

Elevated C-reactive protein levels during cardiac implantations may increase the risk of early complications requiring transvenous lead removal: a preliminary report

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Introduction The growing number of implantations of cardiac implantable electronic devices (CIEDs) increases the population of patients who develop complications from this type of therapy, leading to the need for transvenous lead removal (TLR). This particularly refers to infective complications, the rate of which increases faster than the rate of implantations.¹ The aim of this study was to compare the clinical features of patients treated at the Medical University of Gdansk (Gdańsk, Poland) in the years 2012 to 2016, undergoing TLR during the early and mid-term postoperative period and to identify predictors of complications requiring TLR.

Patients and methods Our retrospective study included patients undergoing early TLR (≤ 6 months) or mid-term TLR (> 6 months and < 2 years after the last procedure) for infective or noninfective indications ($n = 51$ [42%] and $n = 70$ [58%]), respectively, within 2 years after the index procedure of cardiac electrotherapy (implantation, exchange, or upgrade of the system). We analyzed the demographic data of patients, the type of procedure, comorbidities, laboratory test results (measured within 24 hours preceding cardiac implantation), and pharmacological treatment used at the time of the last procedure preceding TLR.

For all comparisons and calculations, the critical P value of less than 0.05 was assumed as statistically significant. The ultimate analysis to determine risk factors of early TLE was based on logistic regression. The multivariable analysis included variables which in the univariate analysis resulted in P values of 0.1 or less. The data were analyzed using the STATISTICA 12 software, licensed for the Medical University of Gdansk.

Results The study included 71 men and 50 women at a mean (SD) age of 66 (17) years, of whom 56 patients had an implanted pacemaker and 65 patients—an implantable cardioverter-defibrillator (ICD). In 60 patients, the early TLR procedure was performed (in 25 patients due to cardiac device infection [CDI], and in 35 patients, for other indications). The remaining 61 patients underwent TLR in the mid-term (26 patients, CDI; 35 patients, other indications). Demographic and clinical data of the study groups are presented in Supplementary material, *Table S1*.

The occurrence of any single disease was not significantly different between the study groups. In the study cohort, the mean (SD) time from the last cardiac implantation to TLR was 291 (263) days. The most frequent indication for early TLR were infective complications within the CIED pocket (32% of the cases), whereas mid-term TLR was performed most frequently due to lead failure (38% of the cases). In addition, it appeared that perforation was a more common indication for early TLR than for mid-term TLR (28% vs 2%; $P = 0.01$). A trend was observed towards lead failure as a more frequent indication for mid-term TLR than early TLR (37.7% vs 20.0%; $P = 0.09$). Data regarding indications for TLR procedures are presented in Supplementary material, *Table S2*.

The results of selected laboratory tests obtained at the time of the last procedure preceding TLR are presented in Supplementary material, *Table S3*. In the early TLR group, higher C-reactive protein (CRP) levels at the time of the last procedure preceding TLR were observed, as compared with the mid-term TLR group (13.5 mg/l vs 3.45 mg/l; $P = 0.03$). The CRP levels of 8.1 mg/l or

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TABLE 1 Predictors of the need for early transvenous lead removal

| Variable | Univariate analysis | | | Multivariable analysis | | |
|---|---------------------|------------|---------|------------------------|------------|---------|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Female sex | 3.16 | 1.49–6.74 | 0.01 | 1.45 | 0.31–6.72 | 0.76 |
| Duration of hospitalization at the time of the last procedure preceding TLR | 1.05 | 0.99–1.11 | 0.07 | 1.02 | 0.96–1.10 | 0.54 |
| Upgrade of CIED | 2.02 | 0.78–5.24 | 0.15 | 1.18 | 0.18–7.62 | 0.63 |
| Implantation of CRT-D system | 3.97 | 0.79–19.97 | 0.09 | 5.67 | 0.76–19.08 | 1.00 |
| CRP >5 mg/l ^a | 5.81 | 1.34–25.17 | 0.02 | 6.33 | 1.41–28.39 | 0.02 |

a Elevated levels according to the reference values of the Central Clinical Laboratory of the Medical University Hospital in Gdańsk, Poland

Abbreviations: CIED, cardiac implantable electronic device; CRP, C-reactive protein; CRT-D, implantable cardioverter-defibrillator with cardiac resynchronization therapy; TLR, transvenous lead removal

higher differentiated patients that required early TLR with a sensitivity of 48% and specificity of 91% (area under the receiver operating characteristic curve, 0.69; $P = 0.02$) (Supplementary material, *Figure S1*).

