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# PROGRESSION OF INFLAMMATORY BIOMARKERS EARLY AFTER CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICE PLACEMENT

## *KARDİYOVASKÜLER İMPLANTE EDİLEN ELEKTRONİK CİHAZ TAKILMASI SONRASI ERKEN DÖNEM İNFLAMATUAR BİYO-BELİRTEÇLERİN SEYRİ*

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## Abstract

**Objective:** There is a lack of data in the current literature regarding the spontaneous progression of inflammatory biomarkers early after cardiovascular implantable electronic device (CIED) placement. In our study we aimed to detect C-reactive protein (CRP) and white blood cell count (WBC) trends in the 5 days following CIED implantation.
**Methods:** We retrospectively investigated a total of 235 patients who received CIEDs between 2012 and 2016 in our heart center. The levels of CRP and WBC for one day before and for the following 5 days after the procedure were noted in 4 serial measurements. The longitudinal course of CRP and WBC and their association with various parameters were analyzed with linear mix model of repeated measurements.
**Results:** Totally 235 patients were screened; 36 patients excluded due to lack of serial CRP and WBC measurements, 44 patients excluded due to occurrence of a factor that may potentially affect CRP and WBC level. Finally 153 patients with a median age of 67 (IQR 58-74), 41 (26.8%) of whom were female, were included in the study. CRP values indicated a significant trend and made a peak in the second estimation (between 48-72 hours) after the procedure (Beta[β]: 0.208; Standard Error [S.E]: 0.015; $p< 0.001$). Age and procedure duration longer than 1 hour emerged as leading factors for high level of CRP (β:0.004; S.E: 0.002; $p=0.05$ and β: 0.208; S.E: 0.015; $p= 0.02$, respectively). The relation between time and WBC count was not statically significant (β: -0.129; S.E: 0.06; $p=0.06$).
**Conclusion:** Progression of CRP after CIED implantation demonstrates a significant trend. Age and procedure duration longer than 1 hour are leading factors for high levels of CRP. There is statistically non-significant relation between WBC levels and time in 5 days of procedure.

**Keywords:** *Pacemaker, implantable defibrillators, C- reactive protein, inflammation, biomarkers*

## Öz

**Amaç:** Güncel literatürde kardiyovasküler implante edilen elektronik cihaz (KİEC) takılması sonrası inflamatuar biyo-belirteçlerin seyri ile ilgili yeterli veri yoktur. Çalışmamızda KİEC takılması sonrası 5 gün içerisinde C- reaktif protein (CRP)ve beyaz kan hücresi (BKH) değişimlerini ortaya çıkarmayı amaçladık
**Yöntem:** Kalp merkezimizde 2012-2016 yılları arasında KİEC takılan toplam 235 hastayı geriye dönük olarak araştırdık. CRP ve BKH sayımı düzeylerinin işlemden 1 gün önce ve işlemden sonraki 5 gün içerisindeki toplamda 4 seri ölçümleri not edildi. CRP ve BKH'nin zaman içerisindeki seyri ve farklı değişkenler ile olan ilişkisi tekrarlayan ölçümler için linear mix model yöntemi kullanılarak analiz edildi.
**Bulgular:** Toplamda 235 hasta tarandı; 36 hasta işlem sonrası seri CRP ve WBC düzeyleri olamaması, 44 hasta CRP ve WBC düzeylerini etkileyebilecek potansiyel bir neden olması sebebiyle çalışma dışı bırakıldı. Sonuç olarak çalışmaya median yaşı 67 (IQR 58-74) 41'i (%26,8) kadın olan toplamda 153 hasta dahil edildi. CRP düzeyleri belirgin değişim gösterdi ve işlem sonrası ikinci ölçümde (48-72 saatler arası) en yüksek değerine ulaştı (Beta[β]: 0,208; Standart Hata [S.H] 0,015; $p<0,001$). Yaş ve işlem süresinin 1 saatten uzun olması yüksek CRP düzeylerine neden olan faktörler olarak ortaya çıktı (sırası ile β: 0,004; S.H 0,002; $p=0,05$ ve β:0,208; S.E:0,015; $p= 0,02$). Zaman ve BKH arasında istatistiksel anlamlı bir ilişki saptanmadı. (β: -0,129; S.E: 0,06; $p=0,06$).
**Sonuç:** KIEC takılması sonrası CRP seyri anlamlı bir değişim gösterir. Yaş ve işlem süresinin 1 saatten uzun olması yüksek CRP düzeylerine neden olan faktörlerdir. İşlem sonrası 5 gün içerisinde zaman ve BKH arasında istatistiksel olarak anlamlı olmayan bir ilişki vardır.

