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

The letter by Dr Korantzopoulos and coworkers draw 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 non-specific 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 phagocytic 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.

Conflict of interest: no conflicts of interest.

References

Six minute walk test

Dr Refsgaard and Dr Hager have commented on our article regarding the 'Six minute walk test' (6MWT), which we concluded that the 6MWT is a simple and inexpensive test, which is not robust enough to evaluate treatment effects in clinical trials. However, it may have a role in clinical practice as a routine part of evaluation (as many patients avoid symptoms by reducing their activity). A recently published trial on 1077 elderly heart failure patients showed that change in symptoms corresponds with change in 6MWT walking distance. The corridor walk test is limited by some very practical considerations such as the length of a quiet corridor where the patient's performance will not be affected by the staff. We agree that encouragement should be administered, not only for improving patients performance on 6MWT, but also to comfort the patient who might find it awkward to walk in silence for 6 min. Standardization of encouragement may be of value. The value of repeated baseline walk tests is disputed. In the statement issued by the American Thoracic Society (ATS) regarding execution of the 6MWT change in walk length from first to second walk varied from 0 to 17% in a variety of diseases including chronic heart failure, and the authors concluded that repeated baseline tests to be unnecessary in most settings. Indeed, 6MWT has proven to yield equally stable results regardless of repeated walk tests.

Ultimately, the 6MWT can be of use in the clinical setting and in evaluating treatment in selected heart failure patients, but in order to ascertain comparable and reliable results there is need for further standardization. We agree with Dr Hager that the statement issued by ATS can provide the framework for this. Regarding peak oxygen uptake as the 'golden standard' of heart failure assessment, we respectfully disagree with the author. Peak oxygen uptake has in our opinion, with the exception of patients eligible for heart transplant, not outperformed 6MWT, neither as a prognostic indicator nor in the evaluation of treatment and is more expensive to use and more cumbersome for the patient.

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References

1. Refsgaard J. 'This is a walking test, not a talking test': the six minute walking test in congestive heart failure. Eur Heart J 2005;26:749–750.

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Six minute walk test: reply

I want to thank the Editor for giving me the opportunity to answer the letter by Dr Swedberg et al. First of all I have to say that as an author it was difficult to discuss the article by Ingle et al., as it was not published when my Editorial was submitted to The European Heart Journal. However, in the article by Ingle et al., the six minute walk test (6MWT) distance is shown to be sensitive to changes in self-perceived symptoms of heart failure. Moreover, the 6MWT test shows satisfactory agreement when repeated 1 year later in 74 patients with congestive heart failure and with unchanged symptoms [intraclass correlation coefficient (ICC) = 0.80 (95% CI = 0.69–0.87)] performed in a 15 m long corridor. What the ICC would have been if the 6MWT had been repeated is unknown from this study, and whether an ICC of 0.80 is an argument for not repeating the test, can be discussed.

Dr Swedberg et al. also refer to the work by Demers et al. They assessed the 6MWT in 768 patients with heart failure (NYHA II–IV) at baseline, after 18 and 43 weeks in the RESOLVD study, and they found a high reproducibility from screening to baseline (baseline 3 weeks after screening) (ICC = 0.90), after 18 weeks (ICC = 0.88) and 43 weeks (ICC = 0.91). However, in their study Demers et al. did not compensate for changes in the patients clinical conditions over time, which is important as shown and discussed by Ingle et al.

I think that a variance in distance from 0 to 17% from the first to the second walk as noticed by Dr Swedberg et al. in their letter is important enough to attempt to minimize, for example by repeating the test as shown by Guyatt et al. And why not, when you have this simple, safe, and inexpensive method? I am therefore still convinced that if the 6MWT is performed in a strict standardized manner in an uncrowded area with a well-prepared instruction without encouragement of the patient during the test, then the test will give valid supplementary information on the treatment effect and the physical status of the patient. The test should be standardized in a strict manner, however, further standardization to make the test more reliable is most welcome.

Finally, I fully agree with Dr Swedberg et al., that the peak oxygen uptake is not a 'golden standard' of heart failure assessment, which I have never stated it is.

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