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Decline in C-Reactive Protein After Successful Ablation of Long-Lasting Persistent Atrial Fibrillation

To the Editor: Increased levels of C-reactive protein (CRP) have been demonstrated to be an independent predictor of atrial fibrillation (AF) and to correlate with AF burden (1,2). In addition, inflammation and endothelial activation have been described as risk factors for adverse events in AF (3,4).

Whether inflammation and endothelial dysfunction are a cause or a consequence of AF remains unknown. Development of CRP levels after cardioversion of AF has shown controversial results, and data on evolution of inflammation after ablation are lacking.

This study investigated whether elimination of AF by ablation could influence the inflammatory state and endothelial dysfunction.

Fifty consecutive patients (49 males, 1 female; age 53 ± 10 years) referred for ablation of persistent or permanent drug-refractory AF were studied. Five patients had long-lasting persistent AF, defined as episodes lasting >7 days (mean 6 months, range 3 to 10 months). Forty-five patients suffered from permanent AF, defined as AF that failed cardioversion or lasted for >1 year. Atrial fibrillation was persisting for a median of 24 months (range 2 months to 20 years).

The ablation procedure was described in detail elsewhere (5). All patients underwent pulmonary vein isolation (PVI). Further substrate modification consisted of linear lesions at the mitral isthmus and at the roof of the left atrium. In patients with ongoing AF after PVI and linear ablation the following additional steps were performed: 1) energy applications at sites showing rapid or heterogeneous activity for 90 to 120 s; 2) an intercaval line joining the superior and inferior caval vein at their posterior aspect; and 3) cardioversion.

A detailed data form including preclinical and procedural data was completed for every patient. At the follow-up examinations (after 1 and 3 months) clinical symptoms were evaluated and transthoracic echocardiography and a 48-h electrocardiogram (ECG) performed. Follow-up blood samples were taken at the 3-month follow-up. Patients suffering from any tachyarrhythmia symptoms or showing any atrial arrhythmia on 48-h ECG were classified as having recurrent arrhythmia. All antiarrhythmics remained unchanged for at least 3 months after the index procedure, as did all other medications, including anticoagulants, beta-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin (AT) II antagonists.

Plasma samples were frozen at −70°C and stored for further examination. All paired blood samples were analyzed on the same day to avoid calibration errors. High-sensitivity CRP (hsCRP) and von Willebrand factor (vWf) activity were measured using commercially available testing kits (hsCRP: BNII analyzer; Dade Behring., Paris, France; vWf: Asserachrom vWf; Diagnostica Stago, Asnieres, France) according to the manufacturers' protocol. The hsCRP assay has a typical detection limit at 0.155 mg/l. Normal activity for the Asserachrom vWf assay ranges from 50% to 150%.

Fifteen patients (30%) suffered from structural heart disease. Fourteen patients were taking amiodarone at the time of the procedure, 11 patients were taking ACE inhibitors or AT II antagonists, 4 patients were taking statins, and 3 patients were taking aspirin. Twenty-five patients were treated with beta-blockers, which were stopped at least five half-lives before the procedure. Mean baseline hsCRP was 2.66 mg/l (range 0.155 to 13.9 mg/l), and mean vWf activity was 132 ± 50%. There were no differences in baseline characteristics for patients with successful ablation or failed maintenance of sinus rhythm 3 months after ablation (Table 1).

All patients underwent a single procedure after collection of baseline data. At 3-month follow-up, 33 patients (66%) were free of arrhythmia, 17 patients (34%) failed to maintain sinus rhythm, 12 suffered from paroxysmal AF, and 5 suffered from atrial tachycardia. Left atrial parasternal diameter decreased significantly in the successfully treated group (45.8 ± 5.6 mm vs. 42.6 ± 4.8 mm; $p = 0.003$ by t test) but showed no change in the group with ongoing arrhythmia (45.2 ± 7.7 mm vs. 45.4 ± 5.3 mm; $p = 0.9$). Left ventricular diameters and LVEF showed no difference before and after ablation in either group. Both groups had comparable cumulative radiofrequency energy delivery (87 ± 32 min vs. 79 ± 30 min; $p = 0.5$).

