

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis

This is a pre print version of the following article:

Original:

Lazzerini, P.E., Capecchi, P.L., LAGHI PASINI, F. (2017). Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. EUROPEAN HEART JOURNAL, 38(22), 1717-1727b [10.1093/eurheartj/ehw208].

Availability:

This version is available <http://hdl.handle.net/11365/1000017> since 2019-04-29T16:52:14Z

Published:

DOI: <http://doi.org/10.1093/eurheartj/ehw208>

Terms of use:

Open Access

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. Works made available under a Creative Commons license can be used according to the terms and conditions of said license.

For all terms of use and more information see the publisher's website.

(Article begins on next page)

European Heart Journal

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis.

--Manuscript Draft--

Manuscript Number:	
Full Title:	Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis.
Article Type:	Clinical review (Invited)
Keywords:	Rheumatoid arthritis; arrhythmic risk; sudden cardiac death; ventricular arrhythmias; atrial fibrillation; systemic inflammation; cytokines.
Corresponding Author:	Pietro Enea Lazzerini, MD University of Siena Siena, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Siena
Corresponding Author's Secondary Institution:	
First Author:	Pietro Enea Lazzerini, MD
First Author Secondary Information:	
Order of Authors:	Pietro Enea Lazzerini, MD
	Pier Leopoldo Capecci, MD
	Franco Laghi-Pasini, MD
Order of Authors Secondary Information:	
Abstract:	<p>Rheumatoid arthritis (RA) is a chronic immuno-mediated disease primarily affecting the joints, characterized by persistent high-grade systemic inflammation. Cardiovascular morbidity and mortality are significantly increased in RA, with more than 50% of premature deaths attributable to cardiovascular disease (CVD). In particular, RA patients were twice as likely to experience sudden cardiac death compared with non-RA subjects, pointing to an increased propensity to develop malignant ventricular arrhythmias. Indeed, ventricular repolarization (QT interval) abnormalities and cardiovascular autonomic nervous system dysfunction, representing two well-recognized risk factors for life-threatening ventricular arrhythmias in the general population, are commonly observed in RA. Moreover, large population-based studies demonstrated that the prevalence of atrial fibrillation is significantly higher in RA subjects than in the general population, thus indicating that these patients are characterized by an abnormal diffuse myocardial electrical instability. Although the underlying mechanisms accounting for the pro-arrhythmogenic substrate in RA are probably intricate, the leading role seems to be played by chronic systemic 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 the inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk in these patients. Intriguingly, these considerations could be more generally applicable to all the diseases characterized by chronic systemic inflammation, and could help elucidate the link between low-grade chronic inflammation and arrhythmic risk in the general population.</p>
Suggested Reviewers:	<p>Peter Libby, MD plibby@rics.bwh.harvard.edu Prof. Libby provided fundamental contributions in clarifying the link between systemic inflammation and cardiovascular risk, particularly in patients with rheumatoid arthritis</p>
	<p>Paul M Ridker, MD pridker@partners.org Prof. Ridker provided fundamental contributions in clarifying the link between systemic</p>

	inflammation and cardiovascular disease, including the risk of sudden death and atrial fibrillation
Opposed Reviewers:	
Additional Information:	
Question	Response
Did you cite ESC guidelines where appropriate?	yes
Some manuscripts may not be able to be published in the European Heart Journal. In such cases, a paper might be considered suitable for another journal from the ESC family. If the editors think your paper may be appropriate for another ESC journal, would you like it to be transferred to that journal's editors for consideration?	No, I do not want my submission to be considered for transfer
As Corresponding Author, I take full responsibility for all information declared in this notification.	Yes
As Corresponding Author, I agree to be the principal correspondent with the Editorial Office, review the edited manuscript and proof, and make decisions about releasing manuscript information to the media, federal agencies, etc.	Yes
All persons who have made substantial contributions to the manuscript (e.g. data acquisition, analysis, or writing / editing assistance), but who do not fulfill authorship criteria, are named with their specific contributions in the Acknowledgements Section of the manuscript.	Yes
All persons named in the Acknowledgements Section have provided the Corresponding Author with written permission to be named in the manuscript.	Yes
If an Acknowledgements Section is not included in the paper then no other persons have made substantial contributions to this manuscript.	Yes
Please enter the names of the authors who <i>Conceived and designed the research</i>	Pietro Enea Lazzerini, Pier Leopoldo Capecchi, Franco Laghi-Pasini
Please enter the names of the authors who <i>Performed statistical analysis</i>	N/A
Please enter the names of the authors who <i>Acquired the data</i>	Pietro Enea Lazzerini, Pier Leopoldo Capecchi, Franco Laghi-Pasini
Please enter the names of the authors who <i>Drafted the manuscript</i>	Pietro Enea Lazzerini, Pier Leopoldo Capecchi, Franco Laghi-Pasini
Please enter the names of the authors	Pietro Enea Lazzerini, Pier Leopoldo Capecchi, Franco Laghi-Pasini

who <i>Made critical revision of the manuscript for key intellectual content</i>	
Please enter the names of the authors who did anything else on the manuscript other than what we have listed:	None
This manuscript represents valid and substantiated work.	Yes
If asked, I will provide or fully cooperate in obtaining and providing the original data on which the manuscript is based so the editors or their designates can examine it.	Yes
The paper under question is being submitted by an ESC Working Group.	No
Each person listed as co-author has been entered as contributing to at least one part of the manuscript	Yes

Dear Professor Lusher,

here you will find enclosed the *Clinical Review article* entitled: “**Inflammation and arrhythmic risk: lessons from rheumatoid arthritis**”, submitted for publication in *European Heart Journal* following your kind invitation.

I state that: 1) the paper is not under consideration elsewhere; 2) each individual named as an author meets the Uniform Requirements for Manuscripts Submitted to Biomedical Journals criteria for authorship; 3) all authors have read and approved the manuscript; and 4) we have no financial relationship with industry to disclosure.

Pietro Enea LAZZERINI, MD

Department of Medical Sciences, Surgery and Neurosciences

University of Siena

Siena, Italy

Running head: Arrhythmic risk in rheumatoid arthritis.

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis.

Pietro Enea LAZZERINI*, MD; Pier Leopoldo CAPECCHI*, MD; Franco LAGHI-PASINI*, MD.

Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy*; Stroke Unit, University Hospital of Siena, Siena, Italy.

Address for correspondence:

Pietro Enea LAZZERINI, MD

Department of Medical Sciences, Surgery and Neurosciences

University of Siena

Policlinico “Le Scotte”, Viale Bracci, Siena, Italy

Tel. +39-0577-5585743; Fax +39-0577-233318

e-mail: lazzerini7@unisi.it

Key words: Rheumatoid arthritis; arrhythmic risk; sudden cardiac death; ventricular arrhythmias; atrial fibrillation; systemic inflammation; cytokines.

Conflict of Interest. None declared.

ABSTRACT

Rheumatoid arthritis (RA) is a chronic immuno-mediated disease primarily affecting the joints, characterized by persistent high-grade systemic inflammation. Cardiovascular morbidity and mortality are significantly increased in RA, with more than 50% of premature deaths attributable to cardiovascular disease (CVD). In particular, RA patients were twice as likely to experience sudden cardiac death compared with non-RA subjects, pointing to an increased propensity to develop malignant ventricular arrhythmias. Indeed, ventricular repolarization (QT interval) abnormalities and cardiovascular autonomic nervous system dysfunction, representing two well-recognized risk factors for life-threatening ventricular arrhythmias in the general population, are commonly observed in RA. Moreover, large population-based studies demonstrated that the prevalence of atrial fibrillation is significantly higher in RA subjects than in the general population, thus indicating that these patients are characterized by an abnormal diffuse myocardial electrical instability. Although the underlying mechanisms accounting for the pro-arrhythmogenic substrate in RA are probably intricate, the leading role seems to be played by chronic systemic 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 the inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk in these patients. Intriguingly, these considerations could be more generally applicable to all the diseases characterized by chronic systemic inflammation, and could help elucidate the link between low-grade chronic inflammation and arrhythmic risk in the general population.

Authors' contributions

P.E.L. , P.L.C., and F.L.P. drafted the manuscript.

P.E.L. , P.L.C., and F.L.P. made critical revision of the manuscript for key intellectual content.

1.Introduction

Rheumatoid arthritis(RA) is a chronic immuno-mediated disease targeting the synovial joints also leading to extra-articular manifestations, characterized by persistent high-grade systemic inflammation. RA affects 0.5-1% of adults in developed countries (global prevalence ~0.25%) and causes significant disability and pre-term mortality, thereby representing a relevant social problem worldwide[1,2].

In this scenario, cardiovascular disease(CVD) plays a prominent role. In fact, cardiovascular morbidity is significantly increased in RA, with ischemic heart disease(IHD) and congestive heart failure(CHF) presenting with a 1.5 to 2.0-times higher prevalence than in the general population[3].

Large evidence indicates that enduring systemic inflammation plays a key role in accelerating heart disease development in these patients[4]. From a pathophysiological point of view, systemic release of pro-inflammatory cytokines (IL-1,IL-6,TNF α) from RA synovial tissue could boost the immuno-inflammatory process underlying atherogenesis either directly,affecting the cells of the plaque, and indirectly,promoting insulin resistance, dyslipidemia,endothelial activation, and prothrombotic/antifibrinolytic effects[5]. Although accelerated progression and higher instability of coronary atherosclerotic lesions may *per se* explain the increased incidence of acute coronary events and left ventricular dysfunction in RA, growing evidence indicates that inflammatory cytokines may also directly mediate a chronic myocardial injury[6,7] possibly further contributing to CHF development.

Cardiovascular disease heavily impacts RA patient survival, being the main driver of the excess of mortality characterizing the disease. Indeed, RA patients have an approximately two-times higher risk of death when compared to the general population, mainly as a result of cardiovascular events accounting for ~50% of premature deaths observed[8]. Notably, exaggerated cardiovascular mortality in RA depends on increased cardiovascular morbidity, but also on higher cardiovascular case fatality, particularly after an acute coronary syndrome(ACS)[9]. This evidence, together with the demonstration that RA patients have a greater risk of sudden cardiac death(SCD) compared to

1 non-RA subjects[10], suggests that an increased incidence of malignant ventricular arrhythmias
2 may explain,at least in part, the higher cardiovascular mortality observed. Moreover, growing recent
3 data from large population-based studies indicate that also the incidence of atrial fibrillation(AF) is
4 significantly increased in RA than in the general population[11], thus further supporting the view
5 that in these patients an abnormal electrical instability is diffusely present throughout the
6 myocardium.
7

8
9 Precise mechanisms accounting for this arrhythmogenic substrate are not completely known. The
10 fact that both IHD and CHF are significantly more prevalent in RA patients than in the general
11 population largely contributing to RA mortality[3] firstly suggests the hypothesis that the structural
12 heart modifications characterizing these conditions may promote arrhythmic risk in RA. Indeed, it
13 is recognized that IHD and CHF are highly associated with life-threatening ventricular
14 arrhythmias,SCD and AF in the general population[12-14].
15

16 Nevertheless, increasing evidence indicates that arrhythmogenicity in RA may be also the result of
17 inflammation-driven non-structural heart abnormalities of electrophysiological origin, possibly
18 amplifying the arrhythmic risk driven by IHD- and CHF-associated structural damage through
19 synergistic unfavourable effects on the myocardial tissue[15].
20

21 This article will review current research on arrhythmic risk in RA in the light of its
22 pathophysiologic relationship with chronic inflammatory activation, and with a particular attention
23 to the potential role of inflammatory cytokines in increasing directly or indirectly myocardial
24 electrical instability of these patients.
25

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 **2.Ventricular arrhythmic risk in rheumatoid arthritis**

52 53 ***2.1.Epidemiology and clinical evidence***

54
55 In the general population the acute onset of malignant ventricular tachyarrhythmias represents the
56 main underlying mechanism leading to SCD, accounting for ~50% of the cardiovascular deaths. In
57 particular,ventricular tachycardia degenerating first to ventricular fibrillation and later to asystole is
58
59
60
61
62
63
64
65

the commonest pathophysiological cascade involved. Bradyarrhythmias and pulseless electrical activity occur less frequently, generally in hearts with a more advanced structural disease[16].

