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Evaluation of atrial conduction properties and atrial arrhythmia propensity in vitiligo patients

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ABSTRACT

Aims: Vitiligo is a skin condition characterized by melanocyte loss. It is thought to have a robust association with various systemic and metabolic disorders, such as insulin resistance, atherosclerotic cardiovascular disease, and metabolic syndrome. Atrial fibrillation (AF) is a prevalent disorder in clinical practice and appears to be predictable by atrial electromechanical delay (EMD). This study aimed to detect atrial conduction time through tissue Doppler echocardiography, a non-invasive method used for patients with vitiligo.

Methods: We conducted this study with 32 patients diagnosed with generalized vitiligo and 38 age and sex-matched controls. This study was designed as a prospective, single-center, and cross-sectional study. West evaluated all participants' blood samples, including neutrophil/lymphocyte ratio (NLR), high-sensitivity C-reactive protein (hs-CRP), and other laboratory parameters. Then, we calculated atrial EMD, intra-atrial EMD, and left atrial EMD.

Results: We found neutrophil count, NLR levels, and hs-CRP levels to be significantly higher in the vitiligo group (6±1.4 vs. 4.5±2.3, p=0.001; 3.5±1.4 vs. 2.5±1.9, p=0.024; 6.2±1.9 mg/dl vs. 4.1±1.3 mg/dl, p<0.001, respectively). In addition, inter-atrial and intra-atrial EMD were significantly higher in the vitiligo group compared to the control group (36.3±8.5 vs. 24.2±10.8, p<0.001; 18.1±8.3 vs. 10.9±5.8, p<0.001, respectively). Finally, left atrial EMD was higher in the vitiligo group, but we could not reach statistical significance (15.3±6.9 vs. 13.2±7.2, p=0.33).

Conclusion: We concluded that intra-atrial EMD and inter-atrial EMD were significantly prolonged in the vitiligo patients. Our results suggest that vitiligo patients are at risk for atrial fibrillation.

Keywords: Atrial conduction time, atrial fibrillation

INTRODUCTION

Vitiligo, a skin condition characterized by selective loss of melanocytes, affects an estimated 0.5-2% of the population worldwide.[1] It is a chronic depigmentation disorder of the skin characterized by white patches. Skin lesions seen in this disorder initially start as hypopigmented lesions and later appear as depigmented macules or patches. Vitiligo is classified as an autoimmune condition and is associated with other autoimmune skin disorders. It also acts as a systemic disease rather than a condition that only affects the skin. It is thought to have a robust relationship with various systemic and metabolic disorders, such as insulin resistance, lipid abnormalities, atherosclerotic cardiovascular disease, and metabolic syndrome.[2,3] Although the etiopathogenesis of vitiligo is not clear, activation of the proinflammatory system involved in the pathogenesis of atherosclerosis and atrial arrhythmias, expression of cytokines/chemokines, increase in oxidative stress, and an elevation in catecholamine discharge play a role in its etiopathogenesis.[4,5]

Atrial fibrillation (AF) is a vital heart rhythm disorder. It is common in clinical practice, causes hemodynamic disorders, frequent hospitalizations, and thromboembolic events, and affects 1-2% of the general population.[6] Although the exact mechanisms that cause AF are not fully understood, diastolic dysfunction, inflammation, endothelial dysfunction, and catecholamine discharge have a place in its pathogenesis.[6]

Atrial conduction time (ACT) refers to the interval between sinus impulses and atrial mechanical contraction. A non-invasive technique called tissue Doppler imaging (TDI) is good at finding heart rhythm problems like atrial fibrillation (AF). It measures atrial electromechanical delay (EMD), which is the lengthening of the conduction time within and between atrial cells.[7,8] Previously, TDI measurement of atrial EMD has been shown to correlate well with invasive measurements.14 Also, atrial EMD was once found to be prolonged in chronic skin disorders such as psoriasis and lichen planus.[9,10]

To the best of our knowledge, cardiac evaluation has not been performed on patients with vitiligo before. Therefore, we aimed to evaluate the atrial conduction time in vitiligo patients with TDI. We also explored a relationship between atrial conduction time, disease severity, and inflammation marker levels.

