High Sensitivity CRP Levels Predict Atrial Tachyarrhythmias in Rheumatic Mitral Stenosis

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Background: The different levels of inflammation in rheumatic mitral stenosis determine its clinical consequences. Atrial fibrillation is frequently encountered in mitral stenosis, though the independent role of chronic inflammation in determining atrial tachyarrhythmia occurrence in rheumatic heart disease has not been demonstrated previously.

Methods: Measurements of C-reactive protein (CRP) with a high sensitivity assay to detect chronic inflammation were performed in a homogenous group of 50 patients with rheumatic mitral stenosis, who were in sinus rhythm. Patients were questioned to exclude confounders of CRP elevation. The patients underwent a twenty-four-hour ambulatory ECG monitoring to check for asymptomatic atrial tachyarrhythmias and were in addition classified according to the presence of atrial tachyarrhythmias.

Results: Forty-four percent of patients showed a total of 100 episodes of atrial tachyarrhythmias where 63% of these episodes were paroxysmal atrial fibrillation. The CRP values in patients with tachyarrhythmias were significantly higher than in patients who remained in sinus rhythm (4.2 ± 0.55 mg/L vs 1.99 ± 0.36 mg/L, $P < 0.001$). A logistic regression analysis revealed only CRP levels and previous history of mitral valvuloplasty significantly determined tachyarrhythmia occurrence where age, left atrial volumes, mitral gradients had no statistically significant effect.

Conclusions: Our data implicated that nearly half of the mitral stenosis patients who are in sinus rhythm develop asymptomatic tachyarrhythmias and the higher levels of CRP in these patients show the significant effect of persistent inflammation on arrhythmia occurrence. **A.N.E. 2008;13(1):31–38**

hs-CRP; mitral stenosis; atrial fibrillation

Although the inciting event of acute rheumatic fever, the acute tonsillopharyngitis caused by group A streptococci, has been known for many decades, the pathophysiologic explanation in the chronic phase leading to rheumatic valvular disease is still speculative. Recently, Carabello reviewed the rheumatic process that not only involves the entire cardiac tissue, primarily the endocardium, but also the myocardium including the atrial myocardium. It is emphasized that chronic valvular damage may be the result of hemodynamic stresses on the now-injured valve or of an ongoing low-grade inflammatory process.¹ In the last years, several investigators showed this chronic inflammation in patients with

rheumatic heart disease with the use of high sensitivity C-reactive protein (hs-CRP) analysis. These studies also revealed that the levels of inflammation may vary among patients causing different clinical outcomes, for example, worse mitral valvuloplasty results in patients with higher hs-CRP levels.^{2,3}

It is also well known that mitral stenosis is a major cause of atrial fibrillation. Although left atrial sizes and pressures are important factors in initiating atrial fibrillation in clinical states other than rheumatic heart disease, it seems that other factors must take roles in initiating atrial fibrillation in patients with mitral stenosis (MS). During daily practice, physicians encounter patients who have

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only mild-to-moderate MS and relatively small left atria though they have already developed atrial fibrillation or other atrial tachyarrhythmias. It is also shown that balloon valvuloplasty, which prevents one from getting higher mitral gradients that would lead to further atrial dilatation, in fact does not result in a lessened risk for developing atrial tachyarrhythmias.⁴ Thus, if the hemodynamic stress of the MS causing a bigger left atrium and/or higher atrial pressures could not be blamed for inducing atrial fibrillation in some patients, then different levels of inflammation in the atrial myocardium induced by the initial rheumatic insult may be the cause of developing atrial fibrillation in these patients. Actually, some studies in the last years detected the role of low-grade inflammation as an underlying factor in patients with paroxysmal atrial fibrillation. The first of these observations was in patients who underwent cardiac surgery, where the highest hs-CRP values in the second postoperative day correlated with the incidence of atrial fibrillation.⁵ Other investigators reported higher hs-CRP and interleukin-6 levels in patients with more frequent episodes of atrial fibrillation.^{6,7} Moreover, hs-CRP values also influenced the conversion rates to sinus rhythm, that is, the higher the values the more resistant is the episode of atrial fibrillation.⁸

