Inflammatory cytokines, life-threatening arrhythmias and premature mortality in chronic inflammatory arthritis: time to focus on

We read with much interest the paper by Ntari *et al*[1] and would like to highlight how the high prevalence of fatal arrhythmic events that they found in Tg197 mice might have relevant implications in the clinical setting.

A solid body of data supports the evidence that in patients with chronic inflammatory arthritis (CIA), particularly rheumatoid arthritis (RA), the risk of death is significantly higher than in the general population, and that such a premature mortality is largely related to fatal cardiovascular events.[2] In this regard, two population-based studies provided evidence that the prevalence of cardiac arrest (CA) and sudden cardiac death (SCD) is ~2 times higher in patients with RA than in those with no RA.[3 4] In addition, in patients with RA, the onset of an acute coronary syndrome is characterised by an increased short-term case fatality, as well as a higher risk to present with SCD when compared with subjects with no RA.[5] Altogether, these data strongly suggest that excess of mortality in patients with CIA is due, at least in part, to an increased incidence of life-threatening ventricular arrhythmias.[6]

In accordance with this view, accumulating evidence indicates that systemic inflammation may promote a pro-arrhythmic substrate in CIA, via multiple effects directly or indirectly increasing myocardial electric instability.[6] Indirect effects, including acceleration of coronary atherosclerosis and myocardial remodelling, are the most recognised. They may lead to an increased risk of ischaemic heart disease and chronic heart failure, which are conditions inherently burdened by a high arrhythmogenic potential.[6] In addition, increasing data demonstrate that inflammatory cytokines, particularly tumour necrosis factor alpha (TNFα), IL-6 and IL-1, directly affect cardiac electrophysiology by modulating the expression and function of specific ion channels in the cardiomyocyte resulting in a prolongation of ventricular action potential duration (APD).[6] Accordingly, QTc interval, reflecting APD on surface ECG and representing a well-recognised risk factor for life-threatening ventricular arrhythmias and SCD in the general population, is frequently prolonged in patients with RA,[6] where it strictly correlates with cytokine levels,[7 8] also independently predicting mortality.[9] In addition, a recent study on a large cohort of women with RA demonstrated that IL-6 levels strongly predicted cardiovascular events, particularly fatal cardiovascular events.[10]

Despite such evidence, prevalence and characteristics of ventricular arrhythmias in RA, and more in general in patients with CIA, are substantially unknown, as to date population studies investigating this subject are surprisingly lacking. Thus, no direct evidence is currently available that the higher risk of SCD/CA in these patients is due to an increased incidence of lethal arrhythmias. Similarly, although increasing data indicate that treatment with antirheumatic drugs decreases the incidence of all cardiovascular events in CIA, such specific outcomes are so far largely unexplored.[11]

In this view, the paper by Ntari *et al*[1] provides important clues in order to fill this gap of knowledge. In fact, the authors provided for the first time direct demonstration that in a murine model of cytokine (TNFα)-mediated chronic polyarthritis, premature mortality of unknown aetiology is markedly increased (~50%) along with a high incidence of fatal arrhythmic events. In addition, the evidence that both premature death and arrhythmias occur relatively early (10–13 weeks of age) after mice had established arthritis (ie, 8 weeks) supports the view that rapidly occurring electrophysiological changes in the heart may represent an important contributing mechanism by which cytokine overexpression increases arrhythmic risk in these animals.

These findings of the study should be emphasised. In fact, in our opinion, they warrant large population-based studies aimed at defining the actual prevalence of life-threatening arrhythmias and SCD in CIA, as well as clinical trials to evaluate the impact of antirheumatic therapies, particularly anticytokine biological agents, on arrhythmic events and premature mortality in these patients. This information, besides helping clarify the pathogenesis of the phenomenon, may open new treatment opportunities in CIA, possibly also including specific antiarrhythmic interventions to date largely overlooked in these patients.

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