Assessment of atrial conduction time in patients with Behçet's disease

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ACTA REUMATOL PORT. 2014:39;29-36

ABSTRACT

Objective: Behçet's disease is characterized by increased inflammatory activity, and there there might be an increased risk of atrial arrhythmia in patients with this disease. Our study is aimed to evaluate a novel method of measuring atrial electromechanical features expressed as interatrial and intraatrial electromechanical delay by tissue Doppler echocardiography in patients with Behçet's disease.

Methods: We evaluated 57 patients (mean age: 36.3±12.1 years) with Behçet's disease and 34 sex and age matched healthy volunteers (mean age: 38.4±8.6 years) as control group. P-wave dispersion (PWD) was calculated from the 12-lead surface ECG, interatrial and intraatrial electromechanical delay were measured by tissue Doppler imaging and conventional echocardiography.

Results: Interatrial electromechanical delay and intraatrial electromechanical delay were prolonged in patients with active Behçet's disease compared with the patients with inactive disease and the controls ($p<0.0001$, $p<0.0001$, $p=0.013$ and $p=0.001$, respectively).

Erythrocyte sedimentation rate and high-sensitivity C-reactive protein values of of patients with active Behçet's were significantly higher than those with inactive Behçet's disease and the controls ($p<0.0001$ and $p<0.0001$, respectively).

High-sensitivity C-reactive protein and erythrocyte sedimentation rate were correlated with interatrial electromechanical delay in patients with Behçet's disease ($r=0.44$, $p=0.001$ and $r=0.64$, $p<0.0001$, respectively).

Conclusions: The prolongation of atrial electromechanical conduction might be related with changes in structure and electrophysiological properties of the atrial myocardium or the conduction system in patients with active Behçet's disease.

Keywords: Behçet's disease; Atrial conduction time; Tissue Doppler echocardiography

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INTRODUCTION

Behçet's disease (BD) is a relatively rare multisystem vasculitis that affects arteries and veins of all sizes.

This systemic inflammatory disorder is chronic and relapsing, and is characterized by aphthous, stomatitis, genital ulcers, and ocular lesions[1].

Cardiac involvement is called cardio-Behçet; its prognosis is extremely poor and mortality has been reported in the literature[2,3] between 7% to 46%.

Main cardiovascular features of BD include pericarditis, myocarditis, endocarditis, endomyocardial fibrosis of the right heart, conduction system disturbances, coronary arteritis, intracardiac thrombus, aortic stenosis, mitral valve prolapse, atrial fibrillation (AF), life-threatening ventricular arrhythmias and sudden cardiac death [2, 4-12].

The hypothesis of this study is that since BD is characterized by increased inflammatory activity, there might be changes of electromechanical coupling that could be associated with an increased risk of atrial arrhythmia in the patients with this disease.

To the best of our knowledge, tissue Doppler echocardiography (TDE) has not been previous used in patients with BD for the detection of atrial electromechanical coupling.

It was our aim to evaluate a novel method of measuring atrial electromechanical features by TDE in patients with BD expressed as interatrial and intraatrial

electromechanical delays and to correlate these measures with disease activity markers.

MATERIALS AND METHODS

PATIENTS

We included 57 patients (40 female, 17 male; mean age, 36.3±12.1 years) with BD who applied to Inonu University Medical School, Departments of Dermatology and Cardiology.

One of the problems was to define the disease activity because there is no currently accepted activity score index in BD; distinct, activation criteria were accepted in different studies because of the obscure etiology of the disease.

After analyzing previous studies[13,14], we decided decided to describe the disease activity as active BD if one of the diagnostic criteria of the International Study Group for BD[15] and/or involvement of at least one organ was present

Inactive BD was defined as the absence of any clinical sign of active BD in the previous month. All the patients with active disease were included before the beginning of the Behçet disease treatment. The inactive BD patients were receiving colchicine.

All the patients were in sinus rhythm during the study period. Exclusion criteria were: clinical evidence of ischemic heart disease, systemic hypertension, diabetes mellitus, thyroid dysfunction, anemia, hypercholesterolemia, renal and hepatic failure, pulmonary disease, active infectious disease, malignancy, immunological disease, atrioventricular conduction abnormalities on ECG, atrial fibrillation, pericardial effusion or electrolyte abnormalities.