METHODS

We conducted the study in dermatology and cardiology clinics at Kayseri City Training and Research Hospital between March and May 2021. Thirty-two (22 females, 10 males) patients diagnosed with generalized vitiligo and age-and sex-matched 38 (24 females, 14 males) controls participated in the study. The approval of the ethics committee, Kayseri City Training and Research Hospital, dated 07.01.2021 and numbered 2021/253 was obtained before the study. All procedures were carried out in accordance with the ethical rules and the principles, and it was conducted in accordance with the Declaration of Helsinki.

This study was designed as a prospective, single-center, and cross-sectional study. From all patients, we obtained a detailed medical history, physical examination, 12-channel electrocardiography (ECG), complete blood count, and serum biochemistry tests. We performed a thorough transthoracic echocardiographic examination on all patients. There was no atrial or ventricular conduction anomaly in the ECG of both the patient and the control groups. In addition, none of the patients included in the study or their families had a history of paroxysmal AF.

Vitiligo is divided into three types: localized, generalized, and universal. We selected our patient group among generalized vitiligo patients since it, the most common form of the disorder, is assumed to be systemic rather than just a depigmenting skin disorder.[2,3]

People who had ischemic heart disease, diabetes mellitus (DM), no sinus rhythm, a pacemaker, severe valvular heart disease, structural heart disease, renal failure, severe comorbidities, use of any cardiovascular medications, obesity [body mass index (BMI) 30 kg/m^2], or abnormal thyroid function or serum electrolyte levels were not allowed to participate.

Echocardiography

We performed 2-dimensional, M-mode, pulse wave, continuous wave, color Doppler, and TDI, as well as conventional echocardiography, using the Philips EPIQ 7 ultrasound system (Andover, Massachusetts, USA). We also recorded ECG simultaneously during all measurements. Conventional echocardiographic images were obtained from parasternal and apical images, according to the guidelines of the American Echocardiography Association. We measured left ventricular (LV) diameter and wall thickness from a parasternal image using the M-mode echocardiography method. Simpson's method was used to calculate the LV ejection fraction. We utilized the parasternal long-axis view in measuring LA diameter, while the left atrial area and mitral inflow rate were measured through the apical window.

Atrial Electromechanical Time

We performed TDI using converter frequencies of 3.5-4.0 MHz We adjusted spectral-pulsed Doppler signal filters until achieving a Nyquist limit of 15-20 cm/sec and used the minimum optimal gain. Myocardial TDI velocities [peak systolic (S'), early diastolic (E'), and late diastolic velocities (A')] were measured by spectral-pulsed Doppler from the apical 4-chamber view. The ultrasound beam tilt did not exceed 15% to achieve the optimal viewing angle. We set the monitor scan rate to 50-100 mm/sec to optimize the spectral display of myocardial velocities. Then, we defined atrial EMD as the time interval from the onset of atrial electrical activity (P wave on surface ECG) to the onset of mechanical atrial contraction (late diastolic A wave) in TDI. All values were averaged over three successive strokes. We called atrial EMD 'PA lateral' when measured from the lateral mitral annulus; called 'PA septal' when measured from the septal mitral annulus; and 'PA tricuspid' when measured from the right ventricle tricuspid annulus. Then, we calculated inter-atrial EMD (difference between PA lateral and PA tricuspid), intra-atrial EMD (difference between PA septal and PA tricuspid), and left-atrial EMD (difference between PA lateral and PA septal).

We randomly selected a total of 20 participants, 10 from the patient group and 10 from the control group, to evaluate the intra-observer variation. We replicated the measurements under the same baseline conditions. Then, we found intra-observer variability to be 4% for lateral PA, 4.4% for septal PA, and 5.1% for tricuspid PA, respectively.

