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Review

# Arrhythmic risk in rheumatoid arthritis: the driving role of systemic inflammation

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ABSTRACT

When compared to the general population, patients with rheumatoid arthritis (RA) have an overall standard mortality ratio of approximately two, with more than 50% of premature deaths attributable to cardiovascular disease (CVD). Moreover, RA patients were twice as likely to experience sudden cardiac death (SCD) compared with non-RA subjects, as a putative consequence of an increased incidence of malignant arrhythmias. Accordingly, mounting data indicate that in patients affected with RA the risk of developing rhythm disturbances, particularly tachyarrhythmias, is high.

Although a number of papers reviewing the problem of cardiovascular involvement in RA are currently available, the main focus is on the mechanisms of accelerated atherosclerosis and related ischemic consequences in the clinical setting. On the contrary, only little consideration has been specifically given to the arrhythmic risk so far. In the light of this concern, in the present paper we reviewed the topic with the aim to put together the apparently fragmentary existing information, with particular attention to the putative role of chronic systemic inflammation characterizing the disease. In fact, although the underlying mechanisms accounting the arrhythmogenic substrate in RA are probably intricate, the leading role seems to be played by inflammatory activation, able to promote arrhythmias either indirectly, by accelerating the development of structural CVD, and directly by affecting cardiac electrophysiology.

In this view, lowering inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk and prevent life-threatening complications in these patients.



**Contents**



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## 1. Introduction

In the last years, a growing body of evidence indicates that patients with rheumatoid arthritis (RA) have an increased risk of death when compared to age- and sex-matched subjects in the general population, with an overall standard mortality ratio (SMR) of approximately two [1,2]. Such an excess of mortality is mainly due to cardiovascular disease (CVD), responsible for about a half of premature deaths observed in these patients [1,2]. The concomitant evidence that in RA the risk of sudden cardiac death (SCD) is two-times higher than it is in non-RA subjects [3], suggests that an increased incidence of malignant arrhythmias may explain, at least in part, the higher mortality observed in RA.

Although the mechanisms accounting for this arrhythmogenic substrate are not well known as yet, the fact that both ischemic heart disease (IHD) and heart failure (HF) are significantly more prevalent in RA patients than in the general population (about 1.5 to 2.0-fold) [4] largely contributing to RA mortality [5,6], suggests that the structural modifications characterizing these heart diseases may promote arrhythmic risk in RA. Indeed, it is well established that IHD and HF are highly associated with the development of life threatening arrhythmias and SCD in the general population [7,8]. Nevertheless, increasing evidence indicates that arrhythmogenicity in RA may be also the result of non-structural heart abnormalities of electrophysiological origin. These factors, by possibly amplifying the arrhythmic risk driven by IHD- and HF-associated structural damage, may help explain the finding that in RA the excess of deaths results not only from an increased CVD morbidity but also from a higher case fatality [2].

## 2. Systemic inflammation and heart involvement in RA

A large amount of data identify enduring systemic inflammation as the pathophysiological basis linking RA to accelerated heart disease development. In fact, although traditional cardiovascular (CV) risk factors are more prevalent in RA than in the general population, they do not adequately account for the increase in CV morbidity and mortality observed in these patients [1,2,4]. Conversely, inflammation markers associated with RA appear to contribute to the risk of CV death, probably by increasing the risk of IHD and HF. In fact, in these patients, both C-reactive protein (CRP) [9] and soluble tumor necrosis factor-α receptor (sTNFR) levels are strong and independent predictors of CV mortality [10]. Moreover, in RA patients IHD histological examination of coronary artery tissue shows a greater evidence of plaque inflammation and instability than in non-RA patients [11], and responsiveness to anti-TNFα biologic therapies markedly reduces the risk of myocardial infarction (about 70%) when compared to non-responsiveness [12]. Furthermore, the excess of risk of HF among RA patients, absolutely not attributable to a higher frequency or effect of traditional CV risk factors and IHD [13], strongly associates with systemic inflammation (elevated erythrocyte sedimentation rate) and disease activity markers (RF positivity, extra-articular manifestations) [14].