At baseline there was no difference in CRP between the successfully treated patients and the patients with ongoing arrhythmia (2.82 ± 3.1 mg/l vs. 2.46 ± 3.6 mg/l; $p = 0.32$). At three months, CRP declined significantly in successfully treated patients

Table 1. Baseline Patients Characteristics

	Success (n = 33)	Failure (n = 17)	p Value
Age (yrs)	53 ± 10	54 ± 10	0.7
AF duration (months)	24 (3–96)	24 (12–60)	0.5
Structural heart disease	9	3	0.7
Amiodarone	9	5	0.9
Statin medication	2	2	0.6
Aspirin medication	2	1	0.6
High-sensitivity CRP (mg/l)	2.82 ± 3.1	2.46 ± 3.6	0.3
vWf activity (%)	128 ± 48	136 ± 30	0.7
Creatinine (μmol/l)	92 ± 12	94 ± 16	0.7
Left atrial parasternal diameter (mm)	46 ± 6	45 ± 8	0.7
LVEF (%)	65 ± 11	62 ± 11	0.5
Radiofrequency duration (min)	87 ± 32	79 ± 30	0.5

AF = atrial fibrillation; CRP = C-reactive protein; vWf = von Willebrand factor; LVEF = left ventricular ejection fraction.

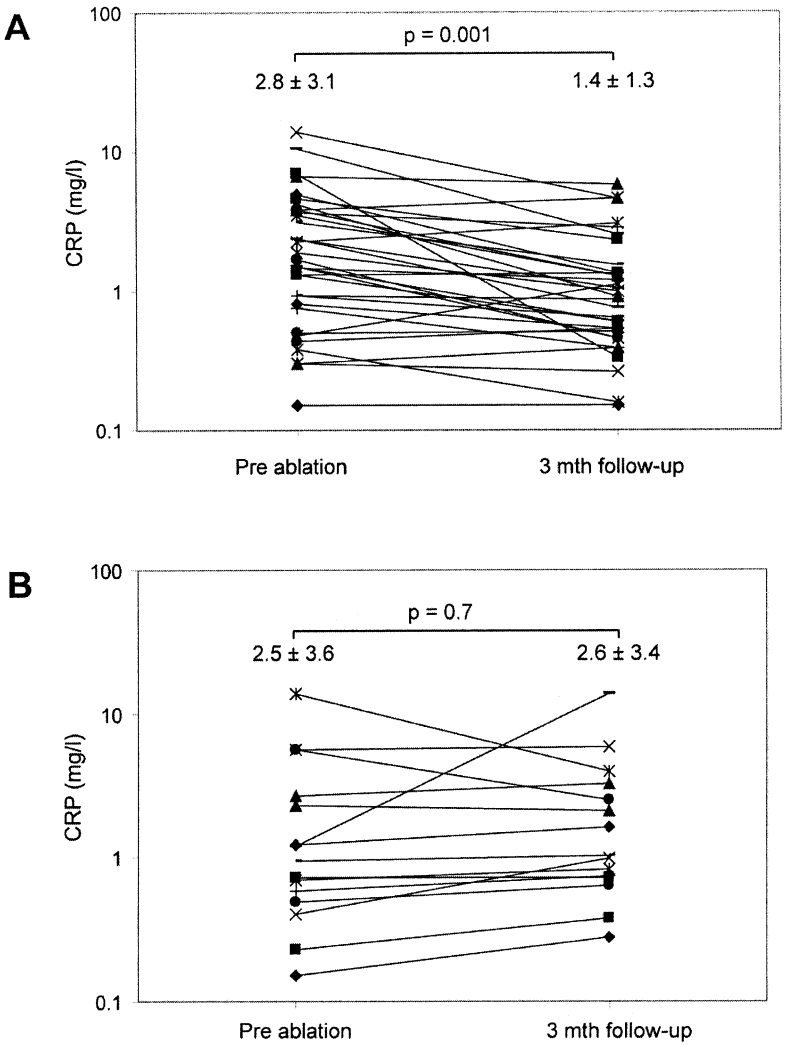

Figure 1. **(A)** Comparison of high-sensitivity C-reactive protein (CRP) values at baseline and 3 months after ablation, showing a significant decline in patients that maintained sinus rhythm. **(B)** Comparison of high-sensitivity CRP values at baseline and 3 months after ablation, showing no change in patients that suffered from recurrent arrhythmia.

(2.82 ± 3.1 mg/l vs. 1.37 ± 1.3 mg/l; $p < 0.001$ by paired t test) (Fig. 1A) but remained unchanged in patients with arrhythmia recurrence (2.46 ± 3.6 mg/l vs. 2.58 ± 3.4 mg/l; $p = 0.16$) (Fig. 1B).

Neither at baseline nor at follow-up a difference could be shown for vWf activity in the two groups (recurrence group: 136 ± 30% vs. 140 ± 26%; $p = 0.7$; sinus rhythm group: 128 ± 48% vs. 132 ± 40%; $p = 0.7$).