Patients were also excluded if they had mitral valve prolapsus, mitral annular calcification or severe valvular disease in echocardiographic examination.

None of the subjects were receiving medications such as antiarrhythmics, tricyclic antidepressants, antihistaminics or antipsychotics.

Using standard laboratory methods, blood samples were drawn after an overnight 12-hours fasting to determine the levels of blood glucose, electrolytes, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

The high-sensitivity C-reactive protein (hs-CRP, mg/l.) was calculated by the nephelometric method. The erythrocyte sedimentation rate (ESR, mm/h) was determined through the Westergreen method. The other biochemical analyses were determined by standard methods.

CONTROL GROUP

Sex and age matched 34 healthy volunteers (24 female, 16 male; mean age, 38.4±8.6 years) were selected randomly as the control group. All of the volunteers were free of any cardiac or systemic disease. Their clinical examinations, electrocardiograms and echocardiographic evaluations were all found to be within normal ranges.

Written informed consent was obtained from all participating patients with BD and the control group members. The study was carried out according to the principles of the Declaration of Helsinki and approved by Inonu University, School of Medicine (Malatya, Turkey), investigational review board.

ELECTROCARDIOGRAPHIC ANALYSIS

All subjects underwent a 12-lead ECG recording, at a paper speed of 50 mm/s and 2 mV/cm, after a 20 minute resting period in supine position. The P-wave duration was measured manually in all simultaneously recorded 12 leads of the surface ECG by 2 of the investigators who had no information about the study's hypothesis. In each lead, the mean values for the 3 complexes were calculated. The onset of the P-wave was defined as the point of first visible upward departure from baseline for positive waveforms and as the point of first downward departure from the baseline for negative wave forms. The return to the baseline was considered to be the end of the P-wave. The maximal P-wave (Pmax) measured in any of the 12 leads of the surface ECG was used as the longest atrial conduction time. The difference between Pmax and the minimum P-wave duration (Pmin) was calculated and defined as P-wave dispersion (PWD) (PWD = Pmax – Pmin).

ECHOCARDIOGRAPHIC ANALYSIS

All echocardiographic examinations were performed with the iE33 ultrasound imaging system (Philips Company, Bothell, WA) while resting at the left lateral decubitis position.

An average of 3 beats was analyzed, and all the measurements were obtained by a single observer who was unaware of the clinical status of the patients.

During echocardiography, 1-lead ECG was recorded continuously. M-mode measurements and conventional Doppler echocardiographic examinations were performed according to the standards of the American

Society of Echocardiography[16].

The average of three consecutive cycles was obtained for each parameter. Left atrial (LA) dimension, left ventricle (LV) end-systolic and end-diastolic diameters were measured. LV ejection fraction was estimated by Simpson's rule. For tissue Doppler, echocardiography was performed by the same echocardiograph machine by adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15 to 20 cm/s was reached and using the minimal optimal gain.

The monitor sweep speed was set at 50 to 100 mm/s to optimize the spectral display of myocardial velocities. In an apical 4-chamber view, the pulsed Doppler sample volume was placed at the level of LV lateral mitral annulus, septal mitral annulus and right ventricular tricuspid annulus.

The time interval from the onset of the P wave on surface ECG to the beginning of the late diastolic wave (A wave), which is called PA, was obtained from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and RV tricuspid annulus (tricuspid PA), respectively (Figure 1). The difference between lateral PA and tricuspid PA (lateral PA – tricuspid PA) was defined as interatrial electromechanical delay; and the difference between septal PA and tricuspid PA (septal PA – tricuspid PA) was defined as intraatrial electromechanical delay[17].

STATISTICAL ANALYSIS

Statistical analysis was performed by using SPSS software package (version 17.0; SPSS Inc, Chicago, IL). Continuous variables were expressed as means ± SD.