In RA patients, the incidence of SCD is ~two-fold higher with respect to the general population, a risk increase as high as that observed in the well-recognized cardiovascular risk factor diabetes mellitus[17]. A large population-based study involving over 600 RA patients followed for a mean period of 15 years, demonstrated that RA patients were twice as likely to experience SCD compared to non-RA subjects[10]. Notably, such a doubling of the risk persisted after supplemental adjustment for history of myocardial infarction, hospitalized or unrecognized, and revascularization procedures[10], thus implying that the finding is not the mere result of the increased incidence of ACS observed in these patients[18,19]. Accordingly, several studies demonstrated that short-term case fatality after a cardiovascular event is higher in RA than in non-RA subjects, particularly following an ACS[9,20,21] which more frequently presented in these patients with collapse[22] or SCD[9](Table 1). Moreover, a recent study on a large cohort of RA women demonstrated that inflammation, as assessed by IL-6 circulating levels, more strongly correlated with fatal than nonfatal CV events[23]. These findings may be putatively explained by the fact that in RA patients ACSs more likely result in large area of myocardial infarction(MI), as a possible consequence of a more extensive inflammation-driven thrombus formation and/or lower rates of post-ACS treatment with acute revascularization and/or cardioprotective drugs[20,21]. However, a number of studies did not confirm that ACS in RA are undertreated[9,22,24,25]. Moreover, the evidence that RA patients did not show a higher risk of CHF at 30-days after a MI[20] suggests that the higher mortality observed is not, or not exclusively, related to a more extensive myocardial damage, as also expected in patients receiving an inadequate acute treatment. Furthermore, in a large nationwide population-based study, it was recently found that the higher short-term ACS-associated mortality observed among RA than control patients was attenuated, but remained statistically significant increased, following adjustment for ACS type(STEMI/NSTEMI) thus indicating that higher case fatality can only partly be explained by increased event severity[9]. Considered all the above data as

1 a whole,a conceivable explanatory mechanism is that following a MI, RA patients have a higher
2 propensity to fatal arrhythmias, possibly as a result of synergistic effects of systemic inflammation
3 and ischemia in promoting myocardial electrical instability. Accordingly,many studies
4 demonstrated that two well-recognized risk factors for life-threatening ventricular arrhythmias in
5 the general population, such as ventricular repolarization (QT-interval) abnormalities and
6 cardiovascular autonomic nervous system (ANS) dysfunction[16], are common in RA, thus
7 providing a possible mechanistic basis for the higher incidence of SCD in these patients.
8

9 A growing number of studies investigated QT-interval parameters(i.e. heart rate-corrected QT-
10 interval,QTc, and QT-interval dispersion,QTd) in RA, consistently demonstrating that both QTc
11 and QTd variables are significantly increased in these patients compared to healthy controls,and
12 associated with disease severity and inflammatory markers[26-35](Table 2). Moreover, direct
13 evidence was provided of a link between QT-interval abnormalities and the risk of ventricular
14 arrhythmias or death in these patients[26,32,34]. In a retrospective population-based study
15 involving 518 RA patients(vs 499 non-RA subjects), QTc prolongation was independently
16 associated with all-cause mortality (HR:2.99, 95%CI 1.93–4.65)[32]. Accordingly, another recent
17 prospective study carried out on 357 RA patients, demonstrated that a prolonged QTc is a strong
18 predictor of death as a 50-ms QTc-increase was associated with a doubling of the risk for all-cause
19 mortality(HR:2.17, 95%CI 1.21–3.90). The evidence that QTc prolongation independently
20 correlated with CRP levels, and that the significance of the association between QTc and all-cause
21 mortality was lost after CRP-adjustment, robustly supported the hypothesis that systemic
22 inflammation plays a key pathogenic role in the phenomenon[34]. As a further confirmation, Adlan
23 et al.[35] found that in RA patients circulating levels of inflammatory cytokines (TNF α ,IL-1 β ,IL-6,
24 IL-10) correlated with QTc duration. Moreover, in RA anti-cytokine therapy with the anti-IL-6-
25 receptor antibody tocilizumab was associated with a rapid and significant QTc shortening, which
26 correlated with the decrease in CRP, and, more strongly, circulating TNF α levels[36](Table 2).
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Cardiovascular ANS dysfunction is highly prevalent in RA, occurring in ~60% of the patients. The main pattern observed is impairment of cardiovascular reflexes and reduced heart rate variability(HRV), indicative of reduced parasympathetic activity and elevated sympathetic activity[37]. Compared to traditional tests, HRV analysis is a non-invasive and reproducible method to detect early cardiovascular autonomic impairment[38]. Moreover, reduced HRV is associated with a high risk of ventricular arrhythmias/SCD in the general population[39]. In the majority of studies focused on RA patients, a significant depression of time- and/or frequency-domain HRV measures when compared to controls was found, suggestive of an increased sympathetic drive of the heart rate[27,40-50](Table 2). These changes seem to be due to enduring inflammatory activation characterizing the diseases. Indeed, HRV impairment significantly correlates with disease duration,disease activity, and inflammation markers[27,41,42,47](Table 2), and treatment with the TNF α -antagonist infliximab produced rapid and evident HRV changes,i.e. decrease in the sympathetic tone with a shift towards a relative vagal prevalence[51].

2.2.Pathogenic mechanisms and pathophysiology

An increased predisposition to develop lethal ventricular arrhythmias is the most likely mechanism accounting for the higher SCD risk in RA. In particular,the increased prevalence of QT-interval and HRV abnormalities observed in these patients strongly suggests that malignant arrhythmias driven by changes in ventricular repolarisation and/or sympathetic overactivity may have a crucial role. In fact,it is well established that the more QTc prolongs, the higher is the risk that abnormal premature depolarisations occur prior to completion of repolarisation(early afterdepolarizations,EADs). EADs can generate malignant ventricular arrhythmias such as torsades de pointes(TdP), which can rapidly progress to ventricular fibrillation and SCD[52]. Notably,a concomitant increased transmural dispersion of repolarisation, a phenomenon accentuated by autonomic influences, is postulated to be a necessary condition for intra-mural reentry circuits underlying TdP[53]. While no studies specifically evaluated TdP prevalence in RA, several case reports are described[54-59]. Moreover,

1 in recent case series/cohorts of TdP patients, an underlying RA was consistently found in 5-8% of
2 the subjects[60-62], an incidence 5-15 times higher than expected in the general population[1].
3

4 Although the pathogenic mechanisms of the pro-arrhythmic substrate in RA are not fully
5 clarified,mounting evidence suggests that systemic inflammation may have a driving role via
6 multiple effects, directly or indirectly favouring arrhythmogenesis[15,63].
7

8 First,by accelerating coronary atherosclerosis[5] or inducing direct myocardial injury and
9 remodelling[6,7], chronic inflammatory activation may lead to an increased risk of IHD and CHF,
10 inherently burdened by a high arrhythmogenic potential as a result of a number of structural
11 (apoptosis, hypertrophy,fibrosis) and functional (biochemical and autonomic changes,ion channel
12 remodelling) myocardial abnormalities[12,13].
13

14 Nevertheless, several clinical and pathophysiological data suggest that systemic inflammation may
15 also be *per se* arrhythmogenic in RA, regardless of any development of structural heart disease.
16 Indeed,in the majority of the studies demonstrating HRV and/or QT-interval abnormalities in RA
17 patients, neither IHD nor CHF were present, as these conditions represented a major exclusion
18 criteria[40-42,44,45,47,51]. Moreover, in the prospective study of Panoulas et al.[32] demonstrating
19 QTc prolongation as an independent predictor for all-cause mortality in RA patients, the authors did
20 not find any association between QTc and the use of common cardiovascular medications, the
21 presence of CVD at baseline, or ECG abnormalities suggestive of myocardial ischemia or left
22 ventricular hypertrophy. Furthermore,as cited above, tocilizumab was able to normalized CRP
23 levels as well as QTc in RA patients within 3 months, a period of time as short as to rule out any
24 structural heart modification, thus suggesting functional changes due to the control of systemic
25 inflammation[36].
26

27 Pathophysiological considerations provide a strong mechanistic support to this view. In fact,many
28 basic studies demonstrated significant direct effects of inflammatory cytokines on cardiac
29 electrophysiology, particularly changes in the expression and function of potassium and calcium
30 channels resulting in a prolonging effect on cardiomyocyte action potential duration(APD)(Figure
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1) (Table 3). Perfused hearts from transgenic mice overexpressing TNF α exhibited a prolonged APD and re-entrant ventricular arrhythmias[64]; ventricular myocytes isolated from these animals revealed a robust decrease of the transient outward current(I_{to}), and a reduced expression of the corresponding potassium-channel protein[65]. Several authors reported consistent findings when rat ventricular myocytes were cultured with TNF α [66-68]. Moreover, Wang et al.[69] showed that TNF α down-regulates in-vitro the rapid component of the delayed rectifier potassium current(I_{Kr}) by impairing the hERG potassium-channel function. Moreover, experiments on pig and mouse ventricular cells proved that also IL-6 and IL-1 prolong APD, by enhancing L-type calcium current(I_{CaL})[70,71]. The previously reported evidence that in RA patients inflammatory cytokine levels correlated with QTc duration[35,36] strongly indicates that also *in-vivo* these mechanisms are of crucial importance.

Systemic inflammation could also produce pro-arrhythmogenic changes in RA in an indirect manner, by inducing ANS dysfunction. Indeed, many basic and clinical studies demonstrated that inflammatory cytokines increase the sympathetic outflow by targeting the autonomic centres of the brain, in turn inhibiting cytokine production and immuno-inflammatory activation by stimulating the β 2-adrenoceptors in circulating lympho-monocytes. Such a self-controlling loop is a crucial component of the so-called *inflammatory reflex*, and in this context sympathetic activation putatively represents an adaptive response to damping excessive immuno-inflammatory activation[72,73]. However, sympathetic system activation affects not only the immune system, but also all the body districts under its control, including the heart, thus possibly favouring the onset of arrhythmias either directly[53], and indirectly by prolonging QT interval parameters. Indeed, cardiomyocyte β 1-adrenergic receptor activation profoundly and complexly affects calcium and potassium conductance with a net effect of APD prolongation[74].

Keeping in mind all these data, it is highly conceivable that systemic inflammation-driven neuro-humoral and molecular changes of myocardial electrophysiology create in RA a vulnerable substrate that is exquisitely sensitive to arrhythmia triggers (Figure 2). Specifically, these

1 considerations may contribute to explain the epidemiological observation that in these patients not
2 only CVD morbidity, but also cardiovascular case fatality is increased, particularly following an
3 ACS[9,19-21], also correlating with the systemic inflammation degree as assessed by circulating
4 cytokine levels[23]. Recent data from animal models strongly support this view, by providing
5 evidence that inflammation can markedly enhance the effects of acute ischemia in increasing
6 ventricular electrical instability. In fact, in a murine model of MI the induction of a state of systemic
7 inflammation via lipopolysaccharide(LPS) injection was associated with APD prolongation, and
8 higher reentrant ventricular arrhythmia propensity than in non LPS-injected animals[75]. Moreover,
9 in another canine model of MI, TNF-alpha-antagonism with etanercept significantly reduces
10 malignant ventricular tachyarrhythmias, and beta-adrenergic receptor activation in the myocardial
11 tissue[76].

30 **3. Atrial arrhythmic risk in rheumatoid arthritis**

31 **3.1. Epidemiology and clinical evidence**

32 Not only ventricular but also atrial arrhythmic risk seems to be increased in RA, with most evidence
33 regarding atrial fibrillation.

34 Atrial fibrillation(AF) is the most prevalent cardiac arrhythmias in the general population. It is a
35 main cause of stroke and strongly associates with CVD, particularly CHF and IHD[77]. A growing
36 body of basic and clinical data strongly suggest that inflammation plays a prominent role in AF
37 development and maintenance, including both post-operative, and non-operative forms. Indeed,
38 large population-based studies demonstrated the existence of a strict link between inflammatory
39 markers, particularly CRP and IL-6 levels, and AF, in both patients with cardiac disease and
40 apparently healthy subjects[78]. Keeping this in mind, and in consideration of the fact that RA is a
41 chronic inflammatory condition burdened by an increased risk of IHD, CHF and stroke[3],
42 increasing interest is recently arising on the potential association between RA and AF.

At the moment, this subject has been evaluated by three large retrospective cohort studies involving ~40,000 RA patients and over 4 million non-RA controls (Table 4). Despite some degree of discrepancy, globally considered the results indicate that the risk of incident AF in RA patients is significantly increased when compared to the general population[11].

