Immunological basis of the cardiac conduction and rhythm disorders

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Introduction

The investigation of cardiac conduction and rhythm disturbances has rested so far on electrocardiography and electrophysiology studies and has mainly addressed patients with coronary artery disease, cardiomyopathies, and heart failure. The contribution of immunological mechanisms in the pathophysiology of these disorders has been under-estimated although the first descriptions of conduction tissue pathology were given by James in 1965, 1966 and 1971[1–3] and by Fairfax and Doniach[4], who described anticonductive tissue antibodies in left bundle branch block in 1976. By the end of 1997, the association of sudden death in babies[5], complete congenital heart block, and maternal connective tissue disease was clearly established[6,7]. Specific Ro/SS-A and La/SS-B antibodies were identified by Weston et al. in 1982[8], Scott et al.[9], and Lee et al.[10] in 1983. In further investigations Villecco et al.[11] demonstrated anticonductive tissue antibodies in rheumatoid arthritis (1983), as did Volta et al.[12] in progressive systemic sclerosis (1985). Maisch et al.[13,14] reported antisinuatrial and antiatrioventricular node antibodies in patients with sick sinus syndrome, atrioventricular block, and myocarditis in 1986 and 1989. More recently, Bacman et al.[15] recognised antibodies against cardiac neurotransmitter receptors, Li et al.[16] demonstrated antibodies to the human endogenous retrovirus-3 expressed in fetal cardiac tissue, and James et al.[17] evaluated the role of apoptosis in the pathophysiology of the gradual development of complete atrioventricular block.

These and other investigations clearly demonstrate that immunological mechanisms may be responsible for certain rhythm and conduction disorders. The aim of this review is thus to summarize the current data on the immunology of the rhythmogenic and conduction system and to analyse their clinical relevance.

Immunological mechanisms in the pathophysiology of the cardiac rhythm and conduction disorders

Genetics

Genetic susceptibility is a possible basic contributor in the pathophysiology of underlying diseases. A high association of HLA-B27 was noted in adults requiring permanent pacemakers for atrioventricular block[18,19], as well as the increased occurrence of HLA-DR3 in mothers of children with complete congenital heart block[20]. This genetic predisposition could allow for breakage of self-tolerance of the host, or for an abnormal response to a cross-reactive determinant or the production of antiidiotypic antibodies bearing the cross-reactive epitopes.

Autoreactivity

Many infectious agents share antigenic determinants not only among themselves, but also with a variety of human tissues, including cardiac rhythmogenic and conduction system tissues. Primarily, this cross-reactivity protects against a wide variety of pathogenic microbes. However, the combination of a certain microbe infecting the genetically susceptible host may result in serious autoimmune consequences (Table 1)[21–24]. In one of the very first contributions to the immunology of the rhythmogenic system, Kasp-Grouchowska and Kingston showed cross-reactivity of antibodies to
Finally, Boutjdir antisera induced a substantial reduction in the slow containing Ro/SS-A and La/SS-B antibodies. The same block in adult rabbit hearts perfused with IgG fractions chain and the M6 protein of eight La/SS-B epitopes that share sequence identity with atrioventricular block occurs extremely rarely and not in correlation with Ro/La, but with antibodies to U1 RNP[31]. Although much more difficult to demonstrate, evidence in acute myocardial infarction[32], rheumatoid arthritis[33], and other autoimmune diseases[34] is accumulating that lymphocytic activation and cellular cytotoxicity, specific for a given target tissue, appears to be at least equally important as the humoral response in the pathogenesis of the disease.

### Table 1 Cross-reactivity in the pathogenesis of cardiac rhythm and conduction disorders

<table>
<thead>
<tr>
<th>Author (reference no.)</th>
<th>Cross-reacting antigens</th>
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</thead>
<tbody>
<tr>
<td>Kasp-Grouchowska[21]</td>
<td>Streptococcus pyogenes/His bundle</td>
</tr>
<tr>
<td>Maisch[25]</td>
<td>Coxsackie B3, B4 (33 and 34 kD)/Sarcolemmal epitopes (220 kD 10%, 110 kD 50%, 72 kD 90%, 67 kD 40%, 45 kD 50% cross-reactivity)</td>
</tr>
<tr>
<td>Horsfall[23]</td>
<td>Human cardiac myosin β heavy chain, laminin B1 chain and the M6 protein of Streptococcus pyogenes/La (SS-B)</td>
</tr>
<tr>
<td>Li[24]</td>
<td>Laminin/La (SS-B) (65–70% cross-reactivity)</td>
</tr>
</tbody>
</table>

Streptococcus pyogenes with the conduction system[21]. A further indication that a microbial infection could be a trigger of an autoreactive process included the demonstration of cytolytic cross-reactive antibodies against Coxsackie B3 and B4 viruses and sarcolemmal epitopes in myocarditis patients[22]. Horsfall et al.[23] revealed eight La/SS-B epitopes that share sequence identity with human cardiac myosin β heavy chain, laminin B1 chain and the M6 protein of Streptococcus pyogenes. Li et al.[24] also noted a significant cross-reaction of mouse laminin and anti-La antibodies from eight of 10 patients with Sjögren’s syndrome. In contrast, purified antibodies to Ro52 from the same patients showed little or no binding to laminin.