None of the previous studies investigated the role of elevated hs-CRP in atrial fibrillation episodes in rheumatic patients. In our study we aimed to determine the evidence of silent atrial fibrillation and other atrial tachyarrhythmia using Holter monitoring and examine its association with ongoing inflammation in rheumatic MS. We hypothesized that continuing low-grade inflammation detected by hs-CRP may be an important factor in causing atrial tachyarrhythmias and atrial fibrillation in rheumatic MS. We designated a study with a homogenous group of relatively young mitral stenosis patients who were in sinus rhythm.

METHODS

Patient Selection and Characteristics

A total of 50 patients (45 women, mean age 38 years; range 25 to 50 years) with rheumatic mitral stenosis who were on sinus rhythm out of 172 patients who were admitted to our valvular heart disease clinic for their yearly control between May 2005 and April 2006 were entered in the study.

Table 1. Clinical Characteristics of the Study Group (n = 50)

Sex (female)	45 (90%)
Age (years)	38 ± 6; 25–50/50
Mild/moderate mitral stenosis	31 (62%)/19 (38%)
Previous mitral balloon valvuloplasty	23 (46%)
Prior ischemic cerebrovascular event	2 (4%)
Palpitations	27 (54%)
Dyspnea NYHA-I	32 (64%)
Dyspnea NYHA-II	18 (36%)
Penicillin therapy	50 (100%)

Only those under 50 years of age and with a mild-to-moderate severe mitral stenosis were selected. A careful screening for confounding factors that could result in higher incidence of supraventricular tachyarrhythmias and elevated CRP levels had been performed and patients with systolic or diastolic heart failure, more than mild valvular regurgitation in any of the heart valves, any rheumatic involvement other than in the mitral valve, known or suspected coronary heart disease, a history of hypertension, hypo- or hyperthyroidism, diabetes mellitus, obesity, any chronic inflammatory diseases such as collagen vascular diseases, acute or chronic infections, malignancy, chronic obstructive pulmonary disease, any minor/major surgical procedure in the last 3 months, and renal failure were excluded. All of the patients were on penicillin therapy because of the high incidence of acute rheumatic fever in the area. None of the study patients were treated with antiarrhythmic drugs including beta-blockers. The clinical characteristics of the study group are shown in Table 1.

Echocardiography, Ambulatory ECG Monitoring, and Blood Samples

Two-dimensional and Doppler echocardiographic examinations were carried out by physicians who were blinded to the study using a phased array scanner with a 2.5-MHZ transducer (Vivid 3, General Electric Company, Hartford, CT). Standard echocardiographic images were obtained in the parasternal long- and short-axis views, apical 2- and 4-chamber views, and when needed, in the subcostal view. A detailed report

of the severity of mitral stenosis, the mitral valve gradients, and right and left atrial volumes with the other usual echocardiographic parameters was obtained for each patient. All patients underwent a single 24-hour period of ambulatory ECG monitoring using a portable 3-channel ECG recorder (Spiderview, Sorin Group Company, ELA medical, Milan, Italy). During the monitoring, patients continued to carry out their normal daily activities. The recordings were analyzed using the SyneScope Ambulatory ECG Software (Sorin Group). Patients were questioned for their symptomatic status and perception of palpitations, drugs taken, and previous invasive procedures on their mitral valves. On the day of ambulatory monitoring, blood samples were obtained for laboratory tests and for the quantitative measurement of hs-CRP levels by enzyme-linked immunosorbent assay method using Immundiagnostik CRP Elisa Kit (Immundiagnostik AG, Bensheim, Germany). All patients underwent routine blood tests, including those for glycemia, creatinemia, blood urea nitrogen, serum electrolytes, transaminase, erythrocyte sedimentation rate, blood cell count, and thyroid function tests.

