

Role of Inflammation in Early AF Recurrence after PV Isolation

Rupa Bala, MD^o

Assistant Professor of Medicine, Division of Electrophysiology, Hospital of the University of Pennsylvania

Introduction

Recently, there has been a great deal of interest in the mechanistic role of inflammation in the initiation, maintenance, and perpetuation of atrial fibrillation (AF)^{1,2}. Several studies have focused on inflammatory biomarkers and acute-phase proteins to further understand the inflammatory milieu in relation to AF. These studies have demonstrated that both interleukin-6 (IL-6) and C-reactive protein (CRP) are elevated in paroxysmal and persistent AF^{3,4,5}. Chung et al. [4] demonstrated an association between elevated CRP levels and AF in a nonoperative setting. In this study, CRP levels were more than 2-fold higher in patients with AF than in control subjects. Moreover, patients with persistent AF had higher CRP levels than patients with paroxysmal AF, suggesting that inflammation may be more relevant to promoting AF maintenance than its initiation. Similarly, Dernellis and Panaretou⁶ demonstrated CRP elevation in patients with paroxysmal AF and that CRP levels were higher in the subgroup that failed pharmacologic cardioversion with amiodarone. Lower CRP levels have been associated with successful cardioversion and maintenance of sinus rhythm. Sata et al.⁷ measured inflammatory markers at different time intervals pre and post cardioversion in 15 patients with paroxysmal AF and found that CRP, IL-6, and tumor necrosis factor (TNF- α) were signifi-

cantly elevated when compared to controls and remained elevated for up to 2 weeks after cardioversion. Although this study was small, the authors suggested that inflammation played a role in the initiation of AF. Whether an increase in inflammatory markers is a cause or a consequence of AF, there is a clear association between the two processes and growing interest in developing therapeutic options to modulate the inflammatory state.

Early recurrence of atrial arrhythmias after pulmonary vein isolation is common and does not necessarily indicate failure of the procedure.^{8,9}

Though, there is data to support that early recurrence of AF is associated with a lower long-term success rate.^{10,11} It is not clear how to manage patients with early recurrence after AF ablation and thus, there is uniform interest in developing treatment strategies to deal with this subset of patients, including reablation and/or medications. A recent consensus document on catheter and surgical ablation of AF¹² suggested a blanking period of at least three months in regards to repeat ablation. The document did state that symptomatic, atrial arrhythmias after ablation are difficult to treat with medications and patients are best managed with repeat ablation. Lellouche et al.¹³ looked at an early reablation strategy to deal

Corresponding Address :Rupa Bala, MD, Assistant Professor of Medicine, Division of Electrophysiology, Hospital of the University of Pennsylvania, 9 Founders Pavilion, 3400 Spruce Street, Philadelphia, PA 19104.

with early recurrences after AF ablation. The authors found that an early reablation strategy had a lower rate of clinical recurrences, but an overall higher number of ablation procedures compared with patients without an early second ablation, suggesting that the optimal timing for the second procedure remains to be defined.

It is unclear if inflammation plays a role in contributing to the early recurrence of atrial arrhythmias after ablation or if these arrhythmias are secondary to recovery of conduction in a previously isolated PV, incomplete PV isolation, or non-PV arrhythmogenic foci and therefore, a marker of late recurrence. An interesting paper by Koyama et al.¹⁴ in the American Journal of Cardiology entitled "Comparison of Characteristics and Significance of Immediate Versus Early Versus No Recurrence of Atrial Fibrillation After Catheter Ablation" sheds light on this topic. The objective of this study was to clarify the relationship between the inflammatory processes related to catheter ablation and recurrence of AF after ablation and to characterize AF recurring within three days after ablation (immediate-AF-recurrence). In this study, 186 patients with symptomatic, par-

oxysmal AF, who were refractory to medications, underwent extensive pulmonary vein isolation by a double lasso technique. The end point of ablation was bidirectional, pulmonary vein block and no AF induction lasting > 3min with decremental burst pacing from the coronary sinus to a cycle-length of 180ms on isoproterenol. Specific attention was paid to symptoms, physical findings, and data relative to an inflammatory response within the first three days after ablation. The variables measured included body temperature (BT) and C-reactive Protein (CRP). During the first three days after ablation, patients were monitored for pericarditis, which was confirmed by ECG diagnosis and echocardiography, and any evidence of frequent atrial premature contractions or nonsustained AF. Successful ablation was defined as the absence of AF on no antiarrhythmic drugs (AAD) after a six-month follow-up period.