It remains controversial whether the cross-reactive antibodies directly initiate the disease process or only reflect prior heart damage. Reichlin et al.[25] were able to elute anti-Ro/SS-A antibodies from a fetal heart affected with complete congenital heart block. Alexander et al.[26] reported the reduction of the plateau phase of cardiac repolarization consistent with alteration of calcium transport in myocardial tissue due to IgG anti-Ro/La antibodies. García et al.[27] obtained atrioventricular block in adult rabbit hearts perfused with IgG fractions containing Ro/SS-A and La/SS-B antibodies. The same antisera induced a substantial reduction in the slow inward calcium current of isolated ventricular myocytes. Finally, Boutjdir et al.[28] were able to show that IgG-enriched fractions of anti-52 kD Ro/SS-A antibodies induce complete atrioventricular block in the human fetal working heart perfused by the Langendorff technique. Inhibition of inward calcium current at the whole cell and single channel level was also confirmed.

Since calcium channel density is lower[29] and sarcoplasmic reticulum less abundant[30] in fetal as compared to adult cardiac cells, the negative consequences of a decreased inward calcium current may be exaggerated in the fetal heart. This would explain the absence of conduction abnormalities in mothers of children with complete congenital heart block, despite the same level of autoantibodies in the maternal and fetal circulation. In adults with systemic lupus erythematosus, high-grade atrioventricular block occurs extremely rarely and not

### Autoantigens and autoantibodies in rhythm and conduction disorders

**Small cytoplasmic ribonucleoproteins (Ro/SS-A and La/SS-B)**

The first antibodies recognized to significantly correlate with the damage to the rhythmogenic and conduction system were autoantibodies reactive with the intracellular soluble ribonucleoproteins 48 kDa La/SS-B, 52 kD Ro/SS-A, and 60 kD Ro/SS-A in mothers and in children with complete congenital heart block[8,30]. Ro/SS-A small cytoplasmic ribonucleoproteins (scRNP) are composed of several proteins complexed with a subset of the La/SS-B associated RNAs, the so-called Y-RNAs (Fig. 1). The Ro60 protein is unusual in containing both an RNP consensus motif for binding RNA and a zinc finger motif for binding to DNA. The Ro52 protein contains multiple zinc fingers and a leucine zipper sequence, but no RNP consensus motif. The function of the Ro/SS-A proteins is thus still unknown.

La/SS-B scRNPs are composed of an RNA polymerase III transcript, to which the La/SS-B protein is bound (Fig. 2). The RNA transcripts include 7S RNA, 5S RNA, U6-RNA, the Y-RNAs as well as a merase III transcript, to which the La/SS-B protein is complexed with a subset of the Ro/SS-A and 60 kD Ro/SS-A in mothers and in children with complete congenital heart block[31]. The La/SS-B protein functions as a termination factor for RNA polymerase III.

All four subclasses of anti-Ro(SSA) and La(SSB) antibodies cross the placenta and were detected in sera obtained from the umbilical cord[32]. In the same study, simultaneous presence of all subclasses was observed in one-third of the anti-52 kDa Ro(SSA) and 48 kDa La(SSB) responses. Anti-60 kDa antibodies were confined to IgG1. Significant differences were observed in the ratio of maternal to neonatal IgG1 and IgG3 antibodies against 52 kDa Ro/SS-A and 48 kDa La/SS-B between pregnancies affected and unaffected with congenital heart block[33]. Ro/La antibody binding sites are located in about 30% in the nucleus and the rest is bound to cytoplasm[34,35] and to the surface antigen[36].

Antibodies to Ro/SS-A and La/SS-B are found in patients with Sjögren’s syndrome, in systemic lupus erythematosus, and in rheumatoid arthritis (Table 2(a) and (b))[37]. In almost all patients with anti-La/SS-B antibodies, anti-Ro/SS-A are also present and their titres significantly correlate. The reverse is not always the case: antibodies to Ro/SS-A often occur alone in systemic lupus erythematosus and systemic sclerosis. In

contrast to anti-dsDNA activity, autoantibody levels against Ro/SS-A and La/SS-B in patients with systemic lupus erythematosus do not correlate with disease activity\[35\].