More in detail, in a Danish nationwide register-based study, Lindhardsen et al.[79] found a ~40% higher overall incidence of this arrhythmia in RA than in non-RA subjects, a value in part reduced but still significantly increased, when cardiovascular drug use and comorbidity were updated during follow-up.

A similar 40% higher risk was reported in a following study based on data from a large US insurance plan. However, in this study the risk of AF was no longer increased in RA compared to non-RA patients when data were fully adjusted for potential confounders of AF, such as demographic factors, comorbidities (including CVD and CHF), medications, and healthcare utilisation[80].

In the third study, performed on a population-based inception cohort of Minnesota residents, the authors found a higher cumulative incidence of AF during follow-up among RA than non-RA subjects, and the difference persisted significantly even after adjustment for AF risk factors. Moreover, this study demonstrated that markers of severe disease, including persistently elevated erythrocyte sedimentation rate, were the strongest risk factors for developing AF thus providing evidence that in RA a strict link exists between arrhythmia occurrence and the degree of systemic inflammation[81].

Very recently, Ungprasert et al.[11] performed a meta-analysis of the pooled data from these three studies demonstrating a ~30% statistically significant increased risk of AF in RA patients compared with non-RA participants (pooling risk ratio 1.29, 95% CI 1.05-1.59) (Figure 3).

3.2. Pathogenic mechanisms and pathophysiology

Available data suggest that the increased risk of AF observed in RA is the combined result of the increased prevalence of structural CVD, and the direct impact of inflammatory mechanisms on the

atrial electrophysiology. Indeed, since both these phenomena represent, directly or indirectly, a consequence of the RA-associated chronic inflammatory activation, it is likely that also for AF, systemic inflammation does represent the main driver of the higher arrhythmic risk.

It is well demonstrated that atrial fibrosis, electro-mechanical remodelling, and myocyte stretch occurring in both CHF and IHD, favour the development as well as the maintenance of AF by creating a susceptible substrate leading to AF in the presence of triggering/modulating factors, including acute ischemia, autonomic changes, and inflammatory activation[82,83]. Thus, the higher prevalence of CHF and IHD in RA may *per-se* explain the increased AF risk observed in these patients[3].

Indeed, in all the above reported studies, the relative-risk of AF reduced when adjusted for comorbidities and medication use, including CHF, IHD and related treatments[79-81]. Notably, in the Danish study[79], the incidence rate-ratio reduction observed after such an adjustment (from 1.41 to 1.24) was primarily driven by the inclusion of loop diuretics (IRR 1.25, 95%CI 1.16-1.34), which are routinely used for CHF.

However, although adjustment for cardiovascular confounders tended in part to reduce the hazard ratio for AF, a significantly higher risk persisted in RA patients in 2 out of 3 studies[79,81]. These findings, together with the evidence provided by Bacani et al.[81] that inflammatory and disease activity parameters represent the most important risk factors for AF in these patients, suggest that systemic inflammation may increase AF risk in RA, not simply by accelerating IHD or CHF development.

Indeed, mounting evidence indicates that inflammation can directly impact atrial electrophysiology by affecting cellular and subcellular signalling cascades known to provoke AF. Large epidemiological studies found a strong association between inflammation markers, particularly TNF α , IL-6, and CRP, and the risk of AF[78], while corticosteroid treatment reduced by ~50% the risk of postoperative AF among cardiac surgery patients[84]. Moreover, a huge amount of data demonstrated that inflammatory cytokines play a key pathophysiological role in AF by promoting

both structural and electrical atrial remodelling through several mechanisms[85], including atrial fibroblast activation[86-89], gap junction impairment via changes in connexins[88,90,91], and intracellular calcium-handling abnormalities[86,92,93]. These phenomena, by both increasing ectopic activity[86,94,95] and slowing atrial conduction[86], impair the homogeneity of impulse propagation throughout the atrium and promote reentry, a key electrophysiological alteration for AF development[96](Figure 4). In accordance with these data, P-wave dispersion (PWD), an electrocardiographic marker of inhomogeneous propagation of sinus impulses in the atrial myocardium representing a sensitive and specific clinical predictor of AF by reflecting the risk of reentry occurrence[97], was found to be increased in RA, and correlated with CRP and disease duration[98,99].

4.Clinical perspectives

The large evidence here provided in support of the driving role of systemic inflammation in increasing RA arrhythmic risk, leads us to put forward some considerations about the clinical impact of these findings, also beyond the specific RA setting.

First, minimizing inflammatory burden through a tight control of disease activity, a goal now more feasible after the introduction of potent biologic therapies targeting the immune system, could represent the most rational way to reduce arrhythmia propensity in RA. Presently, no studies specifically evaluated whether anti-inflammatory therapies can decrease the incidence of arrhythmic events in these patients. Nevertheless, some clinical reports indirectly support this possibility by demonstrating that in RA anti-inflammatory treatment was associated with a significant improvement in QT-interval abnormalities and cardiac autonomic dysfunction, correlating with the control of systemic inflammation[36,51,100,101]. Moreover, a recent prospective analysis provided evidence that intensive anti-inflammatory treatment resulting in a stable low-disease activity was associated with a decrease in CV case fatality in RA patients[102].

Second, given that the link between inflammatory activation and arrhythmic risk in RA seems to be mediated by not disease-specific molecules such as cytokines, it is very likely that the same pathogenic mechanisms (and therapeutic implications) are more generally applicable to any chronic inflammatory disorder. Accordingly, growing evidence indicates that arrhythmic risk is also significantly increased in other autoimmune chronic inflammatory diseases. Large population-based studies demonstrated that in patients with psoriasis, spondyloarthritis and inflammatory bowel disease the incidence of arrhythmic events, including AF, ventricular arrhythmias, and cardiac arrest, is higher than in the general population [103-106], also correlating with disease activity [103,106]. Moreover, in systemic lupus erythematosus, SCD represents the fourth most common cause of death [107], with large studies confirming that cardiac arrhythmias are one of the main specific causes of cardiovascular death in these patients [108,109]. Furthermore, likewise to RA, in all these diseases HRV, QT-interval and PWD abnormalities are rather common, and correlate with disease duration and systemic inflammation [27,63,110-117].

Finally, similar considerations may be also translated to general population individuals with clinically unapparent chronic low-grade systemic inflammation, thus providing a new pathophysiological insight contributing to explain the higher arrhythmic risk observed in these subjects. In fact, large prospective community-based studies have demonstrated that inflammatory markers, particularly high sensitivity (hs)-CRP and IL-6, are strong and independent predictors of SCD and AF in apparently healthy subjects [118-121]. Although the most likely underlying mechanism is the promotion of coronary atherosclerosis, it is also conceivable that low-grade systemic inflammation may be *per se* pro-arrhythmogenic by inducing cytokine-mediated structural and electric myocardial remodelling, and chronic cardiac sympathetic activation. Accordingly, population-based studies demonstrated that likewise RA, also in the general population a significant association exists between inflammatory markers, and QT-interval, HRV and PWD abnormalities [122-126]. This suggests that the link between arrhythmic events and inflammation may be at least in part explained by electrophysiological changes occurring in both ventricular and

atrial myocardium. Such considerations provide further rationale to support the recently increasing interest on anti-inflammatory therapies as a new approach to the treatment of CVD[127]. In particular, the results of several massive trials directly testing the “inflammatory hypothesis” of CVD which are expected to be available in the next 5 years[128] may clarify the actual clinical impact of inflammatory activation on the risk of arrhythmic events.

5.Conclusions

Increasing data suggest that rhythm disturbances, particularly tachyarrhythmias, are prevalent in RA, significantly contributing to the high cardiovascular morbidity and mortality observed in these patients. A leading role seems to be played by chronic systemic inflammation, able to induce arrhythmogenicity both indirectly, by accelerating structural CVD, and directly, by affecting cardiac electrophysiology(Figure 5).

In this view, lowering the inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk in these patients. Intriguingly,these considerations could be more generally applicable to all the diseases characterized by chronic systemic inflammation, and could help elucidate the link between low-grade chronic inflammation and arrhythmic risk in the general population.

References

- [1] Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;376:1094-1108.
- [2] Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, Williams B, Gabriel S, Lassere M, Johns N, Buchbinder R, Woolf A, March L. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1316-1322.
- [3] Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med* 2008;121:S9-14.
- [4] Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. *Eur Heart J* 2015;36:482-489.
- [5] Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *Am J Med* 2008;121:S21-31.
- [6] Puntmann VO, Taylor PC, Barr A, Schnackenburg B, Jahnke C, Paetsch I. Towards understanding the phenotypes of myocardial involvement in the presence of self-limiting and sustained systemic inflammation: a magnetic resonance imaging study. *Rheumatology* 2010;49:528-535.
- [7] Bozkurt B, Kribbs SB, Clubb FJ Jr, Michael LH, Didenko VV, Hornsby PJ, Seta Y, Oral H, Spinale FG, Mann DL. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. *Circulation* 1998;97:1382-1391.
- [8] EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325-331.
- [9] Mantel Å, Holmqvist M, Jernberg T, Wållberg-Jonsson S, Askling J. Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome. *Eur Heart J* 2015 Sep 23. pii:ehv461[Epub ahead of print].

- [10]Maradit-Kremers H,Crowson CS,Nicola PJ,Ballman KV,Ballman KV,Roger VL,Jacobsen SJ, Gabriel SE.Increased unrecognized coronary heart disease and sudden death in rheumatoid arthritis. A population-based cohort study. *Arthritis Rheum* 2005;52:402-411.
- [11]Ungprasert P,Srivali N,Kittanamongkolchai W.Risk of Incident Atrial Fibrillation in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis. *Int J Rheum Dis* 2015 Dec 22. doi:10.1111/1756-185X.12820[Epub ahead of print].
- [12]Tomaselli GF,Zipes DP.What causes sudden death in heart failure? *Circ Res* 2004;95:754-763.
- [13]Di Diego JM,Antzelevitch C.Ischemic ventricular arrhythmias: experimental models and their clinical relevance. *Heart Rhythm* 2011;8:1963-1968.
- [14]European Heart Rhythm Association;European Association for Cardio-Thoracic Surgery.Guidelines for the management of atrial fibrillation:the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology(ESC). *Eur Heart J* 2010;31:2369-429.
- [15]Lazzerini PE,Capecchi PL,Acampa M,Galeazzi M,Laghi-Pasini F.Arrhythmic risk in rheumatoid arthritis: the driving role of systemic inflammation. *Autoimmun Rev* 2014;13:936-944.
- [16]Huikuri HV,Castellanos A,Myerburg RJ.Sudden death due to cardiac arrhythmias. *N Eng J Med* 2001;345:1473-1482.
- [17]Zaccardi F,Khan H,Laukkanen JA.Diabetes mellitus and risk of sudden cardiac death: a systematic review and meta-analysis. *Int J Cardiol* 2014;177:535-537.
- [18]Avina-Zubieta JA,Thomas J,Sadatsafavi M,Lehman AJ,Lacaille D.Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012;71:1524-1529.
- [19]Goodson N,Marks J,Lunt M,Symmons D.Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. *Ann Rheum Dis* 2005;64:1595-1601.

- [20] Van Doornum S, Brand C, King B, Sundararajan V. Increased case fatality rates following a first acute cardiovascular event in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:2061-2068.
- [21] Van Doornum S, Bohensky M, Tacey MA, Brand CA, Sundararajan V, Wicks IP. Increased 30-day and 1-year mortality rates and lower coronary revascularisation rates following acute myocardial infarction in patients with autoimmune rheumatic disease. *Arthritis Res Ther* 2015;17:38.
- [22] Douglas KM, Pace AV, Treharne GJ, Saratzis A, Nightingale P, Erb N, Banks MJ, Kitas GD. Excess recurrent cardiac events in rheumatoid arthritis patients with acute coronary syndrome. *Ann Rheum Dis* 2006;65:348-353.
- [23] Mackey RH, Kuller LH, Deane KD, Walitt BT, Chang YF, Holers VM, Robinson WH, Tracy RP, Hlatky MA, Eaton CB, Liu S, Freiberg MS, Talabi MB, Schelbert EB, Moreland LW. Rheumatoid Arthritis, Anti-Cyclic Citrullinated Peptide Positivity, and Cardiovascular Disease Risk in the Women's Health Initiative. *Arthritis Rheumatol* 2015;67:2311-2322
- [24] Desai SP, Januzzi JL, Pande AN, Pomerantsev EV, Resnic FS, Fossel A, Chibnik LB, Solomon DH. Comparison of symptoms, treatment, and outcomes of coronary artery disease among rheumatoid arthritis and matched subjects undergoing percutaneous coronary intervention. *Semin Arthritis Rheum* 2010;40:215-221.
- [25] Ben-Zvi I, Goldenberg I, Matetzky S, Grossman C, Elis A, Gavrielov-Yusim N, Livneh A. The impact of inflammatory rheumatic diseases on the presentation, severity, and outcome of acute coronary syndrome. *Clin Rheumatol* 2014 Jun 15. doi:10.1007/s10067-014-2695-y [Epub ahead of print].
- [26] Göldeli O, Dursun E, Komsuoglu B. Dispersion of ventricular repolarization: a new marker of ventricular arrhythmias in patients with rheumatoid arthritis. *J Rheumatol* 1998;25:447-450.
- [27] Lazzerini PE, Acampa M, Capecchi PL, Hammoud M, Maffei S, Bisogno S, Barreca C, Galeazzi M, Laghi-Pasini F. Association between high sensitivity C-reactive protein, heart rate variability and

corrected QT interval in patients with chronic inflammatory arthritis. *Eur J Intern Med* 2013;24:368-374.

