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Increased Monocyte Count is Related to the Development of Atrial Fibrillation in Subjects with Heart Failure

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Abstract: Determining subjects with heart failure (HF), who have a high risk of developing atrial fibrillation (AF), is crucial since it is related to an increase in morbidity and mortality. The importance of an increase in inflammatory response cannot be ignored in developing AF in subjects with HF. This study's goal was to evaluate the relationship between the development of AF and monocyte count, the main components of the inflammatory response, in subjects with HF. Medical data of 158 subjects in total with sinus rhythm, admitted to the emergency department and hospitalized with systolic HF between January 2009 and February 2014, were analyzed prospectively. All the subjects followed up in terms of the development of AF. The subjects separated into two groups according to their rhythm at the end of the follow-up period. Group 1 included subjects who maintained sinus rhythm, while Group 2 included subjects with AF. Echocardiographic findings and laboratory data were collected. No statistically significant difference was determined between the groups concerning age, sex (p=0.056), hypertension, diabetes mellitus, and smoking status. The two groups differed significantly regarding the presence of moderate-to-severe mitral regurgitation (MR) [32 (28%) vs. 22 (51%), p=0.010] and monocyte count [560 (20-3100) vs. 800 (380-1510) µL, p<0.001]. The multivariate Cox regression model demonstrated that an association of monocyte count (HR=2.397, 95% CI =1.397-4.112, p=0.002) and moderate-to-severe MR (HR= 2.347, 95% CI=1.276-4.316, p=0.006) with the development of AF remained following the adjustment for the variables, which had determined to be statistically significant as a result of the univariate analysis and related to monocyte count. The present study concludes that increased monocyte count in subjects with HF is related to the development of AF. However, further large-scale research required for confirming the findings, as mentioned above.
Keywords: Monocyte; atrial fibrillation; heart failure

INTRODUCTION

Monocytes account for approximately one-fifth of mononuclear cell fragments in the peripheral blood, and they are essential for inflammatory response.(Curi,2017;Acikgoz 2018) Monocytes take a significant place in inflammatory processes and the occurrence of cardiovascular diseases by promoting the release of immunostimulatory agents, cytokines, growth factors, platelet-derived activation products, oxidized lipids, and eicosanoid proteins. (Gratchev,2012) Monocytes and macrophages result in the release of cytokines that are involved in atrial fibrosis and remodeling the development of atrial fibrillation (AF), as in the case of many other cardiovascular diseases. (Takahashi, 2012)

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Atrial fibrillation represents the arrhythmia type, which is common in heart failure (HF), and its prevalence can reach 30% in HF(Kotecha,2015).

Moreover, atrial fibrillation is an independent indicator of mortality and morbidity in HF(Carlisle,2019). It is, therefore, essential to recognize subjects with HF, who carry a high risk of the development of AF. Inflammation, oxidative stress, and neurohormonal activation are the main physiopathological pathways in developing AF in subjects with HF (January 2014) Several studies have shown elevated levels of interleukin (IL)-22, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) as inflammatory biomarkers, the production of which involves monocytes and macrophages in patients with AF(Oikonomou,2019; Zacharia,2019)

Previous research has shown an association between monocyte count and all-cause mortality, hospitalization, and the New York Heart Association (NYHA) class (Elchinova,2018; Dixon,2011). Nevertheless, there is no research showing a correlation between monocyte count and the development of AF in subjects with HF. The present research aimed to examine the correlation between monocyte count and the development of AF in subjects with systolic HF.

MATERIALS AND METHOD

In our study, the prospective screening of 210 patients with HF, admitted to the emergency department and hospitalized due to systolic HF, was performed. The following exclusion criteria were determined: acute coronary syndrome, cancer, active inflammatory diseases, infectious diseases, sepsis, and myeloproliferative disorders. Finally, 158 patients with systolic HF enrolled in the research. All study procedures were approved by the ethics committee of Cumhuriyet University (Sivas, TURKEY), according to the Declaration of Helsinki. Written informed consent obtained from all subjects.

Systolic HF was diagnosed based on the compatible clinical presentation and history combined with documented systolic left ventricular (LV) dysfunction that described as an LV ejection fraction (LVEF) less than 50% in echocardiography.

The subjects followed up for the development of AF. The subjects separated into two groups according to their rhythm at the end of the follow-up period. Group 1 consisted of subjects who maintained sinus rhythm, while Group 2 included subjects with AF. A comparison between the two groups made in terms of echocardiographic parameters and laboratory data, and cardiovascular risk factors, such as diabetes mellitus (DM), hypertension (HT), and smoking status. Hypertension described as blood pressure higher than 140/90 mmHg on more than two occasions in the course of office measurements or receiving antihypertensive therapy. Diabetes mellitus described as a fasting blood sugar level higher than or equal to 126 mg/dL or undergoing antidiabetic therapy.