Small nuclear ribonucleoproteins (snRNP)

There are two classes of small RNA molecules: the capped small nuclear RNAs (snRNAs or U-RNAs) and the non-capped small cytoplasmic RNAs (scRNAs). U-RNAs are organized into ribonucleoprotein particles (U-snRNPs) and many of them have an important role in messenger RNA processing\[35\]. More than 25 different polypeptides have been identified as constituents of the major snRNPs U1, U2, U5 and U4/U6. Of these proteins, nine are present in each of the individual snRNPs, and are designated as Sm or core proteins. Whereas the antibodies to Sm are exclusively found in patients with systemic lupus erythematosus, antibodies to U1-RNP are considered to be a marker antibody for mixed connective tissue disease\[35\]. Association of anti-U1-RNP antibodies and high-grade atrioventricular block in adult systemic lupus erythematosus patients has been reported (Table 3)\[31,35,59,41,43,46,47\]. Furthermore, antibodies to U1-RNP were shown to be associated with myocarditis and myositis of systemic lupus erythematosus patients\[46\].
Adrenergic and muscarinic cholinergic receptors

IgG autoantibodies to adrenergic and muscarinic receptors have been described in babies with complete congenital heart block\cite{15}. These antibodies activate the receptors in the neonatal tissue. Their occurrence is completely independent of Ro/La antibodies. Both adrenergic and cholinergic reactivities were absent in the sera of normal women of childbearing age and of normal children.

In addition, Fu and co-workers confirmed agonist-like activity of antibodies directed against amino acids 169–193 of the second extracellular loop of the M2 human muscarinic receptor in idiopathic dilated cardiomyopathy patients\cite{47} as well as in the cultured neonatal cardiomyocytes\cite{48}.

Endogenous retrovirus-3

Endogenous retrovirus-3 (ERV-3) encodes an open reading frame for an envelope protein expressed in the placenta. In fetal hearts, high levels of ERV-3 expression occur between 11 and 17 weeks of gestation\cite{16}. Autoimmunization to this protein was observed in normal
pregnancies and in patients with Sjögren’s syndrome and systemic lupus erythematosus. Remarkably, the highest level of anti-ERV-3 antibodies was found in mothers of complete congenital heart block babies[16].

Sinus node antibodies

Antigens in the human conducting tissue and the incidence of autoantibodies was analysed by Maisch[13].[13] in 45 pacemaker patients with sick sinus syndrome, in 17 patients with bradyarrhythmia, and five patients with hypersensitive carotid sinus syndrome (Table 4). Antibodies against the human sinus node (Fig. 2, upper left panel) were demonstrated in 29% of patients with sick sinus syndrome and in 24% of patients with bradyarrhythmia. These observations are in accordance with previous investigations by Helander[49] and Szabo et al.[50] who also detected antigens specific for the cardiac conducting system.

At least two subtypes of antisinus node antibodies (ASNab) were demonstrated: an antibody absorbable

Table 2(a) Frequency of anti-Ro/SS-A antibodies in various autoimmune diseases

<table>
<thead>
<tr>
<th>Author (reference no.)</th>
<th>SLE (%)</th>
<th>CHB (%)</th>
<th>RA (%)</th>
<th>SS (%)</th>
<th>MCTD (%)</th>
<th>PSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smeenk[35]</td>
<td>40</td>
<td></td>
<td>5</td>
<td>70</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Mierau[39]</td>
<td>24–40</td>
<td>95–100</td>
<td>15</td>
<td>70–100</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Tsay[40]</td>
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<td></td>
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</tr>
<tr>
<td>Wang[41]</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Taylor[42]</td>
<td>50</td>
<td>97</td>
<td></td>
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<tr>
<td>Scott[44]</td>
<td>100</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Julkunen[45]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
</tbody>
</table>

SLE=systemic lupus erythematosus; CHB=congenital heart block; RA=rheumatoid arthritis; SS=Sjögren’s syndrome; MCTD=mixed connective tissue disease; PSS=progressive systemic sclerosis.

