The role of inflammation in cardiac arrhythmias pathophysiology

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ABSTRACT

The pathophysiology of cardiac arrhythmias is highly complex. Inflammation causes electrophysiological changes that contribute to increased vulnerability of arrhythmias, a process known as electrical remodeling. There have been many biomarkers and proteins associated with pathophysiology of cardiac arrhythmias such as C-reactive protein, tumor necrosis factor-α, interleukin-2, interleukin-6, interleukin-8, and monocyte chemoattractant protein-1. At present large attention is paid to the clinical studies on the inflammation in the pathogenesis of the atrial fibrillation (AF), given the limited effectiveness of the current therapeutic approaches. Understanding the main process, molecular mechanism and signaling pathways underlying the pathogenesis of the inflammatory dilated cardiomyopathy (iDCM) will be essential for developing new effective therapeutic strategies.

Keywords: inflammation, atrial fibrillation, biomarkers, remodeling.

Introduction

There have been numerous clinical studies supporting the important role of inflammation in the pathophysiology of many cardiovascular diseases including: coronary artery disease, heart failure, hypertension, cardiac arrhythmias. These systemic diseases are associated with low-grade inflammation and increased levels of proinflammatory cytokines [1].

Inflammation plays an important role in pathophysiology of atherosclerosis. It is involved in atherosclerosis from its formation and progression to its final stage, i.e. systemic thrombosis [2]. Inflammation is also involved in the initiation and maintenance of atrial fibrillation as well as its thromboembolic complications [3]. The inflammatory system, comprised of specialized cells and mediators, is responsible for complex responses to all forms of injuries. It stimulates inflammatory reactions by activating leukocytes, macrophages, mast cells, fibroblasts, and endothelial cells. Acute inflammation leads to the tissue repair, while the chronic inflammation can cause damage and pathological remodeling. Nevertheless, these two dimensions of inflammation may coexist with each other.

The immune system, inflammation and oxidative stress are closely related to common pathological responses. Immune factors (e.g. complement) initiate and propagate the inflammatory reactions. If this reaction is not properly controlled, it can exacerbate the chronic inflammation (e.g. granuloma) [4]. Considering the significance of the inflammatory/immune aspects of cardiac diseases, it needs to be emphasized that inflammation might play an important role in the cardiac cells’ function, survival and death. Indeed, inflammatory processes lead to structural and electrical remodeling of the myocardium. Hence, the main pathophysiological mechanisms responsible for the formation of arrhythmias in the cardiac myocardial tissue include ectopic beats, triggered activity and reentry mechanisms. Additionally, inflammation alters electrophysiological properties of the myocardium leading to vari-
ous forms of arrhythmias: from benign supraventricular ectopic beats to malignant forms of ventricular tachycardias and ventricular fibrillation [6]. At present large attention is paid to the clinical studies on the inflammation in the pathogenesis of the AF, given the limited effectiveness of the current therapeutic approaches. In this paper we elaborated pathophysiological aspects of inflammation process in cardiac arrhythmias, emphasized the role of proinflammatory biomarkers involved in atrial fibrillation.

Pathophysiology

Klein et al, have documented the adverse role of inflammation in the pathogenesis of arrhythmias. They described pathological changes in the membrane potential and heterogeneous impulse conduction due to fibrosis and scarring of the myocardial tissue. They also proposed that the formation of cardiac arrhythmias in the inflamed myocardium occurs due to three factors: structural changes, ventricular dynamics and vascular factors. They further remarked that the parameters of ventricular dynamics such as increased wall tension, increased myocardial oxygen consumption and diminished coronary reserve in case of disturbed systolic or diastolic left ventricular function also contribute to the increased incidence of arrhythmias. It was observed that vascular factors can further increase the arrhythmogenicity of the inflamed myocardium through the disturbance of micro- and macrovascular perfusion and the resulting myocardial ischemia. Hence, myocardial biopsy carried out to detect myocarditis is an important additional examination which can improve the differential diagnosis and treatment of patients with cardiac arrhythmias of obscure etiology [7]. Although the inflammatory process of the myocardium may itself be arrhythmogenic, the change in the electrophysiological properties of the myocardium (i.e. electrical remodeling) may also play a role in cardiac arrhythmias [8].

For example, in experimental autoimmune myocarditis (EAM) in rats, demonstrated the changes in the ventricular electrophysiologic properties and in the level of gene expression of cardiac ion channels. During the acute phase of the myocarditis, the ventricular vulnerability was increased and, as a result, the triggered activity was considered to be one of the mechanisms. Also, the ventricular effective refractory period (ERP) and the duration of monophasic action potential (MAPD) were prolonged, showing the “dome-formation” in phase 2 of the MAP trace [9].

