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## Relation of hs-CRP and BNP levels with the atrial spontaneous echo contrast and thrombi in permanent atrial fibrillation patients with different etiologies

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- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
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### Summary

#### Background:

Thromboembolic risk in permanent atrial fibrillation (AF) is strongly associated with the underlying etiology, and inflammatory parameters may contribute. The present study aimed to investigate the relationship of hs-CRP and BNP levels with left and right atrial appendage (LAA and RAA) function, presence of spontaneous echo contrast (SEC) and thrombus.

#### Material/Methods:

Eighty-four permanent AF patients with different etiologies (20 mitral stenosis, 44 hypertension and 20 hyperthyroidism) and 23 patients with sinus rhythm were included. LAA and RAA flow velocities were measured by pulsed-wave Doppler and wall motion velocities with tissue Doppler imaging (TDI) in transesophageal echocardiography.

#### Results:

Hs-CRP and BNP levels significantly differed among the 3 AF groups: levels were highest in mitral stenosis patients ( $8.6 \pm 5.3$  mg/L and  $98.0 \pm 125.7$  pg/mL, respectively), the lowest hs-CRP was in hyperthyroidism patients ( $4.3 \pm 3.8$  mg/L), and the lowest BNP was in hypertensive patients ( $64.8 \pm 44.3$  pg/mL). There were also significant differences between the AF group and controls regarding hs-CRP and BNP levels. In the correlation analysis, BNP level was not significantly correlated with LAA and RAA functions, whereas hs-CRP level was significantly correlated with some LAA and RAA functions. On the other hand, hs-CRP level was significantly related to the presence of mild-moderate SEC and thrombi, mainly in mitral stenosis patients. Moreover, hs-CRP was the most important determinant of RAA thrombus formation, followed by RAA ejection fraction. In contrast, no positive or negative correlation was found between BNP levels and RAA and LAA thrombi.

#### Conclusions:

Higher hs-CRP levels in AF patients may be a predictor for the presence of SEC and thrombi in the atria.

#### key words:

atrial fibrillation • brain natriuretic peptide • C-reactive protein • echocardiography

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## BACKGROUND

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in daily practice that has been associated with an increased mortality and morbidity from thromboembolic complications [1,2]. The prevalence of AF is age-dependent; affecting 1% of the population aged <65 years and 5% of the population aged >65 years [1–3]. Although a better understanding of the underlying pathophysiology of AF may provide prognostic information about future progress and guide clinical practice [2], choosing optimal candidates for anticoagulation treatment among patients with AF is still a matter of debate [3].

It has been shown that left atrial spontaneous echo contrast (SEC) is a significant predictor of thrombus formation and thromboembolic events [4]. Transesophageal echocardiography (TEE) is a useful diagnostic method for both detection of thrombus and visualization of SEC in the left and right atrial appendages (LAA and RAA), which may develop thrombi [3]. Previous studies have pointed out that patients with AF who have a low appendage blood flow velocity (reflecting impaired LAA) measured by TEE pulsed-wave (PW) Doppler have a higher risk of thromboembolism than patients with an appendage flow >20 cm/s [3,5].

There is increasing evidence showing that inflammation is related to AF and may have an important role in AF pathogenesis [6–8]. However, it is not clearly known whether inflammation is the initiator or the result of AF [9]. First, in their study conducted on 12 patients with AF, Frustaci et al. reported that the prevalence of hypertrophy, inflammatory infiltrates, myocyte necrosis, and fibrosis was high in the atrial biopsies taken from patients, whereas biopsies taken from the controls were normal [10]. Moreover, in some previous studies, it has been suggested that inflammation acts as an initiator rather than as a consequence of AF [1,8,11]. C-reactive protein (CRP) is an inflammatory marker that predicts morbidity and mortality in various clinical conditions [12].

Brain natriuretic peptide (BNP) is a polypeptide that is secreted mainly from the cardiac ventricles in response to myocardial stretch as a result of volume overload in heart failure. Contrary to earlier theories that BNP was secreted mainly from the ventricular myocardium, recent studies suggest that the left atrium, not the left ventricle, is the main source of BNP in patients with AF [3,5,13].

In previous studies, it has been found that hs-CRP (or CRP) and BNP (or N-terminal proBNP) are associated with the development and recurrence of AF and can be used to detect vulnerable AF patients at high risk for thromboembolism [5,14–17]. However, possible effects of atrial dysfunction on BNP and hs-CRP levels and association between intra-atrial thrombi and BNP and hs-CRP in various AF etiologies are still the subjects of debate.

Several studies have reported that thromboses are closely related with inflammation, where increased inflammatory markers such as CRP, Nt-proBNP and IL-6 are associated with adverse vascular events [1,9,18–21]. Due to the impaired inflammatory state, endothelial dysfunction, the prothrombotic state in AF may be driven to SEC or thrombus, which can

be a cause of thromboembolic events [2]. Thrombomodulin is a marker of endothelial dysfunction; it was reported that thrombomodulin levels decreased in AF patients with normal ejection fraction who were on anticoagulation therapy [22]. In the present study we aimed to investigate the relation of hs-CRP and BNP with the LAA and RAA functions, and to detect the presence of SEC and thrombus in various AF etiologies.