Table 2(b) Frequency of anti-La/SS-B in various autoimmune diseases

<table>
<thead>
<tr>
<th>Author (reference no.)</th>
<th>SLE (%)</th>
<th>CHB (%)</th>
<th>RA (%)</th>
<th>SS (%)</th>
<th>MCTD (%)</th>
<th>PSS (%)</th>
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<tr>
<td>Smeenk[35]</td>
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<td>1</td>
<td>60</td>
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<td>5</td>
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<tr>
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<td>Wang[41]</td>
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<td>Taylor[42]</td>
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<td></td>
<td>82.8</td>
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<tr>
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<td>15</td>
<td>100</td>
<td></td>
<td></td>
<td>40–50</td>
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</tr>
<tr>
<td>Buyno[44]</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42</td>
</tr>
</tbody>
</table>

SLE=systemic lupus erythematosus; CHB=congenital heart block; RA=rheumatoid arthritis; SS=Sjögren’s syndrome; MCTD=mixed connective tissue disease; PSS=progressive systemic sclerosis.

Table 3 Frequency of anti-U1RNP antibodies in various autoimmune diseases

<table>
<thead>
<tr>
<th>Author (reference no.)</th>
<th>SLE (%)</th>
<th>SLE+AV block gr.III (%)</th>
<th>SLE+myocarditis (%)</th>
<th>RA (%)</th>
<th>MCTD (%)</th>
<th>PSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilazarian[31]</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Smeenk[35]</td>
<td>20</td>
<td>3</td>
<td>100</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mierau[39]</td>
<td>25–40</td>
<td>3</td>
<td>100</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang[41]</td>
<td>21</td>
<td></td>
<td></td>
<td>2–12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott[43]</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td>&gt;95</td>
<td></td>
</tr>
<tr>
<td>Borenstein[46]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

AV=atrioventricular; SLE=systemic lupus erythematosus; CHB=congenital heart block; RA=rheumatoid arthritis; Sjögren’s syndrome=Sjögren’s syndrome; MCTD=mixed connective tissue disease; PSS=progressive systemic sclerosis.
and another one not absorbable with ventricular myocardium\textsuperscript{[13]}. The ASNab were primarily of the IgG, rarely of the IgA or IgM type. Complement (C3) fixation was found in 15% of the sero-positive patients and circulating autoantibodies were found to react primarily with the membrane of cells. ASNab were shown to be highly specific for sinus node disorders, but their sensitivity for identifying patients with sick sinus syndrome is low. A tenfold risk of developing sick sinus syndrome for patients with ASNab can be postulated when compared to age-matched controls without rhythm disturbances. Patients with sick sinus syndrome and prior myocarditis or rheumatic fever had a threefold incidence of the antibodies. Remarkably, the incidence of the ASNab does not increase with the heart failure progression determined by New York Heart Association class, nor with the time elapsed after the pacemaker implantation, indicating that they are rather a causative than a secondary phenomenon.

In a group of 17 patients with bradyarrhythmia 24% were positive for ASNab. If the sera were used pre-absorbed with human ventricular myocardium, 50% of the positive sera in the group of patients with bradyarrhythmia still showed ASNab, but none in the group

Table 4  Antibodies to sinuatrial, atrioventricular node, His bundle and cardiac Purkinje cells

<table>
<thead>
<tr>
<th>Maisch et al\textsuperscript{[13]}</th>
<th>SSS (%)</th>
<th>1st to 3rd degree AV block (%)</th>
<th>Bradyarrhythmia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AntiSA node antibodies</td>
<td>29**</td>
<td>24*</td>
<td>24*</td>
</tr>
<tr>
<td>AntiAV node antibodies</td>
<td>18</td>
<td>22**</td>
<td>29*</td>
</tr>
<tr>
<td>AntiHis bundle antibodies</td>
<td>22</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Anticardiac Purkinje cell antibodies</td>
<td>11*</td>
<td>27*</td>
<td>35*</td>
</tr>
</tbody>
</table>

\textsuperscript{**}P < 0.05 both when compared to non-cardiac controls and age-matched controls without rhythm and conduction disorders; \textsuperscript{*}P < 0.05 when compared to non-cardiac controls.

SSS = sick sinus syndrome; SA = sinuatrial; AV = atrioventricular.

Figure 3  Isolated Purkinje fibres (left panel); antibodies to isolated Purkinje fibres (middle panel); negative controls (right panel). (Left panel=native fibres; middle and right panels=immuno-fluorescent staining with FITC labelled monoclonal antihuman mouse antibodies; F(ab)\textsubscript{2}-IgG fragments staining=white arrows; magnification left 240 x and 160 x magnification respectively). F(ab)\textsubscript{2}-IgG fragment staining avoids non-specific IgG-binding.
with sick sinus syndrome. ASNab could be detected in 24% of the patients with atrioventricular block. In 54% of the patients with both atrioventricular block and ASNab binodal disease was present[13,14].