Data Analysis

Mitral valve morphology was assigned a score on the basis of the Wilkins scoring system for mitral stenosis. To assess the mitral stenosis severity, mitral inflow velocities were measured with continuous-wave Doppler ultrasound scanning from the apical view and peak and mean gradients were calculated. Calculation of the mitral valve area was performed by using the pressure half-time method and planimetry of the mitral valve orifice in early diastole from short-axis view. Patients with mean gradients 5 to 10 mmHg and valve areas 1.0 to 1.5 cm² were classified as moderate and patients with mean gradients less than 5 mmHg and valve areas between 1.5 and 2.0 cm² were classified as mild mitral stenosis. Anteroposterior, mediolateral, and apicobasal diameters of the left atrium were used to calculate its volume with the prolate ellipse method (the product of these three dimensions is further multiplied with the constant value 0.523). Valvular regurgitations were also assessed with color-flow imaging and those with more than mild regurgitation in any of the cardiac valves depending on the spatial extent of color flow in the receiving chamber were

excluded. Patients with any significant aortic and tricuspid rheumatic involvement causing any degree of stenosis were not included as patients with compromised left ventricular functions.

Ambulatory ECG recordings were interpreted by two cardiologists (A.A. and B.G.) separately, who were unaware of the study. All the arrhythmias were printed onto ECG papers. Any arrhythmia was classified accordingly if both of the interpreters agreed. If there was a disagreement the opinion of a third cardiologist (I.C.E.) was obtained. If a consensus was reached the rhythm strip was classified using the following definitions; paroxysmal atrial tachycardia: regular tachycardia with a sudden onset, with a constant P wave morphology, usually different from the sinus P, consisting of more than three consecutive QRS complexes with a rate of >100 beats per minute; paroxysmal atrial fibrillation: sudden burst of totally irregular tachycardia with no discernible P waves; paroxysmal atrial flutter: sudden burst of tachycardia with regular saw-tooth atrial flutter waves; paroxysmal multifocal atrial tachycardia: irregular tachycardia with a sudden onset, with varying P wave morphology, consisting of more than three consecutive QRS complexes with a rate of >100 beats per minute.

The duration and ventricular rate of each tachycardia episode were carefully measured.

Statistics

SPSS for Windows (version 13) statistical package was used for data analysis. Differences between mean values were analyzed by Student's unpaired *t*-test for those with a normal distribution and by Mann-Whitney *U* test for those without a normal distribution. To compare proportions chi-square test was used. For the correlation analysis of the data without a normal distribution Spearman correlation analysis for two variables was used. To determine the sensitivity and specificity of hs-CRP values to predict the presence of any atrial tachyarrhythmia receiver operator characteristic curve analysis was performed. Following independent variables for explanation of the occurrences of atrial arrhythmias were entered in a logistic regression analysis: age, left atrial volumes, mean gradients, history of previous mitral procedures, and hs-CRP values. The results were expressed as odds ratio (OR). A *P* value of ≤ 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A majority of patients were young adult to middle-aged women (90%), which correlates with the higher incidence of rheumatic mitral stenosis in women. For all of the 50 patients, the blood test results taken in the study entry were in the normal range, including white blood cell count, creatinine, sedimentation rate. Sixty-two percent of the group demonstrated mild mitral stenosis and the others had moderate mitral stenosis and all patients had mild tricuspid regurgitation with a calculated pulmonary artery pressure in the mild range. The majority of patients did not report any symptoms associated with valvular disease and those who had symptoms (18 patients) were classified as New York Heart Association Class 2. Twenty-three patients (46%) had undergone percutaneous mitral valvuloplasty in the previous years.