## MATERIAL AND METHODS

As atrial fibrillation is often an electrical manifestation of an underlying cardiac disease or associated conditions, 3 groups of patients were selected to represent 3 main etiologies; mitral stenosis for valvular heart disease, hyperthyroidism for associated conditions, and hypertensive heart disease. Patients with a current episode of permanent AF >12 months due to mitral stenosis, and patients with hypertension or hyperthyroidism were included in the study. Exclusion criteria were age above 80 years; ischemic heart disease; left and right ventricular systolic dysfunction (ejection fraction <55%); moderate to severe pulmonary hypertension (pulmonary artery systolic pressure >40 mmHg); cardiomyopathy; prosthetic heart valve; aortic and tricuspid stenosis; and moderate to severe aortic, mitral or tricuspid regurgitation.

The permanent AF group consisted of 246 patients referred to our TEE laboratory according to etiological inclusion criteria of the study between October 2006 and December 2009. Of these 246 patients, 83 had mitral stenosis, 116 had hypertensive heart disease, and 47 had hyperthyroidism. In patients with mitral stenosis, 32 patients were excluded because of the presence of moderate-severe mitral or tricuspid regurgitation, 17 patients were excluded by having left or right ventricular systolic dysfunction, and 14 patients were excluded for presence of aortic valvular involvement. In hypertensive patients, 36 subjects had known ischemic heart disease, 11 patients had dilated cardiomyopathy, 21 patients had moderate-severe mitral or tricuspid regurgitation, and 4 patients had aortic stenosis. In the hyperthyroidism group, 27 patients were excluded due to associated hypertension. Finally, data analysis was performed in 84 patients – 20 patients with mitral stenosis, 44 with hypertensive heart disease, and 20 with hyperthyroidism.

The control group consisted of patients with sinus rhythm (n=23) who had been referred to echocardiography laboratory for the examination of patent foramen ovale (9 patients), atrial septal defect (3 patients with a Qp/Qs ratio <1.5), cerebrovascular event (4 patients) and transient ischemic attack (7 patients). Of the controls, none had right and left ventricular dysfunction. All patients were informed about the study and written consents were obtained before any study procedures were conducted. The local ethics committee of Kocaeli University Hospital approved the study protocol and informed consent form. The study was conducted in accordance with the latest version of the Helsinki Declaration.

### Transesophageal examination

All patients underwent transthoracic echocardiography using an echocardiograph equipped with a broadband transducer

(Vivid 7, GE Vingmed, Horten, Norway). After conventional transthoracic echocardiography, TEE was performed by an experienced echocardiographer using a 5 MHz multiplane transesophageal transducer (Vivid 7, GE Vingmed, Horten, Norway). All TEE was performed after at least 4 hours of fasting, using 10% lidocaine spray for posterior pharyngeal anesthesia. All images were recorded on a hard disc for subsequent analysis.

### Evaluation of left and right atrial appendage function

LAA was visualized by TEE examination in the transverse plane view at the atrial level. Maximum and minimum LAA areas were measured by planimetry, independent from the ECG cycle. An average of 5 measurements were taken for the patients with AF and 3 measurements for the patients with sinus rhythm. LAA flow measurements were obtained approximately 1cm below the outlet of the LAA cavity using PW Doppler provided with suitable gain and filter adjustments. LAA emptying and filling velocities were measured. The LAA peak emptying flow velocity was defined as the highest positive flow velocity measured on pulse Doppler velocity time scale, and the LAA peak filling velocity was defined as the highest negative flow velocity. Measurements were taken in 5 consecutive cardiac cycles and averaged.

RAA was identified in the longitudinal planes. With the tip of the transducer in the midesophagus, progressive rightward rotation of the endoscope shaft (the array was 90° throughout this maneuver) developed a long-axis view of the superior and inferior vena cava entering the right atrium. Images of RAA were obtained in a continuum of angles from 90° to 140° and were determined anteriorly. Maximum and minimum RAA areas were measured using a trackball by tracing the endocardial borders, and calculated by computed planimetry. Percentage of RAA area was calculated similarly to LAA area. RAA emptying and filling velocities were measured with PW Doppler from the measurements taken in 5 consecutive cardiac cycles.

RAA and LAA velocities measured by tissue Doppler imaging (TDI) were recorded. The sample volume of PW Doppler was placed within the RAA and LAA septal and lateral walls. In the TDI records of the patients, a triphasic TDI profile was obtained in patients with sinus rhythm, and multiphasic fibrillatory emptying and filling velocities were recorded in AF patients, similar to previously described TDI velocities of LAA walls in the study of Parvathaneni et al. [23]. The initial upward velocities in sinus rhythm (D1) were recorded early in diastole (before the P wave). The following biphasic upward emptying and downward filling velocities were named as D2 and D3, respectively. There were no D1 velocities in patients with AF due to the absence of P waves; however, multiple irregular upward D2 and downward D3 velocities in late diastole were recorded in these patients both by Doppler flow and TDI. Therefore, the maximum upward velocity was accepted as D2 and the maximum downward velocity as D3.

