Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 18, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.07.032

EDITORIAL COMMENT

Colchicine After Pulmonary Vein Isolation to Prevent the Early Recurrence of Atrial Fibrillation

Mollifying an Inflammatory Response?*

Gregory M. Marcus, MD, MAS,
Jonathan C. Hsu, MD
San Francisco, California

Atrial fibrillation (AF) is the most common arrhythmia and is associated with a high risk of stroke and an increased risk of death (1). Although an association between AF and inflammation is now well established, the cause-and-effect relationship remains incompletely understood (2,3). Previous studies have demonstrated that increased inflammation may precede AF (4,5), supported by evidence that genetic variants related to inflammatory processes may be more prevalent in AF patients (6,7). Conversely, we and others have shown that AF itself may contribute to an inflammatory state (8–11).

See page 1790

AF likely represents a final common pathway stemming from multiple subtypes. Identifying AF patients with an inflammation-based subtype is important in selecting candidates for anti-inflammatory therapies. In some cases, inflammation-based subtypes already are apparent. For example, building on the sterile pericarditis canine model (12) and observational cardiac surgery studies (13), trials aimed at decreasing inflammation after cardiac surgery with either steroids (14) or colchicine (15) have shown reductions in post-operative AF.

Left atrial catheter ablation to electronically isolate the pulmonary veins now is commonplace for treatment of symptomatic AF (16). Despite ongoing improvements in the procedure, early recurrence after AF ablation (ERAF) often occurs (17). The cause of ERAF remains unknown, but may involve an inflammatory response to thermal injury, pericarditis, or both (18). Because ERAF likely portends a higher risk of late recurrence, it is of particular interest (19,20). Three days of corticosteroid administration after AF ablation reduced immediate recurrence of AF (≤3 days after the procedure) and longer-term AF recurrence (21). However, potentially because of the short course of drug administration, a reduction in AF recurrence between 4 and 30 days was not observed. A longer course of steroids may not be prudent given the risk of adverse effects. We previously showed that the inflammation resulting from AF ablation may persist for more than 1 month (22), suggesting that a longer course of an anti-inflammatory agent may be necessary to combat ERAF.

In this issue of the *Journal*, Deftereos et al. (23) report their findings after randomizing 170 paroxysmal AF patients undergoing pulmonary vein isolation with radiofrequency catheter ablation to 0.5 mg of twice daily colchicine versus placebo. After 3 months of treatment, ERAF was observed in a statistically significantly smaller 16% of those receiving colchicine versus 34% of those receiving placebo.

The study has several strengths. As a blinded and randomized study, the study addressed both known and unknown confounders in an optimal fashion. All patients had paroxysmal AF and all underwent a similar procedure. Vaughn-Williams class I and III antiarrhythmic drugs were not allowed. The colchicine group exhibited significantly lower levels of both C-reactive protein and interleukin 6 by day 4. After adding these markers into a multivariate model, the hazard ratio for colchicine as a predictor of recurrent AF was substantially attenuated. Statistically, this suggests that the effect of colchicine on ERAF was at least in part explained by decreased inflammation. This study likely provides the strongest evidence to date that inflammation is causal in ERAF after ablation.

There are several details worth considering before extending the regular use of post-ablation colchicine to clinical practice. First, the best dose and duration of colchicine remain unknown. Because the primary rationale for the procedure remains quality-of-life improvement, we should avoid replacing one problem (AF) with another (such as gastrointestinal upset, observed in more of those receiving colchicine). Although no serious adverse events were attributed to colchicine, monitoring for both liver toxicity and myelotoxicity occurred. One case of transaminase elevation requiring cessation of colchicine was required. The duration of drug administration was based on our previous findings regarding post-ablation C-reactive protein elevation, measured a median of 49 days after the procedure (interquartile range: 37 to 93 days) (22). It seems that the trial investigators based the 3-month duration of treatment on the 75th percentile of that range. It is possible that a shorter duration would suffice. Discontinuing colchicine for intolerance or adverse reaction before 1 month of therapy was rare,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, University of California, San Francisco, San Francisco, California. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

suggesting that 1 month may be a reasonable duration to maximize tolerance.