Rhythm Analysis

Interpretation of the ambulatory ECGs revealed at least one atrial tachyarrhythmia episodes in 22 patients (44%). The total number of the episodes was hundred 100, 96% of which were totally asymptomatic and all of the episodes were nonsustained. The features of the detected tachycardias were as follows:

- Supraventricular premature beats, couplets and triplets: We encountered isolated premature beats in 39 patients (78%), couplets in 33 patients (66%), and triplets in one (2%) patient. One patient reached a total of 14,893 isolated supraventricular premature beats without demonstrating a sustained tachycardia.
- Paroxysmal atrial tachycardia: There were a total of 33 episodes of paroxysmal atrial tachycardia in 10 patients (20%). The longest episode was 29 seconds with the highest ventricular response of 178 beats per minute.
- Paroxysmal atrial fibrillation: 14 (28%) patients demonstrated 63 episodes of paroxysmal atrial fibrillation. These episodes lasted from 1.0 second to 30.0 second (mean duration 9.8 ± 7.4 s). Ventricular response varied between 110 and 198 beats per minute.
- Paroxysmal atrial flutter: Only 1 episode of atrial flutter in one patient (2%) was encountered,

which lasted 12 seconds with a ventricular rate of 167 beats per minute.

- Paroxysmal multifocal atrial tachycardia: A total of three attacks of multifocal tachycardia were developed in just two patients (4%) with the longest episode lasting 6.8 seconds.

In summary, 63% of the total 100 episodes of supraventricular tachycardia was paroxysmal atrial fibrillation, 33% was paroxysmal atrial tachycardia, 3% was multifocal atrial tachycardia, and 1% was atrial flutter. Of those with tachyarrhythmia only five patients demonstrated more than one type of arrhythmia with four of them having paroxysmal atrial tachycardia and fibrillation and one patient having paroxysmal atrial flutter and atrial tachycardia (Table 2).

Grouping of Patients According to the Presence and Absence of Atrial Tachyarrhythmias

Twenty-two patients had no atrial tachyarrhythmia and were in sinus rhythm. This group was designated as Group S (S for sinus, $n = 28$), while the other group of patients showed the above mentioned types of supraventricular arrhythmias (Group A, A for arrhythmia, $n = 22$). As depicted in Table 3 these two groups did not show any statistically significant difference in their mean age, maximal and peak mitral gradients, mitral valve areas and left atrial volumes, right atrial dimensions, pulmonary artery pressures, and the symptomatic status. On the other hand, there were more valvuloplasty procedures in Group A (28% vs 68%, $P = 0.005$).

Comparing the hs-CRP Levels

Comparison of the hs-CRP levels showed higher values in Group A patients, which was statistically significant (Figure 1).

Correlation analysis revealed moderate association between hs-CRP levels and occurrence of atrial tachyarrhythmias ($r = 0.461$, $P < 0.001$). On the other hand, hs-CRP values were not influenced by age, gender, mitral valve gradients, and previous procedures on the mitral valve.

A logistic regression analysis between hs-CRP levels, age, left atrial volumes, mean gradients, and history of previous mitral valve procedures showed that only higher hs-CRP and previous

Table 2. Distribution of the Tachyarrhythmias Detected in 22 Patients

	Number of Patients (%)	Total Number of Episodes	Min-Max (Mean) Episode Duration	Highest-Lowest Heart Rate
Isolated Premature beats	39 (78%)	N/A	N/A	N/A
SV couplets	33 (66%)	N/A	N/A	N/A
SV triplets	1 (2%)	N/A	N/A	N/A
Px atrial tachycardia	10 (20%)	33	1.2–29 sec (15.8 ± 9.5)	117–178 bpm
Px atrial fibrillation	14 (28%)	63	1–30 sec (9.8 ± 7.4)	110–198 bpm
Px atrial flutter	1 (2%)	1	12 sec	198 bpm
Px multifocal atrial tachycardia	2 (4%)	3	12–16.8 sec (14 ± 2.5)	130–150 bpm

Also included the number of patients demonstrating supraventricular premature beats; SV = supraventricular; Px = paroxysmal.

valvular procedures independently predicted atrial tachyarrhythmias (OR = 1.7, C.I.: 1.2–2.5, $P = 0.004$ and OR = 8.9, C.I.: 1.7–45.1, $P = 0.009$, respectively).

