Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases


Rhythm and conduction disturbances and sudden cardiac death (SCD) are important manifestations of cardiac involvement in autoimmune rheumatic diseases (ARDs). In patients with rheumatoid arthritis (RA), a major cause of SCD is atherosclerotic coronary artery disease, leading to acute coronary syndrome and ventricular arrhythmias. In systemic lupus erythematosus (SLE), sinus tachycardia, atrial fibrillation and atrial ectopic beats are the major cardiac arrhythmias. In some cases, sinus tachycardia may be the only manifestation of cardiac involvement. The most frequent cardiac rhythm disturbances in systemic sclerosis (SSc) are premature ventricular contractions (PVCs), often appearing as monomorphic, single PVCs, or rarely as bigeminy, trigeminy or pairs. Transient atrial fibrillation, flutter or paroxysmal supraventricular tachycardia are also described in 20–30% of SSc patients. Non-sustained ventricular tachycardia was described in 7–13%, while SCD is reported in 5–21% of unselected patients with SSc. The conduction disorders are more frequent in ARD than the cardiac arrhythmias. In RA, infiltration of the atrioventricular (AV) node can cause right bundle branch block in 35% of patients. AV block is rare in RA, and is usually complete. In SLE small vessel vasculitis, the infiltration of the sinus or AV nodes, or active myocarditis can lead to first-degree AV block in 34–70% of patients. In contrast to RA, conduction abnormalities may regress when the underlying disease is controlled. In neonatal lupus, 3% of infants whose mothers are antibody positive develop complete heart block. Conduction disturbances in SSc are due to fibrosis of sinoatrial node, presenting as abnormal ECG, bundle and fascicular blocks and occur in 25–75% of patients.

Introduction

Several autoimmune rheumatic diseases (ARDs) impose an increased risk for the development of cardiovascular comorbidities, either through their impact on progression of atherosclerosis, thrombus formation, vasculitis or myocardial inflammation and/or fibrosis. Rhythm and conduction disturbances and sudden cardiac death (SCD) in ARD have higher incidence than in the general population [1].

In addition to standard 12-lead ECG, 24-h Holter monitoring is most widely applied for evaluation of patients with arrhythmias and conduction abnormalities (Fig. 1). ECG signal averaging can detect a substrate for malignant arrhythmias and identify patients who warrant further investigation. Invasive electrophysiology studies are indicated when spontaneous arrhythmias are infrequent and when a serious sustained arrhythmia is suspected.

Cardiac arrhythmias in autoimmune rheumatic diseases

The nature and severity of underlying ARD is often of greater prognostic significance than the arrhythmia itself. Pathophysiological substrate for rhythm disorders is related to altered automaticity, re-entry or triggered automaticity. Serious arrhythmias require additional diagnostic tests (Fig. 1), to define its cause and exclude coronary, myocardial or arrhythmogenic disorder. Fast supraventricular or ventricular tachyarrhythmias can cause clinically significant haemodynamic compromise.

Cardiac arrhythmias in rheumatoid arthritis

Coronary artery disease (CAD) is a major contributor to the increased risk of SCD in rheumatoid arthritis (RA), leading to acute coronary syndrome and ventricular arrhythmias [2]. Accelerated coronary atherosclerosis, coronary vasculitis, superimposed coronary thrombosis, myocarditis and pulmonary hypertension also contribute to the rhythm disturbances.

Heart rate variability measurement is useful for the risk assessment for ventricular arrhythmias. Significant correlation was observed between RA activity and heart rate variability [3]. In patients with high activity of RA, the decrease of heart rate variability reflects severity of inflammation. Decreased heart rate variability in degree I-II RA activity, is predictor for ventricular arrhythmias, SCD and acute myocardial infarction (MI).

Wisłowska [4] revealed cardiac involvement more frequently in nodular than in non-nodular RA and general population (71.9 vs 42.9 vs 22.9%, respectively). A 24-h Holter monitoring...
did not demonstrate significant differences in frequency of rhythm disorders between the RA patients and the controls.

**Cardiac arrhythmias in systemic lupus erythematosus**

Malignant ventricular arrhythmias are rarely reported in systemic lupus erythematosus (SLE). Sinus tachycardia, atrial fibrillation and atrial ectopic beats are most frequent. Supraventricular arrhythmias are often transient, and may be related to myocarditis and exacerbations of SLE. Sinus tachycardia occurs in 50% of patients and may be the only cardiac manifestation of SLE, resolving under corticosteroid treatment [5].

Anti-small cytoplasmic ribonucleoproteins (anti-Ro/SSA)-associated sinus bradycardia and QT interval prolongation have been described both in children and adults with ARD [6]. Abnormalities in the autonomic tone and ventricular late excitability potentially indicate high risk of developing life-threatening ventricular arrhythmias and SCD [7]. QT interval prolongation and refractory ventricular arrhythmias could also be associated with chronic hydroxychloroquine therapy for SLE [8].

