

Post-Cardiac Implantable Electronic Devices: Inflammation of the Pocket. Should We Be More Aggressive?

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ABSTRACT: **Background:** Pacemaker pocket early post-implantation inflammation (EPII) is defined as clinical signs of local erythema without any systemic signs of infection occurring early after implantation. Data on the best treatment regimen for apparent superficial EPII is scarce.

Objectives: To investigate the prognostic value of medical treatment, rather than extraction surgery, in patients with EPII.

Methods: Data from 6013 consecutive patients who underwent cardiac implantable electronic device (CIED) implantation or replacement from 2007–2015 were retrospectively analyzed; 40 (0.7%) presented with EPII. Our goal was the absence of major complications and to avoidance of extraction.

Results: Patients with EPII were initially treated medically. Nineteen (47%) (group A) recovered with antibiotic treatment only. In the other 21 patients (53%) (group B), CIED extraction was performed. Group B had more major complications compared to group A (15 [71%] vs. 0 [0%], $P < 0.001$). The only significant difference in baseline characteristics was history of non-initial procedure. While 86% of group B patients had a previous non-initial procedure, only 53% of group A patients underwent previous replacement ($P < 0.05$). In multivariate analysis, previous non-initial procedure was the only predictor for need of extraction at 1 year, hazard ratio 3.5, 95% confidence interval 1.001–11.73, $P < 0.05$.

Conclusions: Conservative treatment in patients with EPII after non-initial procedure can lead to serious adverse events resulting in the need for extraction. Close follow-up and aggressive treatment should be considered early in the therapeutic course.

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KEY WORDS: cardiac implantable electronic device (CIED), early post-implantation inflammation (EPII), pocket infection, superficial infection, transvenous lead extraction

incidence of pocket infection associated with bacteremia or device-related endocarditis in the United States is reported to be 1.14/1000 device-years [3]. In established CIED infection, treatment with parenteral antibiotics without hardware removal has been disappointing [4–6]. These findings led to guidelines recommending complete removal of the system, usually performed by percutaneous extraction after infection had been confirmed [7,8].

In contrast to explicit recommendations regarding treatment of device pocket infection, there is a lack of consensus on the best treatment methods for pocket early post-implantation inflammation (EPII). EPII is defined as erythema affecting the CIED implantation incision site without purulent exudate, dehiscence, fluctuance, or systemic signs of infection and occurring within 30 days of implantation [8] and with a clinical resolution within 2 weeks. Medical treatment with a short course of antimicrobial therapy is usually recommended [8]; however, this approach is based on limited data. Since extractions are associated with significant (though small rate) complications [9,10], medical treatment may be an attractive alternative.

While some facilities treat EPII medically, others advocate for a surgical treatment to prevent deterioration of the suspected local inflammation. Hence, medical treatment may delay definitive therapy for underlying misdiagnosed infected pockets, which could lead to abscess formation, sepsis, endocarditis, and death.

In our study we compared our experience with medical treatment using antibiotics to avoid extraction in patients with pocket inflammation versus early extraction. Furthermore, we sought to characterize patients who might benefit from an early surgical approach.

PATIENTS AND METHODS

STUDY POPULATION

We performed a retrospective chart review study of 6013 consecutive patients who underwent a new CIED implantation or replacement between June 2007 and June 2015 at Sheba Medical Center. All patients at our facility are routinely followed at day 1 and day 10 post-procedure. Based on several key words for

Despite the prophylactic use of antibiotics during cardiac implantable electronic device (CIED) implantations, the rate of infection is increasing [1,2]. CIED infection rates range between 0.13% and 19.9%. While the incidence of isolated pocket infection is 1.37/1000 device-years, the

EPII, we performed a search of hospital records from hospitalized patients. Patients were enrolled in the study if they met the criteria of EPII. Thereafter, an individual chart review for confirmation of the diagnosis of EPII was performed. Patient information was anonymized, and the study was approved by the Sheba institutional review board, which adheres to the Helsinki Declaration. As this study was a retrospective analysis, no consent for participation was required.