**Anahtar Kelimeler:** *Kalp pili, implante edilen defibrillatör, C- reaktif protein, inflamasyon, biyo-marker*

## Introduction

Serum C-reactive protein (CRP) level and white blood cell (WBC) count have been used as indicators of inflammation and infection for a long time. The levels of these biomarkers increase in infection as well as in rheumatic disease, cancer, heart failure, atherosclerotic vascular disease, burn, surgery and any tissue damage that causes inflammation.[1,2] Thus, management of the patient with high level of inflammatory biomarkers could be difficult, especially when the clinical condition is confusing. Therefore, if the course of CRP and WBC is known in each circumstance, clinicians can make a correct decision. These biomarkers have also been used to detect new onset systemic infections after surgical procedures. Cardiovascular implantable electronic device (CIED) implantation can be assumed to be a semi-surgical procedure that requires sterile operation room conditions. Additionally, permanent insertion of foreign instruments like pacemaker leads and batteries inside the body renders these procedures prone to infection. In CIED placement, factors leading to infection are assumed to be pocket hematoma, recurrent procedure, lack of antibiotic prophylaxis and procedure duration.[3] Although early monitoring of CIED-related infections is very important, there is no clear recommendation on how to follow inflammatory biomarkers early after the procedure. Data is scarce regarding trend of CRP and WBC early after CIED implantation especially in the implantable cardiac defibrillators (ICDs) and cardiac resynchronization therapy devices (CRTDs) era. In the present study, we aimed to demonstrate the spontaneous progression of CRP and WBC early after CIED implantation and to find out the factors that may affect the level of those markers.

## Methods

### Study Population

In this single center study, patients who received CIEDs between 2012-2016 were evaluated. Inclusion criteria were as follows: being the first CIED implantation procedure of the patient (battery replacement and lead revision-extraction procedures were excluded), having obtained serial measurements of CRP values and WBC count before and 5 days after the procedure. Patients who had pre-procedural infection in any focus were excluded, and the other exclusion criteria were causes that could influence inflammatory biomarker levels (e.g. recent trauma, surgery, burns, malignancy, receiving systemic steroid therapy, active rheumatic disease, decomposed heart failure, acute coronary syndrome in index hospitalization and being on renal dialysis). All CIEDs were implanted with standard methods using left or right (rarely) pectoral region via the subclavian vein. The CIEDs were manufactured by the same company (Medtronic Inc.) in all study participants. Pre-procedural antibiotic prophylaxis was made with cefazoline 2 gram intravenously, and treatment was continued after the implantation as 1 gram intravenously every 8 hours during hospitalization. Most patients were hospitalized for 5 days following the procedure, and the remaining patients were prescribed oral antibiotic for 5 days. Prospectively collected data regarding patients' demographic parameters, type of CIED, primary diagnosis, procedure time (two groups as longer than 1 hour and others), occurrence of hematoma and pocket infection were used. All study patients were aged above 18 years. The medical records of a total of 235 patients were screened retrospectively. Finally, 44 patients were excluded due to the occurrence of any matter that may have potentially affected inflammatory biomarkers including 2 patients who had pocket infection and 36 who had missing values of serial measurements of CRP and WBC. Approval for the study was obtained from the local ethics committee (Near East University 2016/36 Project number: 249)

### Hematoma and Pocket Infection Definition

Swelling in the pocket exceeding the size of the generator without warmth and erythema and change of skin color to purple are accepted as hematoma.[4] Pocket infection is diagnosed when swelling with local erythema, warmth, pain, drainage and purulence, erosion or dehiscence occurred, which required total extraction of the CIED system. Local sign of infection in suture line was followed conservatively and was not accepted as pocket infection.

