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EDITORIAL

Is inflammation a risk factor for recurrent atrial fibrillation?

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This editorial refers to 'Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation' by K.P. Letsas *et al.*, on page 158

Atrial fibrillation (AF) poses an important problem in clinical practice. Restoration and maintenance of sinus rhythm (i.e. secondary prevention of AF) is difficult to achieve.[1] This has led to the fact that acceptance of AF in combination with adequate rate control has become a satisfactory alternative in the management of AF. However, the economic burden due to AF remains high, and morbidity and mortality in patients with AF are still substantial. It would thus seem logical to find methods to prevent AF to ever develop (i.e. primary prevention of AF), and consequently, patients at risk of developing AF must be identified to be able to implement preventative strategies.

Well-known predictors of AF include age, hypertension, valvular disease, myocardial infarction, diabetes mellitus, and congestive heart failure.[2] There are, however, patients with AF with no known underlying disease, classified as 'lone AF'. The question remains whether lone AF in fact is truly lone, and whether there are other risk factors involved in AF. Less well-known risk factors for AF have increasingly been coming to attention, including sleep apnoea, alcohol or other intoxication abuse, excessive physical activity, latent hypertension (i.e. diastolic dysfunction), genetic factors, obesity or body mass index (BMI), and inflammation.[3]

Inflammation has been linked to a variety of cardiovascular conditions, including coronary artery disease, diabetes mellitus, and hypertension, and the association between inflammation and AF is increasingly being substantiated.[4,5] The exact mechanism relating inflammation with AF is still unknown, and it is also unclear whether inflammation is an initiator or rather a consequence of AF. The existence of post-operative AF would suggest that inflammation precedes AF, as surgery causes a strong inflammatory process which involves complement activation and release of pro-inflammatory cytokines. Indeed, it has been reported that markers of inflammation post-operatively are associated with the development of AF. In non-operative AF, there is also increasing evidence that inflammation plays a prominent role in the aetiology and maintenance of AF. Histological studies have shown inflammatory infiltrates and fibrosis in the atria which were not found in controls, even in patients with lone AF in whom inflammation cannot be attributed to other cardiovascular conditions. One of the possible mechanisms causing inflammation and fibrosis in the atria involves the renin–angiotensin–aldosterone (RAAS) system, through angiotensin-II.[6] Increased expression of angiotensin-II, which has been observed in AF, causes increased production of pro-inflammatory cytokines, adhesion molecules, and selectins. On the other hand, inflammation itself stimulates angiotensin-II production.

Markers of inflammation include interleukin (IL)-6, tumour necrosis factor (TNF)-α, transforming growth factor (TGF)-ß, and IL-8.[4,5] Interleukin-6 is a primary cytokine that stimulates the synthesis of acute phase proteins such as C-reactive protein and fibrinogen. Various studies have demonstrated increased levels of IL-6 in both patients with persistent and paroxysmal AF when compared with controls. Increased levels of TNF-α and TGF-ß have also been observed in AF, but evidence has not been as strong. The acute phase protein C-reactive protein has more frequently been investigated using the vascular marker high-sensitivity (hs)-C-reactive protein. Levels of hs-C-reactive protein have been demonstrated to be higher in patients with AF compared with patients in sinus rhythm, and also to be higher in those with persistent AF compared with paroxysmal AF, both having higher levels than controls. Furthermore, hs-C-reactive protein has been shown to be correlated with a success rate of electrical cardioversions. Fibrinogen is less well established as a marker of inflammation in AF. There is also growing evidence that white blood cell (WBC) count, not difficult to assess, is elevated in patients with AF.

