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Mean Platelet Volume in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Aritmojenik Sağ Ventrikül Kardiyomyopatisi/Displazisi olan Hastalarda Ortalama Trombosit Hacmi

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Abstract

Aim: Arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D) is characterized by the gradual replacement of the right ventricular myocardium with fibrous and adipose tissue and can cause ventricular tachyarrhythmia in young patients. Mean platelet volume (MPV) is reported to be an easily measurable marker reflecting platelet activation and plays an important role in the pathophysiology of cardiovascular disorders. In this study, we aimed to assess MPV in patients with ARVC/D.

Methods: Twenty-nine patients (23 men, age: 38.0±13.1 years) with ARVC/D and forty-one healthy subjects (30 men, age: 39.3±11.8 years) were studied. Plasma MPV was measured in ARVC/D patients and control subjects.

Results: The MPV was higher in patients with ARVC/D when compared with the control group (9.87±1.0 vs. 8.2±1.1 fl, p<0.01). To investigate any possible connection between MPV and clinical presentation of ARVC/D, ARVC/D patients were separated into two groups according to the presence of syncope and sudden cardiac death (SCD). MPV was higher in ARVC/D patients with SCD compared to those without cardiac arrest, but the difference was not statistically significant.

Conclusion: Our results suggest that patients with ARVC/D have increased platelet activation.

Keywords: Arrhythmogenic right ventricular cardiomyopathy/dysplasia, mean platelet volume, platelet function

Öz

Amaç: Aritmojenik sağ ventrikül kardiyomyopatisi veya displazisi (ARVC/D) kalp kasının genetik bir hastalığıdır. Sağ ventrikül myokardında fibroz ve yağ dokususu artışı ile karakterize olan bu hastalık gençlerde ventriküler taşikardiye yol açabilmektedir. Ortalama trombosit hacmi, kolayca ölçülebilen bir trombosit fonksiyon göstergesi olup kardiyovasküler hastalıkların patofizyolojisinde önemli rol oynamaktadır. ARVC/D'li hastalarda ortalama trombombosit hacmi ile ilgili bir çalışma bulunmamaktadır. Biz bu çalışmada ARVC/D hastalarında ortalama trombosit hacmini değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya 29 ARVC/D hastası (23 erkek, ortalama yaş: 38,0±13,1 yıl) ve 41 sağlıklı (30 erkek, ortalama yaş: 39,3±11,8 yıl) kişi alındı. Hasta ve kontrol grubu yaş ve cinsiyet bakımından benzer idi. Ortalama trombosit hacmi (OTH) düzeyleri her iki grupta da ölçüldü.

Bulgular: OTH kontrol grubu ile kıyaslandığında ARVC/D hastalarında anlamlı olarak yüksek saptandı (9,87±1,0 vs. 8,2±1,1 fl, p<0,01). OTH'nin, ARVC/D hastalarının klinik prezentasyonu ile olan ilişkisini değerlendirmek için ARVC/D hastaların, bayılma ve ani ölümle başvuranlar diye iki alt gruba ayrıldı. Ani ölümle başvuranlarda OTH yüksek olmakla birlikte istatistiksel olarak anlamlı saptanmadı.

Sonuç: ARVC/D hastalarında OTH değerleri anlamlı olarak yüksek saptandı. Bu sonuçlarımız ARVC/D hastalarında trombosit fonksiyonlarının artmış olduğunu göstermektedir.

Anahtar Sözcükler: Aritmojenik sağ ventrikül kardiyomyopati/displazi, ortalama trombosit hacmi, trombosit fonksiyonu

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Introduction

The first comprehensive clinical description of arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D) was reported by Marcus et al. (1) in 1982. It is a progressive heart muscle disorder and characterized pathologically by myocardial atrophy, loss of myocytes and replacement of myocardial tissue by adipose and fibrous tissue. This process lead to ventricular electrical instability and can result in arrhythmia, syncope, and sudden cardiac death (SCD) (1). The disease is frequently inherited in an autosomal dominant pattern with various expressions. The main factor for the development of ARVC/D is mutations in the genes that encode for desmosomal proteins. Desmosomal dysfunction, that usually affects the right ventricle, and less frequently, the left ventricle and impairs the right ventricular function, leads to insufficient cell adhesion and subsequent myocyte detachment and apoptosis (2-4). Histopathological examinations of patients with ARVC/D reveal fibrous and adipose infiltration of the ventricular myocardium. Fibrous and adipose tissue is commonly localized in the triangle of dysplasia, namely; inflow tract, outflow tract or apex of the right ventricle (4,5). The clinical presentations of ARVC/D are variable. The common symptoms are palpitations and syncope due to nonsustained and sustained ventricular arrhythmias. SCD may be the first presentation of the disease (5).

