Infectious complications of electrotherapy: theory and practice

To the Editor With regard to a recent publication of the updated European Society of Cardiology guidelines focusing on the prevention, diagnosis, and treatment of infective endocarditis (IE),[1] we would like to draw the readers' attention to current challenges in the diagnosis of infectious complications associated with transvenous pacing. We have read a review article by Polewczyk et al[2] with great interest. However, there are some aspects that in our opinion require clarification. Moreover, we believe that the perspective presented by the authors on the matter of cardiac device infections has to be broadened.

The presence of infectious complications has a strong impact on the patient's prognosis and life expectancy and is a Class I indication for transvenous lead extraction (TLE) according to a Heart Rhythm Society expert consensus.[3] In most studies, IE is one of the most important risk factors for mortality after TLE.[4]

Due to different management procedures for patients with various types of infection, it is logical to categorize these types as lead-dependent infective endocarditis (LDIE) and local/pocket infection (without fulfilling criteria for LDIE). Both require a different duration of antibiotic therapy and a delay before cardiac implantable electronic device (CIED) reimplantation. It needs to be highlighted that there are few data on the optimal time for reimplantation.[1] Early reimplantation should be avoided due to the risk of recurrent infection.

The 2009 ESC guidelines provide clear criteria that should be met to diagnose endocarditis, the so called Duke criteria.[5] For patients with CIEDs, 2 additional major criteria have been introduced: the presence of local infection symptoms and pulmonary embolism. In order to diagnose endocarditis, it is necessary to meet either both major criteria, 1 major criterion and 3 minor ones, or 5 minor criteria. A possible LDIE diagnosis can be satisfied with either 1 major and 1 minor criterion, or 3 minor criteria. The authors of the guidelines emphasize the high level of sensitivity and specificity (80%) in the diagnosis of endocarditis, which is characterized by the Duke criteria, based on the clinical picture and the results of echocardiography and microbiological tests. However, due to the fact that the above criteria have certain shortcomings and are still waiting for formal validation, it is important to conduct an in-depth clinical assessment, especially given reduced sensitivity of the criteria, that is, negative blood cultures when infection is related to artificial valves or pacemaker leads.[5] Therefore, in the 2015 ESC guidelines, the Duke criteria were extended to include a positive positron emission tomography (PET) or single-photon positron emission tomography computed tomography–computed tomography (SPECT-CT) results as the major criteria used to aid the diagnosis of IE.[1] Demonstration of abnormal activity with the use of SPECT-CT relates to artificial heart valves only. The existing data are already insufficient to consider SPECT-CT as a diagnostic criterion for LDIE; however, it is an additional tool in patients with suspected LDIE, positive blood cultures, and negative echocardiographic results (Class IIb, C).[1]

The available literature provides evidence on the difficulties in the real diagnosis of IE in the presence of CIEDs. Polish authors published 2 studies in a single patient cohort. In the first study, they did not differentiate between definite and possible IE diagnoses, while in a subsequent study, such a classification was introduced.[6,7] In the first study, they used their own modification of the ESC criteria and diagnosed definite IE in the presence of 1 major and 2 minor criteria. Moreover, in the second publication, they used the ESC criteria, but this did not change the number of IE diagnoses. Notably, the authors neither explained the microbiological methods nor provided the number of positive blood cultures and the pathogens, although the guidelines clearly stated that in order to fulfill the major criterion, it is necessary to obtain the typical IE microorganism from at least 2 different cultures. When a positive blood culture does not meet the major criterion, it adopts the significance of a minor criterion. It should be noted that the presence of *Staphylococcus epidermidis* in a blood culture should lead to the assumption of sample contamination. Furthermore, positive microbiological tests of fragments of the leads or tissue removed during TLE procedures (including blood collected from the Byrd dilator) are not treated

as a minor Duke criterion for LDIE, even if there was no contact with local infection.[1] In the previous version of the guidelines, it was proposed that the positive results of cultures from leads be recognized as a sign of LDIE in the absence of pocket infection or when the lead was removed through an incision distant from the pocket or by cardiac surgical extraction.[5] Currently, it is recommended to collect lead-tip cultures when the CIED is explanted (Class I, C).[1] The purpose of the recommendation in a patient being already treated with antibiotics is not clear.