EPII was defined as: clinical signs of local inflammation (redness, swelling, localized warmth or pain) without any of the following symptoms occurring within 30 days of implantation: fever, fistulas, scar dehiscence, exudate from the pocket, bacteremia, endocarditis, or any signs of sepsis. All cases showed signs and symptoms severe enough to prompt oral antibiotic therapy by the treating physician. Thus, there were no evident signs of pocket infection; but the local signs were more than just superficial inflammation. Our regimen included 14 days of either a first generation cephalosporin, amoxicillin, or clavulanate.

It should be noted that all patients were treated with prophylactic measures before the procedure with cefamezin or clindamycin, in case of penicillin sensitivity.

STUDY OUTCOME

The primary outcomes compared recovery from inflammation versus the need for extraction within 1 year. Comparison between the groups (extracted and non-extracted) included demographic characteristics, implantation techniques, type of device, new implants vs. non-initial procedures, type of antibiotic administered, and time to hospitalization after the index procedure was performed.

STATISTICAL ANALYSIS

Our primary analysis compared the characteristics of the two groups. The differences and the *P* values were calculated using chi-square with Yates correction. Significance was defined as *P* < 0.05.

A Kaplan–Meier cumulative risk of treatment failure according to the occurrence or absence of extraction within 12 months after medical treatment was calculated. Patients were divided into two groups: new implants vs. non-initial procedures. For this analysis, we used Cox proportional hazard regression with two-sided *t*-tests at the 5% level of significance. Measurement of follow-up time started on the date of the last event or after 1 year.

RESULTS

From our entire cohort of 6013 patients, 40 (0.7 %) presented with EPII. Following diagnosis, all started with oral empiric antibiotic therapy. In the first 24 hours after presentation, blood cultures, fever measurements, and laboratory tests were performed.

In group A, 19/40 patients (47%) achieved full recovery after CIED implantation (median of 365 ± 10 days follow-up) and were inflammation free, thus requiring no further treatment or intervention. In the remaining 21 patients (53%) (group B), medical treatment failed, resulting in total CIED transvenous lead extraction (median time to device extraction was 54 ± 14 days after initial presentation).

No differences were seen in baseline characteristics in either group [Table 1].

Twelve patients (30%) presented with EPII after initial implantation. The majority of these patients (9/12, 75%) were treated successfully with medical treatment only. In contrast, 28 patients (70%) presented with EPII after a non-initial procedure. The majority of these patients (18/28, 64%) required device extraction.

Kaplan–Meier analysis showed that at 1 year follow-up, the rate of treatment failure and subsequent extraction need was significantly higher among patients after non-initial procedures

Table 1. Baseline characteristics of patients treated with the medical approach and early post-implantation inflammation

	Non-extracted (n=19)	Extracted (n=21)	<i>P</i> value
Baseline characteristics*			
Gender			
Male	14 (74%)	14 (67%)	0.6
Female	5 (26%)	7 (33%)	0.6
Age, years**	66 ± 16	66 ± 19	0.9
Creatinine ≥ 1.5 mg/dl	8 (44%)	6 (32%)	0.21
Diabetes mellitus	6 (33%)	7 (35%)	0.9
Hypertension	12 (63%)	9 (45%)	0.2
Ischemic heart disease	9 (47%)	10 (50%)	0.8
Congestive heart failure	11 (58%)	10 (50%)	0.6
Atrial fibrillation	9 (47%)	9 (45%)	0.8
Smoking	5 (28%)	5 (28%)	1
immunosuppressive treatment	1 (7%)	1 (7%)	1
Implantation*			
Elective implantation	18 (93%)	20 (95%)	0.9
Pacemaker (DDDR or VVI)	13 (66%)	18 (86%)	0.26
Defibrillator (ICD or CRTD)	6 (34%)	3 (14%)	0.26
Antibiotic prophylaxis	100%	100%	1
White blood cell count (mcl)**	3.9 K	4.5 K	0.7
C-reactive protein (mg/l)***	18 m	27 m	0.5
Initial implantation	9 (47%)	3 (14%)	0.02
Non initial procedure	10 (53%)	18 (86%)	0.02

CRTD = cardiac resynchronization therapy defibrillator, DDDR = dual chamber rate modulated pacemaker, ICD = implantable cardioverter-defibrillator, VVI = ventricular paced and sensed pacemaker

*Categorical variables are reported as absolute frequencies and percentages

**Continuous variables normally distributed

***Continuous variables not normally distributed, as median with 25th–75th range

vs. those with initial implantation [Figure 1]. Notably, separation in event rates between both groups appeared early in the course and was sustained thereafter.