The as yet unanswered question is whether reduction in ERAF will translate into long-term success. It is likely that ERAF represents 2 different groups: those in whom the procedure simply failed versus those with inflammation-induced AF who are destined for success. If these processes are entirely separate, prevention of ERAF may have no bearing on late recurrence. However, it remains possible that ERAF contributes to adverse remodeling, promoting AF in the long term. A trial with longer follow-up is necessary to determine if such inflammation-related remodeling is important.

In conclusion, the authors provide a valuable contribution to the literature regarding post-ablation AF and perhaps AF in general. The study provides strong evidence that inflammation is sufficient to induce ERAF after pulmonary vein isolation using radiofrequency catheter ablation and that administration of colchicine may provide a safe and effective strategy to reduce ERAF. Future studies will be important to determine the optimal dose and duration of colchicine as well as to determine if these early effects lead to lasting success.

Reprint requests and correspondence: Dr. Gregory M. Marcus, Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, University of California, San Francisco, 505 Parnassus Avenue, M1180-B, Box 0124, San Francisco, California 94143-0124. E-mail: marcusg@medicine.ucsf.edu.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:188–97.
2. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997;96:1180–4.
3. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886–91.
4. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108:3006–10.
5. Schnabel RB, Larson MG, Yamamoto JF, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation 2010;121:200–7.
6. Marcus GM, Whooley MA, Glidden DV, Pawlikowska L, Zaroff JG, Olgin JE. Interleukin-6 and atrial fibrillation in patients with coronary artery disease: data from the Heart and Soul Study. Am Heart J 2008;155:303–9.
7. Schnabel RB, Kerr KF, Lubitz SA, et al. Large-scale candidate gene analysis in whites and African Americans identifies IL6R polymorphism in relation to atrial fibrillation: the National Heart, Lung, and Blood Institute's Candidate Gene Association Resource (CARe) project. Circ Cardiovasc Genet 2011;4:557–64.
8. Marcus GM, Smith LM, Glidden DV, et al. Markers of inflammation before and after curative ablation of atrial flutter. Heart Rhythm 2008;5:215–21.
9. Marcus GM, Smith LM, Ordovas K, et al. Intracardiac and extracardiac markers of inflammation during atrial fibrillation. Heart Rhythm 2010;7:149–54.
10. Kallergis EM, Manios EG, Kanoupakis EM, et al. The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. Heart 2008;94:200–4.
11. Rotter M, Jais P, Vergnes MC, et al. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2006;47:1231–3.
12. Ryu K, Li L, Khrestian CM, et al. Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. Am J Physiol Heart Circ Physiol 2007;293:H1231–41.
13. Gaudino M, Andreotti F, Zamparelli R, et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation 2003;108 Suppl 1:II195–9.
14. Halonen J, Halonen P, Jarvinen O, et al. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. JAMA 2007;297:1562–7.
15. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation 2011;124:2290–5.
16. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012;14:528–606.
17. Oral H, Knight BP, Ozaydin M, et al. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. J Am Coll Cardiol 2002;40:100–4.
18. Koyama T, Sekiguchi Y, Tada H, et al. Comparison of characteristics and significance of immediate versus early versus no recurrence of atrial fibrillation after catheter ablation. Am J Cardiol 2009;103:1249–54.
19. Lee SH, Tai CT, Hsieh MH, et al. Predictors of early and late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. J Interv Card Electrophysiol 2004;10:221–6.
20. Bertaglia E, Stabile G, Senatore G, et al. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. Pacing Clin Electrophysiol 2005;28:366–71.
21. Koyama T, Tada H, Sekiguchi Y, et al. Prevention of atrial fibrillation recurrence with corticosteroids after radiofrequency catheter ablation: a randomized controlled trial. J Am Coll Cardiol 2010;56:1463–72.
22. McCabe JM, Smith LM, Tseng ZH, et al. Protracted CRP elevation after atrial fibrillation ablation. Pacing Clin Electrophysiol 2008;31:1146–51.
23. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol 2012;60:1790–6.

Key Words: ablation ■ atrial fibrillation ■ colchicine ■ inflammation ■ pulmonary vein isolation.