Autoimmunity Reviews 18 (2019) 415–425

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Lethal immunoglobulins: Autoantibodies and sudden cardiac death

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ARTICLE INFO

Keywords:
Sudden cardiac death
Autoantibodies
Autoimmunity
Anti-β1 adrenergic receptor antibodies
Anti-muscarinic acethylcholine receptor antibodies
POTS
HPV vaccine
Channelopathies

ABSTRACT

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes that occurs in a short time period (generally within 1 h of symptom onset) in a person with known or unknown cardiac disease. Patients with cardiomyopathies, myocarditis, ischemic heart disease and cardiac channelopathies are at risk of SCD. However, a certain percentage of autopsy-negative cases of SCD in the young (< 35 years) remain unexplained even after a post-mortem genetic testing. Autoantibodies against cardiac proteins may be potentially involved in the pathogenesis of different heart diseases and in the occurrence of unexplained SCD. In this review we analyze clinical and animal studies that elucidate the prevalence of these autoantibodies in patients with different cardiac diseases and their pathophysiological relevance. We propose a classification of the autoantibodies associated with heart diseases and focus on their molecular and cellular effects. Anti-beta adrenergic receptor antibodies and anti-muscarinic acetylcholine receptor antibodies affect myocardial electrophysiological properties and were reported to be the independent predictors of SCD in patients with different heart diseases. Autoimmune mechanism is proposed for cardiac-related adverse reactions following human papillomavirus (HPV) vaccination. The pentapeptid sharing between HPV's antigens, adrenergic receptors and muscarinic acetylcholine receptors supports this assumption. The dysregulating effects of the autoantibodies against calcium and potassium ion channels can be the basis for autoimmune phenocopies of genetic cardiac channelopathies, which are also associated with SCD.

1. Introduction

An increasing number of studies provided insight into pathogenetic roles of autoantibodies (AAb) not only in classical autoimmune diseases e.g. rheumatoid arthritis or systemic lupus erythematosus, but also in those illnesses which are generally not yet accepted as autoimmune ones [1–5]. Moreover, some of the AAb can be considered as predictors of non-autoimmune diseases [6]. Nevertheless, detection of an increased titer of any AAb in serum of patients with a disease, previously considered to be not associated with autoimmunity, is not enough to prove their involvement in the pathogenesis. In each case clinical relevance of the AAb and their effects on cellular level must be explored. In light of the above, this review focuses on the contribution of AAb to the pathogenesis of cardiomyopathies, myocarditis, heart failure, cardiac dysrhythmias, ischemic heart disease and hypertensive heart disease, especially as regards to the mechanisms for SCD. A thorough review, which summarize available literature, was reported by Kaya et al. in 2012 [7]. The AAb can be cytotoxic or involve dysregulating effects (alteration of cell function, growth and signaling). Therefore, they can cause disorder of basic myocardial properties (contractility, conductivity, automaticity, excitability), often even without provoking any inflammation and/or overt structural damage of

Abbreviations: AAb, autoantibodies; Ab, antibodies; ACHB, autoimmune congenital heart block; AMA, anti-mitochondrial antibodies; ANT, adenine-nucleotide translocator; ATP, adenosine triphosphate; ATF6, activating transcription factor 6; AV, atrioventricular; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; cTnI, cardiac troponin I; ERK, extracellular signal-regulated kinase; HPV, human papillomavirus; HSP, heat shock protein; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MyHC, myosin heavy chain; PI3K, phopsphatidylinositol 3-kinase; PKA, protein kinase A; POTS, postural orthostatic tachycardia syndrome; SCD, sudden cardiac death; STAT, signal transducer and activator of transcription.

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https://doi.org/10.1016/j.autrev.2018.12.005
Received 10 December 2018; Accepted 13 December 2018
Available online 14 February 2019
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the cardiomyocytes. SCD (both coronary and non-coronary in origin) as a rule is caused by a lethal episode of arrhythmia (ventricular fibrillation) provoking fatal acute heart failure. An attack of cardiac ischemia may cause such an arrhythmic episode even in an early stage of coronary atherosclerosis. Other frequent causes of SCD are cardiomyopathies and myocarditis. But quite often the myocardium of the victims of SCD is devoid of any significant structural lesions. Unexplained SCD is a serious problem in pediatric and adolescent practice, with a considerable part of cases ascribed to the results of fatal arrhythmias caused by congenital or epigenetic reasons [8]. Cardiac channelopathies are the most known example. However, in the recent 3-year prospective population-based study, that covered a population of 12.59 million young people, 40% cases of SCD were autopsy-negative. 73% of them remained unexplained even after post-mortem genetic testing [9]. In these cases, the possibility of autoantibody-mediated acute disorders of excitability, conductivity and automaticity leading to arrhythmic mechanism of acute heart failure and SCD can be proposed. Are there any anti-myocardial antibodies (Ab) which can be potentially lethal? The following paper reviews the state of the art in this field.