The best hs-CRP cutoff point for predicting atrial arrhythmia occurrence is about 2.8 mg/L. When we repeated the regression analysis for the hs-CRP values above 2.8 mg/L the predictive power became more significant (OR = 4.3, C.I.: 1.1–17.5, $P = 0.043$).

DISCUSSION

Atrial fibrillation and other atrial tachyarrhythmias are common clinical entities encountered in patients with MS. Our study showed that patients who are apparently in sinus rhythm may develop asymptomatic nonsustained atrial tachyarrhythmias throughout the day. This same finding was also reported by Ramsdale et al. where 55% of the 63 patients developed supraventricu-

lar arrhythmias, mainly atrial tachycardias, and atrial fibrillation.⁹ Similarly, atrial fibrillation and other atrial tachyarrhythmias occurred in 44% of our patients, most of which were asymptomatic. Our study, along with the study of Ramsdale, importantly revealed that almost one of every two mitral stenosis patients who seems to be in sinus rhythm, in fact, experiences episodes of atrial tachyarrhythmias. This may have unwanted clinical consequences such as ischemic strokes in those who are undertreated because of undocumented arrhythmias and, therefore, not given anticoagulant and antiarrhythmic therapy.

The findings of recent studies already revealed the chronic, low-grade inflammation detected by hs-CRP in rheumatic heart disease patients.^{3,4,10} But it is not clear whether this inflammation has other consequences than destructing the heart valves. One of the findings in our study is the demonstration of low-grade inflammation in MS patients; moreover, those patients with atrial

Table 3. Comparison of Clinical Characteristics of Patients Divided into Two Groups According to the Presence of Atrial Arrhythmias

	Group S n = 28	Group A n = 22	P
Age (years)	37.6 ± 6.5	40.6 ± 4.7	0.07
Body surface area (m ²)	1.60 ± 0.7	1.60 ± 0.7	0.9
Maximal/Mean MVG (mmHg)	14 ± 5/5.8 ± 2.6	13 ± 4/5.7 ± 2.8	0.54/0.62
Mitral valve area-planimetry (cm ²)	1.63 ± 0.35	1.57 ± 0.24	0.52
Mitral valve area-pressure half time(cm ²)	1.63 ± 0.37	1.60 ± 0.21	0.72
Wilkins score of the mitral apparatus	7 ± 1	8 ± 1	0.13
Left atrial volume (mL)	52 ± 30	55 ± 21	0.70
Right atrium, apicobasal (cm)/mediolateral (cm)	43 ± 6/38 ± 4	45 ± 5/39 ± 5	0.24/0.37
Mean pulmonary artery pressure (mmHg)	32 ± 7	32 ± 8	0.80
Previous mitral balloon valvuloplasty	28%	68%	0.005
Previous ischemic cerebrovascular event	0%	9%	NA
Diuretic therapy	25%	40%	0.231
Palpitations	53%	54%	0.945

Figure 1. Median values and range of distribution of serum CRP in mg/L in patients with mitral stenosis divided into two groups: those with episodes of atrial arrhythmias (Group A) and those without (Group S). Levels in Group A patients are significantly higher, a difference reflecting greater degree of inflammation (mean ranks; 19.61 vs 33, $P < 0.001$).

tachyarrhythmias showed even higher hs-CRP levels than those without arrhythmias. Pathologically, the inflammatory response seen in the acute phase of the rheumatic fever is not limited to the endocardium; in contrast all layers of the heart are affected.¹ One cannot insist that the atrial myocardium can escape this inflammatory insult in the chronic phase of the disease. Thus, hs-CRP levels will rise in the circulating blood as a response of the body to the chronic inflammation and may localize in the atrial myocardium to activate the classic pathway of the complement system.¹¹ It has been shown that a possible ligand for the circulating CRP in the inflamed tissues may be the membranes of myocardial cells.^{12,13} Consequently, long-chain acylcarnitines and lysophosphatidylcholines are generated from phosphatidylcholines in the atrial cell membranes. These changes in the membrane ultrastructure may result in membrane dysfunction where sodium and calcium exchange mechanism in the sarcolemmal vesicles will be inhibited. The dysfunctional sodium/calcium cotransporter in congestive heart failure models is linked to the development of afterdepolarizations and triggered activities, which in turn, lead to ectopic atrial rhythms.¹⁴ This same mechanism may be responsible in the inflamed atrial myocardium in the rheumatic heart disease.