**Cardiac arrhythmias in systemic sclerosis**

Atrial and ventricular arrhythmias are common among asymptomatic patients with systemic sclerosis (SSc) and may be associated with poor outcome. Transient atrial fibrillation, flutter, or paroxysmal supraventricular tachycardia, may be present in 20–30% of SSc patients.

Patchy myocardial fibrosis provides an ideal substrate for tachyarrhythmias, dependent on re-entrant circuits. Ventricular arrhythmias have been demonstrated in 67% [9], and non-sustained ventricular tachycardia (VT) in 7–13% of unselected patients with SSc [10]. Patients with frequent premature ventricular contractions (PVCs) had 50% mortality during 33 months follow-up in contrast to 8% among patients without frequent ectopy. Bulkley et al. [11] noted SCD in 21% of patients with SSc in contrast to no SCD in 61/275 deaths of SSc patients in the study of Lee et al. [12]. In the study of Follansbee et al. [13] SCD was confirmed in 5% of the 1258 patients with SSc. In patients with both skeletal and myocardial involvement ventricular arrhythmias and SCD occur more often.

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**FIG. 1.** Diagnosis and management of patients with rhythm and conduction disorders in autoimmune rheumatic diseases.
Management of cardiac arrhythmias in autoimmune rheumatic diseases

In the management of arrhythmias, the understanding of the aetopathogenesis of ARD is very important. In patients with a chronic disease, often related to significant disabilities, arrhythmias may cause anxiety despite its clinical irrelevance and reassurance is very important.

Anti-arrhythmic drug therapy is the mainstay of management. Drug selection is based upon their electrophysiological effects and the type of arrhythmia. No randomized controlled trials have evaluated any of these therapies specifically for use in patients with rheumatological disease, and therefore, therapy should be tailored to the individual patient. Verapamil-type calcium channel blockers are preferred for the treatment of supraventricular arrhythmias. Digoxin can be used to decrease ventricular response in atrial fibrillation and in end-stage heart failure. The treatment of sinus tachycardia in SLE is generally carried out by β-blockers. Classic β-blockers are contraindicated in patients with SSc and conditions with vasculitis and pulmonary hypertension.

Ventricular fibrillation (except in the first few hours of acute MI) and medicinally intractable life-threatening VT are indications for treatment with implantable cardioverter defibrillators (ICDs) [14]. Preventive ICD implantation was proven to decrease mortality of patients with dilated cardiomyopathy and in combination with resynchronization pacing is nowadays regarded as a treatment of choice for patients with heart failure and advanced left ventricular dysfunction. Importantly, defibrillators do not prevent symptomatic arrhythmias and should be combined with suppressive anti-arrhythmic therapy.

Radiofrequency (RF) ablation has revolutionized the approach to many types of arrhythmias. Patients considered for RF catheter ablation of VT are those with symptomatic, sustained, monomorphic VT when the tachycardia is drug resistant, when the patient is drug intolerant or when the patient does not desire long-term drug therapy; patients with bundle branch re-entrant VT; and patients with sustained monomorphic VT and an ICD who are receiving multiple shocks not manageable by re-programming or concomitant drug therapy. Occasionally, non-sustained VT or even severely symptomatic PVCs require RF catheter ablation. Success rates >90% are expected for accessory pathway tachycardias, para-atrioventricular (AV) nodal re-entrant tachycardia, atrial tachycardia and right ventricular outflow tract tachycardia. AV node ablation (used for ventricular rate control in atrial fibrillation) is possible in >99% of patients. Success rates of 85% are reported for the cure of atrial flutter [15].

Conduction disorders

The conduction disorders occur in ARD mainly in the active disease and are more frequent than rhythm disturbances. They arise through abnormalities of intrinsic automaticity or impaired conduction, principally within the AV node and the His-Purkinje’s network.

Conduction disorders in rheumatoid arthritis

Primary infiltration of the AV node or other conducting tissue by mononuclear cells or rheumatoid granulomas can be revealed in patients with conduction disorders and RA. Other potential mechanisms are vasculitis of the arterial supply to conducting tissue, haemorrhage into a rheumatoid nodule or extension of an inflammatory lesion from the aortic or mitral valve. Rarely, these lesions may be due to amyloid deposition. Villecco et al. [16] described right bundle branch block in 35% of 60 patients with RA. Antibodies to cardiac conducting tissue were found significantly more often in these patients than in those without conduction abnormalities (76% vs 21%). AV block is rare in RA, usually complete, and does not respond to anti-inflammatory and immunosuppressive therapy. Ahern et al. [17] described congenital complete heart block (CHB) in 0.1% of patients with RA, mainly in females, with sudden onset, and more prevalent in patients with subcutaneous nodules. However, no major conduction disorders were noted in anti-Ro/SSA positive RA patients [18].

