Cardiac Arrhythmias in Autoimmune Diseases

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Autoimmune diseases (ADs) affect approximately 10% of the world's population. Because ADs are frequently systemic disorders, cardiac involvement is common. In this review we focus on typical arrhythmias and their pathogenesis, arrhythmia-associated mortality, and possible treatment options among selected ADs (sarcoidosis, systemic lupus erythematosus, scleroderma, type 1 diabetes, Graves' disease, rheumatoid arthritis, ankylosing spondylitis [AS], psoriasis, celiac disease [CD], and inflammatory bowel disease [IBD]). Rhythm disorders have different underlying pathophysiology; myocardial inflammation and fibrosis seem to be the most important factors. Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodeling. Furthermore, chronic inflammation is the pathophysiological basis linking AD to autonomic dysfunction, including sympathetic overactivation and a decline in parasympathetic function. Autoantibody-mediated inhibitory effects of cellular events (i.e., potassium or L-type calcium currents, M_2 muscarinic cholinergic or β_1-adrenergic receptor signaling) can also lead to cardiac arrhythmia. Drug-induced arrhythmias, caused, for example, by corticosteroids, methotrexate, chloroquine, are also observed among AD patients. The most common arrhythmia in most AD presentations is atrial arrhythmia (particularly atrial fibrillation), expect for sarcoidosis and scleroderma, which are characterized by a higher burden of ventricular arrhythmia. Arrhythmia-associated mortality is highest among patients with sarcoidosis and lowest among those with AS; there are scant data related to mortality in patients with psoriasis, CD, and IBD.

Key Words: Atrial fibrillation; Autoimmune disease; Immunosuppression; Inflammation; Remodeling

The prevalence of autoimmune disease (AD) has increased significantly over the past 30 years due to improved detection and surveillance, and currently affects approximately 7.6–9.4% of the world’s population. Because ADs are frequently systemic disorders affecting different structures and organs, cardiac involvement is common among AD patients. The structural changes to heart tissue caused by AD-mediated processes can result in different manifestations (i.e., ischemia-related symptoms, heart failure, frequently arrhythmias, and even sudden cardiac death).

There are different pathophysiological mechanisms underlying the rhythm disorders. However, myocardial inflammation and fibrosis seem to be the most important. Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodeling. Furthermore, chronic inflammation is the pathophysiological link between AD and autonomic dysfunction, including sympathetic overactivation and a decline in parasympathetic function. Autoantibody-mediated and drug-induced arrhythmias are also frequently observed among AD patients.

Currently, there are 80–100 described diseases that occur as a result of autoimmune responses. In this review we focus on typical arrhythmias, their prevalence, and their pathogenesis (Table 1), arrhythmia-associated mortality (Table 2), and proposed possible treatment options among selected ADs, namely sarcoidosis, systemic lupus erythematosus (SLE), scleroderma, type 1 diabetes (T1D), Graves' disease (GD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, celiac disease (CD), and inflammatory bowel disease (IBD).

**Sarcoidosis**

Sarcoidosis is a multisystem inflammatory disease of unknown etiology that manifests as a triad of erythema nodosum, bilateral hilar lymphadenopathy on chest radiograph, and joint pain. The prevalence of sarcoidosis ranges from 2.2 to 160 cases per 100,000 people. Ventricular tachycardia (VT) is the most common rhythm disorder in sarcoidosis, encountered up to 23% of patients. Atrial arrhythmias are less common, occurring in 15–17% of patients, although small studies have reported a 32% risk of supraventricular arrhythmia. The most common observed supraventricular arrhythmia is atrial fibrillation.
Pharmacotherapy is also complicated by the presence of certain acidic acute phase reactants that bind to drugs with a high acid-base dissociation constant, thus interfering with serum concentrations.

Some studies recommend implantable cardioverter-defibrillator (ICD) placement in patients with sarcoidosis and non-sustained VT given the high rate of recurrent VT despite antiarrhythmic and corticosteroid treatment. One systemic review that included 91 patients from 6 papers reported beneficial data on catheter ablation of VT in sarcoidosis and an arrhythmia-free survival rate ranging from 25% to 57% during a 6- to 33-month follow-up. A more extensive arrhythmogenic substrate with more advanced cardiac disease at the time of VT ablation may be the reason for this discrepancy. In that review, the reported rate of procedural complications did not exceed 4.7–6.4%. The most frequent location of the re-entry circuit is the paratricuspid area. In patients with predominant right ventricle (RV) involvement, critical sites in the RV apex have also been described. In patients with epicardial scarring, an epicardial approach may be necessary to eliminate VT.

