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Investigation of atrioventricular block and inflammation interaction versatility and cardiac pacemakers' effects on this versatility

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ABSTRACT

Objectives: This study aimed to examine inflammation markers before and three months after permanent pacemaker implantation in individuals with complete atrioventricular block to establish if cardiac conduction system disorders and pacemaker treatment affect inflammation.

Patients and methods: This retrospective cohort study included 44 complete atrioventricular block patients (24 females, 20 males; mean age: 73.4±9.2 years; range, 64 to 82 years) who underwent dual chamber (DDD) pacemakers implantation between January 1, 2023 and December 31, 2023. The hospital information system provided demographic, clinical, and laboratory data. Preprocedure and postprocedure three-month follow-up C-reactive protein, hemogram-related parameters, and inflammation scores were compared.

Results: The most common comorbidities, listed in order of frequency, were hypertension (95.4%), atherosclerotic heart disease (81.8%), diabetes mellitus (43.1%), heart failure (31.8%), and stroke (11.3%). Regarding laboratory measurements and inflammatory scores of the patients, only the mean platelet volume had a statistically significant difference just before (88.11±6.23 fL) and three months after (87.46±5.43 fL) the procedure was (p=0.002).

Conclusion: As an established indicator of inflammation, the notable decrease in mean platelet volume at the three-month follow-up suggests that inflammation may not only contribute to but also result from atrioventricular block. Long-term follow-up is needed to observe the impact of cardiac pacemakers, and further studies with innovative physiological pacing methods are required to evaluate these effects.

Keywords: Atrioventricular block, cardiac pacemaker, inflammation, inflammation score.

Cardiac diseases, cardiac surgery, and systemic disorders, categorized as infiltrative, rheumatologic, endocrine, and genetic neuromuscular degenerative diseases, can lead to heart block by affecting the myocardium and the conduction system.[1,2] Abnormalities in cardiac conduction are a reliable predictor of mortality and heart failure. Nevertheless, a preventative approach has not yet been formulated. Autopsy examinations indicate the presence of fibrosis in the conduction system, although the underlying reason remains undisclosed. Inflammation is well-acknowledged as an indicator of fibrosis.[3] Studies with follow-up periods of 7 and 11 years have emphasized that high-sensitivity C-reactive protein elevation at baseline can predict incident conduction system disease in the general population.[3,4]

Irrespective of acute heart damage, systemic inflammation can have a detrimental impact on atrioventricular conduction. Gap junctions that include connexin43 and connect cardiomyocytes with inflammation-related cells, including macrophages, are acknowledged as crucial elements regulating conduction in the atrioventricular node. Lazzerini et al.[5] presented evidence that

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an increase in interleukin (IL)-6, which leads to systemic inflammation, might acutely exacerbate atrioventricular conduction by suppressing connexin43.

Recently, novel scoring techniques have been implemented to assess the extent of inflammation. The monocyte-to-lymphocyte ratio, one of these scores, exhibited a substantial association with the occurrence of new-onset cardiac conduction block throughout a follow-up period of roughly 10 years.[6] Patients without preexisting conduction system disorders who underwent transcatheter aortic valve replacement and had elevated neutrophil-to-lymphocyte ratio on the day of the treatment were more likely to require a permanent pacemaker.[7] In recent studies, the systemic immune-inflammation index (SII), which is defined as neutrophils multiplied by platelets/lymphocytes, has been linked to the development of complete atrioventricular block in patients with ST-segment elevation myocardial infarction and the necessity of a permanent pacemaker in patients with drug-related atrioventricular block.[8,9] Çelik et al.[10] discovered a substantial correlation between the occurrence of atrial fibrillation following coronary artery bypass surgery and the neutrophil-to-lymphocyte ratio.

While inflammation is known to cause atrioventricular block, it is worth considering the inverse relationship. If such a scenario is present, it is necessary to scrutinize the impact of cardiac pacemaker therapy on this condition.

This study aimed to assess the inflammation markers before and three months after the permanent pacemaker implantation in patients with complete atrioventricular block and investigate whether cardiac conduction system disorders also affect the inflammation process and, if so, whether permanent pacemaker treatment alters this inflammation process.

PATIENTS AND METHODS

In this retrospective cohort study, the inflammation-related parameters and scores of 44 patients (24 females, 20 males; mean age: 73.4±9.2 years; range, 64 to 82 years) who underwent dual chamber (DDD) pacemakers implantation due to total atrioventricular block at the Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Department of Cardiology between January 1, 2023 and December 31, 2023 were evaluated and compared before and three months after the procedure.

