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The contribution of implantable cardioverter defibrillators to systemic inflammation in heart failure patients

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Abstract
Heart failure (HF) is associated with an increased 'inflammatory burden', which is manifested by the elevation of serum levels of some inflammatory mediators such C-reactive protein (CRP), cytokines. In addition, high levels of inflammatory markers in patients with HF have been associated with poor outcomes. Lethal ventricular arrhythmias such as asystole and ventricular fibrillation-tachycardia are common in patients with HF and implantable cardioverter defibrillators (ICDs) are effective in preventing these situations. But like every foreign object in the body, ICDs also cause fibrosis and inflammation. This study aimed to show additional contribution of ICDs to systemic inflammation in patients with HF. This is a single centrer retrospective study included 140 HF patients with and without ICD (group 1 and 2) and 53 healty control subjects (group 3). Three groups were compared with regard to Hs-CRP and Neutrophil / Lymphocyte ratio (NL ratio). In order that acute inflammation did not affect the results, the earliest 6th month laboratory measures after ICD implantation were recorded. There are not significant difference between all groups in terms of age and gender, and among group 1 and 2 in terms of disease history, ejection fraction, heart rate and creatinine. When compared to the three groups according to Hs-CRP and NL ratio, there was a significant difference between the groups (both $p<0.001$). Hs-CRP levels and NL ratio was high in the group 1(ICD group) than group 2 but it was not significantly. Hs-CRP levels and NL ratio were significantly negative correlated with ejection fraction. CRP and NL that are inflammatory markers were higher in patients with HF. Likewise as every foreign object in the body, ICDs also cause fibrosis and inflammation but in our study, we showed that this additional inflammation was not statistically significant.

Keywords: Systemic inflammation, implantable cardioverter defibrillators, heart failure

Introduction

Heart failure (HF) affected over 23 million people in the world is a major health problem. HF is a clinical syndrome accompanied by typical signs and symptoms that develop as a result of structural and/or functional defects [1]. It is expected that the result of aging the world population, the prevalence of heart failure will increase. Heart failure is associated with an increased 'inflammatory burden', which is manifested by the elevation of serum levels of some inflammatory mediators such C-reactive protein (CRP), cytokines [2]. Previous studies have shown that the neutrophil/ lymphocyte (NL) ratio is as a marker of systemic inflammation. Additionally, there was seen that High NL ratio has associated with cardiovascular mortality [3].

Because of ventricular arrhythmias, bradycardia and asystole, sudden and unexpected deaths are common in patients with heart failure, especially with mild symptoms. Current medical treatments for HF improve or delay the progression of cardiovascular disease, and reduce the annual rate of sudden death. Nevertheless, the effects on lifetime risk of sudden death are more limited and in case occur ventricular arrhythmia, these drugs will not treat it. Implanted cardioverter defibrillators (ICDs) are very effective to correction of the lethal ventricular arrhythmias and ICD implantation is recommended by current guidelines in secondary prevention of ventricular arrhythmias and primary prevention in heart failure patients with reduced ejection fraction (HFrEF) [4]. But like every foreign object in the body, ICDs also cause fibrosis and inflammation [5]. ICD and pace maker leads extend from the vena cava superior to the right ventricular apex. After the implantation process, an inflammatory reaction that will last for years takes place around the entire lead and generator, and these foreign bodies are surrounded with a fibrous capsule [5]. In a previous study, it was found that there was a significant increase in the number of leukocytes after the implantation of ICD or pace maker [6].

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There is no study showing that the contribution of ICDs to systemic inflammation in heart failure patients. This study aimed to show additional contribution of ICDs to systemic inflammation in patients with HF.

Materials and Methods

In this study, the patients who admitted to our cardiology clinic between from 2015 to 2017 were retrospectively screened. Patients with left ventricular ejection fraction (LVEF) <50% on transthoracic echocardiography (TTE) and healthy subjects without any disease were included in the study. Patients that younger than 18 years and older than 90 years and have history of active infection, surgery for any reason, chronic obstructive lung disease, rheumatic disease, severe hepatic dysfunction, stage 4-5 chronic kidney disease were excluded from the study. Similarly, patients with myocardial infarction (MI), percutaneous coronary angioplasty and coronary artery grafting until 6 months before admitted date of clinic were not included. Subjects were divided into 3 groups as heart failure patients with (group 1) and without (group 2) ICD and control group (group 3).

