Journal of the American College of Cardiology Vol. 49, No. 15, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.009

EDITORIAL COMMENT

Atrial Fibrillation and C-Reactive Protein

Searching for Local Inflammation*

Antonio Hernández Madrid, MD,†
Concepción Moro, MD‡
Madrid, Spain

Atrial fibrillation (AF) is the most common arrhythmia. The clinical events leading to AF are multiple, including hemodynamic, electrophysiologic, ischemic, and metabolic abnormalities, acting in concert with genetic factors (1). Histological studies (2) have demonstrated the presence of inflammation in biopsies of patients with isolated AF. It is well-established that several cardiovascular diseases, such as coronary artery disease and hypertension, involve an inflammatory mechanism. However, the idea that AF also might be caused by an inflammatory mechanism is emerging. C-reactive protein (CRP) is an acute-phase reactant that traditionally has been used to detect acute injury, infection, and inflammation and to evaluate the activity of well-known inflammatory processes, which is why several studies have used CRP levels to analyze the level of inflammation in patients with AF (3–7).

See page 1642

Case-control studies have demonstrated a correlation between the levels of CRP and the result of electrical cardioversion (8). In a study from the group of Rotter et al. (9), patients that maintained sinus rhythm at 3 months after radiofrequency catheter ablation showed a significant decrease in CRP levels.

In this issue of the *Journal*, Liu et al. (10) have conducted a systematic review and meta-analysis to examine the association between baseline CRP and recurrence of AF after successful electrical cardioversion. Seven prospective studies with 420 patients were analyzed. Overall, baseline CRP levels were greater in patients who experience a recurrence of AF. The standardized mean difference in the CRP levels between the patients with, and those without AF was 0.35 U (95% confidence interval 0.01 to 0.69). Studies examining the association between CRP and AF have been performed but have not yet been systematically reviewed. Although the number of studies eventually included in the present meta-analysis is not many, the methods, presentation, and conclusion are appropriate. The article is timely and interesting. It provides a reliable demonstration that CRP is associated with AF and it opens the door for mechanistic studies and novel AF therapies targeting inflammation.

However, neither the present meta-analysis nor other studies allow a specific determination of causality (cause, consequence, or simple association). It could happen that the beginning of the AF was activated directly by the inflammation or that the inflammation promoted the beginning and the perpetuation of AF. Nevertheless, both mechanisms can be interrelated. The rapid atrial activation, caused by an automatic focus of pulmonary vein, can produce the beginning of apoptosis in the atrial myocytes. However, the presence of systemic inflammation with increased levels of CRP could help, in patients with abnormally automatic cells, to develop AF.

The findings must be interpreted carefully because they may include a slant of selection and factors of confusion, many still unknown. There are strong and significantly positive associations between CRP levels and several established risk factors and comorbidities that can be potential confounders, such as smoking, hypertension, body mass index, and diabetes (11). The data published recently by Ellinor et al. (12) suggested no difference in CRP levels among patients with lone AF compared with healthy controls patients without hypertension. These facts underscore the importance of evaluating CRP with the use of prospective data and new, unbiased approaches.

In addition, many studies are based on unique measures of CRP and, thus, they cannot reflect the inflammatory process throughout the course of time. Another limitation is the lack of data regarding the parameters of inflammation in the patients before the beginning of AF, as Liu et al. (10) report in the article, and also the methods of AF detection were different between the trials and therefore some asymptomatic episodes of AF may be overlooked.

Although CRP levels were associated with a high relative risk of AF recurrence, reading the data, it would add only little improvement to the prediction of risk in an individual person. The reason is that the distribution of CRP levels in patients with or without AF may overlap considerably, as can be seen from the data of the published studies. It would be of interest to develop a risk estimation equation, incorporating all of the established risk factors for AF and recurrences and know the added utility for each one. The risk stratification is important if it directs us toward the therapy and resources of greater benefit. However, we have to bear in mind that there may be considerable differences between "an inflammatory marker" a "risk marker" or a "risk

*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 †Arrhythmia Unit, Ramón y Cajal Hospital and ‡Department of Medicine, Alcalá University, Madrid, Spain.