Expert echocardiographers performed echocardiographic examinations using the Vivid seven system (GE Healthcare, Milwaukee, WI, USA) and 2.5–5 MHz probes. Digital recordings of echocardiographic examinations assessed offline. The LVEF computed by employing the modified Simpson method. Chamber sizes determined following the recently published guidelines. The measurement of the LA size was performed at the end-ventricular systole by the M-mode linear dimension, acquired from the parasternal long-axis view. Systolic pulmonary artery pressure (sPAP) was computed, as described elsewhere (Galderisi,2017).

The grading of valvular regurgitations was performed in two categories, being 0moderate-to-severe vs. not moderate-to-severe, as a result of combining color flow jet Doppler signal intensity and vena contracta width following the guideline

recommendations(Lancellotti, 2010).

RESULTS AND DISCUSSION

The follow-up of all the subjects was performed for a mean period of 22.1±11 months (range 4–61). The subjects separated into two groups according to their rhythm at the end of the follow-up period. Group 1 consisted of patients who maintained sinus rhythm, while Group 2 included patients who developed AF. Table 1 presents information on baseline features, echocardiographic parameters, and laboratory data. No statistically significant difference was detected between the two groups concerning age, sex (P=0.056), HT, DM, and smoking status.

Table 1. Baseline Characteristics of Study Patients

Variables	All patients (n=158)	Patients with SR (n=115)	Patients with AF (n=43)	p-value
Baseline charecteristics				
Age (yr)	69 ± 10	68±11	70 ±9	0,339
Female	41 (%26)	35(%30)	6(%14)	0,057
Hypertension	83(%53)	56(%49)	27(%63)	0,114
Diabetes mellitus	46(%29)	30(%26)	16(%37)	0,241
Current smoking	54 (%34)	41(%36)	13(%30)	0,652
Echocardiographic findings				
LVEF (%)	30,9±8,2	30,3±8,1	32,4±8,5	0,158
LA(cm)	4,5 ±0,6	4,4±0,6	4,5±0,7	0,395
SPAP (mmhg)	34±12	33±12	34±12	0,689
Moderate-severe MR	54(%34)	32(%28)	22(%51)	0,010
Moderate-severe TR	57(%36)	37(%32)	20(%46)	0,095
Laboratory findings				
Hemoglobin (g/dL)	13,0±2,5	13,0±2,6	13,1±2,4	0,875
BUN(mg/dL)	25(8-103)	24(8-103)	27(11-81)	0,700
Creatinine (mg/dL)	1,1(0,5-5,7)	1,1(0,5-5,70)	1,3(0,6-2,4)	0,524
WBC cells/µl	9190(4090-25840)	8900(4,090-25840)	9800(5140-25000)	0,221
Neutrophil cells/µl	6300(300-22990)	6060(300-22990)	7300(2800-20800)	0,146
Monocyte cells/µl	600(20-3100)	560(20-3100)	800(380-1510)	<0,001
Lymhocyte cells/µl	1400(130-10180)	1400(130-10180)	1460(410-3930)	0,734
Eosinophil cells/µl	105 (0-1260)	100(0-1260)	130(0-970)	0,269
Platelet 10^3x cells/µl	238±84	235±80	248±94	0,376

Abbreviations: SPAP, systolic pulmonary artery pressure; LA, left atrial diameter; MR, mitral regurgitation; SR, sinus rhythm; AF, atrial fibrillation; TR, tricuspid regurgitation; LVEF, left ventricle ejection fraction; BUN, blood urea nitrogen; WBC, white blood cell

The two groups differed significantly regarding the presence of moderate-to-severe mitral regurgitation (MR) [32 (28%) vs. 22 (51%), p=0.010] and monocyte count [560 (20-3100) vs. 800 (380-1510) µL, p<0.001]. As expected, monocyte count

and white blood count, neutrophil, and lymphocyte count were positively correlated (Table 2).

Table 3 presents the findings obtained from the univariate and multivariate Cox regression analyses for the development of AF. In the univariate analysis, an association revealed between moderate-to-severe MR and monocyte count and the development of AF. Furthermore, the multivariate Cox regression model demonstrated that an association of monocyte count (HR =2.397, 95% CI =1.397-4.112, p=0.002) and moderate-to-severe MR (HR= 2.347, 95% CI =1.276-4.316, p=0.006) with the development of AF remained following the adjustment for the variables, which had been determined to be statistically significant in the univariate analysis and related to monocyte count.