All patients had VVI or DDD ICD and in all of them, the procedure had been performed in right or left pectoral area with local anesthesia. Haemogram, biochemistry and CRP values were recorded from the hospital digital registry system. In order that acute inflammation did not affect the results, the earliest 6th month laboratory measures after ICD implantation were recorded (group 1). Haemogram and biochemical analyses had been done with the Sysmex XN-1000 (Sysmex America, Inc. Lincolnshire, IL, USA) and Roche Cobas C501 (Roche Diagnostics GmbH, Penzberg, Germany) devices. Neutrophil to lymphocyte ratio (NLR) was calculated by formula the neutrophil/the lymphocyte count. C reactive protein was measured on routine autoanalysis (Cobas c501, Roche, Manheim, Germany) with high sensitive kit.

In this study, we investigated that whether there is difference in terms of inflammatory parameters between three groups. Our study was approved by the clinical research ethics committee (11.01.2018 and 2018/05).

Statistical analyses were performed using a 64-bit Windows version of SPSS (version 21.0, Statistical Package for Windows, Chicago, Illinois). Continuous variables were analysed for normal distribution by the Kolmogorov-Smirnov test. We reported continuous data as mean and standard deviation. Categorical variables were summarized as percentages, frequencies and compared with the X2 test. We compared parametric variables using the Student's t test, non-parametric variables using Mann-Whitney U. One-way ANOVA and Dunnett's test were used to compare group means. For determine to association between variables, Pearson correlation analysis were used. Analysis results were evaluated within a 95% confidence interval and $p<0.05$ was interpreted as a statistically significant difference.

Results

Demographic, echocardiographic and laboratory characteristics of the patient groups and the control group are shown in table 1. There were no differences between the groups in age, gender, triglyceride, or AST ($p>0.05$). Similarly, between heart failure patients with and without ICD (group 1 vs 2), there were no significant differences in terms of ejection fraction, diabetes mellitus, coronary artery disease, or hypertension ($p>0.005$) (Table 1).

Table 1. Demographic, echocardiographic and laboratory characteristics of patients and control subjects

	Group 1 (ICD+HF patients) n=70	Group 2 (HF patients) n=70	Control Group n= 53	p
Age, year	64.4 ± 11.1	65.4 ± 11.2	61.1 ± 7.1	0.057
Gender, M/F	57/13	49/21	37/16	0.214$^{\beta}$
Disease history:				
Diabetes mellitus	30, % 42.9	31, % 44.3	-	0.865$^{\beta}$
Hypertension	45, % 64.3	47, % 67.1	-	0.722$^{\beta}$
Coronary artery disease	50, % 71.4	52, % 74.3	-	0.704$^{\beta}$
Ejection fraction, %	32 ± 8.7	34.1 ± 9.0	-	0.16
Heart rate, beat/min	79.8 ± 15.6	82.1 ± 10.5	73.2 ± 13.2$^{¥,\pi}$	0.002
Fasting LDL cholesterol, mg/dL	99.9 ± 36.2	113.5 ± 41.2	127.2 ± 34.8$^{¥}$	0.001
Fasting triglyceride, mg/dL	161.6 ± 89.4	146.7 ± 59.5	142.7 ± 61.9	0.296
Creatinine, mg/dL	1.20 ± 0.8	1.25 ± 0.8	0.81 ± 0.13$^{¥,\pi}$	<0.001*
AST, U/L	24.5 ± 16.1	21.9 ± 8.4	24.4 ± 7.2	0.343
Hemoglobin, g/dL	12.7 ± 1.9	12.6 ±1.9	14.7 ± 1.$^{3¥,\pi}$	<0.001
Hs-CRP, mg/L	8.5 ± 6.9	6.8 ± 4.4	2.2 ± 0.7$^{¥,\pi}$	<0.001*
Neutrophil / Lymphocyte ratio	4.46 ± 3.5	3.5 ± 2.8	2.1 ± 0.8$^{¥,\pi}$	<0.001*

* Analyzed with Kruskal-Wallis $^{\beta}$ Analyzed with chi-square
$^{¥}p < 0.05$ Group 1 vs control subjects $^{\pi}p< 0.05$ Group 2 vs control subjects

When heart rate and LDL cholesterol values were examined, it was seen that there was a significant difference between the three groups (p=0.002; 0.001 respectively). In subgroup analyses, heart rate was lower in healthy subjects than other two groups. Additionally, in terms of heart rate, group 1 and 2 were similar. When sub-analysis was performed in terms of LDL values, it was determined that the significance was caused by the difference between groups 1 and 3 (Table 1).

It was found that there was a significant difference between the groups respect to creatinine and heamoglobin (p <0.001 for both). In subgroup analysis, for both parameters, group 3 was significantly different from both group 1 and group 2. But not between group 1 and 2 (Table 1).