The evaluation of the next major criterion for IE, which is the presence of vegetation or abscesses on echocardiography, may also cause diagnostic problems in a patient with endocardial leads. Vegetation is defined as a mobile or fixed intracardiac mass on a valve or other endocardial structure or on the material implanted into the heart. An abscess is a thickened, inhomogeneous area within the valvular annulas or adjacent myocardial structures with increased or reduced echo density. In the guidelines of 2009 and 2015, there is no information as to how to interpret the presence of a thickened fragment of the electrode on echocardiography.[1,5]

The available literature shows that from the time of implantation, the leads undergo a process of wear. In the search for the causes of LDIE, Polish authors have assessed the insulation of the removed leads and reported damage to the lead insulation, resulting in lead unsealing. Breakage in the insulation exposes the inner parts of the lead and creates an "anchor" for bacteria, thus promoting the formation of vegetations in right heart cavities.[8,9] This finding has led to the introduction of a new name for IE in the presence of leads, namely, LDIE.[10] Studies concerning the damage of polymer insulation have gone in 2 directions. One of the teams has attributed the essential role to biodegradation of the silicone insulation with the participation of macrophages.[11] The theory of biodegradation does not explain the occurrence of the insulation damage predominantly in the intracardiac parts of the leads, while macrophages have access to the entire length of the lead in the cardiovascular system. Meanwhile, only the mechanism of the tribological wear of insulation explains the damage of the leads at sites of intensive lead bending during heart contraction.[12] The analysis of pictures from scanning electron microscopy has demonstrated that the silicone insulation undergoes tribological wear in all the assessed leads and the initial stage of tribological wear of the lead is its fatigue and adhesive wear. The unsealing of endocardial leads, along with the exposure of their inner lumen, is the underlying reason for LDIE in most cases. However, the guidelines do not currently recommend that the lead insulation be tested after its removal.

The diagnosis of LDIE in cases of patients with ongoing pocket infection is seemingly easy. Pocket infection is a major Duke criterion for LDIE, and the presence of the leads in the cardiovascular system is a minor Duke criterion for LDIE. This means that any local infection meets the criteria for a possible LDIE. If local infection is accompanied by a fever over 38°C, the probability of LDIE is increased, because 1 major Duke criterion and 2 minor Duke criteria are fulfilled. Such an interpretation, without taking into account the evidence of endocardium involvement in the infectious process, may lead to false-positive diagnoses of LDIE. On the other hand, resignation from taking blood cultures and performing echocardiography in patients referred for TLE with symptoms of pocket infection may result in false-negative diagnoses. It is essential to perform a wide array of diagnostic and imaging tests in each patient with pocket infection to confirm or exclude the diagnosis of LDIE. It has been shown that additional tests, mainly echocardiography, enable the precise identification of LDIE in nearly 20% of 303 patients referred for TLE due to pocket infection.[13]

The presence of the abnormal masses assumed to represent vegetations in the right heart cavities, combined with a minor criterion which is the indwelling endocardial leads, confirms the diagnosis of possible LDIE. At this point, a differential diagnostic process should be initiated to assess whether the masses are vegetations or thrombi. It is worth mentioning that since August 2014, we have been using a novel imaging technique, SPECT-CT with labeled leukocytes, in order to identify the source of infection. SPECT-CT was predominantly used in patients with abnormal masses attached to the leads in the absence of other signs of LDIE. According to the available literature, SPECT-CT reliably excluded device-associated infection during a febrile episode and sepsis, with a negative predictive value of 95%.[14] Similarly, a very high negative predictive value for SPECT-CT was obtained in patients with masses in the right heart cavities assumed to represent vegetations.[15]

In the light of these considerations, it is usually challenging to determine the real extent of infection in patients presenting with either local infection or LDIE. The termination of the diagnostic process before completion of all the required diagnostic tests for LDIE substantially affects diagnosis and treatment. The significant discrepancies in the available reports on the prevalence of various types of infectious complications in patients referred for TLE are largely caused by inconsistencies in the application of diagnostic criteria.

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