Therefore, planning the ablation procedure based on the predominant location of scarring as detected by late gadolinium-enhanced cardiovascular magnetic resonance is helpful in eliminating VT in these patients.

(AF; 18%), followed by atrial tachycardias (7%), atrial flutter (5%), and atrioventricular nodal re-entry tachycardia (2%).

Postulated proarrhythmic mechanisms include active inflammation and enhanced automaticity. The re-entrant pathway can result from active granulomatous inflammation, but can also be found in association with the healing of cardiac granulomas in the inactive phase of the disease. Atrial dilatation or pulmonary involvement are other factors that contribute to the development of atrial arrhythmias. The role of corticosteroids remains inconsistent because they can improve cardiac function and reduce a patient’s arrhythmic burden, but they also promote fibrosis of active granulomas and subsequent re-entrant pathways, leading to recurrent VT. In addition, corticosteroids have been associated with the formation of ventricular aneurysms, leading to a vicious circle of ventricular arrhythmias. Therefore, immunosuppressive therapies are recommended in cases of resistant arrhythmias or as a steroid-sparing strategy.

Ambroginone and sotalol are widely used to treat VT in patients with sarcoidosis, although adverse reactions (pulmonary complications and heart block) in patients with sarcoidosis may limit their applicability. Class I antiarrhythmic agents are not recommended due to frequent myocardial scarring. Pharmacotherapy is also complicated by the presence of certain acidic acute phase reactants that bind to drugs with a high acid-base dissociation constant, thus interfering with serum concentrations.

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Although there is a high VT relapse rate, catheter ablation decreases the overall ventricular arrhythmia burden in 88.4% of sarcoidosis patients. Willner et al described the role of catheter ablation for atrial arrhythmia in 9 patients with cardiac sarcoidosis. Of these 9 patients, 7 remained free from recurrence at 1.8±1.9 years of follow-up and 2 had recurrent atrial arrhythmia. Of the 2 with recurrent atrial arrhythmia, 1 underwent successful repeat ablation of atypical atrial flutter and remained free from recurrence at 2 years, and the second was started on dofetilide and continued on immunosuppressive therapy and was free of recurrence at 10 months.

Nevertheless, resistant VT and severe intractable heart failure, especially in younger patients, are indications for cardiac transplantation in patients with sarcoidosis.

Systemic Lupus Erythematous

SLE is a chronic inflammatory disease with a prevalence ranging from 0.3 to 241 per 100,000 population. SLE is described as a triad of fever, joint pain, and butterfly rash. The causes of premature death associated with SLE are primarily organ failure or cardiovascular disease secondary to accelerated atherosclerosis. More than 80% of SLE patients survive for more than 10 years with proper diagnosis and treatment.

Sinus tachycardia (15–50%), AF, and atrial ectopic beats are the most frequent cardiac rhythm disorders among SLE patients. In the study of Teixeira et al, which included 317 patients with SLE, frequent Holter-monitoring abnormalities were observed in approximately 85% of SLE patients, including supraventricular ectopy (63.4%), ventricular ectopy (45.8%), Bradycardia (31.7%), atrial tachycardia (15.5%), and AF (2.8%). Although, ventricular arrhythmias are infrequent among SLE patients, the Systemic Lupus International Collaborating Clinics Registry revealed a high prevalence of QT prolongation (15.3%) and increased QT dispersion (38.1%), both of which are recognized as independent risk factors for the development of complex ventricular arrhythmias.

The pathophysiology of arrhythmias in SLE includes initial inflammatory cell infiltration and, as the disease advances, myocardial necrosis and fibrotic replacement. Consequently, multiple small areas of fibrosis can affect atrial and ventricular repolarization and conduction, leading to cardiac rhythm disorders. Interestingly, a possible role of autoantibodies, namely anti-Sjögren’s-syndrome-related antigen A (Ro/SSA) autoantibodies, in cardiac rhythm disorders has also been suggested. These antibodies can bind calcium channels and downregulate channel density and protein expression, which results in deregulation of intracellular calcium homeostasis and finally apoptosis of cardiomyocytes. Moreover, previous studies reported a correlation between anti-Ro/SSA antibodies and M3 muscarinic receptors leading to a decrease in parasympathetic activity. Increased titers of anti-SS-A/Ro antibodies described in SLE seem to also be associated with prolongation of the QTc interval. Lazzarini et al reported that in addition to a high prevalence of QTc interval prolongation, anti-Ro/SSA-positive patients also have reduced heart rate variability (HRV) and a high incidence of late ventricular potentials. Case reports have also showed a correlation between new onset AF and methylprednisolone therapy, possibly caused by potassium efflux and the development of late potentials. Finally, sympathetic hyperactivity indicated by elevated norepinephrine levels could play an etiologic role in a wide range of diseases, including SLE.