### Biochemical Analysis

All laboratory analyses were performed in the same day and as early as possible after the blood sample was collected. Pre-procedure blood sample was collected one day before the implantation. The second sample was collected in the next 16 to 24 hours after the implantation, the third sample was collected in the next 48 to 72 hours, and the fourth sample was collected in the next 84 to 120 hours. Serum CRP concentration was analyzed with immune turbid metric method (Tina-quant CRP detection method: Roche Diagnostics) performed on a Cobas C501 automated analyzer. The manufacturer claimed the detection limit to be 0.1 mg/L and the extended measuring range (with reruns) to be 0.1–240 mg/L. WBC count levels was studied with the Sysmex XT-2000 (Roche Diagnostics, USA) automatic analyzer system.

### Statistical Analysis

Continuous variables are expressed as median, and categorical variables are expressed as percentage. Due to the CRP values being highly skewed to the right, logarithmic transformation was performed, and CRP values are expressed as geometric means. Longitudinal processing was used for the analysis of repeated measurements. Linear mix model of repeated measurements was used to analyze the progression of biomarkers. All statistical analyses were proceeded with R-software v.3.5.1 (R Statistical Software, Institute for Statistics and Mathematics, Austria) using "lme4", "ggplot'', "arm" and "jtools" packages.

## Results

Study population consisted of 153 patients with a median age of 67 (IQR 58-74), 41 (26.8%) of whom were females. The number of patients with pocket hematoma was 24 (15.6 %). Clinical and demographic characteristics of the patients are summarized in Table 1. Number of CIEDs according to device type was 15 (9.8 %) for pacemakers (PMs), 102 (66.7 %) for ICDs and 36 (23.5%) for CRTDs. Single lead was used in 34 (22.2%) out of 153 procedures. Linear mix model of repeated measurement was used to demonstrate trends of CRP values and WBC count. Occurrence of hematoma, procedure duration longer than 1 hour, gender and age were put in both models as co-factors. The results were adjusted with interaction of time and hematoma. Serum CRP values represented a trend and made a peak in the third estimation and did not return to baseline in the following 5 days (2.73

mg/dl [IQR 1.82-4.20] 48-72 hours of the procedure; β: 0.208; Standard Error [S.E] 0.015; $p< 0.001$) (Figure 1A).

**Table 1.** Demographic and clinical characteristics of study patients.

| | | |
|---|---|---|
| **Age** | (years, IQR [25-75]) | 67 (58-74) |
| **Male Gender** | (n,%) | 112 (73.2) |
| **Heart Failure** | (n,%) | 115 (75.2) |
| **Hypertension** | (n,%) | 102 (66.7) |
| **Diabetes** | (n,%) | 50 (32.7 ) |
| **Device type** | PM (n,%) | 15 (9.8) |
| | ICD (n,%) | 102 (66.7) |
| | CRT-D (n,%) | 36 (23.5) |
| **Hematoma** | (n,%) | 24 (15.6) |
| **Creatinine Level** | (mg/dl) | 1.13±0.51 |
| **Haematocrit level** | (%) | 39.9±4.9 |

IQR; İnterquartile range, PM; Pacemaker, ICD; implantable cardiac defibrillator, CRT-D; Cardiac resynchronisation therapy defibrillator