Statistical Analysis

We run all statistical analyses using the Statistical Package for the Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The distribution of the data was checked using the Kolmogorov-Smirnov test. While the Independent Samples T-Test was used to compare normally distributed quantitative variables, we ran the Mann-Whitney U test to compare quantitative variables showing a nonnormal distribution. We performed the univariate analysis of categorical variables using the $\chi 2$ test. Continuous variables were shown as mean±SD, whereas categorical variables were given as percentages. We presented medians and interquartile ranges for the variables not normally distributed. A 2-tailed probability value of<0.05 was considered significant.

RESULTS

We presented baseline characteristics and the laboratory findings of the patients and controls in **Table 1**.

There was no significant difference between the patient and the control groups by baseline characteristics (age, sex, hypertension). Considering laboratory findings, we found neutrophil count, neutrophil/lymphocyte ratio (NLR) levels, and high-sensitivity C-reactive protein (hs-CRP) levels to be significantly higher in the patient group (6±1.4 vs. 4.5±2.3, $p=0.001$; 3.5±1.4 vs. 2.5±1.9, $p=0.024$; 6.2±1.9 mg/dl vs. 4.1±1.3 mg/dl, $p<0.001$, respectively).

Table 1. Comparison of baseline laboratory measurements among the study groups

Variables	CONTROL (n=38)	VITILIGO (n=38)	P-value
Age (years)	39,6±8.9	40.7±12.1	0.699
Male/female	14/24	10/22	0.460
HT	9	10	0.380
SBP, mmHg	121.2±9	119±10.3	0.335
DBP, mmHg	74.3±6.6	72.8±7.5	0.795
Heart rate	77.7±8.1	76.4±9.1	0.534
Glucose (mg/dl)	98.8±17.2	102.8±19.8	0.349
Creatinine (mg/dl)	0.83±0.1	0.92±0.3	0.103
AST (U/L)	21.1±5.1	23.3±7.8	0.361
ALT (U/L)	21.2±8.8	24.5±9.2	0.333
WBC (x 10^3/µL)	8.7±3.6	8.8±3.5	0.158
Neutrophil (x 10^3/µL)	4.5±2.3	6±1.4	**0.001**
Lymphocyte (x 10^3/µL)	2±0.4	1.84±0.4	0.201
NLR	2.5±1.9	3.5±1.4	**0.024**
Hemoglobin (g/L)	14.4±1.5	14.9±1.2	0.158
Platelet (x 10^3/mm^3)	256.3±71.6	258.6±60.4	0.881
Hs CRP	4.1±1.3	6.2±1.9	**<0.001**

Data are expressed as mean±standard deviation for normally distributed data and percentage (%) for categorical variables, WBC: White Blood Cell. SBP: Systolic blood pressure DBP: Diastolic blood pressure NLR: neutrophil to lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine transaminase

Table 2 shows echocardiographic and atrial electromechanical time parameters. Accordingly, we could not find a significant difference between the groups by left ventricular systolic and diastolic diameters, left atrial diameter and area, ventricular septum, posterior wall thickness, and left ventricular ejection fractions. Regarding the cardiovascular function parameters of the LV, there was no statistically significant difference between the groups.