### Spontaneous echo contrast and thrombi

The presence of thrombus was diagnosed when an intracavitary echo-dense mass with an echocardiographic appearance different from the atrial endocardium and the

pectinate muscles was detected. The presence of SEC was diagnosed when dynamic and swirling intracavitary smoke-like echoes were detected, which were differentiated from white noise artifact by their characteristic swirling pattern and by careful attention to the gain settings [10,11]. The severity of SEC was scored as follows: (0) absence of echogenicity, (1+) mild (minimal echogenicity detectable in an only part of the left atrial cavity with high gain settings), (2+) moderate (denser swirling during the entire cardiac cycle), and (3+) severe (intense echodensity and very slow swirling patterns in LAA usually with similar density in the main cavity). The same grading was used for SEC in the right atrial cavity.

The intraobserver variability was determined by comparing the measurements of 2 different observations in 10 patients. The correlations for the maximum RAA area, RAA emptying velocity measured by PW Doppler, and D2 were 0.865, 0.850, and 0.947, respectively. The correlations for the maximum LAA area, minimum LAA area, LAA emptying velocity measured by PW Doppler, and D2 were 0.877, 0.865, 0.843, and 0.935, respectively.

### Blood sampling

Blood samples were collected in free tubes and tubes containing EDTA during the intravenous line intervention, just before TEE examination. Hemoglobin and hematocrit levels were determined by standard methods. The samples were immediately transferred into ice-cold water and centrifuged at 10,000 rpm for 10 min at 4°C. Serum levels of hs-CRP were measured with a rate nephelometry method (IMMAGE® Immunochemistry System, Beckman Coulter, California, USA). The measurement range of this method was 0.2–1,440 mg/L and the reference range was <7.44 mg/L.

The measurement of BNP was performed via fluorescence immunoassay (Triage BNP test 2008/04/14, Inverness Medical, San Diego, California, USA). The detection range was 5–5,000 pg/mL.

### Statistical analysis

The statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) for Windows. Results are presented as mean ±SD or as percentages and numbers for categorical data. Normality tests were used for all variables. The inter- and intra-group comparisons of PW Doppler and TDI parameters were performed using the one-way analysis of variance (ANOVA). Homogeneity of variances was tested for all variables with Levene's test. If variances were equal, Tukey HSD post-hoc test; if not, Tamhane's T2 test was used to compare the parameters within the groups. For non-normally distributed variables, Kruskal Wallis test and Mann Whitney U test were used for inter- and intra-group comparisons of variables. Categorical data and proportions were analyzed using the chi-square ( $\chi^2$ ) or Fisher's exact test, where appropriate. The relationship of RAA velocities measured by PW Doppler and TDI and RAA function between BNP and hs-CRP levels of the patients were examined by the Pearson correlation test. In patients with AF, relation of right atrial SEC severity to the LAA and RAA velocities was evaluated using univariate linear regression analysis. All variables

**Table 1.** Baseline characteristics of the AF group and controls.

Parameter	AF group			Control group
	Mitral stenosis (n=20)	Hypertension (n=44)	Hyperthyroidism (n=20)	Sinus rhythm (n=23)
Age	56±11	63±11	59±12	47±16
Gender (Male/Female)	8/12	25/19	11/9	12/11
Hypertension (%)	0	44 (100.0%)	0	13 (56.5%)
Hyperlipidemia (%)	6 (30.0%)	18 (41.0%)	6 (30.0%)	11 (47.8%)
Diabetes mellitus (%)	4 (20.0%)	5 (11.4%)	3 (15.0%)	6 (26.1%)
Smoking (%)	0	6 (13.6%)	3 (15.0%)	6 (26.1%)
Oral anticoagulants (%)	19 (95.0%)	42 (95.5%)	12 (60.0%)	1 (4.0%)
INR (mean±SD)	1.62±0.50	1.8±1.4	1.41±0.47	1.07±0.22
Effective anticoagulation* (%)	6 (31.6%)	9 (21.4%)	1 (8.3%)	0
Beta blockers (%)	14 (70.0%)	19 (43.0%)	11 (55.0%)	4 (17.0%)
Duration of AF (years)	2.4±0.5	2.9±1.0	2.6±0.9	None
Severity of MR (None/Trace-Mild)	0/20	2/42	2/18	13/10
Severity of TR (None/Trace-Mild)	1/19	11/33	6/14	10/13

AF – atrial fibrillation; INR – international normalization ratio; MR – mitral regurgitation; SD – standard deviation; TR – tricuspid regurgitation;

\* Effective anticoagulation is defined as an INR between 2.0 and 3.0.

with a p value <0.10 were then tested in multivariate linear regression analyses using the enter method. Variables were entered if p <0.05 and removed if p >0.10. A p value <0.05 was considered statistically significant.

