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Short communication

The "Subtle" connection between development of cardiac implantable electrical device infection and survival after complete system removal: An observational prospective multicenter study☆

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ABSTRACT

Background: Despite the improvements in transvenous lead extraction (TLE), patients with cardiac implantable device related infection (CIEDI) have a poor prognosis at long term. We explored the possible role of factors associated with development of CIEDI as predictors of post-TLE survival.
Methods: We performed a multi-center prospective observational study in a population of consecutive patients referred for TLE for CIEDI. We adopted a previously developed 10-point scale for CIEDI risk stratification and assessed its performance in predicting post-TLE survival.
Results: We enrolled 169 consecutive patients with CIEDI (systemic infection in 48.5% and vegetations in 24.5%). A Shariff score ≥3 was present in 102/169 (60.4%) of the enrolled patients. Complete radiological success of TLE was obtained in 163 patients. Twenty-seven patients (15.9%) died after a mean follow-up of 20.8 ± 12.0 months. Two factors were independently associated with post-TLE death: a Shariff score ≥3 (HR 10.833, 95% CI 2.544–46.129; p = 0.001) and the presence of vegetations at transesophageal echocardiography (HR 3.324, 95% CI 1.530–7.221; p = 0.002).
Conclusions: Risk factors for development of CIEDI are also predictive of post TLE mortality, together with the presence of vegetations. Improvement of our preventive strategies for CIEDI is crucial for enhancing the outcomes of CIED patients overall.

1. Introduction

Cardiac implantable electrical device infections (CIEDI) represent a type of complications that are known to significantly affect patient outcomes and healthcare costs [1]. Despite a great improvement in techniques and results of transvenous lead extraction (TLE) procedures [2–5], the long-term survival after TLE for CIEDI is still poor [6–8]. The development of leadless pacing systems and entirely subcutaneous defibrillators [9,10] cannot at present satisfy the huge clinical demand. Another approach is to enhance CIEDI prevention, especially for high-risk patients [11]. However more knowledge on post-TLE risk stratification is needed.

We performed this multi-center prospective observational study to test the hypothesis that factors predicting the development of CIEDI [11] are also associated with post-TLE mortality.

2. Methods

2.1. Study population

All consecutive patients >18 years old, affected by local/systemic CIEDI, referred for TLE at two regional referral centers for TLE, were considered for inclusion in a prospective multi-center registry, approved by the institutional ethics committee on human research. All patients provided informed consent and were informed about the study purpose. An exclusion criterion was the presence of any pre-TLE condition for which acute/late cardiac surgery was mandatory.

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2.2. CIED infection management

All patients underwent clinical history, physical examination, blood cultures (≥3 sets), transthoracic and transesophageal echocardiogram (TEE). The diagnosis/suspicion of CIED infective endocarditis (CIEDIE) was formulated according to modified DUKE criteria [12]. All patients underwent an accurate re-assessment of CIED indication, including evaluation of pacemaker (PM) dependency after appropriate wash-out of drugs (whenever feasible).

TLE procedures were performed in accordance with EHRA recommendations [13]. After generator removal, the leads were extracted via subclavian (in selected cases, via femoral) vein, adopting a step-up approach: first a manual traction with non-locking stylets, followed by traction with locking size-matched stylets. When required, a standard mechanical sheath was used, followed in some cases by a rotational/laser potentiated sheath. After TLE, lead tips and CIED were sent for culturing. To minimize the risk of CIEDI recurrence, combined TLE and CIED re-implantation procedure was performed only in PM-dependent patients, preferentially using an epicardial approach [14], while the other procedures were delayed, according to current guidelines [15].

2.3. Data collection and follow-up

The following data were recorded:

Pre-TLE: patient history, clinical findings, CIED characteristics, laboratory data, cultures, TEE data, drugs.

TLE-procedure: TLE approach and results;

Post-TLE: clinical course, re-implantation, follow-up data (phone contact every three-to-six months and periodical in-office follow-up at 6 months and every year thereafter).

2.4. Analytical methods

Previous studies showed several risk factors for CIEDI [16]. We adopted a 10-point scoring system, already tested for CIEDI risk stratification [11]. One point was assigned to each of the risk factors (the modifications made to adapt these factors to pre-TLE setting are reported *in italics*): (1) diabetes mellitus, (2) heart failure, (3) oral anticoagulation, (4) chronic corticosteroid use, (5) renal function impairment *(here defined as a GFR < 60 ml*/min*)*, (6) prior CIED infection *(or CIED pocket revision, after the last CIED procedure)*, (7) more than two leads, (8) presence of epicardial leads, (9) temporary PM at implantation (*PM-dependency*), and (10) CIED system pulse generator replacement or upgrade (*during the last pre-TLE CIED procedure, excluding pocket revisions*). According to Shariff et al. [11], early re-interventions were not included, despite their strong association with CIEDI, since they prove unpredictable before the procedure. This relatively simple score was developed to stratify the pre-operative risk of CIED infection based on the risk factors reported in the literature. Patients with ≥3 points presented an infection rate 2.38 times the rate of the remaining population in a retrospective analysis on >1000 patients.