Circulating antiatrioventricular node antibodies (AAVNab) were found in 18% of patients with sick sinus syndrome and in 29% of patients with bradyarrhythmia (Fig. 2, middle left panel)[13,51]. The relatively high incidence of AAVNab in patients with sinus node disorders may be explained by a binodal disease (first- to third-degree atrioventricular block) in 5/8 sero-positive patients with sick sinus syndrome and 2/4 sero-positive patients with bradyarrhythmia.

AAVNab were detected in the sera of 12/45 pacemaker patients (26.7%) with atrioventricular block, but also in the 10% of age-matched controls without heart block. A 2.2-fold risk of acquiring or already having an atrioventricular block can be calculated if the AAVNab are present[51]. In comparison with non-cardiac controls, who showed no AAVNab, these antibodies are specific for atrioventricular node disorders and could be considered as prognostic markers. The first-degree atrioventricular block was either associated with distal bifascicular block (40%) or binodal disease (60%). AAVNab were primarily of the IgG, rarely of the IgM or IgA class. Complement (C3) fixation was observed in 30% of patients. Since not all of the antibodies could be absorbed by ventricular myocardium, including Purkinje cells, at least two types of antibodies exist: one is a specific antibody directed to the atrioventricular node, the other is an absorbable cross-reacting antibody.

The threefold higher incidence of AAVNab in patients with atrioventricular block and previous rheumatic fever or myocarditis compared to the patients with atrioventricular block (but without a history of this disease) indicates their diagnostic and prognostic value[52].

AntiHis antibodies

AntiHis antibodies (AHISab) were present in 22% of our patients with sick sinus syndrome, and only in 6% of the patients with bradyarrhythmia, which was comparable to the age-matched controls. In patients with atrioventricular block, incidence of AHISab was lower (13%). By absorption experiments, cross-reactivity of the antiHis antibodies with binding sites from normal ventricular myocardium could be shown[13,14].

Anticardiac Purkinje cell antibodies

In patients with sick sinus syndrome, anticardiac Purkinje cell antibodies (ACPCab) were found in 11% of cases (Fig. 2, lower left panel)[13]. Such antibodies can be attached to the membrane of isolated Purkinje fibres (Fig. 3, left panel). A substantial number of such patients had myocarditis and rhythm disturbances. Furthermore, in 35%, bradyarrhythmia-group antibodies to bovine Purkinje-fibres were detected. Purkinje

Figure 4  Initial clinical presentation and prognosis of the 152 mothers of children with congenital heart block. Cumulative data from long-term follow-up studies of Julkunen et al. (31 mothers, mean follow-up 8 years)[52], Waltuck and Buyon (57 mothers, mean follow-up 3-7 years)[74], and Press et al. (64 mothers, mean follow-up 10 years)[75]. □=Asymptomatic; □=Sjögren’s syndrome; □=undifferentiated autoimmune syndrome; □=systemic lupus erythematosus.
cells can be easily located in bovine false tendon and used as antigen for immunofluorescence tests.

In the analysis of sera from 352 patients with atrioventricular block Obbiassi et al.[53] found IgG ACPCab in 14% of patients with systemic lupus erythematosus, 21% in rheumatoid arthritis, 18% in progressive systemic sclerosis, 23% in Sjögren’s syndrome, and in 11% of normal subjects. In 50 patients with permanent pacemakers for chronic non-postinfarction atrioventricular block the prevalence was 30%. In a selected set of 29 patients with idiopathic atrioventricular block located at or below the level of the His bundle the prevalence was 34.5%.

Since sera containing antimyosin or antimitochondrial antibodies could also be reactive with Purkinje cells, diagnosis of a specific ACPCab in the indirect immunofluorescence technique was made only when the residual myocardium did not show ant cardiac or antimitochondrial antibodies, the former expressing a cross-striated, the latter a diffuse cytoplasmic pattern.[13]. In contrast to the study by Obbiassi et al.[53], ACPCab were associated with either anticross striated or anticyttoplasmic antibodies not only in 27% of patients with atrioventricular block, but also in a similar range in the age-matched and disease control population. Therefore, the ACPCab cannot be considered as specific diagnostic or prognostic markers in atrioventricular conduction disturbances.[13,14].

Circulating ACPCab in idiopathic bundle branch fibrosis were first detected by Fairfax and Doniach[59] in 8-6% of patients. The finding was not statistically significant when compared to controls. In our investigations, 60% of the patients with first-degree atrioventricular block and ACPCab simultaneously showed either a left anterior hemiblock or a bifascicular bundle branch block. Based on the heterologous nature of these antibodies, the low incidence and their appearance in controls, they rather seem to be an epiphenomenon and not a pathogenetic marker of left bundle branch block. In 69% to 76% of patients with right bundle branch block and simultaneous rheumatoid arthritis circulating ACPCab of the IgG class could be detected.[13]. The incidence of these antibodies is statistically significant in a selected group with right bundle branch block patients associated to rheumatoid arthritis. Thus, the ACPCab are presently considered to be diagnostic markers for right bundle branch block in patients with rheumatoid arthritis only.