## RESULTS

Baseline characteristics of the study groups are presented in Table 1. Age and sex distribution (except for hypertension and smoking) were similar in the 3 AF groups (patients with mitral stenosis, hypertension, and hyperthyroidism). In the hypertension group, 40 patients (91%) had echocardiographic left ventricular hypertrophy (left ventricular mass index  $\geq 125$  g/m<sup>2</sup> in males and 110 g/m<sup>2</sup> in females). The use of oral anticoagulants was quite high among patients with mitral stenosis and hypertension; however, the frequency of effective anticoagulation (international normalization ratio=2.0–3.0) was 31.6% in patients with mitral stenosis, 21.4% in hypertensives and 8.3% in patients with hyperthyroidism.

The clinical characteristics of the patients and controls are presented in Table 2. There were significant differences between the AF groups and the control group with respect to the levels of hs-CRP and BNP, hematocrit ratio, heart rate, left atrium and right ventricle diameters, right ventricular ejection fraction, and presence of SEC and thrombi in LAA and RAA. In the control group all of the parameters were significantly lower than in the AF group. Among the 3 AF groups, the hs-CRP level of patients was significantly different; the highest levels were measured in the mitral stenosis group (8.6±5.3 mg/L) and the lowest levels were

measured in the hyperthyroidism group (4.3±3.8 mg/L). The highest BNP levels were found in the mitral stenosis group (98.0±125.7 pg/mL) and the lowest levels were found in the hypertensive group (64.8±44.3 pg/mL).

The LAA and RAA characteristics of the patients and controls are presented in Table 3. LAA and RAA PW Doppler and TDI velocities of the control group were significantly higher compared to those in the AF group (p<0.001 for each). On the other hand, patients with mitral stenosis had the lowest LAA and RAA PW Doppler and TDI velocities among the 3 AF groups, and this difference was statistically significant (p<0.001). In the AF group, patients with hypertension and hyperthyroidism had similar LAA and RAA PW Doppler and TDI velocities. Statistical comparison of the parameters given in Tables 2 and 3 is presented in Table 4.

The correlations between BNP and hs-CRP levels and LAA and RAA functions in the AF group are presented in Table 5. According to the correlation analysis, the level of BNP was not significantly correlated with LAA and RAA functions; however, the level of hs-CRP was significantly correlated with some of the LAA and RAA functions. Moreover, in the mitral stenosis group, there was no significant correlation between hs-CRP and LAA PW Doppler velocities, whereas a significant negative correlation was found between hs-CRP and LAA-TDI lateral wall upward and downward velocities (r=-0.51, p=0.022; r=-0.50, p=0.026, respectively). On the other hand, RAA PW Doppler and TDI velocities were significantly correlated with hs-CRP, and the highest correlation levels were detected in those with impaired flow velocities. As the right ventricular diameter increased, the level

**Table 2.** Clinical characteristics of the study patients.

Parameter	AF group			Control group	P
	Mitral stenosis (n=20)	Hypertension (n=44)	Hyperthyroidism (n=20)	Sinus rhythm (n=23)	
hs-CRP (mg/L) (mean±SD)	8.6±5.3	6.5±4.1	4.3±3.8	3.0±2.8	<0.001
BNP (pg/mL) (mean±SD)	98.0±125.7	64.8±44.3	77.3±65.8	27.0±11.8	<0.001
Hematocrit (%)	38.6±3.8	40.9±3.5	39.1±2.3	42.3±3.0	0.001
Heart rate (beat/min)	103±16	102±16	103±13	80±8	<0.001
LA diameter (mm) (mean±SD)	49±5	46±3	45±3	39±3	<0.001
LV EDD(mm) (mean±SD)	48±6	49±4	48±3	50±8	NS
LV EF (%) (mean±SD)	67.3±3.8	68.6±3.4	66.9±2.5	68.7±4.4	NS
RV diameter (mm) (mean±SD)	26.5±1.1	26.0±1.3	25.4±1.2	25.6±2.1	0.026
RV EF (%) (mean±SD)	63.2±2.8	66.4±2.8	68.7±2.8	65.4±6	<0.001
LAA-SEC (1/2/3)	0/3/17	7/13/18	7/6/4	0	<0.001
LAA-thrombus (n [%])	14 (70)	7 (16)	2 (10)	0	<0.001
RAA-SEC (1/2/3)	4/14/1	15/12/2	6/6/0	0	0.002
RAA-thrombus (n [%])	5 (25)	2 (4.5)	0	0	0.007

BNP – Brain natriuretic peptide; hs-CRP – high sensitivity C-reactive protein; LA – left atrium; LV EDD – left ventricle enddiastolic diameter; LV EF – left ventricle ejection fraction; LAA – left atrial appendage; LAA-SEC – spontaneous echo contrast in left atrial appendage; RAA – right atrial appendage; RAA-SEC – spontaneous echo contrast in right atrial appendage; RV – right ventricle; RV EF – right ventricle ejection fraction; SD – standard deviation; \* p values were obtained from the comparison of the AF group with the control group.

of hs-CRP also increased in the patients with mitral stenosis ( $r=0.51$ ,  $p=0.022$ ). In patients with hypertension and hyperthyroidism, LAA and RAA functions were not significantly correlated with the level of hs-CRP. However, in the hyperthyroidism group, there was only a relationship between hs-CRP and hematocrit ratio ( $r=0.42$ ,  $p=0.048$ ).