[28]Cindas A,Gökçe-Kutsal Y,Tokgözoğlu L,Karanfil A.QT dispersion and cardiac involvement in patients with rheumatoid arthritis. *Scand J Rheumatol* 2002;31:22-26.

[29]Alkaabi JK,Ho M,Levison R,Pullar T,Belch JJ.Rheumatoid arthritis and macrovascular disease. *Rheumatology* 2003;42:292-297.

[30]Pirildar T,Sekuri C,Utük O,Tezcan UK.QT dispersion in rheumatoid arthritis patients with and without Sjögren's syndrome. *Clin Rheumatol* 2003;22:225-228.

[31]Ahmad S,Garg S,Dhar M,Srivastava S,Biswas D,Barthwal SP Shirazi N,Srivastava R.Predictors of atherosclerosis in rheumatoid arthritis. *Vasa* 2012;41:353-359.

[32]Panoulas VF,Toms TE,Douglas KM,Sandoo A,Metsios GS,Stavropoulos-Kalinoglou A,Kitas GD.Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: an association driven by high inflammatory burden. *Rheumatology* 2014;53:131-137.

[33]Acar GR,Akkoyun M,Nacar AB,Dirnak I,Yıldırım Çetin G,Nur Yıldırım M,Zencir C,Karaman K,Cetin M,Sayarlıoğlu MEvaluation of Tp-e interval and Tp-e/QT ratio in patients with rheumatoid arthritis. *Turk Kardiyol Dern Ars* 2014;42:29-34.

[34]Chauhan K,Ackerman M.Crowson CS,Matteson EL,Gabriel SE.Population-Based Study of QT Interval Prolongation in Patients with Rheumatoid Arthritis. *Clin Exp Rheumatol* 2015;33:84-89.

[35]Adlan AM, Panoulas VF,Smith JP,Fisher JP,Kitas GD.Association between corrected QT interval and inflammatory cytokines in rheumatoid arthritis. *J Rheumatol* 2015;42:421-428.

[36]Lazzerini PE,Acampa M,Capecci PL,Fineschi I,Selvi E,Moscadelli V,Zimbone S,Gentile D,Galeazzi M,Laghi-Pasini F.Antiarrhythmic potential of anti-cytokine therapy in rheumatoid arthritis:Tocilizumab reduces QTc interval by controlling systemic inflammation. *Arthritis Care Res* 2015;67:332-339.

[37]Adlan AM,Lip GY,Paton JF,Kitas GD,Fisher JP.Autonomic function and rheumatoid arthritis:a systematic review. *Semin Arthritis Rheum* 2014;44:283-304.

- [38]Stein PK,Bosner MS,Kleiger RE,Conger BM.Heart rate variability:a measure of cardiac autonomic tone. *Am Heart J* 1994;127:1376-1381.
- [39]Huikuri HV,Stein PK.Heart rate variability in risk stratification of cardiac patients. *Prog Cardiovasc Dis* 2013;56:153-159.
- [40]Evrengül H,Dursunoglu D,Cobankara V,Polat B,Seleci D,Kabukçu S,Kaftan A,Semiz E,Kilic M.Heart rate variability in patients with rheumatoid arthritis. *Rheumatol Int* 2004;24:198-202.
- [41]Anichkov DA,Shostak NA,Ivanov DS.Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients. *Int J Clin Pract* 2007;61:777-783.
- [42]Kamal A.Assessment of autonomic function in patients with rheumatoid arthritis using spectral analysis and approximate entropy method. *Neurosciences* 2007;12:136-139.
- [43]Vlcek M,Rovensky J,Blazicek P,Radikova Z,Penesova A,Kerlik J,Kvetnanský R,Imrich R.Sympathetic nervous system response to orthostatic stress in female patients with rheumatoid arthritis. *Ann N Y Acad Sci* 2008;1148:556-561.
- [44]Aydemir M,Yazisiz V,Basarici I,Avci AB,Erbasan F,Belgi A,Terzioğlu E.Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus. *Lupus* 2010;19:255-261.
- [45]Milovanović B,Stojanović L,Milićević N,Vasić K,Bjelaković B,Krotin M.Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk. *Srp Arh Celok Lek* 2010;138:26-32.
- [46]Bruchfeld A,Goldstein RS,Chavan S,Patel NB,Rosas-Ballina M,Kohn N,Qureshi AR,Tracey KJ.Whole blood cytokine attenuation by cholinergic agonists ex vivo and relationship to vagus nerve activity in rheumatoid arthritis. *J Intern Med* 2010;268:94-101.
- [47]Yadav RK,Gupta R,Deepak KK.A pilot study on short term heart rate variability & its correlation with disease activity in Indian patients with rheumatoid arthritis. *Indian J Med Res* 2012;136:593-598.
- [48]Vlcek M,Rovensky J,Eisenhofer G,Radikova Z,Penesova A,Kerlik J,Imrich R.Autonomic nervous system function in rheumatoid arthritis. *Cell Mol Neurobiol* 2012;32:897-901.

- [49]Janse van Rensburg DC,Ker JA,Grant CC,Fletcher L.Autonomic impairment in rheumatoid arthritis. *Int J Rheum Dis* 2012;15:419-426.
- [50] Kim HA,Jeon JY,Koh BR,Park SB,Suh CH.Salivary cortisol levels, but not salivary α -amylase levels, are elevated in patients with rheumatoid arthritis irrespective of depression. *Int J Rheum Dis* 2013 Nov 14.doi:10.1111/1756-185X.12224[Epub ahead of print].
- [51]Lazzerini PE,Acampa M,Hammoud M,Maffei S,Capecchi PL,Selvi E,Bisogno S,Guideri F,Galeazzi M,Pasini FL.Arrhythmic risk during acute infusion of infliximab: a prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis. *J Rheumatol* 2008;35:1958-1965.
- [52]Morita H,Wu J,Zipes DP.The QT syndromes: long and short. *Lancet* 2008;372:750-763.
- [53]Verrier RL,Antzelevitch C.Autonomic aspects of arrhythmogenesis: the enduring and the new. *Curr Opin Cardiol* 2004;19:2-11.
- [54]Di Lorenzo M,Schiavo B.Rheumatoid heart: report of a case with endomyocardial injury and severe arrhythmias. *G Ital Cardiol* 1978;8:886-891.
- [55]Tsuji M,Dowaki M,Yamada A,Nakura Y,Takahashi S,Hatano M,Sawada S,Nishinarita S,Ishikawa H.A case of anti-RNP antibody positive malignant rheumatoid arthritis with pulmonary hypertension. *Nihon Naika Gakkai Zasshi* 1991;80:1673-1675.
- [56]Lai D,Brown G,MacDonald I.Clarithromycin-induced prolonged QT syndrome. *Can J Hosp Pharm* 1996;49:33-35.
- [57]Bertino JS Jr,Owens RC Jr,Carnes TD,Iannini PB.Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. *Clin Infect Dis* 2002;34:861-863.
- [58]Bruggisser M,Ratz Bravo A,Brodmer M.Medication associated long QT syndrome. *Praxis* 2009;98:1409-1415.
- [59]Vilaseca-Corbera M,Vázquez-Oliva G,Campoamor-Cela C,Zamora-Cervantes A,Bassanyanes-Vilarrasa J,Massa-Puig R.Extreme QT interval prolongation and helicoid ventricular tachycardia

(torsade de pointes) in non-ST-elevation acute coronary syndrome. *Rev Esp Cardiol* 2012;65:294-296.

[60]Vieweg WV,Hancox JC,Hasnain M,Koneru JN,Gysel M,Baranchuk A.Clarithromycin, QTc interval prolongation and torsades de pointes: the need to study case reports. *Ther Adv Infect Dis* 2013;1:121-138.

[61]Tampi RR,Balderas M,Carter KV,Tampi DJ,Moca M,Knudsen A,May J.Citalopram, QTc Prolongation, and Torsades de Pointes. *Psychosomatics* 2015;56:36-43.

[62]Lazzerini PE,Yue Y,Srivastava U,Fabris F,Capecchi PL,Bertolozzi I,Bacarelli MR,Morozzi G,Acampa M,Natale M,El-Sherif N,Laghi-Pasini F,Boutjdir M.Arrhythmogenicity of Anti-Ro/SSA Antibodies in Patients with Torsades de Pointes. *Circ Arrhythm Electrophysiol* 2016 (resubmitted after minor revision).

[63]Lazzerini PE,Capecchi PL,Laghi-Pasini F.Long QT syndrome:an emerging role for inflammation and immunity. *Front Cardiovasc Med* 2015;2:26.doi:10.3389/fcvm.2015.00026.

[64]London B,Baker LC,Lee JS,Shusterman V,Choi BR,Kubota T,McTiernan CF,Feldman AM,Salama G.Calcium-dependent arrhythmias in transgenic mice with heart failure. *Am J Physiol Heart Circ Physiol* 2003;284:H431-441.

[65]Petkova-Kirova PS,Gursoy E,Mehdi H,McTiernan CF,London B,Salama G.Electrical remodeling of cardiac myocytes from mice with heart failure due to the overexpression of tumor necrosis factor-alpha. *Am J Physiol Heart Circ Physiol* 2006;290:H2098-2107.

[66]Kawada H,Niwano S,Niwano H,Yumoto Y,Wakisaka Y,Yuge M,Kawahara K,Izumi T.Tumor necrosis factor-alpha downregulates the voltage gated outward K⁺ current in cultured neonatal rat cardiomyocytes: a possible cause of electrical remodeling in diseased hearts. *Circ J* 2006;70:605-609.

[67]Fernández-Velasco M,Ruiz-Hurtado G,Hurtado O,Moro MA,Delgado C.TNF-alpha downregulates transient outward potassium current in rat ventricular myocytes through iNOS

overexpression and oxidant species generation. *Am J Physiol Heart Circ Physiol* 2007;293:H238-245.

[68]Panama BK,Latour-Villamil D,Farman GP,Zhao D,Bolz SS,Kirshenbaum LA,Backx PH.Nuclear factor kappaB downregulates the transient outward potassium current I(to,f) through control of KChIP2 expression. *Circ Res* 2011;108:537-543.

[69]Wang J,Wang H,Zhang Y,Gao H,Nattel S,Wang Z.Impairment of HERG K(+) channel function by tumor necrosis factor-alpha: role of reactive oxygen species as a mediator. *J Biol Chem* 2004;279:13289-13292.

[70]Li YH,Rozanski GJ.Effects of human recombinant interleukin-1 on electrical properties of guinea pig ventricular cells. *Cardiovasc Res* 1993;27:525-530.

[71]Hagiwara Y,Miyoshi S,Fukuda K,Nishiyama N,Ikegami Y,Tanimoto K,Murata M,Takahashi E,Shimoda K,Hirano T,Mitamura H,Ogawa S.SHP2-mediated signaling cascade through gp130 is essential for LIF-dependent I CaL, [Ca²⁺]_i transient, and APD increase in cardiomyocytes. *J Mol Cell Cardiol* 2007;43:710-716.

[72]Elenkov IJ,Wilder RL,Chrousos GP,Vizi S.The sympathetic nerve – an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; 52: 595-638.

[73]Tracey KJ.The inflammatory reflex. *Nature* 2002; 420: 853-859.

[74]Wu CT,Nattel S.Triggering of cardiac arrhythmic events in long QT syndrome: lessons from funny bunnies. *J Physiol* 2012;590:1311-1312.