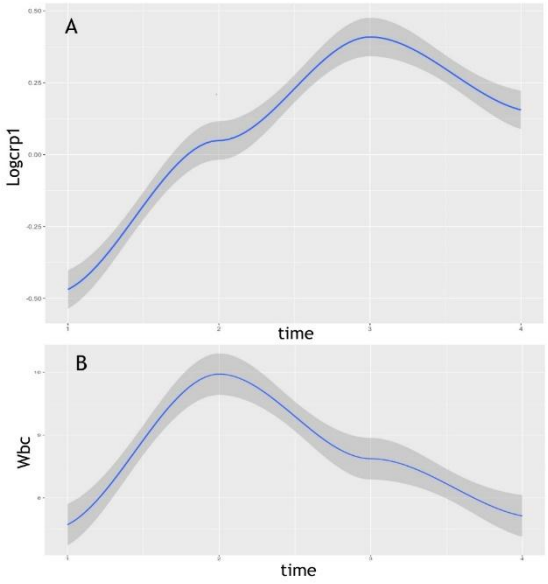


**Figure 1.** Progression curve of C-reactive protein (A); Progression curve of White Blood Cell (B).

WBC count was prone to make a peak in the first day of procedure (9620 µm/ml [IQR 8205-11775] 16-24 hours of the procedure; β: -0,129; S.E: 0.06; $p$=0.06) (Figure 1B). For CRP, procedure duration longer than 1 hour and age were the leading factors for high levels (β: 0.004; S.E: 0.002; $p$=0.05 and β: 0.208; S.E: 0.015; $p$=0.02 respectively) (Table 2, Figure 2). No factor significantly affected the post procedure levels of WBC count (Table 3, Figure 3).

**Table 2.**Association of co-factors and longitudinal changes of CRP levels in linear mix model.

| | Estimate | S.E | *P* value |
|---|---|---|---|
| **Time** | 0.208 | 0.015 | <0.001 |
| **Age** | 0.004 | 0.002 | 0.05 |
| **Hematoma** | 0.164 | 0.110 | 0.14 |
| **Gender*** | -0.07 | 0.05 | 0.20 |
| **Procedure duration**** | 0.14 | 0.06 | 0.02 |
| **Time-hematoma***** | 0.06 | 0.03 | 0.06 |

* Female gender, **Procedure duration longer than 1 hour, ***Time-hematoma interaction

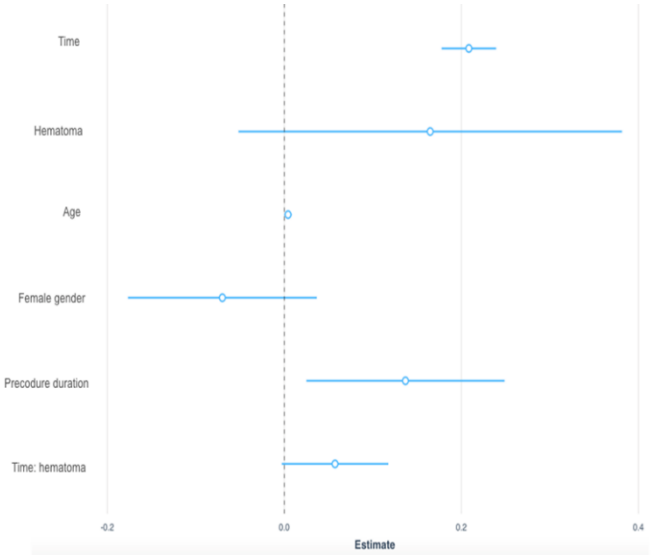


**Figure 2.** Relation between co- factors and CRP levels**.**

**Table 3.** Association of co-factors and longitudinal changes of WBC levels in linear mix model.

| | Estimate | S.E. | *P* value |
|---|---|---|---|
| **Time** | -0.129 | 0.067 | 0.06 |
| **Hematoma occurrence** | 0.599 | 0.448 | 0.18 |
| **Age** | -0.021 | 0.012 | 0.09 |
| **Gender*** | 0.234 | 0.323 | 0.47 |
| **Procedure duration**** | 0.331 | 0.338 | 0.33 |
| **Time-hematoma***** | 0.139 | 0.131 | 0.29 |

*Female gender, **Procedure duration longer than 1 hour, ***Time-hematoma interaction