Patient data from the hospital's information system included basic demographic data, baseline and three-month C-reactive protein values, and hemogram parameters. The calculated inflammation scores included neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, SII (neutrophils×platelets/lymphocytes), and pan-immune-inflammation value (neutrophils × monocytes × platelets/lymphocytes).

This study included only patients diagnosed with complete atrioventricular block and DDD pacemaker implantation. Patients with a previous diagnosis of cardiac conduction system disease, patients with cardiac conduction system disorders other than complete atrioventricular block, patients with pacemaker-related infectious diseases, patients who received cardiac pacemaker treatment other than DDD pacemaker, patients who experienced an acute cardiac syndrome or stroke in the last year, those with uncontrolled hypertension or diabetes mellitus, patients diagnosed with heart failure within the last year not receiving optimal medical treatment for heart failure, acute infection cases, and conditions with a diagnosis of a systemic disease causing an active inflammatory process during an attack episode were excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (date: 26.6.2024, no: E-46059653-050.99-24750597). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The statistical analysis was conducted using the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Initially, the normality of continuous data distribution was assessed using the Kolmogorov-Smirnov test. The mean ± standard deviation (SD) was provided for continuous data, while the number and frequency were used for categorical variables. Student's t-test was employed to compare continuous variables that were continuous. Subsequently, a comparative examination of

Table 1
Baseline clinical and demographic features

Parameters	n	%	Mean±SD
Age (year)	44		73.4±9.2
GFR (mL/min/1.73 m²)	44		64.7±17.4
Sex			
Male	24	54.5	
Hypertension	42	95.4	
Diabetes mellitus	19	43.1	
Heart failure	14	31.8	
Stroke	5	11.3	
Atherosclerotic heart disease	36	81.8	

SD: Standard deviation; GFR: Glomerular filtration rate.

categorical variables was conducted utilizing Pearson's chi-square and Fisher exact tests. A p-value <0.05 was considered statistically significant.

RESULTS

Hypertension, atherosclerotic heart disease, diabetes mellitus, heart failure, and stroke were the most prevalent comorbidities in the study cohort in order of frequency (Table 1). Atrial and ventricular sensing and pacing thresholds and impedance values are shown in Table 2.

The mean platelet volume value was the only statistically significant difference observed when comparing laboratory parameters of the patients just before (88.11±6.23 fL) and three months after (87.46±5.43 fL) the procedure (p=0.002). No differences regarding inflammatory scores were identified in the comparisons (Table 3).

Table 2
Cardiac pacemaker characteristics

Parameters	Mean±SD
Atrial pacing threshold (V)	0.87±0.25
Atrial sensing threshold (mV)	3.27±1.23
Atrial impedance (Ohms)	525.0±112.8
Ventricular pacing threshold (V)	0.81±0.19
Ventricular sensing threshold (mV)	12.53±3.92
Ventricular impedance (Ohms)	689.4±148.6

SD: Standard deviation.

DISCUSSION

The cardiac pacemaker system comprises three main components: cellular ion channels, isolated tissue, and an energy reservoir. This system is influenced by inflammatory processes even during the prenatal period.[11] Research has shown that inflammation adversely affects the cardiac conduction system by triggering fibrotic processes.[1,3,4] It has been shown that IL-6 affects connexin43 gap junctions in cardiomyocytes through a newly revealed mechanism.[5] Inflammation observed during cardiac intervention and surgery has provided indications for the necessity of a permanent pacemaker.[7-9] Moreover, the connection between inflammatory processes and cardiomyopathy and ventricular arrhythmias has recently been uncovered.[12,13]

Cardiac pacemaker therapy has been utilized as a treatment modality since 1960 for patients suffering from cardiac conduction system disorders.[14] Nevertheless, adverse consequences that can impact inflammation due to pacemaker therapy have been noted. These complications include the early lead fixation effect, suture inflammation, postcardiac injury syndrome, and pacemaker- and lead-related infections.[15-18]

These considerations aside, it may come to mind that the atrioventricular block itself is a cause of inflammation after the development of atrioventricular block. To achieve this objective, we investigated the inflammatory markers and scores of patients who developed complete atrioventricular block and