2. Classification of the pathogenic AAb in heart diseases

The spectrum of AAb associated with heart diseases can be classified to several classes according to their targets and hence depending on their possible effects.

1. *Cytotoxic AAb* – those AAb can cause complement-mediated cell death or antibody-dependent cell-mediated death, which manifests on tissue level as a cardiomyocyte loss, accompanied in some cases by severe inflammation. In addition, they may increase the local concentration of tumor necrosis factor (TNF-α), nitric oxide, and cytokines, which amplify the myocardial damage [10]. They also can induce apoptosis. Considering myocardial basic properties, cell death followed by myocardial fibrosis can lead to decreased contractility and/or conduction disorders. Cytotoxic effects are known for anti-cardiac troponin I Ab, anti-HSP60 Ab, anti-α- and anti-β-myosin heavy chain Ab and anti-mitochondrial Ab. Most of their target antigens are structural myocardial cellular proteins (Fig. 1).
2. *Cell-stimulating or cell-blocking autoantibodies* – these AAb can target the following autoantigens (Fig. 2):

1) Neurohormonal regulatory proteins (anti-beta1-, beta2-, beta3-adrenergic receptor Ab, anti-muscarinic 2 acetylcholine receptor Ab and anti-angiotensin II receptor type 1 Ab).
2) Enzymes (including those involved in energy metabolism, like anti-pyruvate dehydrogenase Ab), or membrane transporters – both in mitochondrial membrane (anti-adenine nucleotide transporter Ab) and in plasma membrane (anti-Na/K ATPase Ab).
3) Membrane channels (anti-L-type Ca^{2+} channel Ab, anti-Ro/SSA Ab (cross-react with L-type Ca^{2+} channel, T-type Ca^{2+} channel, hERG1 K^+ channel), anti-KCNQ1 K^+ channel Ab, anti-K_v1.4 K^+ channel Ab and anti-Na_v1.5 Na^+ channel Ab).

However, the classification is not absolute. E.g. anti-52-kD Ro/SSA Ab are known to bind directly to L-type Ca^{2+} channel, thus inhibiting ion current. In the early phase their effect is functional and hence reversible. In some cases, possibly because of a very high titer of AAb or/and individual susceptibility, the chronic exposure to anti-Ro/SSA Ab may induce the calcium channel internalization, in turn responsible for apoptosis. Necrosis is also possible, due to activation of complement, and it leads to local inflammation. In this phase, inflammatory involvement of the conduction system may be responsible for more severe abnormalities (i.e. second-degree AV block) which may become irreversible, if the process goes on towards development of fibrosis [11].