It has been noted that the results of atrial biopsies taken from patients with AF have demonstrated the inflammatory infiltrates and oxidative damage within the atrial tissue [5]. In the study of Frustaci et al, abnormal atrial histology was found in multiple biopsy from patients with lone AF. The histological findings in biopsies taken from the interatrial septum were coincided with a diagnosis of myocarditis in 66% of patients [10]. Presence of circulating autoantibodies against heavy chains of myosin in a the vast majority of patients with idiopathic paroxysmal AF (PAF), raises the possibility of an inflammatory autoimmune processes [11].

AF and inflammatory biomarkers

AF is the most common sustained cardiac arrhythmia in clinical practice [12]. It is associated with an increased risk in mortality and morbidity, and may exert an adverse effect on the quality of life [13]. The pulmonary veins are the key trigger sites initiating AF. So far the exact stimulus for this focal triggering is unknown. Nevertheless, inflammation may provide one explanation. Indeed, inflammation can also act as an ongoing accelerator in the remodeling process [14]. The pathophysiology of AF is highly complex. It is usually associated with organic heart disease but it may also occur without clinically evident abnormalities. The main pathophysiological mechanisms contributing to the AF’s development and progression include both electrical and structural remodeling of the atria. Moreover, AF itself can cause progressive electrophysiological changes during atrial remodeling, which perpetuates the arrhythmia—known as ‘AF begets AF’ phenomenon [15].

There have been many biomarkers associated with pathophysiology of AF such as C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1 [16]. Inflammatory biomarkers related to atrial fibrillation are listed in Table 1. The vascular markers that have been studied most frequently include high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6.

High sensitivity CRP is an acute-phase protein, factor known initially for its capacity to bind to the C-polysaccharide of Streptococcus pneumoniae. It has developed as the most robust and reproducible marker of vascular inflammation. CRP is synthesized primarily by the liver in response to pro-inflammatory cytokines. CRP is involved in the immune response, phagocytosis/opsonisation of the infectious agent and modulates the function of granulocytes and monocytes. Current-
Chemokine is produced by macrophages and epithelial cells associated with atrial fibrillation. One of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Increased levels of MCP-1 have been found in patients with AF and hypertension. The neutrophil/lymphocyte ratio (NLR) has been evaluated as a new predictor of cardiovascular risk, which is an inexpensive, easy to obtain, and widely available marker of inflammation. Additionally, it can be used as an alternative to the traditional markers. For example, in one study, elevated pre- and postoperative N/L ratios were associated with an increased occurrence of AF after coronary artery bypass grafting [20]. Mesut Aydin et al. in retrospective study found significantly higher neutrophil/lymphocyte ratio (NLR) values in patients with documented supraventricular tachycardia (SVT) compared with their control group [21].

**AF and hypertension**

The relation between inflammation and AF in patients with hypertension has not yet been established [5]. So far, in the animal model of hypertension, leucocyte infiltration into the atria as well as inflammation followed by atrial fibrosis have been investigated [22]. It has been observed that the atrial stretch, due to the elevated left ventricular diastolic pressure in patients with hypertension, might activate regional renin–angiotensin–aldosterone system (RAAS), cardiac apoptosis, and oxidative stress, which can subsequently induce the regional inflammation in the heart [23]. Experimental studies have also revealed that angiotensin II possesses several pro-inflammatory properties: blocking of the RAAS by either ACE-inhibitors or angiotensin II receptor blockers have shown to improve endothelial function and reduce inducibility of AF [24].

**Cardiosurgery and ablation**

AF remains one of the most frequent complications after coronary artery bypass graft surgery (CABG). Bruins et al. were first to propose the inflammation-AF hypothesis, following their observations of an increased frequency of AF after CABG [25]. After studying the activation of a complement system during and after CABG, they reported the biphasic complement activation. The first phase occurs during cardiopulmonary bypass itself while the second phase occurs during the first 5 days after surgery, which involves CRP elevation associated with atrial arrhythmias. Interestingly, in the study of Ishida et al. which included patients undergoing off-pump CABG surgery, statistic analysis indicated that the highest quartile of IL-6 level immediately after the surgery varied by patients’ age and can independently predict postoperative AF [26]. It was observed that nonsteroidal anti-inflammatory medications given in the imme-

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**Table 1. Biomarkers of inflammation involved in the pathophysiology of atrial fibrillation [5, 16]**