Clinical expression of the autoimmune injury of the cardiac rhythm and conduction system

The association between rhythm and conduction disorders and autoimmune reactions to cardiac conduction tissue is most obvious in sick sinus syndrome and complete congenital heart block. Furthermore, autoimmune mechanisms are presumably responsible for rhythm and conduction disorders in a significant proportion of patients with systemic connective tissue diseases, myocarditis, and dilated cardiomyopathy.

Sick sinus syndrome

The sick sinus syndrome can present with sinuatrial block, tachycardia-bradycardia syndrome and pathological sinus bradycardia.[54,55]. The anatomical basis of sick sinus syndrome can involve total or subtotal destruction of the sinus node, areas of nodal-atrial discontinuity, inflammatory or degenerative changes of the nerves and ganglia surrounding the node, and pathological changes in the atrial wall.

Direct evidence by immunohistochemistry for the detection of immunoglobulin and complement binding to the sinus node is not available. Indirect evidence can be derived from the demonstration of circulating autoantibodies to cardiac conducting tissue in sick sinus syndrome, by the indirect immunofluorescence technique with human sinus node antigen. The following autoantibodies were revealed in sick sinus syndrome patients[13,14] (Table 4): (1) ASNab in 29%, (2) AAVNab in 18%, (3) AHISab in 22%, (4) ACPCab in 11%, (5) antimyolemmal and antisarcolemmal antibodies in 44% and 29% of patients, respectively[13,14]. When compared to non-cardiac controls, the levels of ASNab, AAVNab and ACPCab were significantly increased[13]. In comparison with age-matched controls without rhythm/conduction disturbances, a significant difference was found primarily for ASNab. Anti-Ro/SS-A and anti-SS-B/La antibodies were absent in all patients.

Sinus node dysfunction was also reported in donor hearts after orthotopic cardiac transplantation[56,57]. Rejection after heart transplantation is a classic injury, immune mediated by allo specific lymphocytes. It was confirmed that the lymphocytes of the recipient are targeting the rhythmogenic and conduction system as well[59]. Due to the anatomical ‘insulation’ of His bundle within the central fibrous body, it exhibits a lesser tendency to be involved in the acute rejection than the other parts of the conduction system. In a series of 90 transplant patients, 45% were found to have sinus nodal dysfunction postoperatively, and 21% required permanent pacing[56]. However, prognosis of this condition was shown to be mostly favourable with no mortality due to sinus node dysfunction in the group of patients that did not undergo pacemaker implantation[57].

Congenital complete heart block

The basic anatomical lesion in complete congenital heart block is discontinuity between the atrial musculature and the atrioventricular node or the His bundle, if the atrioventricular node is absent[59]. The interruption may occasionally be situated between the atrioventricular...
node and the main His bundle, or within the bundle, itself\(^{60}\). Fetal myocarditis, haemorrhage and necrosis involving conduction tissue, and degeneration and fibrosis are the pathohistological entities most often reported from fatal complete congenital heart block independent of the congenital heart anomalies\(^{61,62}\). In addition, initiation of apoptosis has been recently postulated as one of the possible mechanisms of the progression of congenital conduction disturbances to complete heart block, not only in fetuses but also later in childhood and adolescence\(^{63}\).

Transplacental passage of various antibodies and immune complexes from mothers with autoimmune disorders is now widely recognised as the most likely mechanism in the pathogenesis of the disease. The main autoantibodies detected both in children with complete congenital heart block and their mothers are anti-Ro/SS-A and anti-La/SS-B antibodies. The highest risk for giving birth to a child with complete congenital heart block exists in the presence of both antibodies to 52-kD Ro/SS-A and 48-kD SS-B/La and the risk is rather low in pregnant women who do not have antibodies to anti-SSB/La and have anti-SSA/Ro antibodies of low titre\(^{62}\). Maternal antibodies to all components of the Ro/La system are efficiently transported across the placenta\(^{51,63}\). The transport process of the autoantibodies involves binding of an intact Fc portion to specific CD16 placental membrane receptors. The receptors are especially concentrated on the area of the syncytiotrophoblast that makes direct contact with the maternal circulation. There is a close positive correlation between the concentrations of anti-48 La/SS-B, anti-52 Ro/SS-A and anti-60 kDa Ro/SS-A antibodies in the child and that found in the mother\(^{64}\).