Subgroup analysis could not demonstrate any difference between CRP or vWf activity for patients with or without ACE inhibitor treatment or for patients with or without structural heart disease.

To our knowledge, this is the first study to demonstrate that restoration of sinus rhythm in patients with long-lasting persistent AF leads to a decline in hsCRP. This finding was accompanied by a significant reduction in left atrial size. In patients who failed to maintain sinus rhythm, no change in CRP or left atrial size could be demonstrated. These findings suggest that atrial remodeling and modification of the inflammatory state are attributable to the maintenance of sinus rhythm. In addition, this study assessed endothelial dysfunction by measuring vWf activity and showed that neither ablation nor the restoration of sinus rhythm influenced this parameter.

Previous studies have shown that reverse atrial morphological remodeling occurs after successful ablation of atrial fibrillation (6). This remodeling process has been associated with parameters of inflammation and the renin-angiotensin system (7,8), and it has been suggested, in analogy to left ventricular remodeling, that matrix metalloproteinases might be involved (9). Restoration of sinus rhythm decreases wall stress, resulting in a reduced activity of the renin-angiotensin system. Consequently, stimulation of matrix metalloproteinases and inflammation will be reduced; reverse remodeling and a decline in inflammatory parameters will be the effect.

The cause-and-effect relationship between maintenance of sinus rhythm, atrial remodeling, and inflammation remains complex. This study demonstrated that direct atrial tissue destruction by radiofrequency current did not influence atrial size or inflammation but maintenance of sinus rhythm affected both parameters. The relationship between atrial remodeling and inflammation however, needs to be further evaluated, as it remains unclear whether

attenuation of inflammation induces atrial remodeling or vice versa.

Although this study did not include a control group, the levels of CRP measured compare well to previously published data (1). Levels of CRP decreased after successful ablation to levels comparable with patients suffering from paroxysmal AF or patients in sinus rhythm at increased risk for AF. At that point, additional pharmacologic modification of the inflammatory state with an ACE inhibitor or a statin might be useful to reduce the risk of arrhythmia recurrence (10).

Endothelial dysfunction is not influenced by ablation, restoration of sinus rhythm, reverse remodeling, or a decline in inflammatory parameters. This finding confirms previous studies showing sustained endothelial dysfunction despite a restoration of sinus rhythm by cardioversion (11), suggesting that endothelial dysfunction may not be maintained by AF.

In conclusion, we found that restoration of sinus rhythm by ablation leads to a decrease of the patient's inflammatory state and a reverse remodeling of the left atrium.

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doi:10.1016/j.jacc.2005.12.038

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Letters to the Editor

Left Ventricular Noncompaction, Cardiac Magnetic Resonance Imaging, and Neuromuscular Disorders

With interest we read the report by Petersen et al. (1) concerning cardiovascular magnetic resonance imaging (CMRI) in patients with left ventricular hypertrabeculation (LVHT), also termed "noncompaction." Currently, several echocardiographic definitions of LVHT exist, and up to now no CMRI-specific diagnostic criteria for LVHT have been developed (2–4). We have, however, concerns and doubts as to whether the current study will clarify the confusion regarding the diagnosis of LVHT.

According to their definition, the investigators found by CMRI that "areas of non-compaction" were common in healthy volunteers, athletes, patients with hypertrophic or dilated cardiomyopathy, and aortic stenosis. Because these findings were not correlated with echocardiographic or anatomic data, how can Petersen et al. be sure that these areas were indeed "noncompacted" and not just the papillary muscles, false tendons, or aberrant bands, which are common cardiac findings (5)?

When assessing the myocardial layers with different degrees of tissue compaction, how did the researchers differentiate myocardium from flow artifacts? Why did they measure the ratio of noncompacted/compacted myocardial layers in diastole and not in systole, as recommended by one of the echocardiographic definitions (3)? How to explain the discrepancy between the relatively smooth endocardial surface as seen on CMRI and the bizarre morphology of trabeculations and deep intertrabecular recesses when examining LVHT patients echocardiographically and at autopsy?

Echocardiography often does not visualize with clarity the left ventricular apex. Thus, we do not understand why this cardiac region, which can be much better visualized by CMRI than by echocardiography, was excluded from measurements. According to the investigators, a ratio of noncompacted to compacted myocardial layers >2.3:1 in diastole distinguished "pathological" from "nonpathological" noncompaction. Why did they then diagnose "partial expression" of the disease in Patient #2, with a ratio of only 1.1? What is the distinction between "nonpathological" noncompaction and "partial expression" of noncompaction? According to which echocardiographic criteria was LVHT-diagnosed in the seven patients? Why were other family members of Patient #4,