<table>
<thead>
<tr>
<th>Inflammatory Biomarkers</th>
<th>Targets and Effects</th>
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<tbody>
<tr>
<td>IL-2</td>
<td>Secreted by T cells stimulates growth and differentiation of T cell response. IL-2 is also a predictor of AF after cardioversion and after surgery.</td>
</tr>
<tr>
<td>IL-6</td>
<td>Secreted by macrophages and endothelial cells influences adaptive immunity. IL-6 has both proinflammatory and cytoprotective functions. It has been proven that IL-6 is also a predictor of AF after cardioversion and after ablation. Combined with CRP it independently predicts strokes in patients with AF.</td>
</tr>
<tr>
<td>IL-8</td>
<td>Chemokine is produced by macrophages and epithelial cells associated with atrial fibrillation.</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>Secreted by hepatocytes is a predictor of the development of AF after cardiac surgery and after ablation. Increased levels of CRP have been found in patients with new-onset AF. Longer duration of AF is associated with higher CRP levels and larger LA diameter.</td>
</tr>
<tr>
<td>MCP-1</td>
<td>One of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Increased levels of MCP-1 have been found in lone atrial fibrillation.</td>
</tr>
<tr>
<td>HSP27</td>
<td>HSP-27 can downregulate TNF expression and upregulate IL-10 levels. HSP-27 is a predictor of AF recurrence after catheter ablation.</td>
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In patients with AF, inflammatory cytokines IL-6 and CRP were related to the higher risk of vascular death and thromboembolic events independent of clinical risk factors [18]. In another study the circulating biomarkers of inflammation, CRP, and oxidative stress, oxLDL, were higher in lone AF patients compared to healthy individuals and both biomarkers were associated with an increased risk of hypertension in lone AF [19]. The relation between inflammation and AF in patients with hypertension has not yet been established [5]. So far, in the animal model of hypertension, leucocyte infiltration into the atria as well as inflammation followed by atrial fibrosis have been investigated [22]. It has been observed that the atrial stretch, due to the elevated left ventricular diastolic pressure in patients with hypertension, might activate regional renin–angiotensin–aldosterone system (RAAS), cardiac apoptosis, and oxidative stress, which can subsequently induce the regional inflammation in the heart [23]. Experimental studies have also revealed that angiotensin II possesses several pro-inflammatory properties: blocking of the RAAS by either ACE-inhibitors or angiotensin II receptor blockers have shown to improve endothelial function and reduce inducibility of AF [24].

**Cardiosurgery and ablation**

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diately postoperative period of CABG surgery are relatively safe and effective in reducing the incidence of AF and favorably affect the length of hospitalization. In addition, Marcus et al. have proved that CRP and IL-6 levels were elevated in patients with atrial flutter (AFL). These levels of biomarkers fall significantly after ablation of AFL, which proved that arrhythmia is the cause of the inflammation [27]. Indeed, Richter et al. showed that markers of oxidative stress and inflammation were up-regulated 2 days after ablation of atrial fibrillation and their up-regulation was associated with an early recurrence of AF, but it didn’t predict long-term outcome [28].

In the study of Lim the increased levels of inflammatory biomarkers were observed within the first 3 days after radiofrequency (RF) ablation for AF. The level of inflammatory response was directly associated with early AF recurrence. The elevation in the prothrombotic markers, fibrinogen and D-dimer occurred 7 days after ablation and was correlated with the inflammatory response [29].

In another study which compared cryoablation and open-irrigated RF ablation for AFL, the increase in inflammatory markers was significantly greater in the second method. The higher CRP levels during the RF energy might have occurred due to endothelial damage and surface thrombosis. Patients who received cryoablation, had higher levels of myocardial injury (CK, CKMB, TnT) due to cardiomyocyte swelling and irreversible cell death by the rupture of membranes [30].

In the study of Malmborg et al. cryoballon catheter ablation was also associated with greater myocardial injury than the one performed by RF energy-based pulmonary vein ablation catheter (PVAC). Nevertheless, there was no difference in the coagulation and inflammation activity between these two techniques [31].