In general, standard medications for SLE (i.e., glucocorticosteroids and anti-malarial drugs) often caused tachyarrhythmias and QRS prolongation. However, treatment with chloroquine seems to have a protective effect because it reduces the velocity of the action potential of the cells in the conduction system, prolonging the action potential duration and increasing the refractory period of Purkinje fibers. Furthermore, chloroquine can bind to and block the Kir2.1 potassium channel, resulting in an antifibrillatory effect. Conversely, a cumulative chloroquine dose above median of 1,207 g can lead to cardiac toxicity and associated electrocardiogram abnormalities.

Methotrexate and cyclophosphamide may rarely induce ventricular arrhythmias. Mycophenolate mofetil, tacrolimus, and rituximab can cause tachycardia (and AF in the case of rituximab). In contrast, azathioprine and belimumab are assumed to be safe in terms of arrhythmia induction.

In this context, adjusting SLE drug therapy may be a valuable therapeutic option to reduce the burden of clinically relevant arrhythmias.

Catheter ablation seems to be safe in drug-resistant AF. However, dal Piaz et al reported frequent recurrences of AF that could be explained by the presence of thickening of the left atrial (LA) wall associated with extensive atrial fibrosis. Furthermore, electroanatomic mapping frequently reveals large areas of low bipolar voltage in the anterior wall, septum, posterior wall, and roof (~52% of the LA surface).

Scleroderma

Scleroderma may be systemic (SSc), characterized by abnormal hardening and thickness of the skin and organs, or localized (LSc), affecting only the skin. The prevalence of scleroderma varies from 3.1 to 65.9 per 100,000 population.

Patients with scleroderma have been found to have a higher mean heart rate (81±11 beats/min), whereas more cases of sinus tachycardia are reported in LSc than SSc. The most widespread arrhythmias are premature ventricular contractions (PVC; 20–67%) and VT (7–28%). Supraventricular arrhythmias are also frequent and may be present in 32–66% of scleroderma patients. However, the distribution of arrhythmias in pediatric patients is reversed. Cardiac involvement is most frequent in SSc. Of note, a wider spatial QRS–T angle >19.3° and ventricular late potentials have been suggested as independent predictors of ventricular arrhythmias.

Myocardial fibrosis, which disrupts the normal electrical connectivity of cardiac tissue, is the most common pathogenesis of cardiac rhythm disorders. Ventricular arrhythmias are 6-fold more frequent in patients with severe myocardial scleroderma than in those with mild or no scleroderma. Arrhythmogenesis could result from the production of anti-β-adrenergic receptor antibodies, which have been found with idiopathic arrhythmias and autonomic dysfunction, often preceding the development of fibrosis. Arrhythmias may also be a consequence of LA and RV dilation secondary to a higher prevalence of pulmonary hypertension, more severe mitral and tricuspid regurgitation, and terminal renal failure. Moreover, transient coronary vasoconstriction, with reversible myocardial ischemia and dysfunction, has been demonstrated in...
response to peripheral cold exposure in scleroderma patients.\textsuperscript{45}

Vasodilator therapy with dihydropyridine-type calcium channel blockers (CCBs) may improve cardiac perfusion and ventricular function,\textsuperscript{46} potentially reducing the burden of arrhythmias. However, it is worth noting that these agents may have a negative inotropic effect and cause reflex tachycardia, and so their use must be closely monitored.

The benefits of ICD implantation in 10 scleroderma patients with evidence of ventricular arrhythmias were recently reported: over a 3-year-follow up, 30\% of patients were appropriately reverted by shock delivery.\textsuperscript{47} In another study, patients with more than 1,190 PVC per 24h were identified as being at high risk of life-threatening arrhythmias.\textsuperscript{48}

Successful treatment with catheter ablation, even in a hemodynamically unstable scleroderma patients, has been reported.\textsuperscript{49} Patients treated with catheter ablation remained free of VT recurrence for the following 14–25 months.\textsuperscript{48} The origin of the re-entrant VT appears to be the RV, primarily the outflow tract.\textsuperscript{48} Integration of magnetic resonance imaging with 3D mapping systems could also greatly facilitate electrophysiology procedures.