Although it seems exciting that these markers of inflammation are shown to be increased in AF, it is still unknown whether these relations are mere associations or whether they say something about the pathophysiology of AF, implying that they could be used to identify patients at risk for AF or to identify patients in whom therapy for AF will be successful. The paper by Letsas *et al.*[7]

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provides a valuable contribution. In this study, clinical parameters and markers of inflammation, including hs-C-reactive protein, WBC count, and fibrinogen, were determined in 72 consecutive patients with paroxysmal or persistent AF prior to pulmonary vein isolation (PVI). The authors aimed to investigate whether these clinical parameters and markers of inflammation could be related to success of PVI. After a period of 12.5 $\pm$ 5.7 months, 28 patients (39%) had a recurrence of AF. Patients with recurrence of AF more often had the classical risk factors of hypertension, increased left atrial diameter (LAD) and reduced left ventricular ejection fraction, the less well-known risk factor of increased BMI, and furthermore, they had an increased left ventricular end-diastolic diameter. In addition, patients with recurrence of AF less often used statins, and WBC count and hs-C-reactive protein levels (not fibrinogen) were elevated when compared with patients who remained in sinus rhythm. In univariate Cox proportional hazard regression analysis, all these variables except for statin use were significantly associated with recurrence of AF. After multivariate analysis, only hypertension, LAD, and WBC count remained independent predictors of recurrence of AF after PVI.

The present study had a retrospective design with a small number of patients, but it teaches us some interesting lessons and also raises new questions. First, hypertension remains to be the most important risk factor for AF and may also be an important predictor of failure of PVI, as demonstrated in the present analysis. However, no data were provided concerning the actual baseline blood pressures in these patients, and perhaps these patients could have been treated more adequately for their hypertension which may consequently have reduced the recurrence of AF after PVI. Second, the study shows that a simple diagnostic tool, i.e. WBC count, may be a possible predictor of success rate of PVI. WBC count, therefore, may potentially be a factor to be used for better selection of eligible candidates in order to improve the success of PVI and other rhythm control strategies. The other two markers of inflammation that were studied did not predict the success rate of PVI: fibrinogen was not associated with recurrence of AF, but until now fibrinogen has not been well established in association with AF. In addition, hs-C-reactive protein was not an independent predictor of recurrence of AF, in contrary to most previous studies. However, patients with AF recurrence actually did have significantly higher baseline hs-C-reactive protein levels in the present analysis. The fact that hs-C-reactive protein lost its predictive value in multivariate analysis may be a consequence of the small patient numbers. The third interesting observation was that patients with a recurrence of AF had a significantly higher BMI, although this was not confirmed by multivariate analysis, possibly again due to small patient numbers. Obesity has previously been described as a risk factor for AF.[3] Several mechanisms have been postulated to explain why obesity may lead to AF, including left atrial enlargement and chronic low-grade inflammation. In fact, Letsas *et al.* mention that in their study cohort, BMI was significantly correlated with increased LAD and increased inflammation, as expressed by elevated WBC count and hs-C-reactive protein levels.

One question that arises is that if indeed inflammation predisposes to AF, will patients with increased inflammatory markers benefit from therapeutic interventions targeted against processes of inflammation? Statins have been shown to have anti-inflammatory and anti-fibrotic effects and have been associated with a decrease in (recurrence of) AF, either post-operatively, after electrical cardioversion, and in paroxysmal AF, as demonstrated by various retrospective or small observational studies.[6,8] Other promising drugs in the prevention of AF are RAAS blockers, i.e. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor antagonists.[9] Furthermore, anti-inflammatory agents such as glucocorticoids, polyunsaturated fatty acids, and vitamin C could also prevent AF. In the present study, patients with sinus rhythm at follow-up more frequently used statins, but statin use did not predict the recurrence of AF in multivariate analysis. The use of RAAS blockers was not different in patients with and without a recurrence of AF. Perhaps the number of patients was too small to detect differences, but it is also conceivable that RAAS blockade and statin use is predominantly effective in patients with an increased inflammatory status. A totally different therapeutic option that seems to have been underestimated so far in the prevention of AF is exercise: moderate physical activity has been shown to decrease the incidence of AF, which may be explained by inducing and maintaining weight loss, improving glucose control, improving mental well-being, and lowering systemic inflammation, amongst other possible mechanisms.[10]

Due to the small number of patients and the retrospective nature of the present study, the results should be interpreted with caution. However, the study is of additional value with regard to our current knowledge of risk factors for AF and predictors of success of therapy for AF. Obviously, future research is desired to further elucidate which patients are at risk for AF, which patients benefit most from therapies against AF, and which therapies are most effective in the prevention of (recurrence of) AF.

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