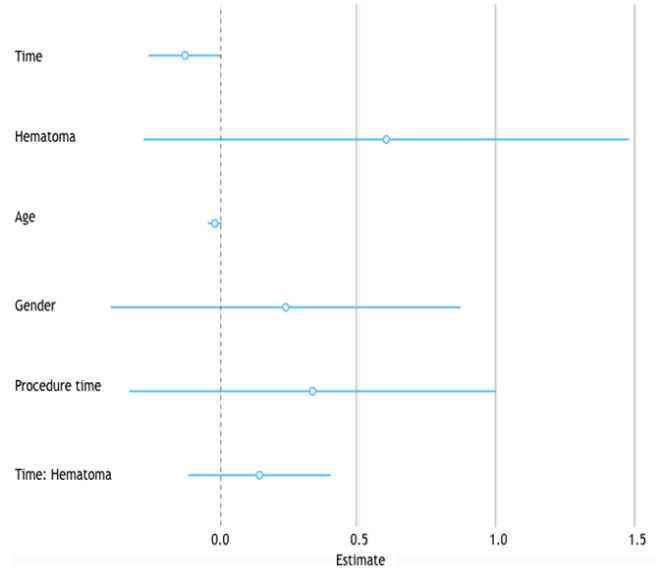


**Figure 3.** Relation between co-factors and WBC count.

## Discussion

In this present study, we demonstrated the course of CRP and WBC early after CIED implantation procedure. Additionally, our other notable findings emerged as CRP values showing a significant trend and making its peak during the 48-72 hours post implantation; procedure duration longer than 1 hour and age were both leading

factors for high level of CRP. Unlike CRP values, WBC count neither exhibited a trend nor had an association with any parameter. This is the first study concerning routine progression of CRP and WBC levels early after CIED implantation. CRP and WBC are both inflammatory biomarkers that are commonly used for the definition of infection and inflammatory diseases and follow-up of treatment. In clinical practice, doing serial measurements is more useful than carrying out a single measurement.[5] Currently, as the number of CIED recipients increases, operators face more CIED-related infections involving approximately 2% of all implantation procedures.[6] The cause of this increasing rate of CIED infection is attributed to increasing patient longevity with CIED, which results in repeated generator changes, increasing comorbidities and increasing implantation rates of complex devices such as ICDs and CRTs.[7] Early detection of systemic infection is crucial in these patients, since the early removal of the infected material can be life-saving and cost-effective, whereby preventing long hospitalization stays and unnecessary antibiotic therapy. On the other hand, some cases exhibiting signs of local infections in confined suture line regions can be managed conservatively without device removals. Additionally, diagnosing a CIED infection can be challenging in some patients due to the fact that many patients may present with nonspecific or even without any obvious signs of infection.[8] In a worldwide survey conducted in the European Hearth Rhythm Association, most responders (140 of 175 centers, 80.0%) reported that infection evaluation was mainly based on complete blood count or CRP (131, 74.9%) regarding the evaluation of patients' infectious status after CIED removal.[9] Klug et al. demonstrated in patients with local signs of pacemaker pocket infections that increased CRP and WBC levels predicted positive blood culture with high specificity but with a very low sensitivity.[8] Zabek et al. showed in patient undergoing trans-catheter lead extraction that WBC count and CRP were within normal range in patient with signs of local infection and markedly elevated those with diagnosed infective endocarditis.[10] They concluded that inflammatory markers were useful to detect systemic infection in patient with local signs of infection. Given that most patients with CIED infection do not present with fever or other symptoms of infection, additional diagnostic tests are needed when infection is suspected. The predictive values of CRP and WBC for infection after various types of surgery have been studied before. In a study by Santonocito et al. on different kinds of major surgery, it was demonstrated that CRP made a peak at post-operative day 3 and did not return to baseline levels even at postoperative day 7.[11] The patients diagnosed with infection exhibited significantly higher values of CRP, and CRP values remained high in those 3 days after the operation. In our study, patients' CRP values made a peak between postoperative 48-72 hours and did not return to baseline in the following 5 days after the procedure. In a retrospective study by Topmkins C. et al., leukocytosis failed to predict infection after CIED implantation.[12] In the study, single WBC value was evaluated after the procedure and compared with pre-procedure levels of WBC count. In another study by Kumar S.D. et al., prior leukocytosis did not predict CIED infection.[13] In our study, we found that WBC count began to fall after 24 hours following CIED implantation. However, the trend of WBC count did not reach statistical significance and no co-factor associated with a high level of WBC was found. Hence, it may be speculated that persistent high levels of WBC count or re-elevation 24 hours after CIED implantation may be more important than pre-procedure or post-procedure single measurement.