Table 2. Echocardiography characteristics of the study population

Variables	CONTROL (n=38)	VITILIGO (n=38)	P-value
LA Diameter, cm	3.38±0.27	3.42±0.26	0.470
LA area, cm^2	21.5±2.2	21.7±1.8	0.679
LVDD, cm	4.66±0.4	4.68±0.4	0.805
LVESD, cm	3±0.4	3.1±0.3	0.601
IVSD, cm	1.06±0.11	1.07±0.14	0.706
PWD, cm	1.02±0.09	1.05±0.13	0.217
LVEF, %	67.3±5.9	65.1±5	0.079
PA Lateral, ms	58.3±12.5	69.1±9	**<0.001**
PA Septum, ms	45.1±9	54.4±6.5	**<0.001**
PA Tricuspid, ms	34.1±9.2	36.7±5.4	**0.145**
PA Lateral-PA Tricuspid (Inter-atrial delay)	24.2±10.8	36.3±8.5	**<0.001**
Pa Septal – PA Tricuspid (Intra-atrial delay)	10.9±5.8	18.1±8.3	**<0.001**
PA Lateral- PA Septal (Left-atrial delay)	13.2±7.2	15.3±6.9	0.330
Mitral E velocity	7.3±1.1	7.5±1.3	0.617
Mitral A velocity	5.8±1.6	6.1±1.4	0.492
DT, ms	180.4±37.2	188.2±35.4	0.817
IVRT, ms			
(S') cm/s	11.8±2.8	11.6±3.2	0.742
(E') cm/s	13.1±2.8	13±3.1	0.887
(A') cm/s	10.1±2.2	10.2±2.6	0.831

LA=Left atrium; LVDD=LV end-diastolic dimension; LVSD=LV end-systolic dimension; IVSD=interventricular septum thickness; PWD=posterior wall thickness; LVEF=LV ejection fraction; DT=deceleration time; IVRT=isovolumic relaxation time. Inter-atrial delay: PA lateral–PA tricuspid; Intra-atrial delay: PA septum–PA tricuspid; Left-atrial delay: PA lateral–PA septum; S': systolic velocity from the mitral annulus; E': early diastolic velocity from the mitral annulus; A': late diastolic velocity from the mitral annulus.

Although we found the PA lateral and PA septum values to be significantly prolonged in the vitiligo group compared to the control group, there was no difference between the groups in the PA tricuspid values (69.1±9 vs. 58.3±12.5, p<0.001; 54.4±6.5 vs. 45.1±9, p<0.001; 36.7±5.4 vs. 34.1±9.2, p=0.145, respectively). In addition, inter-atrial and intra-atrial EMD were significantly higher in the vitiligo group compared to the control group (36.3±8.5 vs. 24.2±10.8, p<0.001; 18.1±8.3 vs. 10.9±5.8, p<0.001, respectively). Finally, left atrial EMD was higher in the vitiligo group, but we could not reach a significant difference between the groups (15.3±6.9 vs. 13.2±7.2, p=0.33).

DISCUSSION

This is the first study showing that intra-atrial and inter-atrial conduction times were prolonged in vitiligo patients. In our study, CRP and NLR levels were found to be significantly higher in the vitiligo patients compared to the control group.

Vitiligo pathogenesis includes cellular defects within melanocytes and autoimmunity targeting these cells. Melanocytes are found in adipose tissue, the eyes, the inner ear, and leptomeninges, as well as in the skin.[11,12] Some studies claimed that melanocytes both exert anti-inflammatory effects and act as an antioxidant system.[12] We found vitiligo patients to have increased levels of interferon-α (IFN-α) (proinflammatory) but decreased levels of interleukin-10 (IL-10) (anti-inflammatory) compared to controls, which supports the idea that inflammation may increase in vitiligo patients.[4] Previous studies documented that the levels of homovanillic acid and vanillylmandelic acid were higher in the urine of vitiligo patients. Mental and physical stress, which is considered to intensify the pathogenesis of vitiligo, can cause vasoconstriction, hypoxia, and catecholamine discharge, leading to excessive production of oxygen radicals that destroy melanocytes and, at the same time, further increasing catecholamine secretion by stimulating the hypothalamic-pituitary-adrenal axis.[4, 13]

Solak et al.[14] and Demirbaş et al.[15] found higher CRP and NLR levels in vitiligo patients and reported a relationship between inflammation level and severity of the disorder. Grimes et al.[16] discovered increased tissue necrosis factor-alpha (TNF-α), and interferon-γ in vitiligo patients. In our study, we revealed that the patient group had higher CRP and NLR levels than the control group, in line with the studies mentioned above.