Moreover, the inflammatory cells will create a rheumatic myocarditis, which results in fibrosis and disorganization with different conduction velocities and nonuniform refractory periods in the atria. The so-called vulnerable atrium is ready to develop short bursts of atrial tachycardia, atrial flutter, and atrial fibrillation as a response to a premature atrial stimulus.¹⁴ Thus, we concluded that the more significant inflammatory reaction expressed by the higher hs-CRP levels in Group A patients is the basis for the more frequent atrial arrhythmias in these patients. In other words, the higher the hs-CRP levels the more susceptible are the atria for developing tachyarrhythmias.

Some discrepancies still exist about whether inflammation as evaluated by hs-CRP levels reflects a response to high atrial rates during episodes of atrial fibrillation or is it a cause of the arrhythmia itself. In their study about paroxysmal atrial fibrillation, Sata et al. reported that inflammatory markers such as CRP, interleukin-6, and TNF- α act as a cause of atrial fibrillation.¹⁵ On the other hand, Dernellis et al. claimed that CRP has a two-sided role, both as a cause and as a consequence of atrial fibrillation.¹¹ We believe that our study supports the argument that inflammation is an inciting factor for atrial tachyarrhythmias, because the episodes seen in our patients did not sustain sufficiently long, with the longest episode of 30 seconds, to result in an elevation of the circulating levels of CRP as a response to high atrial rates.

Another finding in our study is the significantly higher incidence of atrial tachyarrhythmias in those patients with a history of previous mitral valvuloplasty. Our study showed that CRP levels and previous mitral procedures independently predict arrhythmias. It could be assumed that patients who needed a mitral valvuloplasty should sustain more significant inflammation to result in a more destructed mitral valve with a more advanced stage of MS. Thus, this heightened state of inflammation should be depicted in higher CRP levels. Actually, our patients who underwent a previous mitral valvuloplasty procedure showed higher CRP levels, though not statistically significant (3.2 mg/L vs 2.6 mg/L; $P = 0.360$); we believe this might change in a study where more patients could be included. On the other hand, some investigators reported that balloon valvuloplasty did not have an impact on the development of atrial fibrillation in the future.^{2,4,16} According to that concept we came to the conclusion that patients who needed a valvuloplasty

procedure and underwent a successful intervention could not escape the development of atrial tachyarrhythmia; because the higher level of inflammation, which made them a candidate for the intervention, also put them into a higher risk of tachyarrhythmias.

The incidence of atrial fibrillation increases sharply in patients above 60 years, even in people without any other risk factor for atrial fibrillation.¹⁷ We, therefore, did not enter older patients into our study to not overestimate the tachyarrhythmia incidence in our patients.

Our study determined another risk factor for developing atrial fibrillation in patients with mitral stenosis less than 50 years old. CRP levels independently predict atrial arrhythmias with a moderately powered correlation. If a cutoff point of 2.8 mg/L for hs-CRP would be taken, the predictive power would be increased four times. This value is only a bit less than 3 mg/L, which is the proposed value of CRP by the American Heart Association for predicting cardiac risk in the adult population.¹⁸

Left atrial dimensions correlate well with the occurrences of atrial tachyarrhythmias, for example, atrial fibrillation. With increasing atrial volumes the incidence of atrial fibrillation increases and the conversion to sinus rhythm will also be problematic.¹⁷ The universally accepted maximal left atrial volume is 36 mL/m².¹⁹ Using this assumption, we encountered that our patients' left atrial volumes are on average on the higher end of normal or only slightly exceeded this. Therefore, we concluded that in our study group the left atrial volumes should not have determined the arrhythmic outcomes or at least influenced these only slightly. On the other hand, patients with higher CRP levels but with left atrial volumes in almost normal ranges and not different from the patients with no tachyarrhythmias represented significantly more episodes of tachycardia.