Although the specific pathophysiological link between systemic inflammation and CVD is not completely clear, the promotion of accelerated coronary atherosclerosis is considered the most important mechanism of the higher prevalence of IHD in RA. In fact, systemic release of pro-inflammatory cytokines (IL-1, IL-6, and TNFα) in RA synovial tissue could boost the immuno-inflammatory process underlying atherogenesis either directly affecting the cells of the plaque, or indirectly by stimulating a number of proatherogenic functions of liver, adipose tissue, skeletal muscle, and vascular endothelium (including insulin resistance, dyslipidemia, endothelial activation, and prothrombotic and antifibrinolytic effects) [15].

Less information is available on the pathogenesis of HF in RA patients. However, the evidence that the proportion of the HF risk attributable to IHD is lower than it is in non-RA patients [13] suggests the involvement of factors other than accelerated atherosclerosis. Indeed, a number of recent studies have demonstrated that in RA patients, also in the absence of HF, signs of subclinical myocardial damage (including increased left ventricular mass, diastolic dysfunction, myocardial inflammation/fibrosis at cardiac magnetic resonance, pro-BNP and troponin I level elevation) are highly frequent [16–20]. The fact that these markers strictly correlate with disease activity and inflammatory indicators [16–19], also tending to normalize under treatment with biologic drugs in parallel with disease control [21–23], suggests that systemic inflammation mediates a chronic myocardial injury possibly resulting in HF in the long-term.

Recently, increasing data indicate that inflammatory burden may play a key role in increasing arrhythmic risk in RA. Keeping in mind the above considerations, the first hypothesis arising is that this harmful link is mainly indirect, being related to the ability of systemic inflammation in favouring the development of structural heart disease. However, the evidence from several basic and clinical studies that inflammatory mediators (in particular pro-inflammatory cytokines) may directly and indirectly induce significant changes in cardiomyocyte electrophysiology as the result of specific effects exerted at the molecular level, suggests the existence of a more complex interplay connecting inflammation and arrhythmias in RA.

## 3. Rheumatoid arthritis and arrhythmic risk

Despite the huge amount of studies investigating CVD morbidity and mortality in RA, the attention has been mainly focused on the mechanisms of accelerated atherosclerosis and related ischemic consequences in the clinical setting. On the contrary, although the evidence that the hazard of SCD in RA is high dates almost 10 years ago [2], relatively few and fragmentary information is currently available specifically regarding arrhythmic risk in these patients.

The present paper is aimed at reviewing this latter topic, particularly focusing on the putative role of chronic systemic inflammation characterizing the disease. Literature data mostly deal with the risk of ventricular arrhythmias and SCD, and atrial fibrillation.

### 3.1. Ventricular arrhythmias and sudden cardiac death

#### 3.1.1. Clinical data

In the general population, SCD accounts for about half of the cardiovascular deaths and, in the large majority of cases, it is caused by acute ventricular tachyarrhythmias. In fact, ventricular tachycardia degenerating first to ventricular fibrillation and later to asystole appears to be the most common pathophysiological cascade involved [24]. Bradyarrhythmias and pulseless electrical activity occur less frequently, and generally in hearts with a more advanced structural heart disease [7].

In RA patients, the risk of SCD is significantly increased with respect to the general population. This evidence came out from a large population-based cohort study using data resources of the Rochester Epidemiology Project, in which 603 RA patients and 603 non-RA subjects were followed for a mean period of about 15 years. RA patients were twice as likely to experience SCD (hazard ratio 1.94, 95% CI 1.06–3.55, after multivariable-adjustment for age, sex, smoking status, body mass index, and the presence or absence of diabetes mellitus and hypertension) compared with non-RA subjects. Accordingly, the estimated cumulative incidence of SCD at 30 years of follow-up, adjusted for competing risk death by other cause, was 6.7% in the RA cohort versus 3.8% in the non-RA cohort [2]. These findings are impressive, particularly if we consider that a comparable two-fold increase in SCD risk is observed in a well recognized cardiovascular risk factor such as diabetes mellitus [25].

In face of such evidence, the exact prevalence and severity of ventricular arrhythmias in RA are not known, as only few and rather dated studies are currently available, also involving relatively small groups of patients. In fact, just three 24-hour ECG monitoring studies analyzed



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