Table 2. Spearman Correlation Coefficients for Monocyte Count

Variable	Monocyte Count	p-value
WBC	0,591	<0,001
Neutrophil	0,472	<0,001
Lymphocyte	0,324	<0,001

Abbreviations: WBC; white blood cell

Table 3. Univariate and Multivariate Analyses for Predicting Atrial Fibrillation

	Univariate			Multivariate		
Variable	p	HR	(95% Cl)	P	HR	(95% Cl)
Statistically significant variables						
Monocyte	0,003	2,189	1,308-3,665	0,002	2,397	1,397-4,112
Moderate - severe MR	0,010	2,196	1,204-4,006	0,006	2,347	1,276-4,316
Variables correlated with monocyte count						
WBC	0,354	0,960	0,880-1,047			
Neutrophil	0,384	0,960	0,875-1,053			
Lymphocyte	0,532	1,106	0,807-1,514			

In the present research, an independent association of elevated monocyte counts with the development of AF determined in subjects with HF.

Heart failure represents a complex syndrome accompanied by hemodynamic and neurohormonal disturbances, involving the release of various cytokines, sympathetic nervous system activation, and the activation of the renin-angiotensin-aldosterone system (Ponikowski P,2016). Atrial fibrillation represents the arrhythmia type that most frequently observed in subjects with HF, and HF subjects with AF have a poorer prognosis than subjects maintaining sinus rhythm (Wang,2003; Carlisle,2019). It is, therefore, significant to determine subjects at high risk of developing AF. Much research has demonstrated that atrial and ventricular wall stress plays a significant role in developing AF(Yang, 2014; Cullington,2014).

On the other hand, inflammation takes a central part in the pathophysiology of the development of AF, as in many cardiovascular diseases. Several studies have indicated elevated levels of inflammatory biomarkers, including IL-2, IL-6, IL-8, and TNF-α, in subjects with AF (Conway,2004; Zacharia,2019).

Monocytes are the primary cell line involved in the inflammatory response, although they constitute only 5 to 10% of leukocytes in the peripheral blood. Monocytes increase inflammatory response by secreting cytokines, on the one hand,

and they increase their cell fragments, on the other hand (Franca,2017; Kratofil,2017). Previous studies have revealed the clinical significance of monocyte activation and increased monocyte count in cardiovascular diseases, such as stable coronary artery disease, stroke, and HF(Rogacev,2012; Kim,2014; Wrigley,2011). The importance of monocyte activation for the development and progression of HF has been shown (Wrigley,2011; Shahid,2018).

Furthermore, proinflammatory and anti-inflammatory cytokines, such as IL-6, TNF-α, and IL-10, for which activated monocytes are the primary source, have been demonstrated to correlate with the progression and severity of HF and the associated mortality (Wrigley,2011; Shirazi, 2017; Bartekova,2018). However, no previous study has evaluated the relationship between monocyte count and developing AF in subjects with HF. As far as we know, the current research represents the first study demonstrating an association of the high monocyte count with the development of AF in subjects with HF. In a study, Karatas et al. found a relationship between monocyte count and the development of AF(Karatas,2016). Another study found a relationship between monocyte activation and AF development following cardiac surgery(Tekkesin,2017). Observational and *ex vivo* studies also demonstrated a relationship between AF and inflammation and oxidative stress-mediated by monocytes(January 2014). Endomyocardial biopsies obtained from the right atrial septum of patients with AF showed the widespread inflammatory infiltrates of monocytes (Smorodinova,2017). Deng et al. showed that monocytes attach to adhesion molecules that proceed into the sub-endothelial space of the atrial wall, by producing cytokines including TNF-a and IL-6, which can be associated with the mechanism of AF development (Deng,2011).

On the other hand, monocytes secrete various cytokines that are closely related to the development of AF, and these cytokines play a central role in atrial remodeling by affecting myocytes and fibroblasts in the atrial tissue (Takahashi,2012; Li,2010; Guo,2012). According to the findings obtained from this research, monocyte activation induced by various causes in patients with HF may cause AF through an escalated inflammatory process.

In the present study, we also showed that the development of AF in subjects with HF could be predicted by moderate-to-severe MR, as expected. Similar to the data reported in previous studies, the current research also found a relationship between the severity of MR and the development of AF (Yokota,2018; Grigoini 2018). This finding may be associated with an increase in the left atrial diameter resulting from the increasing severity of MR and atrial fibrosis, which is the source of reentry resulting in AF.

The present research represents a single-center study, which has a comparatively small sample size. Another limitation is that the present study did not create subsets and perform the functional analysis of peripheral monocytes. Cytokine analysis could not be performed in the study due to its high cost. Although patients with active inflammatory disease, infectious disease, sepsis, or myeloproliferative disorders excluded from the study, it is another limitation of the present study that other inflammatory clinical problems, which could increase monocyte count, may have been possibly overlooked.

CONCLUSION

In conclusion, our study results suggest that there is an association of the high monocyte count with the development of AF in subjects with HF. Therefore, we

recommend that subjects with HF and increased monocyte count should strictly be monitored for the development of AF.

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CONFLICT OF INTEREST

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript.

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