Patients were divided into immediate-AF-recurrence (within 3 days), early-AF-recurrence (4-30 days) and no AF recurrence groups following ablation. During the initial one-month follow-up period, 45 patients (24%) were in the immediate-

AF-recurrence group, 27 patients (14%) were in the early-AF-recurrence group, and 114 patients (61%) were in the no AF recurrence group. In the first 3 days after the ablation procedure, the immediate-AF-recurrence group had the highest body temperature, greatest change in body temperature, highest CRP level, and greatest change in CRP level from baseline compared to the early-recurrence and no recurrence groups. Nonsustained AF and frequent atrial premature contractions were more prevalent in the early-AF-recurrence group compared to the immediate-AF-recurrence and no AF recurrence groups. It is important to note that recurrent AF episodes in the immediate-AF-recurrence group were decreased at the 1 and 6 month follow-up visit. In the immediate-AF-recurrence, 45 patients had recurrent AF in the first three days post ablation, which decreased to 10/45 patients and 11/45 patients at 1 and 6 months of follow-up respectively. In contrast, the prevalence of AF recurrence was > 70% at 1 and 6 months in the early-AF-recurrence group.

In this study, the AF-free rate after 6 months of follow-up was greater in the immediate-AF-recurrence group (76%) than in the early-AF-recurrence group (30%). The authors concluded that immediate-AF-recurrence was associated with an acute inflammatory response after ablation with a high BT, increased CRP levels, and signs and symptoms of pericarditis. In most cases, AF recurrence in the immediate-AF-recurrence group resolved spontaneously within 1 month and AF freedom persisted at 6 months, indicating that immediate-AF-recurrence may have a different mechanism than early-AF-recurrence. In contrast, an early-AF-recurrence (4-30 days) was the most powerful predictor of AF recurrence at the end of the 6 month follow-up period and suggested a different mechanism for AF recurrence: recovery of conduction between the pulmonary veins and the left atrium or the presence of non-pulmonary vein foci.

This study introduces an interesting concept: AF recurrence in the setting of an acute inflammatory response. The majority of patients in the immediate-AF-recurrence group did well at the 6-month follow-up and did not require repeat ablation. Thus, it would have been wrong to assume failure in this select group and from this study, it is apparent that immediate-AF-recurrence had different characteristics than early-AF-recurrence. Richer

et al.¹⁵ recently published a study on the prognostic value of early AF recurrence within 48 hours after ablation and its impact on long-term outcome. This study included both paroxysmal and persistent patients using two, different ablation strategies and pulmonary vein entrance block as the endpoint of ablation. Although the authors found that early recurrence of AF within 48 hours after ablation was a significant predictor of a poor long-term ablation outcome, they noted that 46% of patients with early AF recurrence were AF free during long-term follow-up. These two studies support the concept of an acute inflammatory process at work, which may confer a benefit in the overall outcome as the healing process occurs.

Richter et al. also looked at the use of statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers in relation to ablation outcome and found that none of these medications resulted in an improved ablation outcome.¹⁶ Roux et al. recently studied the use of antiarrhythmics after ablation of atrial fibrillation (5A Study).¹⁷ This study randomized patients with paroxysmal AF undergoing ablation to empiric versus no antiarrhythmic drug (AAD) therapy for the first six weeks after ablation and found that AAD therapy reduced the incidence of clinically significant atrial arrhythmias and need for cardioversion.