Mean platelet volume (MPV) which corresponds to the average of size of platelets in the blood is reported to be an easily measurable marker reflecting platelet activation. It is significant in the mechanism of cardiovascular events (6,7). MPV is gaining interest as an independent cardiovascular risk factor (8). MPV increases when there is increased platelet production (9). Large platelets increase thrombotic potency (10).

To our best knowledge, the association between MPV and ARVC/D has not been examined previously. This study was designed to investigate MPV values in patients with ARVC/D.

Methods

Study Population

Twenty-nine ARVC/D patients (23 men, mean age: 38.0±13.1 years), who were followed by the Arrhythmia Outpatient Clinics of the İstanbul Medical Faculty between November 2005 and February 2011, were included in the study. The control group consisted of forty-one age-, gender-, and body mass index-matched healthy subjects. The diagnosis of ARVC/D was based on the criteria set by the Task Force of the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology (11), and was re-checked according to the 2010 revised Task Force Criteria (12). Electrocardiographic and echocardiographic examinations, cardiovascular magnetic resonance imaging, and catheter angiography were performed in all patients. Definite ARVC/D was characterized by the presence of ≥2 major criteria, 1 major and 2 minor criteria or 4 minor criteria (12). We obtained the patients' general and laboratory characteristics by review of medical records. Furthermore, data on major clinical events, including ventricular tachycardia (VT), syncope, catheter ablation and implantable cardioverter/defibrillator (ICD) implantation were taken from the medical records. The control group consisted of forty-one healthy individuals (30 men, mean age: 39.3±11.8 years) without any cardiac or other chronic disorders. Age and gender distributions between the patients and controls were similar.

Laboratory Analysis

In all cases, fasting venous blood samples were taken from the antecubital vein without stasis between 8:00 and 9:00 in the morning. Lipid profile, creatinine and glucose levels were measured using standard methods. Tubes with K3-EDTA were used to collect the blood samples. MPV was measured using automatic blood counter Coulter LH 780 Hematology Analyzer (Beckman Coulter). In addition, the measurements were performed within 30 minutes after sampling to avoid from EDTA-induced platelet swelling.

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS version 16.0, Chicago, Illinois, USA). All data were presented as mean + standard deviation. Comparison of parametric and nonparametric values between the two groups was performed by Student t-test and the Mann-Whitney U test. Categorical variables were compared by the Chi-square test. A p value of less than 0.05 was interpreted as statistically significant.

Ethics

This retrospective study was performed according to the Helsinki declaration and approved by the Ethics Committee of İstanbul University İstanbul Medical Faculty.

Results

The study population consisted of 29 ARVC/D (23 men, mean age: 38.0±13.1 years) and 41 age- and sex-matched control participants (30 men, mean age: 39.3±11.8 years). Age and gender distributions between the patients and controls were similar. Basal characteristics of the study population are listed in Table 1. The MPV was higher in patients with ARVC/D when compared with controls (9.87±1.0 vs. 8.2±1.1 fl, $p<0.01$). Furthermore, there were no significant differences between the groups regarding the platelet counts, hemoglobin levels, blood lipid levels,

creatinine and glucose levels (Table 2). Fifteen patients (51.7%) had syncope, while eight patients (27.5%) were resuscitated from SCD. Electrophysiological study was performed in twenty-five patients; in two patients (8.0%) ventricular fibrillation and in 16 patients (64.0%) VT) was induced. There was no arrhythmia induced in the remaining seven patients (28.0%). In eight patients (27.5%), radiofrequency catheter ablation was performed successfully. ICD was implanted in 17 patients (58.6%). To investigate any possible connection between MPV and clinical presentation of ARVD, ARVD patients were separated into subgroups according to the presence of syncope and SCD. The MPV values were higher in ARVD patients with SCD compared to those without cardiac arrest, but the difference was not statistically significant.

Discussion

ARVC/D is a genetic disease of the heart muscle and associated with syncope and SCD (13). It is characterized by a gradual right ventricle apoptosis and fibrofatty replacement. Left and biventricular involvement is also common. Apoptosis is induced by inflammatory cytokines. Inflammation plays an important role in the disease progression and outcome (14). Infiltration of inflammatory cells in necrotic or degenerative cardiac tissue has been determined in ARVC/D patients (15,16).