Multivariate analysis (including age, gender, creatinine levels, diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, and atrial fibrillation) showed that the only significant predictor for need of extraction at 1 year in cases of EPII was non-initial procedure (hazard ratio 3.4, 95% confidence interval 1.00–11.73, $P < 0.05$).

No deaths were reported in either case (extracted and the non-extracted) during follow-up.

REASONS FOR EXTRACTION IN GROUP B

Figure 2 shows the complications associated with failure of medical treatment resulting in extraction. Eight patients (38%) developed endocarditis, seven (33%) were diagnosed with sepsis/bacteremia, and six (28%) presented with persistent or a recurrence of local pocket inflammation despite medical treatment of up to 2 weeks. Among patients with endocarditis, 50% had valve vegetations and 50% had lead vegetations on transesophageal echocardiography.

The majority of this patient group was evaluated after non-initial implantation [Figure 3].

EXTRACTION PROCEDURE

Twenty-one patients underwent extraction. Of those, 21 leads were removed with simple traction, 14 with mechanical tools and 15 with laser-assisted lead extraction. Two patients pre-

sented with major bleeding that was treated with blood products without the need for further operative treatment.

DISCUSSION

Infected CIED systems can lead to life-threatening complications, and the need for subsequent extraction is well established. Nevertheless, there are no recommendations regarding treatment of EPII. At best, the published guidelines of the British Society for Antimicrobial Chemotherapy suggest that medical treatment may be considered for EPII [8]. The term “inflammation,” in the context of EPII, implies that a definite diagnosis of microbial infection has not been established and starting antimicrobial therapy is not mandatory.

To the best of our knowledge, our study is the first to evaluate outcomes of CIED recipients with EPII while being treated medically. Our main finding was that medical therapy with a

Figure 1. Kaplan–Meier cumulative risk of treatment failure according to the occurrence or absence of extraction within 12 months after medical treatment. Patients were divided into two groups: initial and non-initial procedures

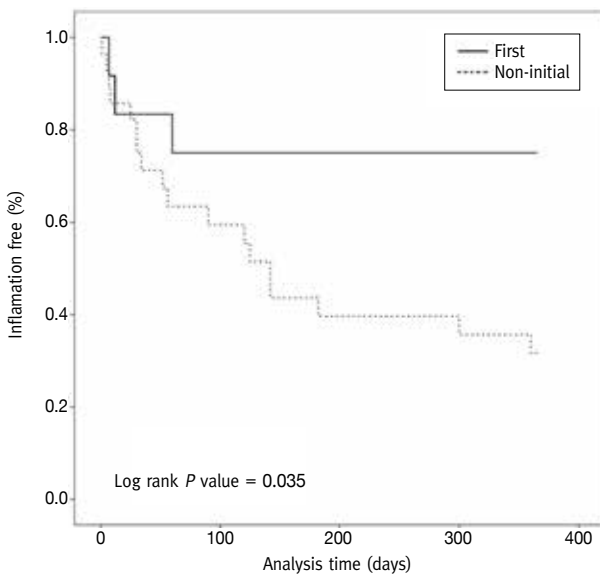


Figure 2. Complication among the group B patients. Among endocarditis patients, 50% had valve vegetations (pink), the rest had electrode vegetations (grey)