Table 3
Clinical laboratory findings

	Procedure Day*			After 3 month			
	Mean±SD	Median	Q1, Q3	Mean±SD	Median	Q1, Q3	*p*
CRP (mg/dL)	10.84±8.77			10.44±8.61			0.835
WBC (10^3/μL*)	7.93±2.29			7.98±2.78			0.889
Neutrophil (10^3/μL*)	6.76±2.81			5.40±2.25			0.349
Lymphocyte (10^3/μL*)	1.84±0.74			1.74±0.73			0.203
Monocyte (10^3/μL*)	0.55±0.21			0.54±0.21			0.948
Hemoglobin (gr/dL)	12.14±1.91			12.48±1.98			0.093
Hematocrit (%)	37.03±5.50			37.86±5.65			0.191
MCV (fL)	88.11±6.23			87.46±5.43			0.156
RDW (%)	14.40±1.70			14.55±1.46			0.480
MPV (fL)	9.90±1.24			9.58±1.39			**0.002**
Platelet (10^3/μL*)	225.00±78.77			232.46±76.23			0.265
M/L	0.38±0.34			0.38±0.26			0.986
N/L		2.65	1.84-4.41		2.90	1.89-4.67	0.326
P/L		120.66	80.71-151.60		132.08	89.96-190.17	0.090
SII		532.14	343.93-1187.90		871.15	378.56-1249.71	0.578
PIV		265.38	153.67-673.30		541.03	177.92-718.95	0.669

SD: Standard deviation; CRP: C-reactive protein; WBC: White blood cell; MCV: Mean corpuscular volume; RDW: Red cell distribution width; MPV: Mean platelet volume; M/L: Monocyte/lymphocyte; N/L: Neutrophil/lymphocyte; P/L: Platelet/lymphocyte; SII: Systemic immune-inflammation index; PIV: Panimmune-inflammation value; * Just before the procedure.

underwent DDD pacemaker implantation before and three months after the procedure.

The prevalence of inflammation-related atrial high-rate episodes in patients with cardiac pacemakers, as reported in the literature, prompted us to consider this subject.[19-21] The results of our study did not reveal any statistically significant differences, except for a decrease in mean platelet volume in the third month of the follow-up compared to baseline (87.46±5.43 fL *vs.* 88.11±6.23 fL; p=0.002).

A literature review showed that MPV could be an indicator of platelet activation and microvascular complications, as well as a marker of inflammation. Furthermore, it has been demonstrated that minor postcardiac surgery may be associated with the development of atrial fibrillation.[22-24] Therefore, our study's findings provide limited but relevant insights that align with its objectives.

The potential effects of the atrioventricular block on inflammation may not be adequately observed by restricting the follow-up period of the study to three months, as it is known in the literature that the effects of inflammation on the development of new atrioventricular block begin approximately two years later.[4] The investigation is also scheduled to undergo long-term follow-ups.

Another point that needs to be focused on is the recently implemented His-Purkinje conduction system pacing method. This novel cardiac pacing method has demonstrated the ability to maintain stable pacing thresholds over mid-term follow-ups and achieve low rates of lead revision in patients diagnosed with atrioventricular block.[25] The more physiological nature of this system for the cardiac conduction system may result in more suggestive results for the objectives of our study. This subject may be clarified in future research, specifically through innovative pacing methods like left bundle pacing.

The study's limitations include the fact that it is retrospective, it can be conducted in a single

center with a limited number of patients, and the limited follow-up period. Despite the exclusion of patients with newly diagnosed acute coronary syndrome, stroke, uncontrolled hypertension, and diabetes mellitus within the past year to mitigate the impact of comorbidities on inflammation, the results of the study may have been influenced by the presence of these conditions. Although we excluded all pacemaker-related infectious diseases, the study may have been exposed to unforeseeable effects.

In conclusion, inflammation is a cause of cardiac conduction system disorders, but it is unclear whether these disorders also lead to inflammation. In the present study, the difference in the mean platelet volume observed in the follow-up after DDD pacemaker application in patients with complete atrioventricular block may be a clue in clarifying this situation. Although we believe that our study will give ideas for future studies, it is evident that long-term follow-ups are necessary to clarify this issue.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization: O.A., E.Y.; Data collection: O.A., E.A.D.; Data analysis and investigation: O.A., E.Y., S.K.O., E.A.D.; Methodology: O.A., E.Y., T.G.; Reviewing-editing: O.A., E.Y., S.K.O., E.A.D., T.G., M.K.; Writing: O.A., E.Y., T.G., M.K.

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