early post-myocardial infarction phase; this is particularly true in the case of a marker such as troponin, which has a slow wash-out and a delayed peak. To eliminate the potential effect of high pre-procedural cardiac marker levels on the results of our study, we also performed a separate analysis after excluding the patients whose baseline marker levels were above the upper reference limit and obtained similar results. We would finally like to point out that increasing the troponin cut-off value to considerably above the 99th percentile of the distribution of a reference control group would probably have shown an association between cTnI elevation and a worse outcome; in this case, however, the post-procedural increase in cTnI would have been easily associated with a simultaneous increase in CK-MB, thus leaving the issue of the prognostic significance of elevated troponin I after percutaneous coronary intervention. For this reason, we performed a separate analysis of a reference control group who would probably have shown an association between cTnI elevation and worse outcome;4 in this study, we also performed a separate analysis of a reference control group who would probably have shown an association between cTnI elevation and worse outcome;4 in this case, however, the post-procedural increase in cTnI would have been easily associated with a simultaneous increase in CK-MB, thus leaving the issue of the prognostic significance of the minor post-procedural myocardial damage, revealed by an isolated cTnI elevation, unaddressed. Our data now suggest that isolated cTnI elevations do not influence long-term mortality.

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The emerging role of inflammation in atrial fibrillation and the potential of anti-inflammatory interventions

We read with considerable interest the article by Engelmann and Svendsen, providing a concise overview of the current knowledge about the association of inflammation with atrial fibrillation (AF). A continuously increasing number of investigations examine the role of inflammation in AF. Interestingly, two recent studies indicated that C-reactive protein relates to the left atrial size and AF duration before cardioversion, providing evidence of an association between inflammation and atrial structural remodelling. Moreover, it has been demonstrated that baseline C-reactive protein levels prior to cardioversion of persistent AF represent an independent predictor of sinus rhythm maintenance after cardioversion. Of note, in a recent small study, we examined the variation of inflammatory indexes during the first week after successful cardioversion of persistent AF. We found that fibrinogen levels increased significantly in patients who relapsed into AF, but remained stable in patients who remained in sinus rhythm. In the latter patients, C-reactive protein values tended to decrease post-cardioversion, but white blood cell (WBC) count was significantly lower on the seventh day when compared with baseline values. Thus, we concluded that the variation of inflammatory indexes post-cardioversion might have prognostic implications with regard to sinus rhythm maintenance.

There is substantial evidence that inflammation augments oxidative stress and vice versa, whereas such interaction has also been implicated in the pathophysiology of AF. were the first to show that an antioxidant intervention with vitamin C ameliorates atrial electrical remodelling in experimental animals and significantly reduces the incidence of post-operative AF in patients undergoing coronary bypass surgery. Very recently, we demonstrated that treatment with vitamin C reduces the early recurrence rates after electrical cardioversion of persistent AF and attenuates the associated low-level inflammation. A significant variance was found in the serial measurements of WBC counts and of fibrinogen levels in the two groups (vitamin C and control), whereas in the vitamin C group, C-reactive protein levels were lower on the seventh day post-cardioversion when compared with baseline. It can therefore be speculated that antioxidant interventions might have an impact against AF-associated inflammation.

As mentioned by Engelmann and Svendsen, accumulating evidence suggests that anti-inflammatory interventions might exert favourable effects on AF. It has been recently shown that administration of n-3 fatty acids in patients undergoing coronary bypass surgery substantially reduces the incidence of post-operative AF. Besides direct electrophysiological effects, it has been proposed that the anti-inflammatory effects of these natural compounds may favourably affect the atrial remodelling. Finally, we agree with the authors that angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers represent a promising approach. We have further proposed that aldosterone antagonists such as spironolactone might exert beneficial effects on AF, as aldosterone induces inflammation, oxidative stress, and fibrosis. Undoubtedly, more studies are needed to elucidate the exact role of inflammation and to clarify the impact of anti-inflammatory interventions in the setting of AF.

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The emerging role of inflammation in atrial fibrillation and the potential of anti-inflammatory interventions: reply

The letter by Dr Korantzopoulos and coworkers drew attention to some new studies which were not published when the review ‘Inflammation in the genesis and perpetuation of atrial fibrillation’ was written. Dr Korantzopoulos mentions four studies on markers of inflammation and AF, studies which are interesting and adds to the body of evidence in favour of an association between AF and inflammation, although it should be emphasized that the observed associations cannot be interpreted as indicating a role for C-reactive protein in the pathogenesis of AF. It is possible that elevated C-reactive protein levels are simply indicative of a generalized inflammatory state antedating AF. Moreover, the majority of studies are limited by the use of C-reactive protein as the only marker of inflammation. C-reactive protein is a nonspecific acute-phase protein primarily produced in the liver in response to most forms of tissue damage, infection, inflammation, and malignant neoplasia. Studies in patients with acute myocardial infarction have indicated that cytokines, i.e. interleukin-6 (IL-6) is produced locally in the heart, whereas C-reactive protein is produced mainly in the liver and taken up locally by phagocytosing white blood cells. Thus, measurement of cytokines (IL-6, TNF-α, etc.) may be more specific than C-reactive protein and may hold important information in AF patients. This is underlined in the study by Psychari et al., who measured C-reactive protein and IL-6. Both markers of inflammation were significantly elevated in AF patients and both were independent predictors of left atrial size. In addition, IL-6 levels were positively related to AF duration which may indicate a role for inflammation in the process of atrial remodelling. Interestingly, IL-6 levels were not independently related to the presence of AF, which is in contradiction to our findings in patients with persistent AF, where IL-6 was a significant independent predictor of AF. These differences may be due to patient selection, i.e. duration of AF, proportion of persistent and permanent AF, co-morbidities, etc. However, studies on multiple markers of inflammation in AF are scarce and more studies in larger populations should be encouraged.

If one accepts inflammation as being significant in the genesis and perpetuation of AF, a logical step is to clarify the role for anti-inflammatory interventions in the setting of AF. In this regard, we reviewed the impact of glucocorticoids, statins, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. The list of drugs with anti-inflammatory properties is long and Dr Korantzopoulos and coworkers draw attention to vitamin C, n-3 fatty acids, and aldosterone antagonists as potential and indeed exciting treatment strategies. However, these drugs are only the tip of the iceberg and the need for large randomized, placebo-controlled longitudinal studies should be emphasized. Such studies may herald a new area in the treatment of an arrhythmia, where the effects of pharmacological interventions so far have been disappointing.

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