[75]De Jesus NM,Wang L,Herren AW,Wang J,Shenasa F,Bers DM,Lindsey ML,Ripplinger CM. Atherosclerosis exacerbates arrhythmia after myocardial infarction: Role of myocardial inflammation. *Heart Rhythm* 2015;12:169-178.

[76]Yu X,Patterson E,Huang S,Garrett MW,Kem DC.Tumor necrosis factor alpha, rapid ventricular tachyarrhythmias, and infarct size in canine models of myocardial infarction. *J Cardiovasc Pharmacol* 2005;45:153-159.

[77]Falk RH.Atrial fibrillation. *N Engl J Med* 2001;344:1067-1078.

- [78]Guo Y,Lip GY,Apostolakis S.Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012;60:2263-2270.
- [79]Lindhardsen J,Ahlehoff O,Gislason GH,Madsen OR,Olesen JB,Svendsen JH,Torp-Pedersen C,Hansen PR.Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- [80]Kim SC,Liu J,Solomon DH.The risk of atrial fibrillation in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73:1091-1095.
- [81]Bacani AK,Crowson CS,Roger VL,Gabriel SE,Matteson EL.Increased incidence of atrial fibrillation in patients with rheumatoid arthritis. *Biomed Res Int* 2015;2015:809514.
- [82]Lubitz SA,Benjamin EJ,Ellinor PT.Atrial fibrillation in congestive heart failure. *Heart Fail Clin* 2010;6:187-200.
- [83]Nattel S,Maguy A,Le Bouter S,Yeh YH.Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. *Physiol Rev* 2007;87:425-456.
- [84]Halonen J,Halonen P,Järvinen O,Taskinen P,Auvinen T,Tarkka M,Hippeläinen M,Juvonen T,Hartikainen J,Hakala T.Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. *JAMA* 2007;297:1562-1567.
- [85]Hu YF,Chen YJ,Lin YJ,Chen SA.Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol* 2015;12:230-243.
- [86]Saba S,Janczewski AM,Baker LC,Shusterman V,Gursoy EC,Feldman AM,Salama G,McTiernan CF,London B.Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor- α . *Am J Physiol Heart Circ Physiol* 2005;289(4):H1456-1467.
- [87]Porter KE,Turner NA,O'Regan DJ,Ball SG.Tumor necrosis factor alpha induces human atrial myofibroblast proliferation, invasion and MMP-9 secretion: inhibition by simvastatin. *Cardiovasc Res* 2004;64:507-515.

- [88]Liew R,Khairunnisa K,Gu Y,Tee N,Yin NO,Naylynn TM,Moe KT.Role of tumor necrosis factor- α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. *Circ J* 2013;77:1171-1179.
- [89]van Nieuwenhoven FA,Hemmings KE,Porter KE,Turner NA.Combined effects of interleukin-1 α and transforming growth factor- β 1 on modulation of human cardiac fibroblast function. *Matrix Biol* 2013;32:399-406.
- [90]Sawaya SE,Rajawat YS,Rami TG,Szalai G,Price RL,Sivasubramanian N,Mann DL,Khoury DS.Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. *Am J Physiol Heart Circ Physiol* 2007;292:H1561-1567.
- [91]Baum JR,Long B,Cabo C,Duffy HS.Myofibroblasts cause heterogeneous Cx43 reduction and are unlikely to be coupled to myocytes in the healing canine infarct. *Am J Physiol Heart Circ Physiol* 2012;302:H790-800.
- [92]Zarain-Herzberg A,Estrada-Avilés R,Fragoso-Medina J.Regulation of sarco(endo)plasmic reticulum Ca²⁺-ATPase and calsequestrin gene expression in the heart. *Can J Physiol Pharmacol* 2012;90:1017-1028.
- [93]Duncan DJ,Yang Z,Hopkins PM,Steele DS,Harrison SM.TNF- α and IL-1 β increase Ca²⁺ leak from the sarcoplasmic reticulum and susceptibility to arrhythmia in rat ventricular myocytes. *Cell Calcium* 2010;47:378-386.
- [94]Mitrokhin VM,Mladenov MI,Kamkin AG.Effects of interleukin-6 on the bio-electric activity of rat atrial tissue under normal conditions and during gradual stretching. *Immunobiology* 2015;220:1107-1112.
- [95]Mitrokhin VM,Mladenov MI,Kamkin AG.IL-1 provokes electrical abnormalities in rat atrial myocardium. *Int Immunopharmacol* 2015;28:780-784.
- [96]Nattel S,Burstein B,Dobrev D.Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol* 2008;1:62-73.

- [97]Dilaveris PE,Gialafos JE.P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* 2001;6:159-165.
- [98]Yavuzkir M,Ozturk A,Dagli N,Koca S,Karaca I,Balin M,Işık A.Effect of ongoing inflammation in rheumatoid arthritis on P-wave dispersion. *J Int Med Res* 2007;35:796-802.
- [99]Guler H,Seyfeli E,Sahin G,Duru M,Akgul F,Saglam H,Yalcin F.P wave dispersion in patients with rheumatoid arthritis: its relation with clinical and echocardiographic parameters. *Rheumatol Int* 2007;27:813-818.
- [100]Syngle A,Verma I,Krishan P,Garg N,Syngle V.Disease-modifying anti-rheumatic drugs improve autonomic neuropathy in arthritis: DIANA study. *Clin Rheumatol* 2015;34:1233-1241.
- [101]Syngle A,Verma I,Krishan P.Interleukin-6 blockade improves autonomic dysfunction in rheumatoid arthritis. *Acta Reumatol Port* 2015;40:85-88.
- [102]Meek IL,Vonkeman HE,van de Laar MA.Cardiovascular case fatality in rheumatoid arthritis is decreasing; first prospective analysis of a current low disease activity rheumatoid arthritis cohort and review of the literature. *BMC Musculoskelet Disord* 2014;15:142.
- [103]Chiu HY,Chang WL,Huang WF,Wen YW,Tsai YW,Tsai TF.Increased risk of arrhythmia in patients with psoriatic disease: A nationwide population-based matched cohort study. *J Am Acad Dermatol* 2015;73:429-438.
- [104]Ahlehoff O,Gislason GH,Jørgensen CH,Lindhardsen J,Charlot M,Olesen JB,Abildstrøm SZ,Skov L,Torp-Pedersen C,Hansen PR.Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. *Eur Heart J* 2012;33:2054-2064.
- [105]Keller JJ,Hsu JL,Lin SM,Chou CC,Wang LH,Wang J,Bai CH,Chiou HY.Increased risk of stroke among patients with ankylosing spondylitis: a population-based matched-cohort study. *Rheumatol Int* 2014;34:255-263.
- [106]Kristensen SL,Lindhardsen J,Ahlehoff O,Erichsen R,Lamberts M,Khalid U,Torp-Pedersen C,Nielsen OH,Gislason GH,Hansen PR.Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace* 2014;16:477-484.

- [107]Abu-Shakra M,Urowitz MB,Gladman DD,Gough J.Mortality studies in systemic lupus erythematosus. Results from a single center. I. Causes of death. *J Rheumatol* 1995;22:1259-1264.
- [108]Mok CC,Kwok CL,Ho LY,Chan PT,Yip SF.Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. *Arthritis Rheum* 2011 May;63(5):1182-9.
- [109]Thomas G,Mancini J,Jourde-Chiche N,Sarlon G,Amoura Z,Harlé JR,Jougla E,Chiche L.Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. *Arthritis Rheumatol* 2014;66:2503-2511.
- [110]Simsek H,Sahin M,Akyol A,Akdag S,Ozkol HU,Gumrukcuoglu HA,Gunes Y.Increased risk of atrial and ventricular arrhythmia in long-lasting psoriasis patients. *ScientificWorldJournal* 2013;2013:901215.
- [111]Bacaksiz A,Erdogan E,Tasal A,Vatankulu MA,Kul S,Sevgili E,Ertas G,Dizman D,Onsun N,Uysal O.Electrocardiographic P-wave characteristics in patients with psoriasis vulgaris. *Ups J Med Sci* 2013;118:35-41.
- [112]Borman P,Gokoglu F,Kocaoglu S,Yorgancioglu ZR.The autonomic dysfunction in patients with ankylosing spondylitis: a clinical and electrophysiological study. *Clin Rheumatol* 2008;27:1267-1273
- [113]Acar G,Yorgun H,Inci MF,Akkoyun M,Bakan B,Nacar AB,Dirnak I,Cetin GY,Bozoglan O.Evaluation of Tp-e interval and Tp-e/QT ratio in patients with ankylosing spondylitis. *Mod Rheumatol* 2014;24:327-330
- [114]Lazzerini PE,Acampa M,Guideri F,Capocchi PL,Campanella V,Morozzi G,Galeazzi M,Marcolongo R,Laghi-Pasini F.Prolongation of the corrected QT interval in adult patients with anti-Ro/SSA-positive connective tissue diseases. *Arthritis Rheum* 2004;50:1248-1252.
- [115]Dogdu O,Yarlioglu M,Kaya MG,Ardic I,Kilinc Y,Elcik D,Kelesoglu S,Akpek M,Sahin O,Cosgun S,Oguzhan N,Oguzhan A.Assessment of atrial conduction time in patients with systemic lupus erythematosus. *J Invest Med* 2011;59:281-286.

- [116]Curione M,Aratari A,Amato S,Colotto M,Barbato M,Leone S,Tego A,Panetti D,Parlapiano C.A study on QT interval in patients affected with inflammatory bowel disease without cardiac involvement. *Intern Emerg Med* 2010;5:307-310.
- [117]Dogan Y,Soylu A,Eren GA,Poturoglu S,Dolapcioglu C,Sonmez K,Duman H,Sevindir I.Evaluation of QT and P wave dispersion and mean platelet volume among inflammatory bowel disease patients. *Int J Med Sci* 2011;8:540-546.
- [118]Albert CM,Ma J,Rifai N,Stampfer MJ,Ridker PM.Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595-259.
- [119]Empana JP,Jouven X,Canoui-Poitaine F,Luc G,Tafflet M,Haas B,Arveiler D,Ferrieres J,Ruidavets JB,Montaye M,Yarnell J,Morange P,Kee F,Evans A,Amouyel P,Ducimetiere P.C-reactive protein, interleukin 6, fibrinogen and risk of sudden death in European middle-aged men: the PRIME study. *Arterioscler Thromb Vasc Biol* 2010;30:2047-2052.
- [120]Hussein AA,Gottdiener JS,Bartz TM,Sotoodehnia N,DeFilippi C,See V,Deo R,Siscovick D,Stein PK,Lloyd-Jones D.Inflammation and sudden cardiac death in a community-based population of older adults: the Cardiovascular Health Study. *Heart Rhythm* 2013;10:1425-1432.
- [121]Peña JM, MacFadyen J,Glynn RJ,Ridker PM.High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. *Eur Heart J* 2012;33:531-537
- [122]Kim E,Joo S,Kim J,Ahn J,Kim J,Kimm K,Shin C.Association between C-reactive protein and QTc interval in middle-aged men and women. *Eur J Epidemiol* 2006;21:653-659.
- [123]Medenwald D,Kors JA,Loppnow H,Thiery J,Kluttig A,Nuding S,Tiller D,Greiser KH, Werdan K,Haerting J.Inflammation and prolonged QT time: results from the Cardiovascular Disease, Living and Ageing in Halle (CARLA) study. *PLoS One* 2014;9:e95994

- [124]Sajadieh A,Nielsen OW,Rasmussen V,Hein HO,Abedini S,Hansen JF.Increased heart rate and reduced heart-rate variability are associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. *Eur Heart J* 2004;25:363-370
- [125]Sloan RP,McCreath H,Tracey KJ,Sidney S,Liu K,Seeman T.RR interval variability is inversely related to inflammatory markers: the CARDIA study. *Mol Med* 2007;13:178-184.
- [126]Medenwald D,Dietz S,Tiller D,Kluttig A,Greiser Kh,Loppnow H,Thiery J,Nuding S,Russ M,Fahrig A,Haerting J,Werdan K.Inflammation and echocardiographic parameters of ventricular hypertrophy in a cohort with preserved cardiac function. *Open Heart* 2014 Feb 8;1:e000004.
- [127]Ridker PM,Lüscher TF.Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014;35:1782-1791.
- [128]Couzin-Frankel J.Cardiovascular disease. Massive trials to test inflammation hypothesis. *Science* 2012;337:1158.