Similarly, in terms of inflammatory parameters which we investigated Hs-CRP and NLR in this study, Levels of the parameters were significantly different between three groups (p<0.001) and we found that this condition emerging from difference of group 3 and other groups (Table 1). Correlation analyzes of inflammatory markers with important variables for heart failure are given in table 2. We demonstrated a negative and significate correlation between Hs-CRP and ejection fraction (r= -0.329, p<0.001). Likewise, there were seen that NLR correlated with ejection fraction and creatinine (r= 0.324, p<0.001, r=-0.245 p= 0.003 respectively) (Table 2, Figure 1).

Table 2. Correlation analysis between inflammatory markers and major parameters.

	Age, year		Creatinine, mg/dL		Ejection fraction, %		Hemoglobin, g/dL	
	r	p	r	p	r	p	r	p
Hs-CRP	-0.142	0.094	0.073	0.394	-0.329	<0.001	-0.120	0.158
NL ratio	0.081	0.343	0.324	<0.001	-0.245	0.003	-0.147	0.084

Analyzed with Spearman correlation test

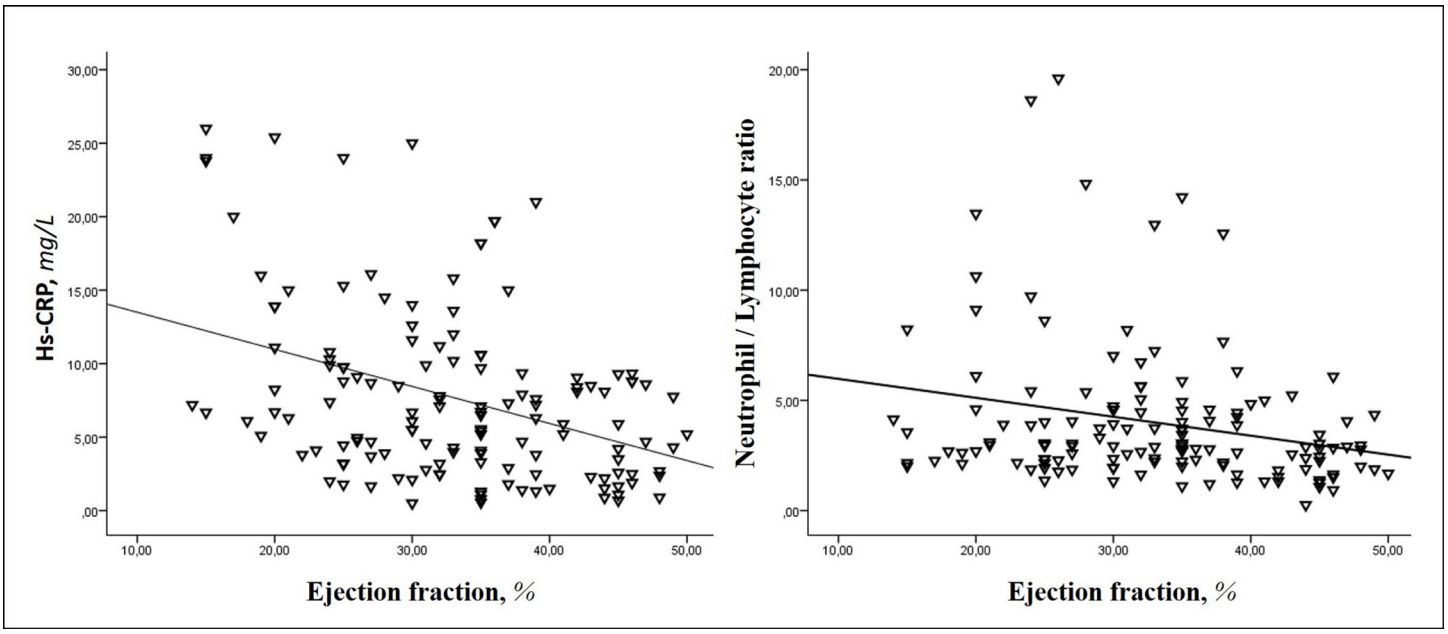

Figure 1. The correlation curves between ejection fraction and Hs-CRP and NL ratio

Discussion

The results of our study showed a significant increase in inflammatory parameters in HF patients as compared to controls. Additionally, these parameters in the patients with ICD was a little higher than in patients without ICD, although the difference was not significant.