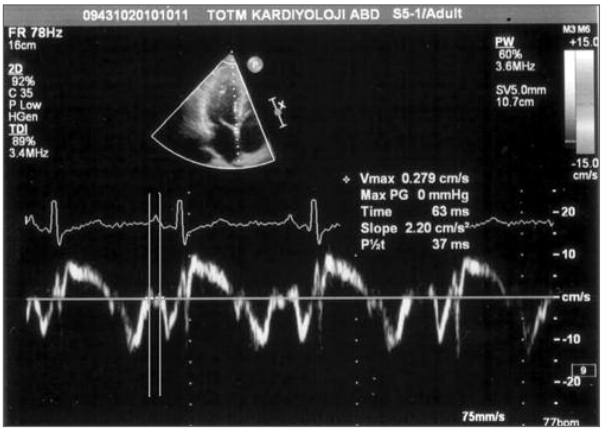

FIGURE 1. Measurement of the time interval from onset of the P wave on surface ECG to beginning of the A wave (PA) with tissue Doppler echocardiography

Categorical variables were expressed as counts and percentages. Interatrial electromechanical delay, intraatrial electromechanical delay, Pmax, PWD, the plasma level of ESR, the plasma level of hs-CRP values and other continuous variables of the patient group and the control group were compared by using one-way ANOVA test. The Post-Hoc analysis was done by Tukey test. Comparison of categorical variables was made by the Pearson Chi-square test.

Correlations were examined by Pearson correlation. The intraobserver and interobserver reproducibility of the P-wave measurements and electromechanical delays were assessed by coefficient of variation between measurements. The coefficient of variation is calculated as the SD of the differences between the repeated measurements divided by the averages of the repeated measurements and is expressed as a percentage. P values less than 0.05 were considered to be significant.

RESULTS

The demographic characteristics and echocardiographic features of the patients with BD and of the control group are given in Table I.

The two groups were similar regarding age, sex, blood pressure, body mass index, total cholesterol, LDL, HDL and smoking status. In addition, interventricular septum thickness, left ventricle (LV) posterior wall thickness, LV end-diastolic dimension, LV end-systolic dimension, LV ejection fraction and LA dimension of BD were similar to those of the control group. Clinical features of patients with active BD are shown in Table II.

Interatrial electromechanical delay, intraatrial electromechanical delay and PWD were not correlated with age, diastolic blood pressure, LV ejection fraction, LA diameter or disease duration.

The atrial electromechanical coupling parameters of different sites measured by TDE are shown in Table III. Lateral PA was significantly higher in patients with active BD. Than in the patients with inactive BD and the controls ($p < 0.0001$). PA lateral did not differ significantly between the patients with inactive BD and the controls (p=NS).

Interatrial electromechanical delays were prolonged in the patients with active BD compared with the patients with inactive BD and the controls ($p<0.0001$ and $p<0.0001$, respectively).

Besides, intraatrial electromechanical delays were

TABLE I. THE STUDY GROUP'S DEMOGRAPHIC AND ECHOCARDIOGRAPHIC CHARACTERISTICS

		Active BD patients (n=22)	Inactive BD patients (n=35)	Controls (n=34)	p value
Age (year)		37.3±12.0	35.7±12.3	38.4±8.6	NS
Sex, n(%)	Male	9 (%40.9)	8 (%22.9)	16 (%47.1)	NS
	Female	13 (%59.1)	27 (%77.1)	24 (%52.9)	NS
Blood pressure	Systolic	118.6±8.7	118.2±7.7	119.1±9.1	NS
(mmHg)	Diastolic	72.1±6.8	72.3±6.8	72.6±8.1	NS
Total cholesterol (mg/dl)		197.7±25.5	190.2±17.1	189.7±26.9	NS
Low-density lipoprotein (mg/dl)		127.4±19.8	120.9±18.8	117.3±21.5	NS
High-density lipoprotein (mg/dl)		39.7±5.7	41.3±4.9	40.2±5.2	NS
Triglyceride (mg/dl)		136.5±39.8	135.0±60.7	165.5±68.1	NS
Smoking, n(%)		10 (45.5%)	13 (37.1%)	17 (50%)	NS
Body mass index(Kg/m2)		20.5±2.1	21.0±2.3	20.8±2.4	NS
Disease duration (months)		12.2±10.3	10.8±8.4	–	NS
Left atrial dimension (mm)		35.1±4.8	33.9±3.5	33.3±3.3	NS
Left ventricular end-systolic diameters (mm)		33.1±7.5	30.4±3.7	28.6±2.2	NS
Left ventricular end-diastolic diameters (mm)		48.5±6.4	47.0±3.4	45.9±2.6	NS
Interventricular septum thickness (mm)		9.8±1.4	9.9±1.1	9.8±1.5	NS
Left ventricular posterior wall thickness (mm)		9.7±1.4	9.7±0.9	9.7±1.3	NS
Left ventricular ejection fraction (%)		61.6±7.3	64.1±4.1	61.7±8.2	NS