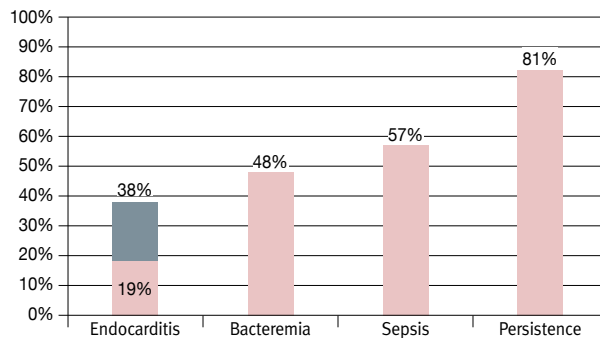
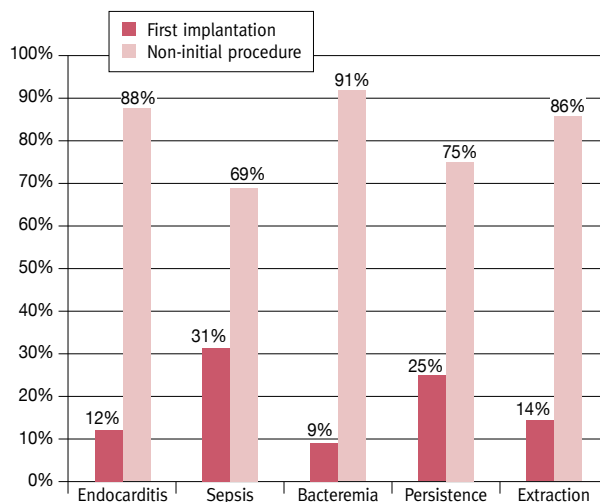


Figure 3. Percentage of patients with complications after initial implantation vs. non-initial procedure



short course of antimicrobial antibiotics is an alternative treatment protocol for patients presenting after primary device implantation. However, this approach failed in most cases following non-initial procedures.

Other studies have shown a strong correlation between kidney disease, atrial fibrillation, and heart failure with the onset of pocket infection [11,12]. Our study looked specifically into EPII, which might differ from later onset pocket infection. The noted pocket infection predictors did not predict failure of medical therapy in EPII. We did not compare our results to cases without EPII, but our main aim was to investigate whether the recommendation for medical treatment should apply to all. The only predictor for need of extraction was EPII after non-initial procedure.

Moreover, in patients who did not respond to medical therapy, severe complications were observed and extraction was needed. Nevertheless, it did not result in an increase in mortality, probably due to the fact that extraction was performed promptly at the time of the appearance of complications.

Of note, other authors reported higher rates of complications following non-initial implants (i.e., system upgrade, lead revision, or pulse generators change), including worse outcomes when considered with CIED extraction [13].

Our data show that a closer follow-up, and perhaps even an earlier surgical approach (i.e., extraction), are indicated in patients presenting with EPII following non-initial procedure. In contrast, patients with EPII following initial implantation may fully recover with medical treatment.

STUDY LIMITATIONS

The main limitation of our study is that distinguishing between superficial, EPII, and pocket infection can be subjective. However, all physicians in our clinic are experienced electrophysiologists and this study examined common practice patterns.

Although all extraction cases were uneventful in the long term, extraction remains a procedure with definite, though small, risks. The risks and benefits should be evaluated individually for each case.

Our retrospective study was conducted at a single academic medical center with no control group. The risk of information bias is low, as information on exposure variables and outcomes was collected without knowledge of this study.

To diagnose EPII, relevant patient files were identified using a computer search for key words. The relevant files were then individually reviewed to identify those with EPII diagnoses. We believe that this retrospective data search method results in an underestimation of EPII recognition.

Since some patients were referred to our center from other hospitals, we lack the duration and dose of the prior antibiotic treatment for those cases.

CONCLUSIONS

Medical treatment can be attempted in patients presenting with EPII after first implantation when close monitoring and close follow-up and/or a prolonged course of antibiotics may be necessary. Further prospective studies should be conducted to validate our findings.

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“A man does not die of love or his liver or even of old age; he dies of being a man”

Miguel de Unamuno y Jugo, (1864–1936), Spanish Basque essayist, novelist, poet, playwright, philosopher, professor of Greek and Classics, and later rector at the University of Salamanca