In a large multicentre study, Buyon et al.\(^{65}\) addressed the questions of Ro/La antibody frequency, titre, and specificity in complete congenital heart block. Ro/La antibodies were assessed in mothers of children affected with complete congenital heart block initially presented as systemic lupus erythematosus (15/55 patients), undifferentiated autoimmune syndrome (11/57 patients), Sjögren’s syndrome (8/57 patients), and in 23 asymptomatic mothers. Anti-Ro/SS-A and anti-La/SS-B antibodies were identified in 100% and 76% of the mothers respectively. The risk of having another child with complete congenital heart block was 16%\(^{65}\).

Cumulative data on the presentation and prognosis of 152 mothers to the children with congenital heart block from the long-term follow-up studies of Julkunen et al.\(^{45}\), Waltluc and Buyon\(^{66}\), and Press et al.\(^{67}\) are shown in Fig. 4. At the initial presentation, 19 mothers (12.5%) had systemic lupus erythematosus, 11 (7.2%) Sjögren’s syndrome, 26 (17.1%) undifferentiated autoimmune syndrome, 16 (10.5%) had other diseases, and 80 (52.6%) were asymptomatic. All 19 mothers with systemic lupus erythematosus remained stable during the follow-up. Out of 11 patients with Sjögren’s syndrome one developed systemic lupus erythematosus. Undifferentiated autoimmune syndrome was the initial diagnosis in 26 mothers. Three of them developed systemic lupus erythematosus, two Sjögren’s syndrome, and one became asymptomatic. Eighty mothers were asymptomatic throughout entire pregnancy. Eight of them developed systemic lupus erythematosus, an additional eight Sjögren’s syndrome, nine undifferentiated autoimmune syndrome, one hyperthyroidism, and one ankylosing spondylitis. During the follow-up, three initially asymptomatic mothers died, one of acute myocardial infarction, the second due to complications of systemic lupus erythematosus, and the third patient from the alcoholic liver disease.

In contrast to the rather mild maternal disease, as demonstrated in Fig. 4, morbidity and mortality of children with complete congenital heart block is high. According to Buyon et al.\(^{65}\) 19% of the 113 children with complete congenital heart block died, 73% within 3 months after birth. Sixty-seven (63%) of 107 live-born children required pacemakers: 35 within 9 days of life, 15 within 1 year, and 17 after 1 year. In addition, Julkunen et al.\(^{45}\) demonstrated 15% total mortality and 1·9 relative risk for a female child compared with a male child to have complete congenital heart block.

Fetal contribution to the pathogenesis is also important. Idiotypes of DNA antibodies different from that of those detected in mothers have been found in newborns\(^{45,68}\). Furthermore, the hearts of affected children show deposition of immunoglobulins of isotypes not transferred from the mother, suggesting that autoantibody synthesis is also occurring in the child. In the recent study of Siren et al.\(^{69}\) children with complete congenital heart block were shown to be often identical to their mothers in alleles of DR-B, DQ-A and DQ-B loci, thus affecting fetomaternal recognition and suggesting that cell-mediated mechanisms could be involved in the injury of the conduction system.

### Rhythm and conduction disorders in adults with autoimmune diseases

#### Rheumatoid arthritis

The conduction system of the heart is affected in the setting of active disease. Histologically, cases of heart block reveal primary infiltration of the atrioventricular node or other conducting tissue by mononuclear cells or rheumatoid granulomas. Rarely, these lesions may be due to amyloid deposition. Villecco et al.\(^{11}\) described complete or incomplete right bundle branch block in 35% of 60 patients with rheumatoid arthritis. Antibodies to cardiac conducting tissue were found significantly more often in these patients than in those without conduction abnormalities (76% vs 21%). Volta et al.\(^{12}\) detected right bundle branch block in 32% of 110 patients with rheumatoid arthritis and cardiac conducting tissue antibodies in 69% of them. The same antibodies were found in an additional 20% of patients with rheumatoid arthritis without right bundle branch block.
Atrioventricular block is rare in rheumatoid arthritis but when it occurs it is usually complete and permanent upon presentation\(^1\,\text{[23]}\).