NS - indicates not significant

TABLE II. CLINICAL FEATURES OF PATIENTS WITH ACTIVE BD

Clinical manifestation	Patients (n =22) Number (%)
Oral aphthous ulcers	22 (100%)
Genital ulcers	14 (63.6%)
Vascular lesions	4 (18.2%9)
Skin lesions	11 (50%)
Ocular lesions	8 (36.4%)
Arthritis/arthropathy	5 (22.7%)
Central nervous system involvement	7 (31.8%)
Postive pathergy test	14 (63.6%)

prolonged in the patients with active BD compared with the patients with inactive BD and the controls (p=0.019 and p=0.003, respectively). When compared with the controls, interatrial and intraatrial electromechanical delay times were not different from those of patients with inactive BD

Intraobserver and interobserver variability was calculated from 40 subjects selected randomly from the study participants (20 patients with BD and 20 control subjects) by repeating the measurements under the same basal conditions. The coefficient of variation was 4.8% for PA lateral, 5.2% for PA septal and %4.5 for PA tricuspid, respectively. Interobserver variability was 4.1% for PA lateral, 3.9% for PA septal and 4.9% for PA tricuspid, respectively.

P-wave measurements are given in Table III. Pmax and PWD were significantly higher in the patients with active BD compared with the other two groups (p<0.0001 and p<0.0001, respectively). Pmin did not differ among among the groups (P=*NS*).

Intraobserver and interobserver coefficients of variation were 3.4% and 3.1% for maximum P-wave duration, and 3.7% and 3.3% for PWD, respectively.

The mean values of ESR and hs-CRP concentrations of the patients with active and inactive BD and the controls are given in Table IV. ESR and hs-CRP values of the active BD patients were significantly higher than those of with inactive BD and the controls (p<0.0001 and p<0.0001, respectively). The ESR and hs-CRP values of the patients with inactive disease were higher than the individuals in the control group (p=0.013 and p=0.03, respectively).

TABLE III. COMPARISON OF PWD AND INTRA-/INTERATRIAL MECHANICAL DELAY VALUES OF THE ACTIVE BD, INACTIVE BD AND THE CONTROL GROUPS

	Active BD patients (n=22)	Inactive BD patients (n=35)	Controls (n=40)	P[1] value	P[2] value	P[3] value
Leteral PA (ms)	74.2±7.0	55.2±7.8	55.3±8.3	< 0.0001	< 0.0001	NS
Septal PA (ms)	47.0±6.9	43.9±7.8	44.4±6.7	NS	NS	NS
Tricuspid PA(ms)	36.5±5.1	36.4±7.3	37.8±6.2	NS	NS	NS
Interatrial electromechanical delay (ms)	37.7±5.9	18.8±7.4	17.3±5.7	< 0.0001	< 0.0001	NS
Intraatrial electromechanical delay (ms)	10.5±4.4	7.5±4.5	6.5±2.8	0.019	0.003	NS
Pmin (ms)	68.1±7.1	69.0±13.6	68.7±8.3	NS	NS	NS
Pmax (ms)	114.7±4.9	98.7±11.5	95.3±9.7	< 0.0001	< 0.0001	NS
PWD (ms)	46.5±10.0	29.7±8.7	26.6±10.3	< 0.0001	< 0.0001	NS

P[1]: Between Active BD patients and Inactive BD patients
P[2]: Between Active BD patients and the Controls
P[3]: Between Inactive BD patients and the Controls

TABLE IV. MEAN VALUES OF ESR AND HS-CRP CONCENTRATIONS IN ACTIVE AND INACTIVE BD AND CONTROLS

	Active BD patients (n=22)	Inactive BD patients (n=35)	Controls (n=34)
ESR (mm/s)*#&	41.3±17.0	13.0±5.0	6.7±1.9
CRP (mg/dl)*#δ	33.8±24.1	11.4±9.5	3.2±1.1

