right-sided vegetations >2 cm are considered to be an indication for surgery. In this issue of JACC, investigators from the MEDIC (Multicenter Electrophysiologic Device Cohort) registry report the importance of vegetation size in a group of 129 patients with pacemaker lead-associated endocarditis (LAE) (2). LAE accounts for approximately 20% of cardiac implantable electronic device (CIED) infections (3). Although there is an early incidence of infection after CIED insertion, it can also present months or years later. Device infections are commonly associated with more complex and prolonged procedures such as implantable cardioverter-defibrillator device implantation (with or without cardiac resynchronization therapy). This is known to pose the most risk to a subgroup of older patients (more commonly men) with co-morbid diseases (heart failure, diabetes, hypertension, and renal impairment) undergoing early pocket re-exploration or an upgrade procedure (4). Unfortunately, although the problem occurs in <0.5% to 1.5% within 1 year of implantation (4,5), the rate of infections seems to be increasing.

Like endocarditis in general, LAE is a malignant disease, with a 1-year mortality of 12% for pocket infections and 25% for endovascular infections in patients referred to the Cleveland Clinic between 2002 and 2007 (4), and a mortality of >10% in this study by Greenspon et al. (2). About one-half of the incremental long-term mortality occurs after discharge (5). Current treatment is based upon the use of parenteral antibiotics and lead removal (6), which may be surgical if vegetations are large. CIED infection not only causes increased acute and long-term mortality, but also carries a substantial cost burden, related mainly to intensive care (5). In that cost analysis, the standardized adjusted incremental cost that is due to infection was $14,360 to $16,498. A better method for evaluating risk might allow prioritization of interventions.

The results of this study by Greenspon et al. (2) show that patients with small (<1 cm) vegetations were more likely to present with features of pocket infection. The same database has previously been used to document that LEA with small vegetations usually occurs early after implantation (6) (probably from spread of pocket infection to the leads) and that 55% of patients with CIED pocket infection present <12 months following their last CIED-related procedure (7). Patients with early infection present with localized inflammation and are more likely to be female and on anticoagulation. By contrast, larger (>1 cm) vegetations—known to present later after implantation—were more likely associated with evidence of systemic infection, likely related to hematogenous spread from other foci. Patients with larger vegetations were older and more likely to have co-morbid disease, including coronary disease. Previous
work has shown both Staphylococcus aureus and coagulase-negative staphylococci to be involved in CIED, with no differences in microbiology to support a 1-year cutoff between early and late CIED infection (8). About 20% of all CIED-related infections are due to non-staphylococcal organisms, although outcomes seem similar in all groups (9).

The publication emphasizes the value of registries in gathering insight regarding the presentations and outcomes of uncommon illnesses by gathering data at multiple high-volume centers (2). Nonetheless, some design aspects are imperfect. A systematic process for reviewing images would have reassured the reader that the same approach was used for image acquisition as well as measurement. The selection of a 1-cm cutoff as a meaningful number regarding vegetation size is arbitrary. Length measurement may be difficult in a highly mobile lesion that may be partially out of the ultrasound plane. Recent work has emphasized that vegetation length from 2-dimensional (2D) transesophageal echocardiography was 3.2 mm (95% confidence interval: 2.1 to 4.2 mm) less than the length estimated from 3D imaging, which was more accurate than 2D imaging for the prediction of embolic events (10). Even 3D imaging may not permit accurate measurement if the lesion is moving across planes, and the spatial resolution of this technique may introduce other challenges to the detection of thin, friable structures.

In the context of these findings, vegetation length should not be considered to be central in clinical management of LAE. First, lead masses do not necessarily constitute vegetations, and as mentioned earlier in the text, the measurement of vegetation length can be difficult. Second, LAE is a malignant illness, with a mortality of >10%, with no difference in the outcomes of the groups based upon vegetation size (2). Third, the differences between groups may simply reflect time bias leading to confounding by the duration of illness. Finally, complete removal of hardware is necessary and widely performed in LAE (11), and the appropriateness of this strategy was confirmed by the finding in this study (2) that patient outcomes seemed to be better with device removal than in those treated medically. Indeed, in a recent study of 151 patients with device infections who underwent successful treatment including extraction and reimplantation showed no difference in all-cause mortality, with patients with biventricular devices never known to become infected (p = 0.21). The finding of similar outcomes with small and large vegetations in the current paper (2) supports the performance of lead extraction once there is evidence of systemic infection or evidence of lead or valvular endocarditis (12).

The best strategy for CIED infection is prevention, including meticulous aseptic technique and prophylactic antibiotics, minimizing exposure and handling of the device, and potentially including an antibacterial envelope (13). If this fails, the results of this study support early diagnosis and aggressive intervention. LAE is associated with short- and long-term mortality, independent of age, renal failure, heart failure, cancer, and immune suppression (14). Suspected LAE should provoke performance of transesophageal echocardiography—preferably 3D because it has higher sensitivity for infection (9). Vegetations are easily missed in the superior vena cava, which requires careful evaluation in the bicaval view. As recently published in JACC, labeled autologous white blood cell scintigraphy has a high sensitivity (94%) for device infection, especially LAE (15), exceeding those of echocardiography (81%) and Duke criteria (31%). Likewise, 18F-fluorodeoxyglucose positron emission tomography has a potential role when the diagnosis is suspected but not confirmed (16).

The use of these imaging in LAE is to ensure early diagnoses. Once the diagnosis is made, the management policy should be clear, irrespective of the imaging findings.

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