**Systemic lupus erythematosus**

The small vessel vasculitis in systemic lupus erythematosus may cause injury to nodal or other conducting tissue. Infiltration of the sinus or atrioventricular nodes by fibrous or granulation tissue has been found in pathohistology\(^7\,\text{[30,71]}\). Various degrees of heart block and bundle-branch block have been described. Although it was first reported in 1965\(^7\,\text{[3]}\), complete atrioventricular block in adults with systemic lupus erythematosus is extremely rare, and is not associated with anti-Ro/La antibodies as in newborns, but with anti-U1-RNP antibodies\(^8\,\text{[11]}\). In the study of O'Neill et al.\(^7\,\text{[72]}\) 12/33 patients with Ro/La antibodies had no rhythm/conduction defects, but conduction defects were present in 2/33 patients, without Ro/La antibodies. A significantly higher prevalence of myocarditis and conduction defects occurred in the anti-Ro positive systemic lupus erythematosus patients (8/36) when compared to the ones who were anti-Ro negative (1/31) and healthy controls (1/50) was reported by Logar et al.\(^7\,\text{[73]}\). In contrast to rheumatoid arthritis, conduction abnormalities may regress when the underlying disease is controlled. Arrhythmias such as atrial fibrillation and flutter may transiently occur in association with peri-carditis, especially during periods of active disease. However, sinus tachycardia may be the only manifestation of cardiac involvement and has been noted to resolve with corticosteroid treatment for exacerbation of extracardiac disease.

**Systemic sclerosis**

Bundle and fascicular blocks, first-, second-, and third-degree atrioventricular block as well as the rhythm disturbances occur in up to 50% of patients with systemic sclerosis, sometimes even preceding cutaneous lesions\(^7\,\text{[34]}\). Autopsy studies have demonstrated myocardial fibrosis involving the sinusatrial node more often than the atrioventricular node and also the His-Purkinje system\(^7\,\text{[5,76]}\). In the study of Volta et al.\(^7\,\text{[12]}\) 8/32 patients (25%) with progressive systemic sclerosis had cardiac conducting tissue antibodies. Out of these eight patients, six (75%) had a right bundle branch block.

**Conclusions**

The immunopathogenesis of cardiac rhythm and conduction disorders in sick sinus syndrome, complete congenital heart block, and connective tissue diseases is well established.

Patients with ASNab have a tenfold higher risk of developing sick sinus syndrome, compared to age-matched controls. ASNab were shown to be highly specific for sinus node disorders, but their sensitivity for identifying patients with sick sinus syndrome is low. Patients with sick sinus syndrome and prior myocarditis or rheumatic fever had a threefold incidence of the antibodies. The incidence of the ASNab did not increase with the progression of heart failure, nor with the time elapsed after the pacemaker implantation.

A two- to threefold risk of acquiring an atrioventricular block was found in patients with AAVNab in comparison to controls. The incidence of AHISab was low and not significant when compared either to the non-cardiac or the age-matched controls. ACPCab seemed to be an epiphenomena and not a pathogenetic marker of conduction disorders.

In complete congenital heart block contribution of the fetal genetic susceptibility, associated with HLA-B27 and HLA-DR3 is a possible prerequisite in the pathophysiology of the underlying diseases, although transplacental passage of various antibodies and immune complexes from mothers with autoimmune disorders is widely recognised. The main autoantibodies detected both in children with complete congenital heart block and their mothers are anti-Ro/SS-A and anti-La/SS-B antibodies. Inhibition of the inward calcium current at the whole cell and single channel level by these antibodies has been confirmed. Induction of Ro and La antigens on the surface of myocardial fibres during fetal development may be critical in the localization of the specific autoantibodies and subsequent evolution of complete congenital heart block. The cross-reactivity of laminin with anti-La antibodies could be important in the initiation of the autoimmune process.

Mothers, who do not possess anti-La/SS-B antibodies, but have anti Ro/SS-A antibodies of low titre that do not recognize either the 60 kD or 52 kD component on SDS-immunoblot, appear to be at low risk for giving birth to a complete congenital heart block infant. Asymptomatic mothers do not invariably become ill and if an asymptomatic mother does develop systemic lupus erythematosus it is not likely to be life-threatening. Autoantibody levels against Ro/SS-A and La/SS-B in patients with systemic lupus erythematosus do not correlate with disease activity.

Autoantibodies against adrenoceptors and muscarinic cholinergic receptors of neonatal heart and human ERV-3 expressed in fetal cardiac tissue could also play a role in the pathogenesis of complete congenital heart block. Of note, apoptosis could be one of the possible mechanisms of the progression of the congenital conduction disturbances to the complete heart block.

Experience from investigations on cardiac involvement in systemic diseases also implies that immunological mechanisms are important in the pathophysiology of rhythm and conduction disorders. In addition, evidence in rheumatoid arthritis and other autoimmune diseases is accumulating that cellular activation and cellular cytotoxicity specific for a given target tissue appears to
be at least equally important in the pathogenesis of the disease as the humoral response.

References


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