In patients with mitral stenosis, no positive or negative correlation was detected between BNP levels and PW Doppler and TDI velocities of LAA and RAA. In the hypertension group, there was a negative correlation between BNP levels and LAA ejection fraction ( $r=-0.30$ ,  $p=0.049$ ), LAA PW Doppler emptying velocity ( $r=-0.30$ ,  $p=0.049$ ), and RAA lateral wall downward velocity ( $r=-0.33$ ,  $p=0.028$ ); whereas a positive correlation was found between BNP levels and left atricular diameter ( $r=0.32$ ,  $p=0.039$ ). In patients with hyperthyroidism, there was a negative correlation between BNP levels and LAA-TDI septal and lateral wall downward velocities ( $r=-0.45$ ,  $p=0.045$ ;  $r=-0.42$ ,  $p=0.047$ , respectively) and also between RAA-PW Doppler emptying and filling velocities ( $r=-0.56$ ,  $p=0.010$ ;  $r=-0.41$ ,  $p=0.07$ , respectively); whereas there was a positive correlation between BNP levels and right ventricular diameter and duration of AF ( $r=0.50$ ,  $p=0.025$ ;  $r=0.64$ ,  $p=0.002$ , respectively).

In the AF group, the level of hs-CRP was significantly related to the presence of mild-moderate SEC and thrombi. However, when the AF group was evaluated according to etiologies, it was observed that this significant correlation mainly originated from patients with mitral stenosis (Table 6).

The highest correlation was found between the hs-CRP levels and RAA-SEC and thrombus ( $r=0.54$ ,  $p=0.01$  and  $r=0.45$ ,  $p=0.03$ , respectively). In multivariate analysis, hs-CRP level was found to be the most important determinant of RAA thrombus formation ( $p=0.002$ ), followed by RAA ejection fraction ( $p=0.009$ ). In the other study groups, especially in the hyperthyroidism group, level of hs-CRP was not related to the presence of SEC and thrombi. In all AF groups, no positive or negative correlation was found between BNP levels and both RAA and LAA thrombi.

## DISCUSSION

AF is the most common arrhythmia encountered in clinical practice that has been associated with an increased mortality and morbidity from thromboembolic complications [1,2]. TEE is frequently used to identify left atrial thrombus and to guide cardioversion in AF patients. Aortic atheroma, which may cause an embolus, can also be detected by TEE examination [24].

During a routine TEE study, RAA is examined only visually, and quantitative analysis is generally ignored. Several studies and case reports suggest that impaired RAA function may be a source for right-sided embolus in AF [13,20,25,26].

Previous studies on AF are generally based on treatment of AF; however, information about the role of inflammation in various AF etiologies is limited and open to question. It is also unclear whether a high level of inflammatory markers

**Table 3.** Left and right atrial appendage characteristics of the study patients.

Parameter	AF Group			Control Group	P
	Mitral stenosis (n=20)	Hypertension (n=44)	Hyperthyroidism (n=20)	Sinus rhythm (n=23)	
LAA-E (cm/s)	24±6	35±12	35±12	61±16	<0.001
LAA-F (cm/s)	24±7	34±12	35±12	50±9	<0.001
LAA EF (%)	15±6	31±16	39±19	69±4	<0.001
RAA-E (cm/s)	22±5	29±10	27±6	53±15	<0.001
RAA-F (cm/s)	22±6	29±9	30±11	42±12	<0.001
RAA EF (%)	20±7	35±15	39±17	63±3	<0.001
RAA-S-D2 (cm/s)	6.2±2.3	8.7±3.1	8.9±2.9	16.7±4.8	<0.001
RAA-S-D3 (cm/s)	6.3±2.5	9.0±2.9	8.4±3.0	14.2±4.1	<0.001
RAA-L-D2 (cm/s)	5.5±2.3	7.7±2.9	7.7±1.8	16.4±5.7	<0.001
RAA-L-D3 (cm/s)	6.0±2.5	8.3±2.9	8.0±2.7	14.7±4.1	<0.001
LAA-S-D2 (cm/s)	4.5±1.4	7.3±2.8	8.8±3.3	13±5	<0.001
LAA-S-D3 (cm/s)	5.0±1.3	6.6±2.4	7.7±2.5	10.3±3.6	<0.001
LAA-L-D2 (cm/s)	4.2±1.3	6.9±3.6	7.8±2.6	14.9±5.9	<0.001
LAA-L-D3 (cm/s)	5.0±1.3	7.2±2.7	7.6±2.5	11.4±5.1	<0.001