Conduction disturbances in systemic lupus erythematosus

The small vessel vasculitis and the infiltration by fibrous or granulation tissue are major causes of the dysfunction of sinus or AV nodes in SLE. Correlation of autoimmunity-related destruction with conduction disorders has been documented. Conduction defects may also represent a sequel of myocarditis in 34–70% of patients with SLE [19]. First-degree heart block is often transient. CHB in adults with SLE is extremely rare (11 cases described so far), and is associated with appearance of anti-U1-RNP (U1 nuclear ribonucleoprotein) antibodies, and not with anti-Ro/La antibodies as in newborns [7]. Myocarditis and conduction defects occur more frequently in the anti-Ro-positive than in anti-Ro-negative SLE patients and healthy controls. In contrast to RA, conduction abnormalities may regress when the underlying disease is controlled.

Conduction disturbances in neonatal lupus

Neonatal lupus is a rare syndrome related to the transplacental passage of autoantibodies from mothers positive for anti-Ro/SSA (and/or anti-La/SSB) to their newborns. Approximately 3% of infants whose mothers are antibody-positive develop CHB [20]. The risk of recurrence is 10 times higher in the following pregnancies [21]. CHB is usually permanent (despite steroid therapy), and can be isolated or associated with other structural heart diseases. Incomplete heart block is often reversible, but may also progress to CHB despite therapy. Rarely, CHB can be associated with VT [22].

Direct arrhythmogenic activity of anti-Ro/SSA antibodies, immunoglobulin and complement deposition in cardiac tissues were demonstrated in several studies. Inhibition of L- and T-type calcium channels, seems to play an important role in the pathophysiology of the syndrome [23]. Fetal susceptibility may be influenced by specific human leukocyte antigen complex (HLA) alleles [24]. However, the discordance of CHB in identical twins suggests that an in utero factor plays a more important role than genetic differences [25]. Maternal–fetal microchimerism may be important in neonatal lupus, as demonstrated by finding of female (maternal) cells in the myocardium of the males who died of CHB [26]. Women with elevated levels of anti-Ro/SSA and anti-La/SSB could be treated with glucocorticoids for prevention of CHB during pregnancy. CHB did not develop in any of 26 infants born to mothers undergoing such a treatment before 16 weeks’ gestation [27]. However, such a preventive approach exposes 80% of expectant mothers and fetuses to the risks of unnecessary glucocorticoid treatment.

Immunoadsorption was recently suggested by Hickett et al. [28] as a possible treatment for pregnant women with high titers of SSA-antibodies and clinical complications. Infants with CHB may require a cardiac pacemaker, especially if the heart rate before delivery is <50 beats/min [20].

Conduction disturbances in systemic sclerosis

Conduction disturbances in SSc are mostly due to the fibrosis of the sinoatrial node, but direct involvement of the cardiac conduction tissue and its arterial blood supply has also been reported. In the study of Volt et al. [29] 25% of the patients with progressive SSc had antibodies against cardiac conducting tissue. Abnormal ECG; bundle and fascicular blocks occur in 25–75% of patients with SSc; sometimes even preceding cutaneous lesions, and are independent predictors of mortality. Fortunately, second and third degree AV block, are rare (<2%) [30].
Conduction disturbances in polymyositis and dermatomyositis

Polymyositis and dermatomyositis (PM/DM) are frequently complicated by conduction disturbances either by direct lesion of the conduction system or by myositis with contraction band necrosis and/or focal myocardial fibrosis. The block is localized distally to the His bundle, with no alterations in sinus node and AV nodal function. Cardiac involvement is mainly subclinical, but up to 23% of patients have conduction block in ECG that can occur in the absence of cardiomyopathy and may be progressive [7].

Management of conduction disturbances in autoimmune rheumatic diseases

Pacemaker implantation is the method of choice for the treatment of CHB and other serious conduction abnormalities. Sophisticated pacing modalities and programmability as well as low-energy circuitry and new battery designs have increased device longevity and enabled wide clinical application. A simple VVI pacemaker (paces and senses the ventricle and is inhibited by a sensed ventricular event) may be adequate for transient or infrequent bradyarrhythmia. For frequent or persistent bradyarrhythmia, prolonged dependence on ventricular pacing may warrant use of a rate-responsive demand unit or, if no atrial or sinus node abnormalities are present, a dual-chamber system (DDD—both chambers are capable of being sensed and paced). New devices enable resynchronization therapy in patients with dilated cardiomyopathy and severely impaired contractility, with beneficial effect on haemodynamics and long-term survival.

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References