2.1. Anti-cardiac troponin I (anti-cTnI) Ab

The effect of anti-cTnI Ab on disease progression (especially in cardiomyopathies) drew much attention during last 10 years. The prevalence of these Ab in healthy individuals ranges from 0% to 20%, but in a large cohort study tends to be around 10% [12,13]. Wide range of positivity could be partly explained by subclinical cardiovascular disease in some individuals and is related to the different specificities and sensitivities of methods for their detection [12]. The prevalence of these Ab in patient with dilated cardiomyopathy, ischemic cardiomyopathy, myocardial infarction and acute coronary syndrome also vary considerably. Almost in all of the studies on anti-cTnI Ab reported, they were more frequently detected in cases than in the control groups [13]. One more reason for a wide range of anti-cTnI Ab positivity in patients could be the existence of different subgroups of diseases, which have been considered to be the nosologic entities. In this case, certain AAb could play an important role in the pathogenesis and prognosis only in particular subgroups. It was shown that immunization of mice with cardiac troponin I induced severe inflammation in the myocardium followed by fibrosis and heart failure with an increased mortality [14]. But apart from that, administration of anti-cTnI Ab to mice augmented the voltage-dependent L-type Ca^{2+}-current of cardiomyocytes independent of protein kinase A and induced ventricular dilatation and heart failure. These findings indicate, that cytotoxic effects of the AAb are not limited to the complement-mediated cell lysis, but a second mechanism could be proposed, namely initiation of downstream signaling by a cross-reaction with cardiomyocytes surface proteins [15]. The presence of cTnI on the plasma membrane was proven in mice [16]. An alternative hypothesis is that anti-cTnI Ab are able to interact with cTnI by penetrating into the cells. It is purely conjectural [17], although principal ability of certain IgG to penetrate into living cells and even into their nuclei has been proven [18,19]. Presumably, at least some effects of anti-cTnI Ab develop due to epitope spreading: immunization of mice with murine cTnI peptide resulted in a late increase of anti-myosin AAb, indicating cardiomyocyte damage and exposure of autoantigens to the immune system, thus causing an autoimmune reaction against antigens other than cTnI [12]. The anti-cTnI Ab themselves have not only pathogenic effects; in a subset of patients with dilated cardiomyopathy (but not with ischemic cardiomyopathy) anti-cTnI Ab were associated with an increased Il-10 secretion that can cause the reduction in systemic concentrations of C-reactive protein. They also decrease the prevalence of advanced diastolic dysfunction in these patients compared with those without anti-cTnI Ab [20]. Concerning the impact on clinical state or outcome in heart disease mentioned above, conflicting results correspondingly have been published: Leuschner et al. showed that the absence of AAb against cardiac troponin I predicted an improvement of the left ventricular function after myocardial infarction [21]. While Doesch et al. described a beneficial effect of anti-troponin I AAb in the setting of dilated cardiomyopathy (improved survival), but not in patients with ischemic cardiomyopathy [22]. With regard to acute coronary syndrome and particularly myocardial infarction, several studies show that anti-cTnI Ab are not independent predictors of myocardial infarction and death during follow-up. They do not correlate with the 12-month outcome [23–25]. However, they can serve as independent predictors for left ventricular remodeling and their presence correlated with a higher troponin release in non-ST elevation acute coronary syndrome [23,25]. As for dilated and ischemic cardiomyopathies, in several studies anti-cTnI Ab were detected more frequently in both groups of patients, compared to controls, but correlations between the levels of these Ab and clinical state or outcome were not always demonstrated [13]. Haghikia et al. studied a group of 70 patients with peripartum cardiomyopathy. The presence of AAb to troponin I was associated with a significantly lower baseline left ventricular ejection fraction, more frequent pericardial effusion and a lower rate of full cardiac recovery at follow-up [26]. According to Erer et al. anti-cTnI Ab level was significantly higher in