JACC Vol. 49, No. 15, 2007
April 17, 2007:1649–50

factor." We have to define what exactly CRP is: if CRP is associated with AF by its participation in the causal pathway, then it can be a risk factor. It would be a risk marker if it is statistically associated with AF but need not be causally linked; it may be simply a response to other, established, risk factors (e.g., obesity, hypertension, dyslipidemia) and, thus, the therapeutic strategy also may be different. Another task would be to establish the link between inflammation in AF and the risk of thromboembolism through alterations of hemostasis, endothelium, fibrinolysis, and platelets.

The relative inefficiency of the present treatments stimulates us to dedicate resources to develop new strategies of treatment for the patients with AF. Drugs like statins as well as exercise and weight loss have demonstrated their effectiveness in reducing the levels of CRP (13). Similarly, drugs like inhibitors of the angiotensin-converting enzyme, antagonists of the receptors of angiotensin II, among others, have shown effectiveness in reducing the recurrence of AF (14). Part of this possible antiarrhythmic effect can be explained through its anti-inflammatory activity.

Nevertheless AF, at least in the great majority of cases, is a multifactorial and complex process, and the development of the substrate for AF requires probably a long period of time of evolution. The question remains: What is the meaning of an increased level of CRP in a long and complex process? The exact role placed by CRP in AF needs to be elucidated by further study. Furthermore, it would be interesting to know the local degree of inflammation at the atrial level or in the pulmonary veins, which could not be correctly assessed from a systemic point. If the inflammation hypothesis proves to be correct and the management of AF on the basis of the results of CRP eventually is possible, then analysis of cost effectiveness will be required, because AF is a major public health problem, due to its high incidence.

And meanwhile, waiting for more investigations in the field of CRP and AF, we must advise our patients all the measures that we know that diminish the levels of CRP and the incidence of AF: maintain normal weight or lose weight if overweight, reduce sodium intake and control hypertension, undertake at least 30 min of physical activity daily, and do not smoke.

Reprint requests and correspondence to: Dr. Antonio Hernández Madrid, Arrhythmia Unit, Ramon y Cajal Hospital, Ctra Colmenar Viejo, km 9.100, Madrid 28034, Spain. E-mail: antoniomadri@gmail.com.

REFERENCES

1. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108:3006–10.
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. Engelmann M, Hastrup Svendsen J. Inflammation in the genesis and perpetuation of atrial fibrillation. Eur Heart J 2005;26:2083–92.
4. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for health-care professionals from the Center for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.
5. Hernández Madrid A. Proteina C reactiva y fibrilación auricular. Un viejo marcador en busca de un nuevo sitio. Rev Esp Cardiol 2006; 59:94–8.
6. Boos C, Anderson R, Lip G. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006;27:136–49.
7. Wilson P. CDC/AHA workshop on markers of inflammation and cardiovascular disease. Circulation 2004;110:e568–71.
8. Zarauza J, Rodriguez MJ, Farinas C, et al. Relación entre niveles de proteína C reactiva y recurrencia precoz de la fibrilación auricular tras cardioversión eléctrica. Rev Esp Cardiol 2006;59:125–9.
9. Rotter M, Jäis P, Vergnes MC, Takahashi Y, Sanders P, Rostock T, Hocini M, et al. Decline in C-reactive protein after successful ablation of long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2006; 47:1231–3.
10. Liu T, Li G, Li L, Korantzopoulos P. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. J Am Coll Cardiol 2007;49:1642–8.
11. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363–9.
12. Ellinor PT, Low A, Patton KK, Shea MA, Macrae CA. C-reactive protein in lone atrial fibrillation. Am J Cardiol 2006;97:1346–50.
13. Patti G, Chello M, Candura D, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery. Circulation 2006;114:1455–61.
14. Lällier PL, Ducharmen A, Keller PF, et al. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J Am Coll Cardiol 2004;44:159–64.