Continuous variables are expressed as mean ± standard deviation, if normally distributed, otherwise as median and interquartile ranges. Significance of between-groups differences was assessed by two tailed Student's *t*-test, or by the equivalent non-parametric test, when appropriate. Discrete variables are expressed as frequencies and percentages. Significance of different distribution was tested by using the Chi-squared or Fisher's exact test (as appropriate) for binary variables, and the Mann-Whitney test for ordinal variables. Kaplan–Meier survival curves estimated the unadjusted survival distributions from death after TLE. Log-rank test was adopted to assess between groups survival and Cox proportional hazards regression analysis was performed to determine clinical predictors of outcome. Hazards risks (HR) were reported with 95% confidence intervals (95%CI). We used SPSS Version 23.0.0 (Statistical Package for Social Sciences Inc.) for statistical analysis, with significance set at $p < 0.05$.

This report adheres to the statement of ethical publishing as appears in the International Journal of Cardiology [17].

3. Results

169 CIEDI patients who underwent TLE were included in the analysis: 87 with rejected CIEDIE (no vegetations at TEE), 45 with possible CIEDEIE (8 with vegetations) and 37 with definite CIEDIE (34 with vegetations). Twelve patients were excluded because of a primary indication for heart surgery. A Shariff score ≥3 was present in 102 (60.4%) of the enrolled patients. Complete radiological success of TLE was obtained in 163 (96.4%), in 118 with the use of powered sheath (49 rotational, 67 laser sheaths and two patients with both type of sheaths). Four subjects experienced a major complication (two vascular tears and two pericardial effusions) requiring urgent surgical intervention in two cases. Only 88 (52.1%) patients underwent CIED re-implantation before hospital discharge: 56 within 72 h of TLE (all with local CIED infection, Table 1), the remaining within 5–10 days. In particular, among the 41 PM-dependent patients 28 were re-implanted at the time of TLE (either with epicardial device: 8 CRT, 15 single/dual chamber PM, 2 single/dual chamber ICD; or with transvenous devices in selected patients with local infection: 3 PM), while the others were all re-implanted before discharge (5 CRT, 2 ICD and 6 PM). The two patients with vascular tear were re-implanted epicardially during the same procedure. Twenty-seven were re-implanted within 6 months of discharge based on clinical judgment. After a mean follow-up of 20.8 ± 12.0 months, we observed 27 deaths. The estimated death rate in our population, according to Kaplan–Meier curves, was 4.1% at 90 days, 12.5% at 1 year and 23.5% at 3 years follow-up. Table 1 reports the characteristics of CIEDI patients according to their vital status at the end of follow-up. At univariate Cox regression analysis (Table 1), several risk factors were associated with survival status at three years; notably, five of them are actually included in the Shariff score, which also proved to be significantly associated with survival status at three years, in particular with a score ≥3, the cut-off value proposed by the original study for CIEDI prediction [11] (Fig. 1). At multivariate Cox regression analysis, only two factors were independent predictors of death for any cause: a Shariff score ≥3 (HR 10.833, 95% CI 2.544–46.129; $p = 0.001$) and presence of vegetations at TEE (HR 3.324, 95% CI 1.530–7.221; $p = 0.002$). Notably, both variables became significant at 6 months after TLE (respectively HR 8.894, 95%CI 1.126–70.264 and HR 4.976, 95%CI 1.508–16.416), with a tendency at 90 days only for Shariff score ≥3 ($p = 0.07$). Finally, the C statistic of Shariff score for prediction of pot-TLE survival was 0.707.

4. Discussion

CIEDI is probably the worst complication among CIED carriers, since it is associated with high morbidity, mortality and resource consumption [1]. We found an overall mortality of 4.1% at 90 days after TLE, 12.5% at 1-year and 23.5% at 3-year follow-up. While in the post-discharge phase our results were below the lower tier, at 1 year they appear broadly in line with previous, mainly retrospective, data (13%–20% vs. 12.5%) [6,7]. A possible explanation, beside the study design, is a lower prevalence of systemic involvement, according to modified Duke criteria (possible/defined CIEDI 48.5% vs. 58.9% [6] - 80.0% [7]) and presence of vegetations at TEE (24.5% vs. 70.4% [7]) which likely reflects an earlier referral for TLE, justified by the increasing sensitization of the medical community on this topic (in line with the results of the Electra registry showing a 2:1 ratio of local vs. systemic CIEDI) [18]. This is also reinforced by our finding that presence of vegetations at TEE was one of the two independent predictors of long-term survival in our population.

The most relevant result of our study is the high predictive value of the Shariff score for post-TLE mortality, both at medium (6 months) and long-term. This score was previously demonstrated to be predictive