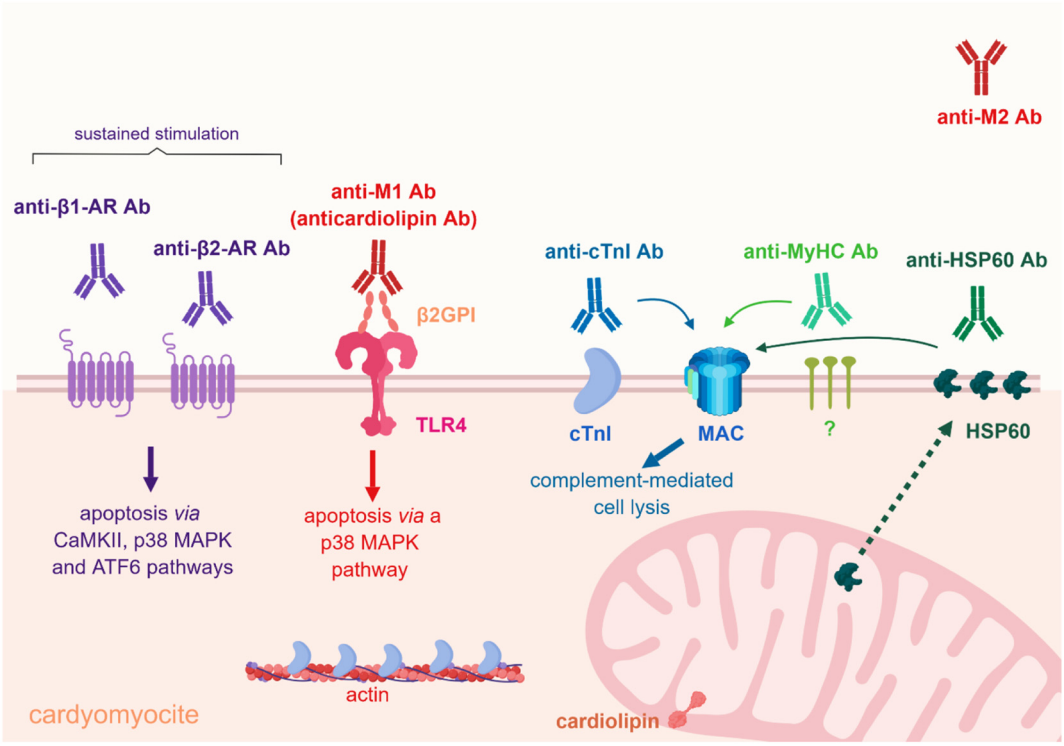

Fig. 1. Targets of cytotoxic autoantibodies (AAb). The target antigen of anti-myosin heavy chain (MyHC) Ab (antibodies) on the plasma membrane has not been defined. The mechanism of cytotoxic effect of anti-M2 Ab is also to be explored. The presence of cardiac troponin I (cTnI) on the plasma membrane was shown in mice. Translocation of human heat shock protein 60 (HSP60) to the plasma membrane following induction of heart failure in rats (see below). AR: adrenergic receptor; ATF6: activating transcription factor 6; β2GPI: beta2-glycoprotein-I; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; MAC: membrane attack complex; MAPK: mitogen-activated protein kinase; TLR: toll-like receptor.

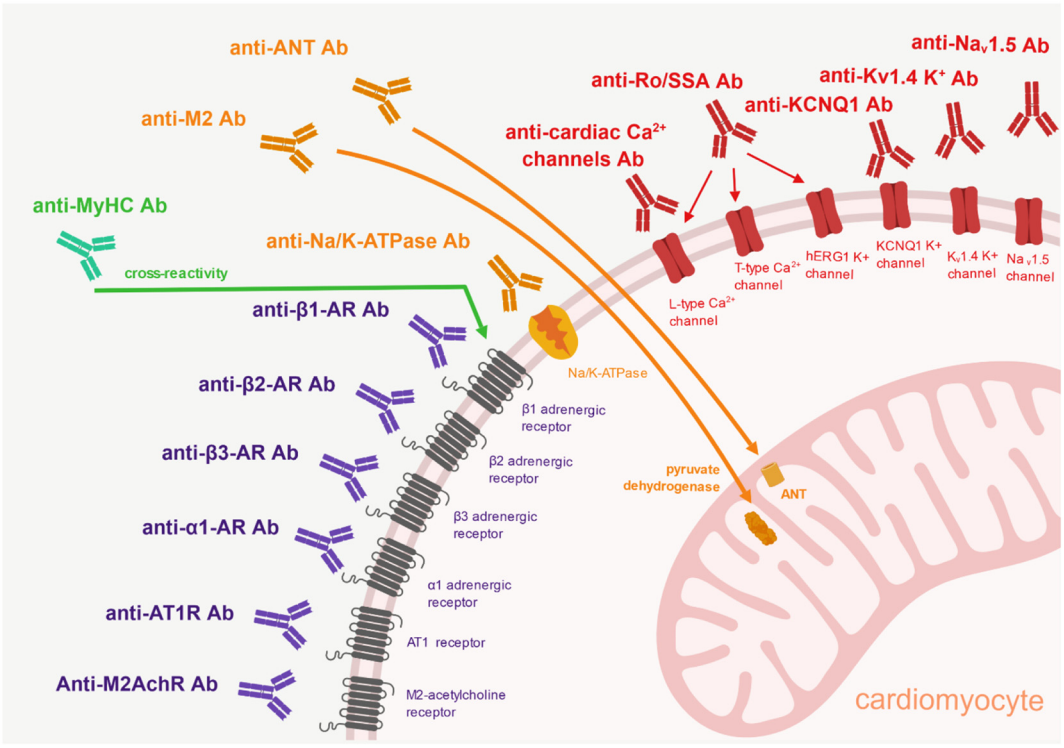

Fig. 2. Targets of cell-blocking and cell-stimulating autoantibodies (AAb). Ab: antibodies; ANT: adenine nucleotide transporter; AR: adrenergic receptor, AT1R: angiotensin II receptor type 1, M2AchR: muscarinic 2 acetylcholine receptor Ab and anti-angiotensin II receptor type 1 Ab); MyHC: myosin heavy chain.

patients with left ventricular hypertrabeculation/non-compaction compared with a control group. The authors claim that increased titers of cTnI and anti-cTnI Ab precede the decline in systolic function and could indicate an ongoing myocardial damage in left ventricular hypertrabeculation/non-compaction [27].