*p<0.0001 (active and inactive BD patients); #p<0.0001 (active BD patients and the control group); &p=0.013 and δp=0.03 (inactive BD patients and the control group)

In correlation analysis, interatrial electromechanical delay was positively correlated with PWD as well as Pmax (r=0.55, p<0.0001, r=0.63, p<0.0001, respectively) in all the patients with BD. Plasma level of hs-CRP was singificantly correlated with interatrial electromechanical delay (Figure 2), intraatrial electromechanical delay, PWD and Pmax in all the patients with BD (r=0.44, p=0.001; r=0.28, p=0.035; r=0.43, p=0.001; r=0.36, p=0.006, respectively). The plasma level of ESR was also significantly correlated with interatrial electromechanical delay, intraatrial electromechanical delay, PWD and Pmax in all the patients with BD (r=0.64, *p*<0.0001; r=0.31, p=0.02; and *r*=0.56, p<0.0001; r=0.58, p<0.0001, respectively).

DISCUSSION

In this study, atrial electromechanical delay was evaluated in the patients with BD by using TDE which is a novel echocardiographic noninvasive technique. Generally, atrial conduction abnormalities have been evaluated with electrophysiological studies. However, the invasive nature of this technique limits its availability.

Recent developments in tissue velocity imaging allow getting precise parameters of atrial motion from different regions of the RV and LV with high temporal resolution. Recently, it has been shown that interatrial electromechanical delay measured by TDE is significantly longer in patients with paroxysmal AF, ankylosing spondylitis and type I diabetes mellitus[18-20].

In the present study, it was demonstrated that interatrial and intraatrial electromechanical delays are significantly increased in patients with active BD compared with controls and patients with inactive BD.

Interatrial and intraatrial electromechanical delays of patients with inactive BD were also prolonged but not significantly different from controls. The ESR and hs-CRP levels of the patients with active BD were significantly higher than in the controls and the patients with inactive disease. Moreover, the ESR and serum CRP levels of the patients with inactive BD were also higher than in the controls. Additionally, another important finding of this studies was that the plasma le-

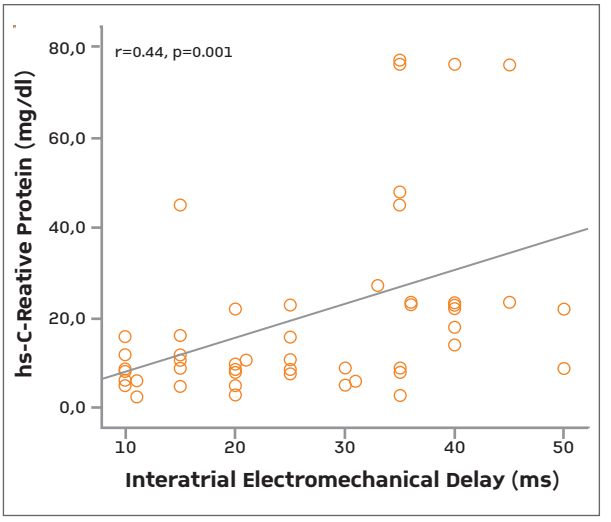

FIGURE 2. Positive correlation between the plasma level of hs-CRP and interatrial electromecanical delay

vels of ESR and CRP were closely associated with interatrial and intraatrial electromechanical delays.

The prolongation of P-wave duration is an accepted indicator of a disturbance in the interatrial conduction and is depicted as a prolonged P-wave (>110 msec) on an electrocardiogram[21].

A lead-variable P-wave duration is an indicator of site dependent propagation of the sinus impulse and is generally evaluated using PWD[21]. PWD has been associated with the inhomogeneous and discontinuous atrial conduction of the sinus impulses.

Magnani et al detected that P-max was related to long-term AF risk in a population consisting of people over 60 years; however, they could not find any relation with PWD[22].

On the other hand, increases in PWD have been related with the risk of subsequent development of AF in patients with a wide range of cardiovascular disorders and in those undergoing aorto-coronary bypass grafting or hemodialysis[23, 24].

In addition, increased PWD has been reported to represent an increased risk for AF in the patients with no underlying heart disease[25, 26].