**Type 1 Diabetes**

T1D is a chronic disease caused by insulin deficiency following the destruction of insulin-producing pancreatic \( \beta \)-cells. The reported prevalence of T1D across the world ranges from 6.7 to 427.5 per 100,000 population.\textsuperscript{50}

One of the best described arrhythmias among T1D patients, especially in young females, is AF.\textsuperscript{51} The risk of AF in men and women with T1D is 9–13\% and 26–50\%, respectively, than that in the general population.\textsuperscript{52} Furthermore, QT interval prolongation has been reported in T2D.\textsuperscript{53}

The pathophysiology of arrhythmias in T1D includes inflammation and oxidative stress. Cytokines (interleukin-6, IL-2, tumor necrosis factor [TNF]-\( \alpha \), transforming growth factor [TGF]-\( \beta \), connective TGF) promote collagen deposition, myocyte apoptosis, and fibrosis.\textsuperscript{54} Increased levels of systemic oxidative stress coupled with production of reactive oxygen species via the mitochondrial pathway\textsuperscript{55} induce the nuclear factor (NK)-\( \kappa \)-B pathway, leading to atrial remodeling.\textsuperscript{56} T1D-related oxidative stress attenuates potassium, L-type calcium, and sodium-potassium and sodium-calcium exchanger currents, resulting in a small depolarization in the resting membrane potential that prolongs the action potential duration.\textsuperscript{57} Moreover, advanced glycation end-products and their receptors,\textsuperscript{58} the Rho-associated protein kinase pathway,\textsuperscript{59} and decreased expression of peroxisome proliferator activated receptor \( \gamma \)\textsuperscript{60} and the paired-like homeodomain transcription factor 2 (\textit{Pitx2}) gene\textsuperscript{61} can play a role in the development of atrial fibrosis in diabetic hearts. In addition, left ventricular dysfunction and hypertrophy, the first proarrhythmic changes in patients with impaired glucose tolerance, increase LA afterload pressure, leading to atrial dilation and AF.\textsuperscript{62} In addition, in many animal models, increased expression of connexin-43 and cathepsin A (the expression of which is associated with impaired LA emptying function, increased LA fibrosis, and regions of slow conduction) has been noted as a potential proarrhythmic mechanism.\textsuperscript{63} T1D-related enhanced sympathetic and decreased parasympathetic activity are also crucial contributors to increased AF in diabetics.\textsuperscript{64}

Moreover, sudden sympathetic activation in response to hypoglycemia also contributes to the occurrence of AF and ventricular arrhythmias in certain cases.\textsuperscript{65}

It has been suggested that stringent glycemic control could reduce the incidence of AF in T2D.\textsuperscript{66} However, the Action to Control Cardiovascular Risk in Diabetes trial failed to show a benefit of intensive vs. standard glycemic control on the occurrence of new-onset AF in T2D.\textsuperscript{67} Nevertheless, various antiarrhythmic agents have been shown to reduce AF risk since metformin,\textsuperscript{68} rosiglitazone, pioglitazone,\textsuperscript{69} and thiazolidinediones\textsuperscript{70} were reported to attenuate oxidative stress, inflammation, fibrosis, and associated atrial remodeling.

Compared with antiarrhythmic drug therapy, catheter ablation of AF was associated with improved quality of life, reduced AF hospitalizations (8.6\% vs. 34.3\%; P=0.01) and a decreased likelihood of AF recurrence (20\% vs. 57.1\%; P=0.001).\textsuperscript{71} However, in the study of Tang et al, pulmonary vein isolation was similarly effective in patients with and without T2D, but T2D patients were more prone to develop post-procedural complications.\textsuperscript{72} Of note, in patients undergoing catheter ablation for AF, maintenance of sinus rhythm was higher and the need for a second ablation was lower in the group of patients treated with pioglitazone.\textsuperscript{73} Finally, in patients with T1D/T2D (no information regarding diabetes type in the article), low-voltage areas were more frequently observed than in the control group.\textsuperscript{74}

**Graves’ Disease**

GD is characterized by hyperthyroidism due to circulating thyrotropin receptor antibodies. The annual prevalence of GD ranges from 200 to 500 cases per 100,000 population.\textsuperscript{75}