**AF and electrical remodeling**

The key features of electrical remodeling are shortening of the atrial refractory period, the loss of rate adaptation, an increase in dispersion, slowing down of conduction velocity, and the presence of triggering foci. The shortening of the atrial effective refractory period takes place due to accumulation of calcium within atrial myocytes and, as a result, leads to the reduction of the inward L-type Ca\(^{2+}\) current, which in turn contributes to the promotion and maintenance of multiple wavelet-reentry circuits. Decreased Na current (I\(_{\text{Na}}\)), impaired connexin channel function and enhanced fibrosis deposition, by contrast, slow conduction and promote AF-maintaining reentry [32]. Calcium homeostasis in cardiomyocytes is regulated by TNF, PDGF, and IL-2, which are associated with increased triggering and shortening of the action potential duration. Abnormal intracellular Ca\(^{2+}\) handling is emerging as a key contributor to AF that promotes both ectopic activity and reentry. Delayed afterdepolarization is initiated by diastolic Ca\(^{2+}\) leak from the sarcoplasmic reticulum [5, 32] According to Lee et al., TNF induces abnormal Ca\(^{2+}\) handling and arrhythmogenicity in pulmonary vein cardiomyocytes [33]. TNF can also decrease the expression of sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\) ATPase 2a (SERCA2a) by enhancing methylation in the promoter region [34]. PDGF-A, which promotes cell proliferation and collagen expression in cardiac fibroblasts, increases atrial fibrosis and susceptibility to AF [35]. In clinical studies, high CRP and IL-6 levels, are associated with increased atrial size, which further contributes to inflammation in atrial remodeling [36]. Indeed, the levels of myeloperoxidase in atrial tissue are higher in patients with AF than in individuals with sinus rhythm. Also, the increased blood myeloperoxidase level has been associated with early AF recurrence after catheter ablation [37].

**Ventricular arrhythmias, inflammation and the prevention of sudden cardiac death**

Approximately 50% of cardiac arrests occur in case of individuals without a known heart disease but most of them suffer from a concealed ischaemic heart disease. Nevertheless, it is known that inflammatory heart diseases lead to malignant ventricular arrhythmias and sudden cardiac death [38]. In nested, case-control study of apparently healthy male physicians, baseline plasma CRP levels were positively associated with risk of sudden cardiac death (SCD) over the ensuing 17 years of follow-up. The meantime to SCD was 9.2 years (range 0.7 to 16.8 years). One clinical implication of these data is that markers of inflammation may be useful in identifying men at higher risk of SCD who have no obvious signs of coronary heart disease (CHD) many years before the fatal event [39]. In another study of six hundred seventy eight healthy middle-aged and elderly subjects with no apparent heart disease and frequent ventricular premature complexes (VPC), a CRP values > 2.5 μg/mL were associated with a significantly higher risk of death and acute myocardial infarction [40].
Myocarditis

Myocarditis is the pathological myocardial infection and autoimmunity that causes active inflammatory destruction of myocytes. Aetiologically, a wide spectrum of infectious agents, including viruses, bacteria as well as toxic and hypersensitivity reactions might be involved. Enteroviruses, especially Coxsackie B, adenoviruses and parvovirus B19 are among the most common causal agents. The typical microscopic image involves the presence of inflammatory cells together with necrotic myocytes [41].

Ventricular premature beats are typical forms of cardiac arrhythmias in myocarditis. Nevertheless, they may also include malignant ventricular tachycardia or ventricular fibrillation. Myocarditis can also be a factor responsible for sudden cardiac death in young people [42]. The electrocardiogram (ECG) is a sensitive tool used for diagnosis of myocarditis (in case of abnormal ST – T waves and conduction block are frequently observed in myocarditis). ECG manifestations are diverse, and include atrioventricular block (I to III degree), intraventricular conduction delay (widened QRS complex), frequent premature beats, supraventricular tachycardia, atrial fibrillation, sinus arrest, ventricular tachycardia, ventricular fibrillation, and asystole [43].

Considering malignant arrhythmias associated with myocarditis, two distinct clinical settings have to be distinguished: acute fulminant myocarditis and inflammatory cardiomyopathy. The first is associated with refractory malignant ventricular tachycardia in the context of severe acute heart failure (HF), and adverse short-term prognosis with early death due to multisystem failure. On the other hand long-term evolution to inflammatory cardiomyopathy with LV dysfunction results in a high risk of sudden cardiac death (SCD) similar to that for dilated cardiomyopathy (DCM). Patients with fulminant myocarditis have a high mortality rate and a severe risk of life-threatening refractory ventricular tachyarrhythmias. The important association between undiagnosed myocarditis and SCD is emphasized by post-mortem data, which have implicated myocarditis in SCD of young adults at rates of 8.6–44% [38].

In fulminant myocarditis most patients have markedly increased leucocytes (WBC) and CRP. Moreover in the study of Aoyama et al., all readmitted patients had abnormally increased WBC and CRP during their follow-up [44]. In another study creatine kinase (CK) and CRP levels declined sharply during the therapy of fulminant myocarditis by intravenous methylprednisolone, which was associated with hemodynamic improvement measured by the improved left ventricle ejection fraction (LVEF) [45].