Dogan et al. showed that PWD increased in patients with BD. They speculated that inhomogeneous impulse propagation due to myocardial involvement or increases of sympathetic tone, changes in excitation–contraction coupling and myocardial fibrosis could be the possible explanations. Differently from their study, we found that the patients with active BD had increased PWD and Pmax compared with both the patients with inactive BD and the controls. Compared to the control group, PWD and Pmax tended to increase in the patients with inactive BD, although the differences were not statistically significant. Besides, there was a strong positive correlation between PWD, Pmax and, inter-intraatrial electromechanical delays in all patients with BD.

BD is a chronic, relapsing, multisystemic and immuno-inflammatory disorder involving vessels of all sizes[27]. There is no specific diagnostic laboratory test for BD, and therefore, assessment of the disease activity is mainly based on clinical features[15]. It has been reported that ESR and CRP levels are not reliable parameters to assess the clinical activity of BD[27]. However, ESR and CRP are valuable acute-phase reactants of hepatic origin with a high sensitivity revealing systemic inflammation.

Boos CJ et al.'s laboratory and epidemiological research suggest that systemic inflammation can play a role in AF etiology[28]. In our study, plasma level of hs-CRP and ESR were higher in patients with active and inactive BD than in the control group. Additionally, these inflammatory parameters were closely associated with atrial electromechanical conduction delays and PWD. Therefore, we could speculate that increased PWD and delayed atrial electromechanic conduction in patients with active BD may be indicators of the effect of systemic inflammation in the conduction system. In fact, the exact mechanism of increased PWD and delayed atrial electromechanical conduction in patients with BD are not well known, but they may be related to the changes in the structure and electrophysiology of the atrial myocardium. Moreover, chronic inflammation may cause atrial fibrosis which prolongs the atrial activation time[29].

It is well known that BD causes microcirculation abnormalities without the involvement of epicardial vessels[30]. As a result of disturbance of coronary microcirculation, small areas of myocardial fibrosis may develop. Gullu et al.'s study has shown that there are perfusion defects by using thallium myocardial scintigraphy in BD patients who have normal coronary angiography[30]. Analyzing only patients in sinus rhythm and in the absence of follow-up is not possible through this study evaluate the risk of AF. This ideia is already depicted in the "limitations of the study"

Delayed atrial electromechanical conduction and increased PWD could also be due to autonomic dysfunction especially in patients with active BD. The au-

tonomic nervous system has modulating effects on electrophysiological properties, such as heterogeneity of atrial conduction time, and also, it has a profound influence on the occurrence of AF[31]. Slowed atrial conduction may contribute to reentry circuits and vulnerability for AF. A possible explanation of slowed atrial conduction may relate to autonomic dysfunction, which is present in patients with BD[32,33]. It is known that autonomic dysfunction involves different pathophysiological mechanisms, according to the underlying disease. Indeed, the causes of autonomic dysfunction are not well-defined in patients with BD. Aksoyek et al. have shown an abnormality of autonomic tone in the form of increased sympathetic and decreased parasympathetic activity by using power spectral analysis of HRV in patients with BD[32]. They have suggested that the responsible mechanism of autonomic dysfunction may be the vasculitis by reason of immunological mechanism.

LIMITATIONS OF THE STUDY

The most important limitation was the cross-sectional design of the study, in which the patients were not prospectively followed up for future arrhythmic events. Therefore, we do not know whether prolongation of PWD and atrial electromechanical delay predict atrial arrhythmias in patients with BD.

The second limitation of this study is that we calculated Pmax and Pmin manually using magnifying lens instead of a more reliable computer-assisted P-wave calculating system [34].

CONCLUSION

In conclusion, our study confirmed that in patients with active BD there is a delayed atrial electromechanical conduction correlated with the increase of the PWD and Pmax. Besides, plasma levels of hs-CRP and ERS were strongly correlated with atrial electromechanical coupling values, PWD and Pmax. Therefore, we speculated that the prolongation of atrial electromechanical conduction and P wave indices might be related to the changes in the structure and electrophysiology of the atrial myocardium or the conduction system in the patients especially with active BD. This might contribute to the development of adverse functional and electrophysiological atrial characteristics in these patients.

In future, these findings should be corroborated with electrophysiological investigation of the atrial conduction delay. Long-term follow-up studies are essential to identify the value of PWD and of the inflammation markers in the prediction of AF in patients with BD.

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