The most common cardiac rhythm disorder among GD patients is AF.\textsuperscript{76} Sawin et al reported a 2.8-fold increased risk of AF in individuals with subclinical hyperthyroid aged >60 years.\textsuperscript{77} There is also a single report of ventricular arrhythmias among GD patients.\textsuperscript{78} AF in hyperthyroid patients is explained by a decreased atrial refractory period, increased sympathetic tone with decreased HRV, and automaticity in the pulmonary vein.\textsuperscript{79}

Watanabe et al found that decreased the atrial refractory period is caused by thyroid hormone-mediated decreases in the expression of L-type calcium channel mRNA and increased expression of the K-1.5 potassium channel.\textsuperscript{80} The presence of autoantibodies to both \( \beta \)-adrenergic and M\textsubscript{2} muscarinic cholinergic receptors results in increased sympathetic function and a decreased atrial refractory period.\textsuperscript{81} The correlation between hyperthyroidism and ventricular arrhythmia is explained by the effects of thyroid hormone on cardiac myocyte Na\textsuperscript{+}/K\textsuperscript{+}-ATPase, further increasing intracellular potassium levels, hyperpolarizing the membrane and prolonging repolarization, which manifests as a prolonged QTc interval.\textsuperscript{82}

Berker et al reported that improvements in atrial conduction were associated with euthyroidism regardless of the chosen therapy.\textsuperscript{83} Patients with GD and AF who become hypothyroid are more likely to revert to sinus rhythm than those who are rendered euthyroid during this period.\textsuperscript{84} Surgical treatment of GD resulted in rapid clinical improvement of impaired left ventricular systolic function as well as the resolution of tachycardia and AF in 68.8\% and 100\% of patients, respectively.\textsuperscript{85} Disopyramide, bepridil, and prednisone therapy resulted in conversion to sinus
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rhythm in 1%, 81.3%, and 86% of patients, respectively.84 In addition, prednisone therapy proved to be beneficial in reverting AF into sinus rhythm among GD patients, with a reversion rate of 86% and a mean reversion time of 3.8 months.85

Ma et al studied the efficacy of circumferential pulmonary vein ablation and found that AF relapsed over a mean follow-up period of 15.8 months in 44% of 16 patients with thyrotoxic AF.86 In addition, non-pulmonary vein triggers are significantly more often observed in patients with hyperthyroidism and there is a higher risk of occurrence of AF after a single ablation compared to controls.87 It is worth noting that elevated thyroidin levels increase the risk of a thrombotic event by increasing Factor VIII, Factor IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1 levels and by decreasing antithrombin III.88 and anticoagulation treatment may be considered.89

**Rheumatoid Arthritis**

RA primarily attacks the synovial tissues within the small joints, leading to limitation of movements. The prevalence of RA varies between 180 and 1,070 per 100,000 population.90

The most frequent arrhythmia among RA patients is AF, especially in young (<50 years) females with sedimentation rates >60 mm/h or anti-TNF-α antibodies.91 In a Danish cohort study of 4,182,335 participants, including 18,247 with RA, the overall incidence of AF was approximately 40% higher than in the general population.92 However, in the subsequent meta-analysis of 3 retrospective cohort studies, the pooled risk ratio of developing AF in patients with RA vs. controls was only 1.29, because in 2 of those studies no increased risk of incident AF was observed after adjusting for comorbidity and medication.93 Although described by smaller cohort studies, other frequent arrhythmias among RA patients are PVC and VT.94

The basis for rhythm disorder is diffuse cardiac involvement (rheumatoid nodules or inflammatory lesions), as well as coronary vasculitis and coronary atherosclerotic disease, which lead to perfusion defects of the myocardium with proarrhythmic effects.95 Moreover, antibodies against the cardiac conduction system,96 found in 35% of patients with RA, which increase P-wave dispersion (PWD) and LA diameter,97 may play important a role in conduction abnormalities in RA patients. Increased sympathetic and decreased parasympathetic activity could play a crucial role in the development of VT in RA patients.101 Reports suggest that the anti-inflammatory drug infliximab may be associated with new-onset ventricular tachyarrhythmias.98

Early therapy with disease-modifying antirheumatic drugs has been demonstrated to have beneficial effects on the lipid profile and to reduce atherosclerotic processes and endothelial dysfunction by decreasing inflammation.102 The success rate of catheter ablation for AF in patients with RA is comparable to that in patients without RA. However, RA patients tend to develop early atrial tachyarrhythmia recurrence after AF ablation compared with controls, as shown in a small group of patients (n=15).103