Non-invasive measurement of atrial EMD with TDI, as an alternative to invasive electrophysiological measurements, is considered successful in evaluating the risk of AF.[7] Cui et al.[17] showed that the atrial conduction delay measured by TDI was significantly prolonged in patients with paroxysmal AF compared to the control group. Roshanalli et al.[18] reported that atrial electromechanical interval is a predictor of AF developing after coronary artery bypass grafting and that preoperative amiodarone administration decreases the incidence of postoperative AF in patients with prolonged atrial electromechanical interval. Previous studies proved that atrial EMD is prolonged in many clinical disorders, such as diabetes mellitus, psoriasis, and inflammatory bowel disease.[19-22] In addition, the incidence of AF in these diseases is significantly higher compared to the normal population. As a result, atrial EMD is prolonged in paroxysmal AF and considered a predictor of incipient AF.[23] Our research showed

that intra-atrial and inter-atrial EMD, a method that predicts the chance of developing AF in the future, lasted a lot longer in people with vitiligo compared to healthy controls.

AF has a rather complex pathophysiology, and the mechanisms promoting AF have not been completely elucidated. These mechanisms are thought to depend on remodeling mechanisms (electrical, structural, and autonomic) that allow the initiation and maintenance of AF (sympathetic activity in AF). The substantial evidence from various animal models suggests that autonomic dysfunction, namely increased sympathetic activity and, thus, autonomic remodeling, have an impact on AF.[24,25] It was previously concluded that increased sympathetic activity leads to heterogeneous changes in atrial refractoriness, reinforcing the reentrant wave.[26,27]

It has long been known that inflammation is an integral part of the pathogenesis of AF. Patients suffering from inflammation due to myocardial infarction, acute myopericarditis, chronic rheumatic heart disease, or cardiac surgery have increased AF rates. Some inflammatory markers, including many of the interleukins (IL-2, IL-6, and IL-8), as well as CRP, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), are associated with a predisposition to AF.[28,29] Inflammatory interaction in atrial cardiomyocytes causes changes in the effective refractory period, conduction slowdown, hypertrophy, and fibrosis.[30] In line with the findings in this study, Solak et al.[14] previously showed that systemic inflammation increases in AF. Although we did not evaluate sympathetic activation, considering the previous results, it is reasonable to accept that the patients in our study had elevated catecholamines. Our study found that the longer intra-atrial and inter-atrial EMD in people with vitiligo compared to controls may have been caused by inflammation and atrial remodeling because of sympathetic hyperactivity.

Even though our research was not a follow-up study, we concluded that intra-atrial and inter-atrial EMD, techniques that predict cardiac arrhythmias, were significantly prolonged in patients with vitiligo. Considering the relevant literature, it is not wrong to assert that vitiligo patients are at risk for AF.

Study Limitations

The present study bears some limitations. First, it was difficult for us to predict how long participants had been suffering from the disorder. Secondly, the sample size was relatively small. Besides, we evaluated atrial EMD, a helpful marker for AF development, but this is not a follow-up study. Thus, we did not directly investigate AF development. The last limitation is that, unfortunately, we could not perform Holter monitoring to detect AF and other atrial arrhythmias. Overall, further studies need to consider examining the variables over a longer time period and including more participants.

CONCLUSION

As the European Society of Cardiology emphasizes in its latest AF guidelines, it is critical to identify and manage risk factors and comorbidities that predispose to AF prior to the development of atrial remodeling and fibrosis. Identifying individuals with vitiligo who have a higher risk of developing AF in the community may facilitate early AF detection. Therefore, we consider the results of this study to be clinically significant.

ETHICAL DECLARATIONS

Ethics Committee Approval: The approval of the ethics committee, Kayseri City Training and Research Hospital, dated 07.01.2021 and numbered 2021/253 was obtained before the study, and it was conducted in accordance with the Declaration of Helsinki.

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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