In summary, the concept of an acute inflammatory response in relation to early recurrence supports an extended blanking period after the initial ablation procedure. The data from Koyama et al.¹⁴ suggest that immediate recurrence of AF after ablation may be related to an inflammatory response and that conservative treatment in this group, until the inflammatory state subsides, is prudent. AAD therapy after ablation should be encouraged in the group with immediate recurrence of AF in the short-term. While conservative treatment is also reasonable for patients with early AF recurrence, one should be vigilant for late AF recurrence in this subgroup of patients and have a low threshold for repeat ablation if AF persists. Additional prospective clinical trials utilizing anti-inflammatory treatment after ablation seems warranted to determine if modification of the inflammatory state will diminish early AF recurrences after ablation.

References

- Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *Eur Heart J* 2005; 26:2083-2092.
- Issac TT, Dokainish H, Lakkis NM. Role of Inflammation in Initiation and Perpetuation of Atrial Fibrillation: A Systematic Review of the Published Data. *J Am Coll Cardiol* 2007;50:2021-2028.
- Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a Risk Factor for Atrial Fibrillation. *Circulation* 2003;108:3006-3010.
- Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive Protein Elevation in Patients with Atrial Arrhythmias: Inflammatory Mechanisms and Persistence of Atrial Fibrillation. *Circulation* 2001;104:2886-2891.
- Psychari S, Apostolou T. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol* 2005;95:764-7.
- Dernellis J, Panaretou M. C-reactive protein and paroxysmal atrial fibrillation: evidence of the implication of an inflammatory process in paroxysmal atrial fibrillation. *Acta Cardiologica* 2001;56:375-80.
- Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, Miyahara K. C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? *Jpn Heart J* 2004;45:441-445.
- Bertaglia E, Stabile G, Senatore G, Zoppo F, Turco P, Amellone C, De Simone A, Fazzari M, Pascotto P. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. *Pacing Clin Electrophysiol* 2005;28:366-371.
- Themistoclakis S, Schweikert RA, Saliba WI, Bonso A, Rossillo A, Bader G, Wazni O, Burkhardt DJ, Raviele A, Natale A. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008;5:679-685.
- Oral H, Knight BP, Ozaydin M, Tada H, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F, Jr., Strickberger SA, Morady F. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. *J Am Coll Cardiol* 2002;40:100-104.
- Dixit S, Gerstenfeld EP, Ratcliffe SJ, Cooper JM, Russo AM, Kimmel SE, Callans DJ, Lin D, Verdino RJ, Patel VV, Zado E, Marchlinski FE. Single procedure efficacy of isolating all versus arrhythmogenic pulmonary veins on long-term control of atrial fibrillation: A prospective randomized study. *Heart Rhythm* 2008;5:174-181.
- Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Ie-saka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, She-min RJ. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation Developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and Approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace* 2007;9:335-379.

13. Lellouche N, Jais P, Nault I, Wright M, Bevilacqua M, Knecht S, Matsuo S, Lim KT, Sacher F, Deplagne A, Bordachar P, Hocini M, Haissaguerre M. Early Recurrences After Atrial Fibrillation Ablation: Prognostic Value and Effect of Early Reablation. *J Cardiovasc Electrophysiol* 2008;19:599-605.
14. Koyama T, Sekiguchi Y, Tada H, Arimoto T, Yamasaki H, Kuroki K, Machino T, Tajiri K, Zhu XD, Kanemoto M, Sugiyasu A, Kuga K, Aonuma K. Comparison of Characteristics and Significance of Immediate Versus Early Versus No Recurrence of Atrial Fibrillation After Catheter Ablation. *Am J Cardiol* 2009;103:1249-1254.
15. Richter B, Gwechenberger M, Socas A, Marx M, Gossinger HD. Frequency of Recurrence of Atrial Fibrillation Within 48 Hours After Ablation and Its Impact on Long-Term Outcome. *Am J Cardiol* 2008;101:843-847.
16. Richter B, Derntl M, Marx M, Lercher P, Gossinger HD. Therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins: No effect on ablation outcome after ablation of atrial fibrillation. *Am Heart J* 2007;153:113-9.
17. Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Russo AM, Hutchinson MD, Cooper J, Verdino R, Patel V, Joy PS, Gerstenfeld EP. AntiArrhythmics After Ablation of Atrial Fibrillation (5A Study). *Circulation* 2009; In Press.