Basso et al. (17) detected patchy inflammatory infiltrates in 20 cases (67%) of 30 hearts with ARVC/D in autopsy. Additionally, Campuzano et al. (14) reported a relationship between the presence of inflammatory infiltrates in ventricular myocardium and the severity of structural heart alterations in ARVC/D. Myocarditis plays another significant role in the onset and progression of ARVC/D. A common finding upon pathological examination of ARVC/D biopsies is myocarditis (18). It is acknowledged that myocarditis can be induced by a viral infection. Infiltration of inflammatory cells might be a response to pro-inflammatory cytokines induced by such a viral infection (19).

C-reactive protein (CRP) is a biomarker of inflammation. High levels of CRP predict cardiovascular events such as coronary heart disease, stroke or peripheral vascular disease (20). It is known that inflammation is associated with arrhythmia occurrence. This association has clearly been established during atrial fibrillation. It has been shown that high levels of CRP are associated with a greater risk of atrial fibrillation recurrence after electrical cardioversion (21,22). Bonny et al. (22) found that the baseline CRP level was significantly higher in patients with ARVC/D compared to that in right ventricle outflow tract tachycardia patients.

Platelets make an important contribution in the pathogenesis of inflammation and thrombosis (23). Evidence has accumulated suggesting a significant role of MPV as a biomarker of inflammation (24). MPV indicates the platelet stimulation and production. Platelet volume is arranged at the stage of the megakaryocyte. Researchers proved that inflammatory cytokines affect megakaryocyte ploidy and can lead to the production of more active and larger platelets (24,25). Therefore, inflammatory cytokines, which are increased in patients with ARVC/D, cause an increase

Table 1. Basal characteristics of the study and control groups

	ARVC/D (n=29)	Controls (n=41)	p value
Age	38.0±13.1	39.3±11.8	0.67
Gender (male) (n-%)	23 (79.3%)	30 (73.1%)	0.89
Body mass index (kg/m^2)	26.04±3.91	24.76±3.83	0.73
Hypertension (n-%)	2 (7.1%)	2 (4,9%)	0.82
Smoking (n-%)	12 (42.9%)	12 (29.2%)	0.18

ARVC/D: Arrhythmogenic right ventricular cardiomyopathy or dysplasia

Table 2. Laboratory characteristics of the Arrhythmogenic right ventricular cardiomyopathy or dysplasia patients and controls

	ARVC/D (n=29)	Controls (n=41)	p value
Glucose (mg/dl)	94.0±18	96.8±12	.34
HDL cholesterol (mg/dl)	41.9±9.3	41.3±8.6	.91
LDL cholesterol (mg/dl)	149±55.4	138.7±45.1	.37
Triglyceride (mg/dl)	151.9±55.4	144.5±36.0	.65
Hemoglobin (g/dl)	14.1±1.4	14.7±1.3	.23
Mean platelet volüme (fL)	9.87±1.0	8.2±1.1	<0.01
Platelet count	249±49	251±58	0.83

ARVC/D: Arrhythmogenic right ventricular cardiomyopathy or dysplasia, HDL: High density lipoprotein, LDL: Low density lipoprotein

in MPV values by stimulating the megakaryocyte ploidy. Inflammation might be one of the reasons of increased MPV in patients with ARVC/D. This study demonstrated that MPV was significantly increased in patients with ARVC/D compared with healthy control subjects.

Our study has some limitations. The small sample size of patients was the major limitation. ARVC/D is a rare and inherited progressive disease of the heart muscle. Because of that reason, our sample size was small. Another limitation of this study was that the analysis was based on a simple baseline determination, but a single measurement of MPV may not reflect lifetime status.

Conclusion

In this study, MPV values were significantly higher in patients with ARVC/D when compared with the controls. Elevated MPV indicated that patients with ARVC/D have increased platelet activation. We recommend further prospective studies in order to establish the pathophysiological and clinical significance of increased MPV in patients with ARVC/D.

Author Contributions

Ethics Committee Approval: We offer in the form of retrospective academic and ethical committee approval has been obtained in this study, Informed Consent: Retrospective chart scanning (from medical records) was conducted as, Concept: İbrahim Altun, Fatih Akın, Murat Biteker, Nuri Köse, Göksel Güz, Fahrettin Öz, İmran Önür, Ahmet Kaya Bilge, Kamil Adalet, Design: İbrahim Altun, Ahmet Kaya Bilge, Kamil Adalet, Data Collection or Processing: İbrahim Altun, Göksel Güz, Fahrettin Öz, İmran Önür, Analysis or Interpretation: Fatih Akın, Murat Biteker, Nuri Köse, Literature Search: İbrahim Altun, Fatih Akın, Murat Biteker, Nuri Köse, Göksel Güz, Fahrettin Öz, İmran Önür, Writing: İbrahim Altun, Ahmet Kaya Bilge, Kamil Adalet, Peer-rewiev: Internal peer-reviewed, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared that this study has received no financial support.

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