LEGEND TO FIGURES

Figure 1. Electrophysiological basis of inflammation-mediated QTc prolongation, from the cell to the surface electrocardiogram. TNF α , tumor necrosis factor alpha; IL-1, interleukin-1; IL-6, interleukin-6; INa, sodium current; Ito, transient outward current; ICaL, L(long-lasting)-type calcium current; IKr, rapid component of the delayed rectifier potassium current; IKs, slow component of the delayed rectifier potassium current; IK1, inward rectifier potassium current.

Figure 2. Systemic inflammation and ventricular arrhythmic risk: non-structural myocardial changes induced by inflammatory cytokines. TNF α , tumor necrosis factor alpha; IL-1, interleukin-1; IL-6, interleukin-6; CNS, central nervous system; β_1 , beta-1 adrenergic receptor; β_2 , beta-2 adrenergic receptor; APD, action potential duration.

Figure 3. Risk of atrial fibrillation in rheumatoid arthritis patients: a meta-analysis of population-based studies. RA, rheumatoid arthritis; CI, confidence interval; SE, standard error.

Reprinted with permission from: Ungprasert P, Srivali N, Kittanamongkolchai W. Risk of Incident Atrial Fibrillation in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis. *Int J Rheum Dis* 2015 Dec 22. doi: 10.1111/1756-185X.12820.[11]

Figure 4. Inflammatory cytokines in atrial fibrillation.

TNF α , tumor necrosis factor alpha; IL-1, interleukin-1; IL-6, interleukin-6; MMPs, matrix metalloproteinases; Cx40, connexin 40; Cx43, connexin 43; SR, sarcoplasmic reticulum; Ca $^{++}$, calcium; SERCA2, sarco/endoplasmic reticulum calcium-ATPase 2; DADs, delayed after-depolarizations.

Figure 5. Systemic inflammation in the pathogenesis of cardiac arrhythmias in rheumatoid arthritis. IHD, ischemic heart disease; CHF, congestive heart failure.

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 1. Population-based studies showing an increased risk of sudden cardiac death and/or short-term case fatality after an acute coronary syndrome in patients with rheumatoid arthritis.

<i>Author, year</i>	<i>Study design</i>	<i>RA patients</i>	<i>Control group</i>	<i>Results</i>
Maradit-Kremers et al., 2005 [10]	Retrospective cohort	603 73% female Age: 58.0±15.2 years Follow-up: 14.7 years	603 73% female Age: 58.2±15.2 years Follow-up: 16.8 years	RA patients had a two-times higher risk of SCD compared with non-RA subjects (HR 1.94, 95%CI 1.06-3.55, after multivariable adjustment for age, sex, smoking status, body mass index, and the presence of diabetes mellitus or hypertension). The doubling of the risk persisted after supplemental adjustment for history of hospitalized or unrecognized MI and revascularization procedures
Van Doornum et al., 2006 [19]	Retrospective cohort	359 66.9% female Age: 74.8±10.6 years	29,565 41.6% female Age: 71.9±12.9 years	RA patients had an increased risk of 30-day case fatality following MI, but not stroke, compared with non-RA patients (OR 1.9, 95%CI 1.3-2.7, after multivariable adjustment for age, sex, smoking status, presence of diabetes mellitus, hypertension or hyperlipidemia, type of intervention after cardiac event, comorbidities, ethnicity, healthcare accessibility and socioeconomic factors). No difference in the rates of CHF between RA and non-RA patients following a MI was observed (OR 1.2, 95%CI 0.9-1.7, after multivariable adjustment)
Van Doornum et al., 2015 [20]	Retrospective cohort	666 64.4% female Age: 76(68-82) years	77,981 39.1% female Age: 74(61-82) years	RA patients had an increased risk of 30-day case fatality following MI compared with non-RA patients (OR 1.51, 95%CI 1.24-1.84, after multivariable adjustment for age, sex, comorbidities, healthcare accessibility and socioeconomic factors)
Mantel et al., 2015 [9]	Contemporary cohort	1135 62.6% female Age: 73.8±10.3 years	3184 59.6% female Age: 73.6±9.8 years	RA patients had an increased risk of short-term case fatality following ACS compared with non-RA patients (7-day HR 1.50, 95%CI 1.19-1.90; 30-day HR 1.43, 95%CI 1.18-1.72; multivariable adjustment for age, sex, comorbidities, medications and educational level). The risk reduced, but remained significantly increased, after additional adjustment for ACS severity as assessed by MI type (7-day HR 1.44, 95%CI 1.14-1.82; 30-day HR 1.36, 95%CI 1.13-1.64). ACS more frequently presented with SCD in RA than non-RA patients.

SCD: sudden cardiac death; RA: rheumatoid arthritis; MI: myocardial infarction; CHF: congestive heart failure; ACS: acute coronary syndrome; HR: hazard ratio; OR: odds ratio; CI: confidence interval.

Table 2. Clinical studies on QT interval and heart rate variability parameters in patients with rheumatoid arthritis.

Author, year	Study population	Results
QT INTERVAL PARAMETERS		
Goldeli et al.,1998 [26]	42 RA (34.0 y; ♀76%) vs 42 HC (age and sex-matched)	QT dispersion variables (QTD,QTcD,JTD,JTcD) increased in RA. <i>No difference in QTc.</i>
Cindas et al.,2002 [28]	40 RA (51.9 y; ♀87%) vs 48 HC (53.5 y; ♀85%)	QT dispersion variables (QTD,QTcD) increased in RA, and correlated with disease duration
Alkaabi et al.,2003 [29]	40 RA (56 y; ♀50%) vs 40 HC (55 y; ♀50%)	QTD increased in RA, and correlated with extra-articular manifestations, erosive disease, steroid use
Pirildar et al., 2003 [30]	58 RA (40.2 y; ♀86%) vs 29 HC (41 y; ♀86%)	QT dispersion variables (QTD,QTcD) increased in RA, and correlated with extra-articular manifestations (secondary SjS)
Ahmad et al.,2012 [31]	100 RA (48.5 y; ♀68%) vs 100 HC (45.8 y; ♀68%)	QTD increased in RA, and correlated with disease duration, DAS28, ESR, steroid use
Lazzerini et al.,2013 [27]	25 RA (51.8 y; ♀52%) vs 21 HC (46.7 y; ♀50%)	QTc increased in RA, and correlated with CRP levels. <i>No difference in QTcD.</i>
Panoulas et al.,2014 [32]	357 RA (60.2 y; ♀75%); prospective cohort study (FU 73 months)	QTc prolongation was independently associated with CRP levels and predicted all-cause mortality (HR:2.18, 95%CI 1.09-4.35, per 50 ms QTc-increase; predictive value was lost after CRP-adjustment)
Acar et al., 2014 [33]	96 RA (43.8 y; ♀75%) vs 50 HC (44.2 y; ♀70%)	QT dispersion variables (Tp-e, Tp-e/QT ratio) increased in RA, and correlated with DAS28, ESR, CRP
Chauhan et al.,2015 [34]	518 RA (58.5 y; ♀68%) vs 499 non-RA (58.7y; ♀69%); retrospective cohort study (FU:12/13 y in RA/non-RA)	Cumulative incidence of QTc prolongation higher in RA than non-RA patients; any QTc prolongation independently associated with all-cause mortality; idiopathic QTc prolongation correlated with ESR
Adlan et al., 2015 [35]	112 RA (62 y; ♀71%)	QTc prolongation correlated with circulating levels of inflammatory cytokines
Lazzerini et al., 2015 [36]	17 RA (52.3 y; ♀88%); prospective cohort study (FU:6 months)	High prevalence of QTc prolongation in patients with high disease activity (73%). Anti-IL-6 therapy was associated with QTc shortening, which correlated with the decrease in both CRP and TNF α levels
HRV PARAMETERS		
Everengul et al.,2004[40]	48 RA (47 y; ♀73%) vs 50 HC (45 y; ♀66%)	Time- (SDNN) and frequency-domain (LF,HF,LF/HF) measures were reduced/impaired in RA. <i>No association between HRV and disease duration, Steinbrocker's classification or ESR</i>
Anichkov et al.,2007 [41]	23 RA (48 y; ♀100%) vs 23 HC (47 y; ♀100%)	Time-domain (SDNN,SDANN,rMSSD) and non-linear (SD1,SD12) measures were reduced in RA, and correlated with disease duration, disease activity scores and leucocyte count
Kamal et al.,2007 [42]	52 RA (49 y; sex NA) vs 51 HC (46 y; sex NA)	Time-domain (SDNN) and non-linear (ApEn) measures were reduced in RA, and correlated with DAS28, rheumatoid factor positivity
Vlcek et al., 2008 [43]	8 RA (30.5 y; ♀100%) vs 8 HC (30.5 y; ♀100%)	<i>No difference in frequency-domain measures</i>
Aydemir et al.,2010 [44]	36 RA (48.7 y; ♀83%) vs 40 HC (42.5 y; ♀78%)	Frequency-domain measures (LF,HF) were reduced in RA
Milovanovic et al.,2010[45]	52 RA (43.3 y; ♀88%) vs 41 HC (37.4 y; ♀41%)	Time-domain (SDNN,pNN50) and frequency-domain (VLF,LF,HF) measures were reduced in RA
Bruchfeld et al.,2010 [46]	13 RA (52 y; ♀69%) vs 10 HC (32 y; ♀54%)	Frequency-domain measures (HF) were reduced in RA
Yadav et al., 2012 [47]	45 RA (40.6 y; ♀87%) vs 45 HC (36.8 y; ♀87%)	Time-domain (SDNN,rMSSD,SDSD,pNN50) and frequency-domain (TP,LF,HF) measures were reduced in RA, and correlated with DAS28, rheumatoid factor positivity
Vlcek et al.,2012 [48]	45 RA (30.6 y; ♀100%) vs 45 HC (29.9 y; ♀100%)	<i>No difference in frequency-domain measures</i>
Janse van Rensburg et al.,2012 [49]	45 RA (44.5 y; sex NA) vs 39 HC (46.5 y; sex NA)	Time-domain (SDNN,RMSSD,pNN50), non-linear (SD1,SD2) and frequency-domain (LF,HF) measures were reduced in RA
Kim et al.,2013 [50]	94 RA (49.7 y; ♀100%) vs 43 HC (37.9 y; ♀100%)	<i>No difference in frequency-domain measures</i>
Lazzerini et al.,2013 [27]	25 RA (51.8 y; ♀52%) vs 21 HC (46.7 y; ♀50%)	Frequency-domain (TP,LF,HF) measures were reduced in RA, and correlated with CRP

RA: rheumatoid arthritis; HC: healthy controls; y: years; ♀: females; QTD: QT interval dispersion; QTc: heart-rate corrected QT interval; QTcD: heart-rate corrected QT interval dispersion; JTD: JT interval dispersion; JTcD: heart-rate corrected JT interval dispersion; Tp-e: interval from the peak to the end of the T wave; Tp-e/QT ratio: interval from the peak to the end of the T wave/QT interval ratio; SjS: Sjögren's syndrome; DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ms: milliseconds; FU: follow-up; HR: hazard ratio; CI: confidence interval.

confidence interval. HRV: heart rate variability; SDNN: standard deviation of all R-R intervals; SDANN: standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; rMSSD: square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50: number of pairs of adjacent R-R intervals differing by more than 50 ms in the entire recording divided by the total number of all R-R intervals; SDSD: standard deviation of successive differences between adjoining normal cycles; SD1: standard deviation of the points perpendicular to the line-of-identity; SD2: standard deviation of the points along the line-of-identity; SD12: SD1/SD2 ratio; TP: total power; VLF: very low frequency; LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio; ApEn: approximate entropy index; NA: not available.