Longer procedure duration is related with CIED infection.[7] Our results showed that procedure durations longer than 1 hour caused high post-procedural CRP values. We hypothesized this because increased duration is related to more complicated procedures and prolonged external exposure of the wound can lead to bacterial inoculation. These factors increase inflammatory response in the wound and cause higher levels of CRP as a result.

In our study, age emerged as a factor related with a high level of CRP. Aging has a negative impact on the cellular immunity system by means of suppressing T cell function, decreasing the number of T cell and poorer B cell humoral response. On the other hand, CRP is released by liver and it is hypothesized that during an inflammatory process, elderly people demonstrate stronger immune-mediator response than adults.[14,15] Thus, the association between high levels of post-procedural CRP and age in our study cohort can be explained with increased mediator response to inflammation in elderly patients.

About 2-9% up to 33 % of CIED implantation procedures result in pocket hematoma.[4,16] Prior anticoagulant and/or antiplatelet therapy and switching oral anticoagulant drugs to heparin facilitates pocket hematoma.[17] In our study cohort, two-thirds of the patients continued their antiplatelet medications. Also bridging to heparin strategy was used in patients on oral anticoagulant therapy. Additionally, the incidence of pocket hematoma is highly related the criteria used to define. In this study, we accepted even small swelling with color change of skin to purple as hematoma, therefore, the number of pocket hematoma remained higher in our study population than prior reported. Hematoma causes inflammation and tension in the pocket, which precipitates ischemia-necrosis to the skin, thereby creating a suitable ground for microorganisms. Thus, occurrence of hematoma is a leading factor of pocket infection. In our study, considering the time-hematoma interaction as a co-factor in the model, we found that hematoma did not predict post implantation higher levels of CRP and WBC. Although hematoma frequently occurs during the first 24 hours after the procedure, it potentially occurs in the following days. Therefore, when the time interaction is taken into account, hematoma did not significantly affect the results.

Although some biomarkers other than WBC and CRP do exist to define new onset infection, these are not suitable for use in daily practice. For instance, procalcitonin has emerged as a diagnostic tool for early diagnosis of sepsis, but it has not yet completely been validated for CIED-related infections. Accordingly, use of other cytokines such as interleukin-6 and TNF-alpha has remained limited in clinical research and did not take place in routine use. Therefore, we believe that, although they are old and basic biomarkers, CRP and WBC still have a central role in diagnosis and follow-up of infection and other inflammatory diseases. Having presented the progression of CRP and WBC levels early after CIED implantation -which has not been studied with serial measurements before- will shed light on the follow-up of CIED recipients, especially when clinicians apply these biomarkers in case of suspicion of a CIED-related infection.

**Limitations**

This study had several limitations. CRP and WBC levels were studied in a time interval, and the estimations were

therefore expressed as time intervals. Measurements were limited with the following 5 days of the procedure, thus the return of CRP levels to baseline values could not be demonstrated. There are several methods to estimate CRP levels, and the results may change depending on the method used. However, we used 4 repeated measurements of CRP with the same method to demonstrate the progression of CRP, and the progression curve would not change if a different method was used. Hence, our results can be used in daily clinical practice, regardless of the method used to estimate CRP levels. In our study cohort, we observed pocket infection in two patients, and this inadequate number limited us to validate our results only in uninfected patients.

**Conclusion**

The course of CRP levels indicate a progression curve early after CIED implantation. Age and procedure duration longer than 1 hour lead to higher post-procedural CRP levels. Occurrence of hematoma is not predictive for high levels of post procedural CRP and WBC. Post- implantation level of WBC does not indicate such a trend and no any factor predict high post procedure levels of that biomarker.

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**Conflict of Interest**

The authors have no conflicts of interest to disclose.

**Compliance with Ethical Statement**

The research was approved by the Near East University Ethical Committee (Near East University-2016/36; Project number:249)

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**Author Contributions**

KG: Design; KG: Project development; KG, LC, CC: Data collection; KG, BA, HD: Analysis; FÖ: Literature search; KG, HD: Manuscript writing; HD, OA: Critical review

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