In the study of Bironaite et al. the concentration of IL-6 and hsCRP in the inflammatory dilated cardiomyopathy (iDCM) was increased. Persistent myocardial stressors increase T-lymphocytes in myocardium of iDCM patients. Moreover, chronic myocardial inflammation affected mitochondria and triggered significant release of Hsp-60, MMP-9/TIMP1 suggesting apoptotic pathways [46].

The pathogenesis of cardiac arrhythmias in the myocarditis is complex. The process was explained in the murine model of myocarditis. One of the triggers is the active process of inflammation related to the presence of the virus in the first stage of the disease. This process leads to the activation of immune system, characterized by the invasion of the natural killer cells and macrophages followed by T-lymphocytes. In this stage various cytokines including IL-1β, TNF-α, IFN-γ, and IL-2 are produced. The next process called subacute myocarditis is defined by activated virus-specific T lymphocytes. These cells play critical role in eliminating infected myocardial cells and limiting viral replication [47]. Pathological changes in the myocardium especially myocardial necrosis and replacement fibrosis (favoring re-entry mechanism) seem to be the major arrhythmogenic substrate. Proarrhythmic effects of the cytokines and inflammatory mediators may be related to the changes in the ion channel function (especially in the potassium and calcium channels). These modifications lead to the prolongation of the ventricular effective refractory period.

Pericarditis

The etiology of pericarditis may be similar to myocarditis with infective (viruses, bacteria) an non-infective (i.e. autoimmunity) agents. Acute pericarditis in isolation does not seem to be frequently associated with ventricular arrhythmia but is often present as perimyocarditis with a burden of arrhythmia related to the myocardial component [43]. Furthermore, SCD in these patients has mostly a haemodynamic and not an arrhythmogenic cause.

According to Imazio et al. C-reactive protein, WBC levels were higher in patients with pericarditis compared with those with myopericarditis/perimyocarditis [48]. In another study hs-CRP levels were elevated at the initial presentation in 78% of patients and com-
Inflammation plays an important role in the formation and maintenance of cardiac arrhythmias. Inflammatory biomarkers may prove useful in predicting the onset of cardiac arrhythmias and their complications. Inflammation and oxidative stress directly affect myocyte apoptosis and cardiac fibrosis, thus lead to progressive electrophysiological changes of the myocardium, which consequently contribute to arrhythmias. A better knowledge of the role of inflammation in the pathophysiology of cardiac arrhythmias is necessary to individualize treatment and develop future therapeutic strategies. New therapies might require the specific targeting of inflammatory biomarkers in addition to the modification of other factors to produce beneficial results [5]. Also, further clinical trials are necessary for the development of anti-inflammatory therapies in the prevention of AF. Identifying unique methods to improve imaging, autonomic modulation, inflammatory biomarkers will help us to better understand the patients with cardiac arrhythmias.

**List of abbreviations**

- AF – atrial fibrillation
- PAF – paroxysmal atrial fibrillation
- CRP – C-reactive protein
- IL – interleukin
- TNF – tumor necrosis factor
- MCP – monocyte chemoattractant protein
- EAM – experimental autoimmune myocarditis
- NLR – neutrophil/lymphocyte ratio
- SVT – supraventricular tachycardia
- RAAS – renin–angiotensin–aldosterone system
- CABG – coronary artery bypass graft
- AFI – atrial flutter
- RF – radiofrequency
- SCD – sudden cardiac death
- CHD – coronary heart disease
- VPC – ventricular premature complexes
- ECG – electrocardiogram
- HF – heart failure
- DCM – dilated cardiomyopathy
- IRAP – idiopathic recurrent acute pericarditis
- MAPD – monophasic action potential duration
- ERP – effective refractory period

**Conclusion**

A better knowledge of the role of inflammation in the pathophysiology of cardiac arrhythmias is necessary to individualize treatment and develop future therapeutic strategies. New therapies might require the specific targeting of inflammatory biomarkers in addition to the modification of other factors to produce beneficial results [5]. Also, further clinical trials are necessary for the development of anti-inflammatory therapies in the prevention of AF. Identifying unique methods to improve imaging, autonomic modulation, inflammatory biomarkers will help us to better understand the patients with cardiac arrhythmias.

**References**


**Acknowledgements**

**Conflict of interest statement**

The authors declare no conflict of interest.

**Funding sources**

There are no sources of funding to declare.


Acceptance for editing: 2016-06-10
Acceptance for publication: 2016-06-23

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