Table 3. Effects of inflammatory cytokines on ventricular myocyte action potential: electrophysiological and molecular mechanisms

<i>Cytokine</i>	<i>Effects on ventricular myocyte ion currents</i>	<i>Molecular mechanisms</i>	<i>Effect on APD</i>
TNF α	IKr decrease ⁶⁹	impairment of hERG potassium channel function (via stimulation of ROS) ⁶⁹	Prolongation ^{64,67,69}
	IKs decrease ⁶⁵	reduced expression of Kv1.5 potassium channel ⁶⁵	
	Ito decrease ⁶⁵⁻⁶⁷	reduced expression of Kv4.2 and Kv4.3 potassium channels ⁶⁵⁻⁶⁷ (via iNOS induction ⁶⁷ , ROS generation ⁶⁷ , NFkB activation ⁶⁸ and KCHIP-2 inhibition ^{66,68})	
IL-1	ICaL increase ⁷⁰	lipoxygenase pathway-mediated ⁷⁰	Prolongation ⁷⁰
IL-6	ICaL increase ⁷¹	enhancement of Cav1.2 calcium channel function (via SHP2/ERK-mediated phosphorylation) ⁷¹	Prolongation ⁷¹

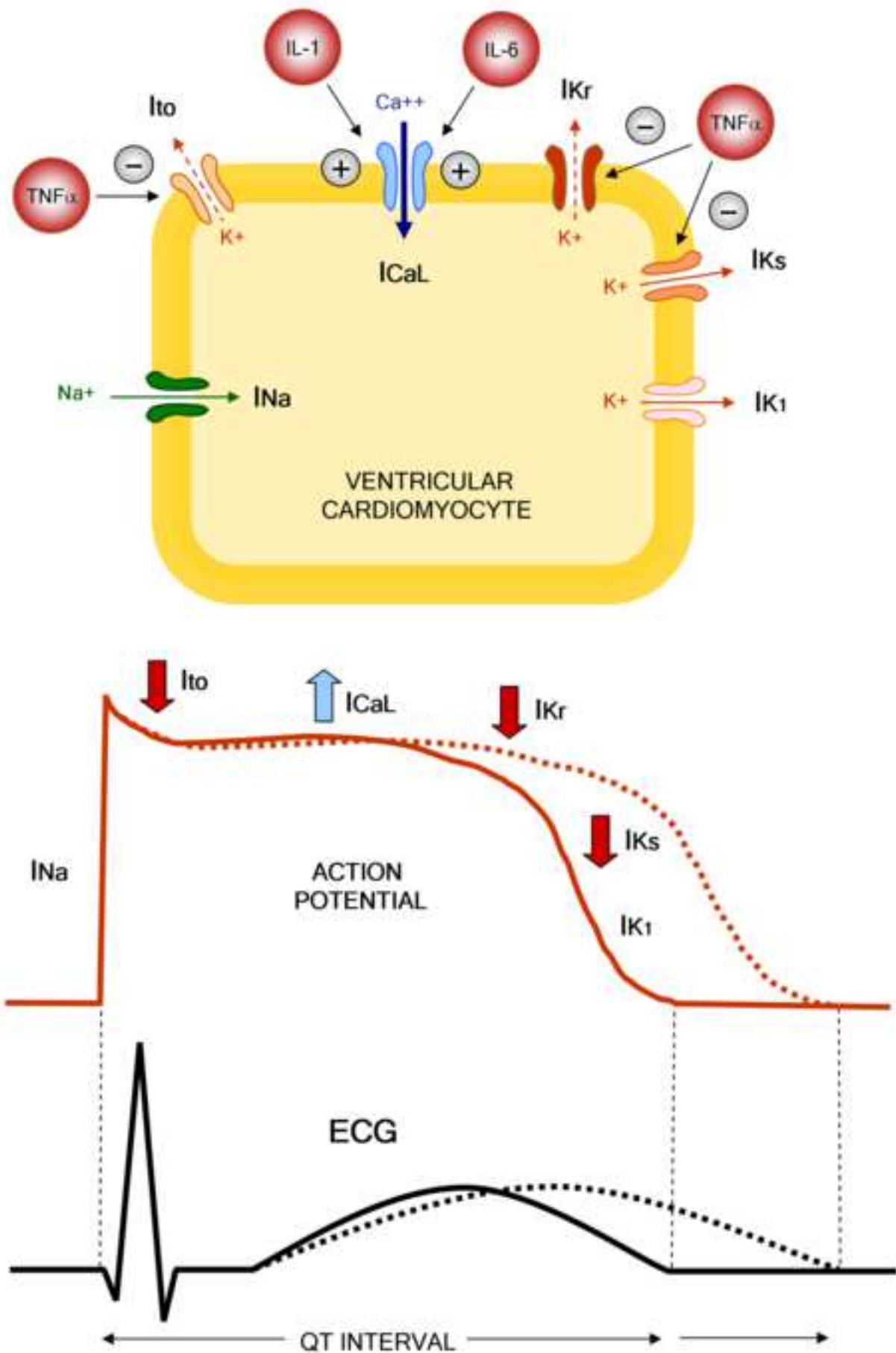
TNF α : tumor necrosis factor α ; IL-1: interleukin-1; IL-6: interleukin-6; ROS: reactive oxygen species; iNOS: inducible nitric oxide synthase; NFkB: nuclear factor-kappa-B; KCHIP-2: K(+) Channel-Interacting Protein; SHP/ERK: Src homology 2 domain-containing phosphatase/ extracellular signal-regulated kinase; APD: action potential duration.

Modified from: Lazzerini PE, Capecchi PL, Laghi-Pasini F. Long QT syndrome: an emerging role for inflammation and immunity. *Front Cardiovasc Med* 2015;2:26.doi:10.3389/fcvm.2015.00026[reference 63].

Table 4. Population-based cohort studies on the incidence of atrial fibrillation in patients with rheumatoid arthritis.

<i>Author, year</i>	<i>Study design</i>	<i>RA patients</i>	<i>Control group</i>	<i>Results</i>
Lindhardsen et al., 2012 [79]	Retrospective cohort	18,247 69.7% female Age: 52.4±14.9 years Follow-up: 5.2 years	4,164,088 50.9% female Age: 45.6±18.4 years Follow-up: 11.5 years	AF incidence was increased in RA patients compared to controls, also after adjustment for age, sex, calendar year, socioeconomic status, and baseline cardiovascular drugs and comorbidity (IRR 1.41, 95%CI 1.31-1.51). The risk reduced, but remained significantly increased when cardiovascular drug use and comorbidity were updated during follow-up (IRR 1.24, 95% CI 1.15-1.35)
Kim et al., 2014 [80]	Retrospective cohort	20,852 74% female Age: 51.9±12.1 years Follow-up: 2.0 years	104,260 74% female Age: 51.9±12.1 years Follow-up: 2.0 years	AF incidence was increased in RA patients compared to controls, also after adjustment for age, sex and cardiovascular disease (IRR 1.44, 95%CI 1.21-1.71). The increased risk disappeared after full adjustment for potential confounders, also including combined comorbidity, medications and healthcare utilisation (IRR 1.11, 95% CI 0.8-1.39)
Bacani et al., 2015 [81]	Retrospective cohort	813 68% female Age: 55.9±15.7 years Follow-up: 9.6 years	813 68% female Age: 55.9±15.7 years Follow-up: 9.6 years	AF incidence was increased in RA patients compared to controls, also after adjustment for age, sex, and calendar year (HR 1.60, 95% CI 1.17-2.18). The risk reduced, but remained significantly increased after additional adjustment for current smoking status and development of hypertension (HR 1.46, 95% CI 1.07-2.00). Markers of severe disease were the strongest risk factors for AF development, particularly the presence of severe extra-articular manifestations (HR 3.29, 95% CI 1.98-5.48) and ESR>60 mm/hr on 3 occasions (HR 2.04, 95%CI 1.19-3.50).

AF: atrial fibrillation; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; IRR: incidence rate ratio; HR: hazard ratio; CI: confidence interval.



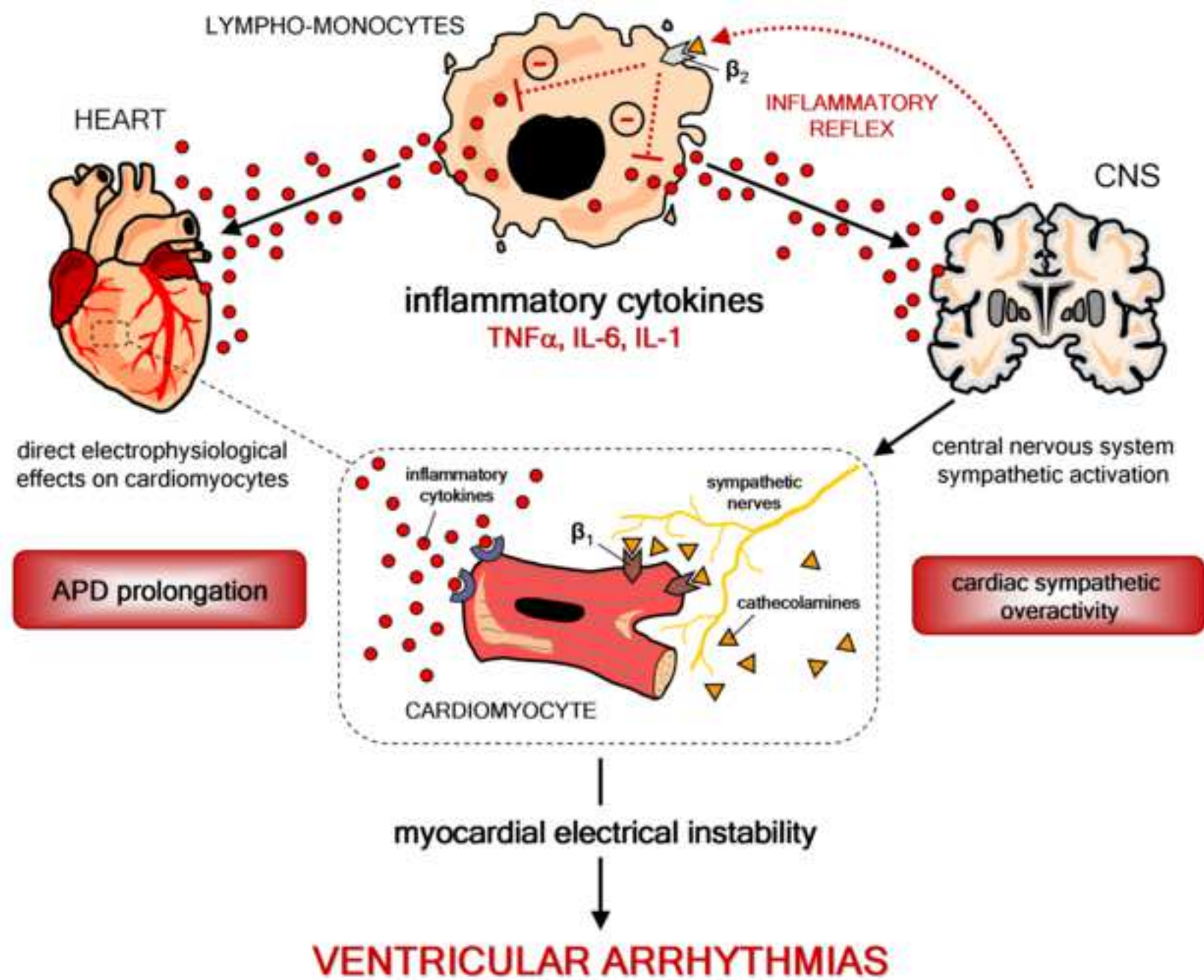
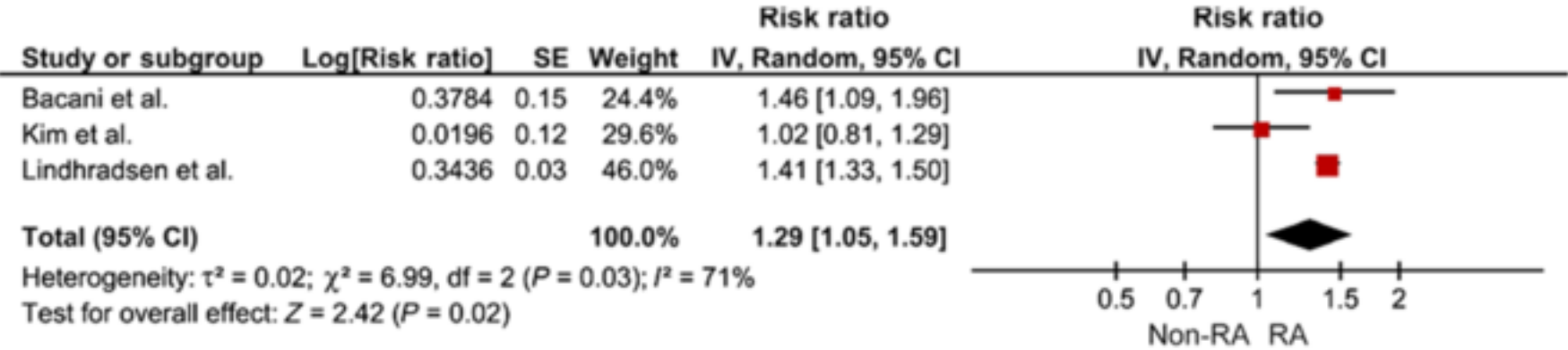