Ischemic cerebrovascular events constitute a very important clinical problem in mitral stenosis. The current guidelines about valvular heart diseases support therapy with warfarin in patients with prior attacks, with atrial fibrillation, or with left atrial thrombus that is given a class 1 recommendation.²⁰ Patients without these risk factors who are in sinus rhythm are given a class IIb recommendation for anticoagulant therapy if they have severe mitral stenosis and a left atrium diameter >55 mm. In our study two patients had prior cerebrovascular attacks due to mitral stenosis, both in the atrial tachyarrhythmia group. They have mild

mitral stenosis, but one of these had undergone a mitral balloon valvuloplasty for moderately severe stenosis in the past. The stroke developed 2 years after intervention. Both the patients had no known history of atrial tachyarrhythmias. Actually, systemic emboli constitute the initial manifestations of mitral stenosis in 20% of the patients.²¹ Similarly, with some other studies Ramsdale et al. also reported that 14% of the patients in his study group who were apparently in sinus rhythm had had systemic emboli previously.^{9,22-24} He concluded if the occurrence of systemic embolism is associated with a changing atrial rhythm, including the type of non-sustained atrial tachyarrhythmias in his study, then even patients with predominantly sinus rhythm carry a high risk for systemic embolism.⁹ These two patients in our study also had frequent attacks of atrial fibrillation and tachycardia with a total of 13 and 18 episodes, respectively, on their ambulatory ECG recordings. Moreover, these two patients had much higher CRP values than the average, 6.1 mg/L and 5.8 mg/L, respectively. According to these findings, we agree with Ramsdale et al., but we also would like to argue that patients with higher CRP values, for example, higher than 2.8 mg/L, have higher risk for a supraventricular tachyarrhythmia, especially for atrial fibrillation and atrial tachycardia, which can also be seen as a precursor for atrial fibrillation, and thus for stroke and may benefit from anticoagulant therapy.

Study Limitations

A relatively small study group and lack of a healthy control group are the main limitations in our study.

It is possible that rhythm follow-ups longer than 24 hours would increase the proportion of patients who develop asymptomatic tachyarrhythmias. Also, some sustained episodes could be detected on such longer follow-ups.

Comparative studies in patients with severe mitral stenosis should be undertaken. We have intentionally excluded such patients to investigate data in relatively lower risk patients, who were especially undertreated with anticoagulants.

Although we tried to exclude completely all the disease states that could influence hs-CRP levels, there may be some conditions not covered in the exclusion criteria because of the lack of knowledge about a possible interaction. Nevertheless, in a population with a majority of young to middle-aged women, it is unlikely to expect CRP elevation due

to other causes than rheumatic heart disease. Two studies with similarly aged women revealed median CRP levels 1.3 mg/L and 1.6 mg/L, significantly less than in our study group (2.1 mg/L).^{25,26}

Clinical Implications

Our data implicated that nearly half of the mild-to-moderate mitral stenosis patients who are in sinus rhythm develop asymptomatic tachyarrhythmias during the day. These are in decreasing order: paroxysmal atrial fibrillation, paroxysmal atrial tachycardia, multifocal atrial tachycardia, and atrial flutter. Evaluating of CRP levels with high sensitivity tests may help in identifying those patients with a higher risk of having supraventricular tachycardias where CRP values above 2.8 mg/L indicate a four times increased risk. Therefore, oral anticoagulant therapy in mild-to-moderate mitral stenosis patients with higher CRP levels will prevent unwanted clinical outcomes.

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