**Psoriasis**

Psoriasis is a chronic inflammatory condition characterized by excessive growth of the epidermal layer of the skin and associated patches of abnormal, thickened skin. The reported prevalence of psoriasis ranges between 100 and 200 per 100,000 population.111 Patients with psoriasis are more susceptible to AF than the general population,112,113 with a severity-adjusted risk of 1.50–2.98 in patients aged <50 years and 1.16–1.29 in those aged ≥50 years.114 Commonly seen arrhythmias in patients are also single supraventricular beats115 and ventricular arrhythmias, including VT related to commonly observed increased PWD and QT dispersion.116

Chronic inflammation mediated by systemic inflammatory cytokines, such as TNF-α, IL-6, and IL-17, is the most important contributor linking psoriasis to increased AF incidence.117 Another structural remodeling factor with increased bioactivity in psoriasis is platelet-derived growth factor α (PDGFα), which promotes cell proliferation and collagen expression in cardiac fibroblasts. Moreover, TNF-α and PDGFα are responsible for electronic remodeling: TNF-α interferes with calcium influx into pulmonary vein cardiomyocytes,118 whereas PDGFα reduces the action potential duration and calcium transients.119 Sympathetic nervous system dysregulation,120 inflammation-related structural mitral valve changes,121 and depression122 may be other possible reasons for the high incidence of AF among those with psoriasis.

Methotrexate and TNF inhibitors are associated with a decreased risk of cardiovascular disease morbidity and mortality, whereas ustekinumab appears to be neutral.123 Patients using TNF inhibitors have a lower risk of cardiovascular events that those undergoing phototherapy. In
addition, phototherapy has been reported to have no major cardiovascular effect and may reduce levels of proinflammatory cytokines. Statins, with anti-inflammatory and antioxidative effects, also reduce the incidence of both AF and psoriasis.

Celiac Disease

CD is a life-long gluten-sensitive AD primarily involving the small intestine, but with potential effects in other organ systems, genetically affecting susceptible individuals. The worldwide prevalence of CD is 660 per 100,000 population.

The most common cardiac arrhythmia in CD is AF, with a reported incidence 30% higher than in the general population. An elevated risk of ventricular arrhythmias (multiform and repetitive couplets of PVCs) has been also reported.

This increased risk of AF has been attributed to inflammation and fibrosis, the coexistence of other autoimmune conditions (T1D, RA, and thyroid disease), and hyperhomocysteinemia, resulting from vitamin B deficiency, which affects sodium and potassium channels in the atria.

In the study of Corazza et al, a QTc interval >440 ms, associated with the development of ventricular arrhythmias, was found in 32% of 53 untreated coeliac patients but in only 3% of 30 patients on a gluten-free diet. These findings are in line with those of Frustaci et al, who observed downgrading from Lown Class III–Ia to I in 187 patients following a gluten-free diet.

Inflammatory Bowel Disease

IBD is a chronic, inflammatory disease of the gastrointestinal tract and includes ulcerative colitis and Crohn’s disease. The annual prevalence of IBD is 4.9–505 per 100,000 population for ulcerative colitis, and 0.6–322 per 100,000 population for Crohn’s disease.

AF represents the most common sustained cardiac arrhythmia among patients with IBD, and its incidence increases more than 2-fold during active flare-ups of IBD.

The very powerful inflammatory cytokines implicated in AF development are C-reactive protein (CRP) and IL-6. Studies suggest that IL-6 is significantly correlated with increased LA size by stimulating matrix metalloproteinase-2 whereas increased circulating CRP may localize in atrial tissue, inducing myocarditis and electrical changes in the atrium. Furthermore, PWD and electromechanical delay, well-described predictors of AF, were high in IBD patients. These results confirm the significant decrease in parasympathetic function in patients with IBD as an important factor triggering arrhythmia.

The observed prolongation in QT interval and significant QT dispersion in IBD patients using cardiotoxic medications like infliximab or ciprofloxacin highlights the need for the continued surveillance of these patients. There are some reports in the literature focusing on the effects of azathioprine on ion channels, which may be the cause of cardiac rhythm disturbance.

Conclusions

Arrhythmias are important and frequent manifestations of cardiac involvement in patients with AD. Early recognition of life-threatening arrhythmias is crucial to improve the overall prognosis of AD patients. It is of note that most of cardiac rhythm disorders are transient and can be the first presentation of autoimmune conditions, resolving when the underlying disease is controlled. Further prospective studies and unifying registers encompassing ADs with their accompanying arrhythmias are warranted in order to explore the pathogenesis and to improve the early diagnosis of cardiac rhythm disorders.

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Conflict of Interest

None declared.

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