Figure 3



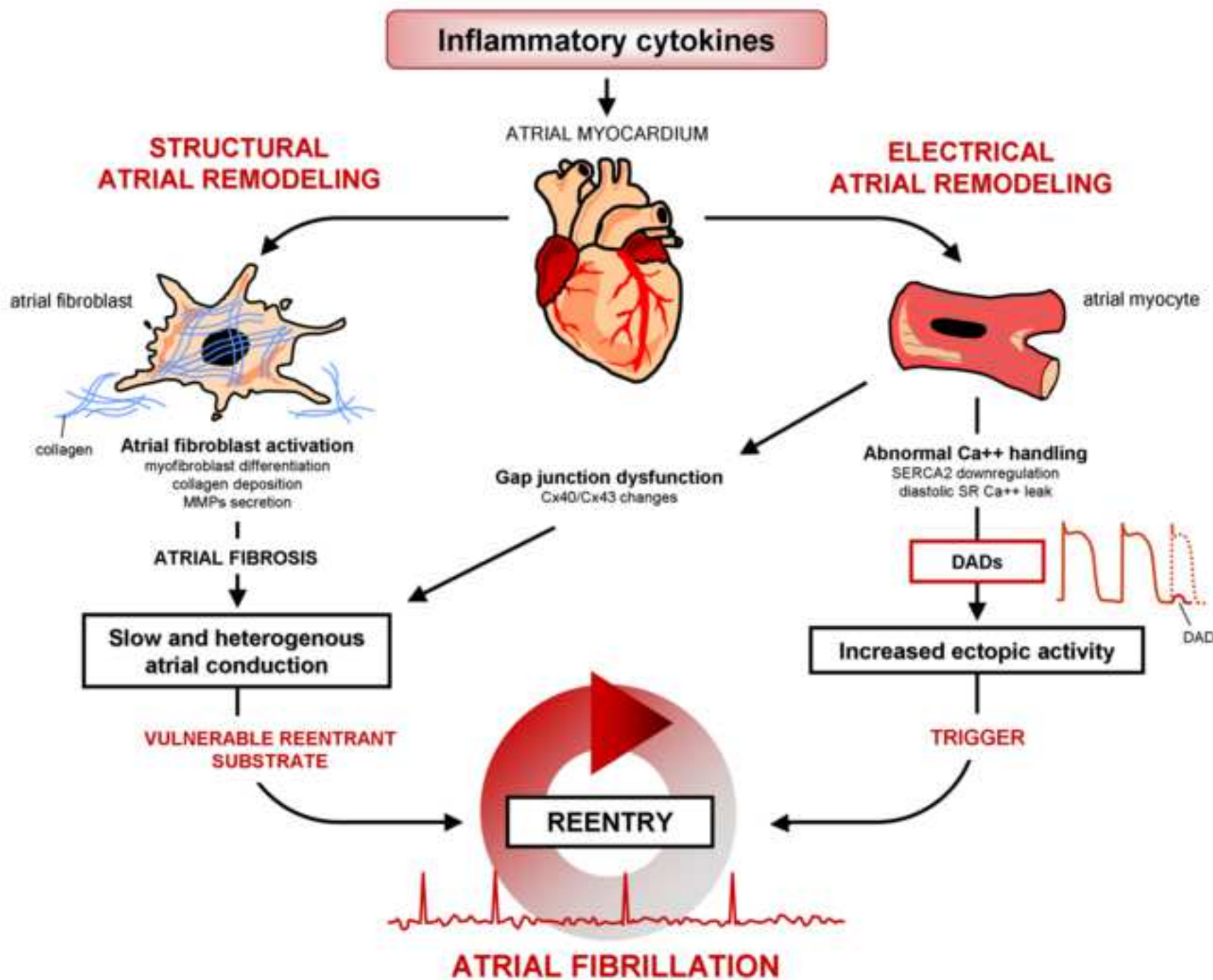
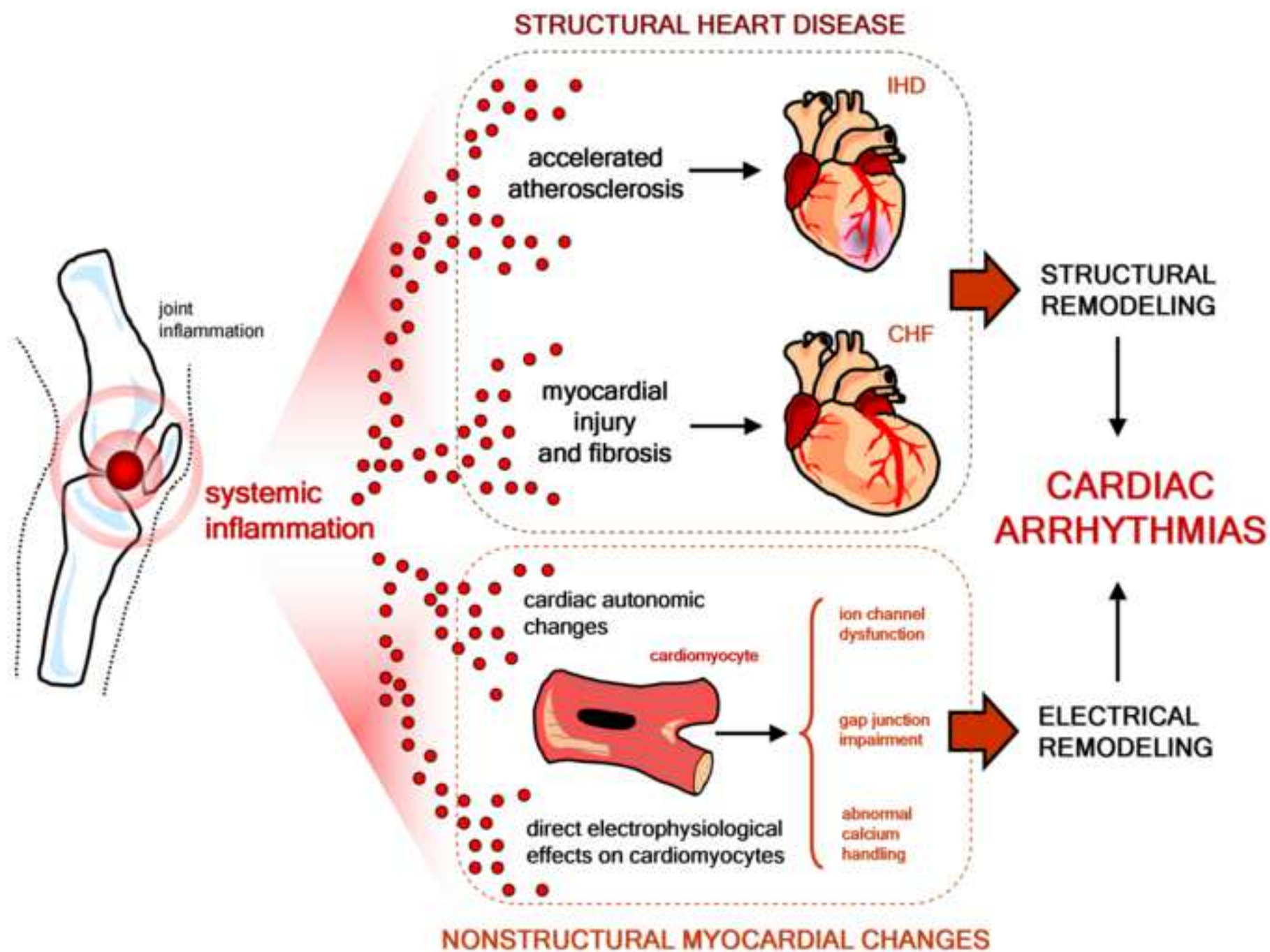


Figure 5



Word count: 4,924 words (including: main test and the first 50 references).

JOHN WILEY AND SONS ORDER DETAILS

Jan 25, 2016

This is an Agreement between ("You") and John Wiley and Sons ("John Wiley and Sons"). It consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

Order Number	501094595
Order date	Dec 23, 2015
Licensed Content Publisher	John Wiley and Sons
Licensed Content Publication	International Journal of Rheumatic Diseases
Licensed Content Title	Risk of incident atrial fibrillation in patients with rheumatoid arthritis: a systematic review and meta-analysis
Licensed Content Author	Patompong Ungprasert,Narat Srivali,Wonngarm Kittanamongkolchai
Licensed Content Date	Dec 22, 2015
Pages	1
Type of use	Journal/Magazine
Requestor type	University/Academic
Is the reuse sponsored by or associated with a pharmaceutical or medical products company?	no
Format	Electronic
Portion	Figure/table
Number of figures/tables	1
Original Wiley figure/table number(s)	Figure 2
Will you be translating?	No
Title of new article	Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis.
Publication the new article is in	European Heart Journal
Publisher of new article	Oxford University Press
None	
Author of new article	Pietro Enea Lazzerini, Pier Leopoldo Capecchi, Franco Laghi Pasini
Expected publication date of new article	May 2016
Estimated size of new article (pages)	12
Requestor Location	Pietro Enea Lazzerini Viale Bracci,16 Siena, Italy 53100 Attn: Pietro Enea Lazzerini
Billing Type	Invoice

Billing Address

Pietro Enea Lazzerini
Viale Bracci,16

Siena, Italy 53100
Attn: Pietro Enea Lazzerini

Total

0.00 EUR

Terms and Conditions

TERMS AND CONDITIONS

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or handled on behalf of a society with which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at <http://myaccount.copyright.com>).

Terms and Conditions

- The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.
- You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, **and any CONTENT (PDF or image file) purchased as part of your order**, is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.
- With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner. **For STM Signatory Publishers clearing permission under the terms of the [STM Permissions Guidelines](#) only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts**, You may not alter, remove or suppress in any manner any copyright, trademark or

other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

- The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto
- NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.
- WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.
- You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.
- IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.
- Should any provision of this Agreement be held by a court of competent jurisdiction

to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

- The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.
- This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.
- Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.
- These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.
- In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.
- WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.
- This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.
- This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS

Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription

journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only, the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License

The [Creative Commons Attribution License \(CC-BY\)](#) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-

Creative Commons Attribution Non-Commercial License

The [Creative Commons Attribution Non-Commercial \(CC-BY-NC\)License](#) permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.(see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License

The [Creative Commons Attribution Non-Commercial-NoDerivs License](#) (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Use by commercial "for-profit" organizations

Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee.

Further details can be found on Wiley Online Library <http://olabout.wiley.com/WileyCDA/Section/id-410895.html>

Other Terms and Conditions:

v1.10 Last updated September 2015

ABSTRACT

Rheumatoid arthritis (RA) is a chronic immuno-mediated disease primarily affecting the joints, characterized by persistent high-grade systemic inflammation. Cardiovascular morbidity and mortality are significantly increased in RA, with more than 50% of premature deaths attributable to cardiovascular disease (CVD). In particular, RA patients were twice as likely to experience sudden cardiac death compared with non-RA subjects, pointing to an increased propensity to develop malignant ventricular arrhythmias. Indeed, ventricular repolarization (QT interval) abnormalities and cardiovascular autonomic nervous system dysfunction, representing two well-recognized risk factors for life-threatening ventricular arrhythmias in the general population, are commonly observed in RA. Moreover, large population-based studies demonstrated that the prevalence of atrial fibrillation is significantly higher in RA subjects than in the general population, thus indicating that these patients are characterized by an abnormal diffuse myocardial electrical instability. Although the underlying mechanisms accounting for the pro-arrhythmogenic substrate in RA are probably intricate, the leading role seems to be played by chronic systemic 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 the inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk in these patients. Intriguingly, these considerations could be more generally applicable to all the diseases characterized by chronic systemic inflammation, and could help elucidate the link between low-grade chronic inflammation and arrhythmic risk in the general population.



[Click here to access/download](#)

ICMJE Conflicts of Interest form (1 for each author listed)

[coi_disclosure-5 Lazzerini.pdf](#)





[Click here to access/download](#)

ICMJE Conflicts of Interest form (1 for each author listed)

coi_disclosure-5 Capecchi.pdf





[Click here to access/download](#)

ICMJE Conflicts of Interest form (1 for each author listed)

coi_disclosure-5 Laghi-Pasini.pdf