LAA-E – left atrial appendage PW Doppler peak emptying velocity; LAA EF – left atrial appendage ejection fraction; LAA-F – left atrial appendage PW Doppler peak filling velocity; LAA-L-D2 – left atrial appendage lateral wall upward velocity; LAA-L-D3 – left atrial appendage lateral wall downward velocity; LAA-S-D2 – left atrial appendage septal wall upward velocity; LAA-S-D3 – left atrial appendage septal wall downward velocity; RAA-E – right atrial appendage PW Doppler peak emptying velocity; RAA EF – right atrial appendage ejection fraction; RAA-F – right atrial appendage PW Doppler peak filling velocity; RAA-L-D2 – right atrial appendage lateral wall upward velocity; RAA-L-D3 – right atrial appendage lateral wall downward velocity; RAA-S-D2 – right atrial appendage septal wall upward velocity; RAA-S-D3 – right atrial appendage septal wall downward velocity; \* p values were obtained from the comparison of the AF group with the control group.

is the initiator or result of AF [27]. Moreover, the association between AF and inflammation, particularly in the intense inflammatory conditions such as myocarditis, pericarditis and post-coronary artery bypass graft surgery, may be considered as evidence of the role of inflammation in AF. On the other hand, the high levels of CRP and IL-6 in AF patients may also be considered as evidence of this association [28–30].

Increasingly, it is becoming accepted that there is a significant relationship between occurrence and persistence of AF and inflammation; furthermore, AF appears to result due to degeneration and fibrosis of atrial muscles with different etiologies. BNP and hs-CRP levels are higher in patients with AF because of inflammation, atrial pressure overload and atrial muscle dysfunction [5,6,31,32]. In the present study we investigated the relationship of hs-CRP and BNP with LAA and RAA, and the presence of SEC and thrombi in AF patients with different etiologies whose left and right ventricular functions were both normal. Thus, our study compared 3 groups of AF patients with different etiologies (mitral stenosis, hypertension, and hyperthyroidism) and a control group with sinus rhythm.

In the present study, hs-CRP and BNP levels were significantly different among the 3 AF groups ( $p<0.001$ ). The highest

levels of hs-CRP and BNP were measured in mitral stenosis patients ( $8.6\pm 5.3$  mg/L and  $98\pm 125.7$  ng/mL respectively), whereas the lowest level of hs-CRP was measured in patients with hyperthyroidism ( $4.3\pm 3.8$  mg/L), and the lowest level of BNP was measured in patients with hypertension ( $64.8\pm 44.3$  ng/mL). The patients with AF and those in the control group did not have heart and/or renal failure; thus their plasma BNP levels were not likely influenced by renal function or conventional cardiac function.

Contrary to earlier theories, today we know that BNP is secreted mainly from the left atrium in patients with AF [3,5,13] and it has been shown that atrial pressure overload leads to elevation in plasma BNP levels in patients with pure mitral stenosis [5,33,34]. In this study, patients with mitral stenosis had the highest BNP and hs-CRP levels, while the control group had the lowest levels. Frustaci et al. suggested a variety of changes (eg, severe hypertrophy, fibrosis, and inflammation) from patients with lone AF [10]. Saito et al. reported that LAA of patients with valvular AF showed significantly greater hypertrophy of cardiomyocytes, nuclear enlargement, bizarre nuclei, intercellular fibrosis and endocardial thickening [34]. A previous study reported that N-terminal pro-BNP, which is the biologically inactive fragment of BNP, increases in AF and decreases after cardioversion, and it is also useful in monitoring rhythm stability

**Table 4.** Statistical comparison of the clinical characteristics between the study groups.

Parameter	P1	P2	P3	P4	P5	P6
hs-CRP (mg/L)	<0.001	0.001	0.003	0.002	0.004	0.038
BNP (pg/mL)	<0.001	<0.001	0.004	NS	NS	NS
Hematocrit (%)	0.002	NS	<0.001	NS	0.027	0.018
Heart rate (beat/min)	<0.001	<0.001	<0.001	NS	NS	NS
LA diameter (mm)	<0.001	<0.001	<0.001	0.006	0.007	NS
LV EDD(mm)	0.039	NS	NS	0.042	NS	NS
LV EF (%)	NS	NS	NS	NS	NS	NS
RV diameter (mm)	0.046	0.09	NS	0.009	NS	0.033
RV EF (%)	0.006	NS	0.05	<0.001	<0.001	0.005
LAA-E (cm/s)	<0.001	<0.001	<0.001	<0.001	0.004	NS
LAA-F (cm/s)	<0.001	<0.001	<0.001	0.001	0.003	NS
LAA EF (%)	<0.001	<0.001	<0.001	<0.001	<0.001	NS
RAA-E (cm/s)	<0.001	<0.001	<0.001	<0.001	0.004	NS
RAA-F (cm/s)	<0.001	<0.001	0.005	0.001	0.035	NS
RAA EF (%)	<0.001	<0.001	<0.001	<0.001	<0.001	NS
RAA-S-D2 (cm/s)	<0.001	<0.001	<0.001	0.003	0.003	NS
RAA-S-D3 (cm/s)	<0.001	<0.001	<0.001	0.001	0.021	NS
RAA-L-D2 (cm/s)	<0.001	<0.001	<0.001	0.004	0.002	NS
RAA-L-D3 (cm/s)	<0.001	<0.001	<0.001	0.001	0.021	NS
LAA-S-D2 (cm/s)	<0.001	<0.001	0.002	<0.001	<0.001	0.088
LAA-S-D3 (cm/s)	<0.001	<0.001	0.005	0.006	<0.001	0.058
LAA-L-D2 (cm/s)	<0.001	<0.001	<0.001	<0.001	<0.001	0.07
LAA-L-D3 (cm/s)	<0.001	<0.001	0.002	<0.001	0.001	NS