HF is a clinical syndrome associated with typical signs and symptoms resulting from structural and/or functional cardiac diseases [1]. HF with reduced EF, HF with preserved EF and HF with mid-range EF was considered as EF <40%, ≥50% and 40-49% respectively according to 2016 ESC Heart Failure Guidelines [4]. Although hypertension, cardiac valvular diseases, and cardiomyopathy may cause to HF, ischemic heart disease is the underlying etiology in most cases. While HF is already associated with an increased risk of morbidity and mortality, nearly 60% of the patients with ischemic heart failure die from arrhythmias such as ventricular tachycardia, bradycardia, or asystole [7]. Although some antiarrhytmic drugs may decrease deaths associated with tachy-arrhytmia in these patients, a reduction in all-cause mortality could not be shown. In these patients, ICDs may be implanted for primary and secondary prevention of sudden cardiac death. ICD implantation for reduce to risk of sudden cardiac death and all-cause mortality has been recommended in subjects with recovered from a ventricular arrhythmia [4]. Similarly, An ICD is recommended in patients with symptomatic HF, and an LVEF ≤35% despite ≥3 months of optimal medical treatment (OMT), provided they are expected to survive substantially longer than one year with good functional status [4]. Even if the above criteria are met, it is not recommended since the absence of a proven benefit of ICD implantation within 40 days after acute MI [8].

The neutrophil/lymphocyte (NL) ratio has been utilized as an inflammatory marker for several cardiac and non-cardiac diseases, and has been used for prognostic estimations in a number of diseases including acute myocardial infarction (MI), stroke, or heart failure [9,10]. Also, poor prognosis in heart failure was shown to be associated with elevated levels of Hs-CRP, which is another inflammatory marker [11]. Furthermore, statin treatment has been found to suppress the increased cardiovascular risk associated with inflammation (Hs-CRP) [12].

Patients with congestive HF has been known to have elevated levels of inflammatory mediators. CRP is an acute phase reactant and a non-specific inflammation marker primarily produced by hepatoyctes [13]. Previous studies have clearly established that HF patients have elevated levels of CRP as compared to controls [14]. In our study, in accordance with previous data, HF patients with or without ICD had higher Hs-CRP than controls. Once again, neutrophil/lymphocyte ratio, which is considered a marker of systemic inflammation, was higher in both groups as compared to healthy controls. However, although HF patients with ICD had higher Hs-CRP and NL than those without ICD, the difference was statistically insignificant. Despite the underlying mechanisms responsible for the elevated CRP in HF patients is not completely understood, it is thought that it may be due to hepatocellular injury as a result of hepatic congestion [15]. Also, CRP levels have been shown to be more markedly elevated during periods of decompensation, with return to baseline levels after failure is compensated [16]. On the other hand, the elevation in inflammatory markers due to HF is associated with poor prognosis per se. Although this was explained on the basis increased myocardial stiffness, neurohormonal activation, and immune response etc., the exact mechanisms remain unclear [2].

ICDs consists of batteries that are able to deliver shocks to the myocardium, which may lead to right ventricular injury and development of local fibrotic areas. Furthermore, the foreign body reaction due to ICD leads may also result in injury of the right ventricular apex together with areas of fibrosis [17]. Although subtle in most patients with ICDs, these may also be partially responsible for the increased inflammatory response. Even if not significant in patients with ICD, these may be responsible for the increased inflammatory response.

In a study by Stumpf et al., a negative and significant correlation between CRP and LVEF was found among MI patients [18]. Again, Wojciechowska et al. found a similar correlation between LVEF and CRP. In our study, there was also a correlation between LVEF and both CRP and NL ratio, suggesting that lower ejection fraction is associated with an increased inflammatory burden [14].

Anemia is a common comorbidity in HF patients that has been shown to be associated with poor functional capacity as well as increased morbidity and mortality [19]. Anemia has been reported in up to 70% of the patients with heart failure [19]. In our study, HF patients had lower hemoglobin levels than controls, while the difference between HF patients with or without ICD was not significant. HF patients frequently have sinus tachycardia, both as a result of increased sympathetic activity and as an attempt to compensate for the reduced ventricular function. Also, tachycardia in patients with HF negatively affects the prognosis of the diseases. Patients with lower baseline heart rate or pharmaceutically reduced hear rate are known to have better clinical outcomes [20]. In our study, while resting heart rate was similar between patients with or without ICD, both groups had significantly elevated pulse rate as compared to healthy controls.

Conclusion

HF patients have increased levels Hs-CRP and NL ratio, which are inflammatory markers. Furthermore, statically a significant correlation exists between these inflammatory markers and LVEF. As with every foreign body, ICDs are also caused fibrosis and inflammation, although in our study their effect on inflammatory markers was statistically insignificant.

Limitations of our study

Major limitations of our study include the relatively smaller sample size and its retrospective design. Also, the history of device shocks in patients with ICD was not inquired. More comprehensive studies on the subject should be planned.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
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Ethical approval
Our study was approved by the clinical research ethics committee (11.01.2018 and 2018/05)

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