A univariate analysis proved that female sex (odds ratio [OR], 3.16; 95% CI, 1.49–6.74; $P = 0.01$) and elevated CRP levels (OR, 5.81; 95% CI, 1.34–25.17; $P = 0.02$) were associated with a higher risk of complications requiring early TLR (**TABLE 1**).

A multivariable analysis identified the elevated CRP level at the time of the cardiac implantation as the only independent predictor of the future need for an early TLR procedure (**TABLE 1**).

Discussion The available literature data confirm that the most frequent indications for transvenous lead extraction procedures are lead failure and infective complications.^{2–5} In our cohort, those 2 indications for TLR were also predominant. TLR was more frequently performed due to CIED pocket infection than infective endocarditis, which is in accordance with the results of other available studies.^{2,6} However, in our cohort, a relatively high number of patients undergoing TLR had an indication for the exchange or upgrade of the CIED system. We noted a relatively high percentage of patients who had TLR due to an upgrade or exchange of CIED for another device (8.2%), in comparison with literature data (0.7%–7.8%).^{2,6}

In our study, higher CRP levels at the time of the procedure preceding TLR predicted a future need for early TLR. The CRP level of 8.1 mg/l or higher differentiated patients that required early TLR from the remaining patients. The measurement of CRP levels during the diagnostic workup for infective complications of electrotherapy procedures is well established.^{7–9} Of note, our study is the first to propose the cutoff level for CRP that defines the increased risk of early complications requiring TLR. Our results confirm that the measurement of CRP levels is an important part of the diagnostic workup, not only when cardiac device-related infective endocarditis is

suspected but also when the first cardiac electrotherapy procedure is performed. This simple tool allows an identification of patients at high risk of early complications requiring TLR.

In the multivariable logistic regression model, we proved that the only independent predictor of complications requiring early TLR was the increased concentration of CRP at the time of the last procedure preceding early TLR. Therefore, the measurement of CRP levels may help reduce the risk of infective complications requiring TLR. The CRP assay is an inexpensive and widely available method. By monitoring the values of repetitive assays, it may be possible to plan the optimal timing for the initial procedure, that is, when the CRP concentration is within the normal range.

Importantly, it is difficult to explain why the elevated CRP level at the initial procedure predicted the need for early TLR, especially when the total rate of infective complications in both groups was almost equal. It is possible that this correlation indicates the earlier development of infective complications in patients with elevated CRP concentrations at implantation. In the early TLR group, complications occurred within 6 months, and in the mid-term TLR group, the same absolute number of complicated cases was observed over the 4-fold longer time. This means means that the ratio of the number of complications to the time period is higher in the early TLR group.

It could be speculated that the higher CRP levels are not a marker of the risk of infective complications but of the early development of infective complications (within 6 months). The analysis of the type of infection revealed a higher rate of more generalized infections in the mid-term TLR group, while pocket infections were more common in the early TLR group. Pocket infections seem to be associated more with the procedure itself, whereas systemic infections may also be blood-mediated and related to other causes. Perhaps the elevated CRP level may be predominantly a marker of pocket infections, associated with the procedure itself. Owing to the limited number of patients in our study, it is difficult for us to

prove those hypotheses, and further research is needed to draw more reliable conclusions.

Of note, our results may not refer to all cases in the study groups. The elevated CRP level was apparently not associated with the need for TLR due to perforation of lead failure. The study group was too limited in size to allow for an additional subgroup analysis, in which patients would be divided according to the type of indications for TLR.

We would also like to comment on the fact that some patients had elevated CRP levels at the time of the initial CIED procedure, which might have indicated ongoing infection. This group included patients who had an indication for an urgent procedure but also patients in whom an active infection had been excluded by additional tests.

Our univariate analysis revealed that female sex may be a potential predictor of early complications of CIED-related procedures. This observation is concordant with the literature data reporting that women have a significantly higher risk of complications related to a de-novo implantation of an ICD during the first postprocedural 45 days.¹⁰

Study limitations The retrospective design constitutes one of the limitations of the study. Data were derived from several centers performing prior CIED-related procedures in our patients, and thus some laboratory data were missing. Moreover, the relatively small size of the study group limits the reliability of our statistical analysis; therefore, this publication should be considered as a preliminary report.

Conclusions Elevated CRP levels at the time of a cardiac implantation may indicate a higher risk of complications requiring TLR during the 6 months after the index procedure. The need for early TLR is also correlated with female sex.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

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