BNP – brain natriuretic peptide; hs-CRP – high-sensitivity C-reactive protein; LA – left atrium; LV EDD – left ventricle enddiastolic diameter; LV EF – left ventricle ejection fraction; LAA-E – left atrial appendage PW Doppler peak emptying velocity; LAA EF – left atrial appendage ejection fraction; LAA-F – left atrial appendage PW Doppler peak filling velocity; LAA-L-D2 – left atrial appendage lateral wall upward velocity; LAA-L-D3 – left atrial appendage lateral wall downward velocity; LAA-S-D2 – left atrial appendage septal wall upward velocity; LAA-S-D3 – left atrial appendage septal wall downward velocity; NS – non-significant; P1 – control vs. mitral stenosis; P2 – control vs. hypertension; P3 – control vs. hyperthyroidism; P4 – mitral stenosis vs. hypertension; P5 – mitral stenosis vs. hyperthyroidism; P6 – hypertension vs. hyperthyroidism; RAA-E – right atrial appendage PW-Doppler peak emptying velocity; RAA EF – right atrial appendage ejection fraction; RAA-F – right atrial appendage PW-Doppler peak filling velocity; RAA-L-D2 – right atrial appendage lateral wall upward velocity; RAA-L-D3 – right atrial appendage lateral wall downward velocity; RAA-S-D2 – right atrial appendage septal wall upward velocity; RAA-S-D3 – right atrial appendage septal wall downward velocity; RV – right ventricle; RV EF – right ventricle ejection fraction.

after cardioversion [35]. Chronic AF and NT pro-BNP have been reported to be independent prognostic predictors in patients with systolic heart failure. In these patients, NT pro-BNP levels have been found to be higher in those with AF compared to those with sinus rhythm [36]. Most patients with chronic heart failure (CHF) have atherothrombotic disease, such as coronary artery disease and hypertensive heart disease; a high level of high-sensitivity C-reactive protein (hs-CRP) indicates a risk of vascular death from atherothrombotic disease in CHF patients. In addition, the serum level of hs-CRP is elevated in CHF patients regardless of the cause [37,38]. Patients with normal LV and RV end-diastolic diameters, LVEF and RVEF were included in our

study. We excluded heart failure patients and investigated the effect of AF with different etiologies on hs-CRP levels.

LA diameter, left ventricular ejection fraction and AF status (paroxysmal or permanent or both) have been reported to be associated with NT-proBNP levels. A higher LA diameter has been found to be associated with increased BT-proBNP levels [39]. The prolongation of AF duration results in increased LA diameters and failure in restoration of sinus rhythm. In a previous study it was suggested that AF duration is a significant predictor of the restoration and maintenance of sinus rhythm after successful cardioversion [40]. In the mitral stenosis group of this study, LA diameter was the

**Table 5.** Correlations between LAA and RAA functions and BNP and hs-CRP levels in patients with atrial fibrillation.

Atrial fibrillation group	BNP Level		hs-CRP Level	
	r	p	r	p
LAA EF (%)	0.11	NS	0.23	0.046
RAA EF (%)	0.27	0.012	0.23	0.036
LAA-E (cm/s)	0.22	0.041	0.09	NS
LAA-F (cm/s)	0.23	0.04	0.12	NS
RAA-E (cm/s)	0.32	0.03	0.12	NS
RAA-F (cm/s)	0.29	0.07	0.09	NS
LAA-S-D2 (cm/s)	0.10	NS	0.15	NS
LAA-S-D3 (cm/s)	0.28	0.011	0.26	0.015
LAA-L-D2 (cm/s)	0.14	NS	0.10	NS
LAA-L-D3 (cm/s)	0.22	0.043	0.14	NS
RAA-S-D2 (cm/s)	0.12	NS	0.17	NS
RAA-S-D3 (cm/s)	0.28	0.011	0.13	NS
RAA-L-D2 (cm/s)	0.21	0.05	0.25	0.022
RAA-L-D3 (cm/s)	0.29	0.007	0.13	NS
RV EF (%)	0.16	NS	0.30	0.004
RV diameter (mm)	0.13	NS	0.36	0.001

BNP – brain natriuretic peptide; hs-CRP – high sensitive C-reactive protein; LAA-E – left atrial appendage PW-Doppler peak emptying velocity; LAA EF – left atrial appendage ejection fraction; LAA-F – left atrial appendage PW-Doppler peak filling velocity; LAA-L-D2 – left atrial appendage lateral wall upward velocity; LAA-L-D3 – left atrial appendage lateral wall downward velocity; LAA-S-D2 – left atrial appendage septal wall upward velocity; LAA-S-D3 – left atrial appendage septal wall downward velocity; NS – non-significant; RAA-E – right atrial appendage PW-Doppler peak emptying velocity; RAA EF – right atrial appendage ejection fraction; RAA-F – right atrial appendage PW-Doppler peak filling velocity; RAA-L-D2 – right atrial appendage lateral wall upward velocity; RAA-L-D3 – right atrial appendage lateral wall downward velocity; RAA-S-D2 – right atrial appendage septal wall upward velocity, RAA-S-D3 – right atrial appendage septal wall downward velocity; RV – right ventricle; RV EF – right ventricle ejection fraction.

**Table 6.** The levels of hs-CRP and BNP according to the presence of thrombi in atrial fibrillation patients with different etiology.

Etiology	Thrombus	hs-CRP Level (mg/L)		BNP Level (pg/mL)	
		Mean ±SD	p values*	Mean ±SD	p values*
Mitral Stenosis	0	7.8±3.8	0.044	55.6±21.8	0.035
	+	8.9±5.9		116.2±107.4	
Hypertension	0	6.4±4.3	NS	60.4±44.4	NS
	+	7.2±2.9		87.8±38.7	
Hyperthyroidism	0	4.2±3.7	NS	67.0±28.3	NS
	+	5.4±2.9		78.4±68.1	

BNP – brain natriuretic peptide; hs-CRP – high sensitivity C-reactive protein; NS – non-significant; SD – standard deviation; \* P values are the comparisons of the hs-CRP/BNP levels between those patients with and without thrombi.

largest (49±5 mm) and LAA EF was lowest (15±6%) compared to other groups. Also, there was a marked decline in right and left atrial appendage velocities of all groups compared to control patients with sinus rhythm. The magnitude of the impairment was significantly related to the etiology

of atrial fibrillation, being most severe in patients with mitral stenosis and moderate in patients with hypertension and hyperthyroidism [41,42]. Thus, as a result of these data, we suggest that BNP and hs-CRP correlate with the degree of degeneration and atrial dysfunction, and that valvular AF

carries a higher risk for thromboembolic events than does non-valvular AF.

Velocities recorded with the TDI technique showed changes similar to classical PW-Doppler velocities. All TDI velocities recorded at the 2 sides of the right and left atrial appendages were lowest in patients with mitral stenosis and slightly higher (but still worse than the controls) in non-valvular AF patients. LAA TDI velocities showed significant correlations to RAA functional parameters. This finding suggests that the impairment of atrial function in AF is a global phenomenon, and the degree of impairment in left atrial function is significantly related to the degree of right atrial dysfunction.

AF is a prothrombotic or hypercoagulable state that may increase the risk of stroke and thromboembolism. Previous studies pointed out the apparent link between thrombogenesis and inflammation, in which increased CRP is associated with an increased risk of SEC and vascular events [9,17]. Plasma BNP and hs-CRP seem to reflect LA and RA functions and might be useful markers of vulnerability to thromboembolism in AF patients without overt heart failure [19]. In the previous studies it has been indicated that CRP is significantly associated with fibrinogen and plasma viscosity in AF, and that there is an association between CRP and SEC (which is believed to represent an interaction between erythrocytes and macromolecules and to be associated with a depressed mechanical LAA function) [43–45]. Additionally, Maehama et al. [46] suggested that a high CRP is related to LA thrombus in patients with non-rheumatic AF. It has been reported that BNP levels can be used as an indicator of LA function, and high plasma BNP levels may indicate a hypercoagulation state in non-valvular AF patients [5]. Furthermore, LAA dysfunction was directly related to a prothrombotic state [5]. In our study, LAA SEC was seen in all patients with mitral stenosis (100%), 88% of hypertensive patients and 85% of hyperthyroid patients ( $p < 0.001$ ). Moreover, the grade 3 SEC ratio was 85%, 40% and 20%, respectively. LAA thrombus was seen in 70% of patients with mitral stenosis, 16% of hypertensive patients and 10% of hyperthyroid patients ( $p < 0.001$ ).

The left and right atrial appendage TDI velocities were not superior to classical parameters of appendage function for predicting the severity of right and left atrial SEC. TDI evaluates only 1 particular segment of the atrial appendage; thus a more global parameter of right and left atrial appendage function may be more predictive for thromboembolic events than is regional evaluation.

There were some limitations of the present study. As the design of the present study was cross-sectional, the relation between RAA function and thromboembolic events could not be examined. Also, while abnormalities in haemostatic markers like fibrinogen and fibrin D-dimer are associated with the occurrence of SEC and thrombi in LAA, their effects were not studied in the different AF groups in this study.

## CONCLUSIONS

In conclusion, in patients with permanent AF, especially in those with mitral stenosis, there is a significant negative correlation between hs-CRP and atrial appendage function.

Higher hs-CRP levels in these patients may be a predictor for the presence of SEC and thrombi in the atria. Patients with high hs-CRP levels might profit from close monitoring and may be suitable candidates for anticoagulant, anti-inflammatory and anti-oxidant therapy.

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