2.2. Anti-human heat shock protein 60 (anti-HSP60) Ab

It is hard to evaluate the prevalence of anti-HSP60 Ab in a healthy population, because apart from pathogenic Ab against endogenous HSPs and Ab against the HSPs of pathogens, the presence of a pool of natural anti-HSP AAb has been demonstrated [28]. Anti-HSP60 Ab are known to take part in immunologically mediated promotion of atherosclerosis. Translocation of HSP60 to the cell surface occurs during cell stress response that correlates with apoptosis and exacerbation of the disease [29]. Anti-HSP60 Ab can lyse the endothelial cells in a complement-mediated fashion or *via* antibody-dependent cellular cytotoxicity [30]. But anti-HSP60 Ab are not endothelial-specific. Lin et al. showed that HSP60 following induction of heart failure in rats (by coronary ligation of left anterior descending artery) was translocated to the plasma membrane and thus being a potential target for Abs or for the effectors of the innate immune system. In this study the percentage of rats, positive for anti-HSP60 Ab raised in group with heart failure reaching 100% in 12-week heart failure rats at a 1:2500 plasma dilution *versus* 60% in a sham group. In the same study the expression level of HSP60 on plasma membrane in human heart samples was higher not only in hearts with an ischemic cardiomyopathy, but also in hearts with dilated cardiomyopathy [31]. Mándi Y et al. showed that 80% of patients with ischemic heart disease and in 65% of patients with dilated cardiomyopathy were seropositive for anti-HSP60 Ab (seropositive category was defined as mean value in healthy controls +2 SD). At the same time the frequency of anti-HSP60 positivity in patients with hypertrophic cardiomyopathy or aortic stenosis did not differ from those in the normal blood donors [32]. In dilated cardiomyopathy, the cause of the increased anti-HSP60 Ab titers is obscure. One possible explanation is that HSP60 shares sequence homologies with cardiac myosin heavy chain (65% of patients with dilated cardiomyopathy with Hsp60 positivity were seropositive against myosin and actin) [32]. With regard to the natural anti-HSP Ab, it is important to distinguish them from the pathogenic ones. A strong link was established between the specificity and the pathogenicity of anti-HSP60-Ab: some of them were specific for ischemic heart disease epitopes, while some other - for epitopes associated with the severity of atherosclerosis [33,34].

2.3. Anti-myosin heavy chain (anti-MyHC) Ab

Abnormal titers of anti-myosin Ab were described in the sera of 0–12.5% healthy individuals [16,35]. The increased titers of anti-myosin Ab have also been reported in patients with rheumatic heart disease [36], myocarditis (17%–52%) [37,38], dilated cardiomyopathy (20%–66%) [16,39–41], ischemic cardiomyopathy (4%–30%), Chagas' cardiomyopathy (11%–38%), peripartum cardiomyopathy (24%) and myocardial infarction (16%–43%) [16,35]. As for myocardial infarction, IgG levels (but not IgM) remain elevated beyond the 6 months after myocardial infarction and therefore could take part in ventricular remodeling, resulting in heart failure [35]. Anti-MyHC Ab were shown to induce myocarditis and dilated cardiomyopathy in susceptible mice in the absence of a viral infection (animal models) [42,43]. Presumably, myosin, which is exclusively intracellular protein, can become accessible to T-cells through presentation on the major histocompatibility complex type II of inflamed myocytes and local antigen presenting cells. Another reason, which is perhaps relevant for rheumatic heart disease and myocarditis, is molecular mimicry. Anti-MyHC Ab are cross-reactive with streptococcal M protein [44], but in regard with the most common viral causes of myocarditis, there is no data on cross-reactivity with Parvovirus B19 or human herpesvirus 6. Moreover, it was shown that anti-MyHC Ab do not cross-react with Coxackie virus [45]. One possible explanation is that anti-MyHC Ab arise due to epitope spreading, while some other self-molecules are cross-reactive with viral epitopes. The cross-reactivity of Coxackie virus with actin favors this hypothesis [46]. Since the titer of anti-MyHC Ab is increased after infection with Coxsackie virus, and immunization with myosin itself induces severe myocarditis and high titers of Ab in genetically predisposed mice [47], it is possible that anti-MyHC Ab are not just a bystander in myocarditis, but rather cause their cytotoxic effects. Recently, it has been demonstrated that human cardiac antigenic myosin fragments activated human monocytes *via* binding to their toll-like receptors, which suggests that cardiac myosin and its pathogenic T cell epitopes may link innate and adaptive immunity in a novel mechanism that could promote chronic inflammation in the myocardium [16]. Besides myocardial damage, some other effects of anti-MyHC Ab (such as inhibition of cardiomyocytes' contraction and raised diastolic level of Ca_i^{2+}) [48] have also been studied in functional assays and several mechanisms for these effects have been suggested, including:

1) Cell membrane penetration and interference of Ab with functionally significant epitopes of the myosin protein [49].
2) Interference of the intracellular signaling by Ab interaction with membrane protein due to dual specificity.

The anti-MyHC Ab's ability of cell membrane penetration have not been confirmed to date, while cross-reactivity of anti-MyHC Ab with β-adrenergic receptor have been described [50]. Cytotoxic and cell-stimulating effects of Ab converge here, because β-AR has also role in controlling apoptosis [51] (see below).

2.4. Antimitochondrial antibodies (AMA)

Most of the papers on the role of AMA in heart diseases date back to the 1990s or earlier period. According to these papers anti-M7 Ab were detected in 31–36% of the patients with dilated cardiomyopathy, in 13–25% of those with myocarditis, in 33% of patients with hypertrophic cardiomyopathy, but not in control subjects with other cardiac disease or in healthy controls [52,53]. In one study 29 of 48 patients with idiopathic dilated cardiomyopathy and all 6 patients with dilated cardiomyopathy after suspected viral myocarditis were anti-M2 Ab positive. While just 1 of 26 patients with ischemic cardiomyopathy and none of 30 healthy controls demonstrate the same titer of anti-M2 Ab [54]. Ab against adenine-nucleotide translocator (ANT) were found in 57–91% of the myocarditis/dilated cardiomyopathy sera, not in healthy controls or those with ischemic heart disease [55]. The debates on the role of increased level of anti-M1 Ab (anticardiolipin Ab) in acute and recurrent cardiac events are ongoing and the results are controversial [56]. Experimentally induced affinity-purified anti-ANT Ab cross-related with calcium channel complex of rat cardiac myocytes, induced enhancement of the transmembrane calcium current and produced Ca-dependent cell lysis in the absence of complement [55]. However, Ab-dependent cell lysis has not been reported using the AAb from patients' sera. Anti-ANT Ab are bimodal (combining cell-destructive and cell-dysregulating effects) and the latter are described below. Anticardiolipin Ab are known to cause endothelial dysfunction and hypercoagulation [57]. However, their direct impact on cardiomyocytes have also been described in *in vitro* hypoxia/reoxygenation injury model – they enhance rat neonatal apoptosis *via* p38 MAPK [58]. The effects of anti-M7 and anti-M2 are poorly understood. While anti-M7 Ab seemed to have no pathogenic effects [59], interstitial infiltration of CD3-positive T-cells was revealed in the ventricular myocardium of a patient with anti-M2 associate cardiomyopathy [60]. Although anti-M2 were shown to activate macrophages, and to bind to their target on apoptotic bodies in biliary cirrhosis [61], their effects on the heart are to be clarified.

As for the reason for elevated AMA titers to distinct antigens in heart

Table 1
Pentamer sharing between HPV L1s antigens and alpha-1A adrenergic receptor, beta-1 adrenergic receptor, beta-adrenergic receptor kinases, and muscarinic-2 acetylcholine receptor. HPV strains examined: 6, 11, 16, 18.

Epitopic sequence	Human proteins
Strain 6	
RKRAK	ARBK1.Beta-adrenergic receptor kinase 2
Strain 11	
SKSAT	ARBK1. Beta-adrenergic receptor kinase 1
Strain 16	
LQPPP	ADA1A. Alpha-1A adrenergic receptor
KPNNN	ACM2. Muscarinic acetylcholine receptor M2
Strain 18	
LHYHL	ARBK1. Beta-adrenergic receptor kinase 1
LHYHL	ARBK2. Beta-adrenergic receptor kinase 2
SPSPS	ADRB1. Beta-1 adrenergic receptor

disease, it was shown that anti-ANT Ab cross-react with viral capsid protein (VP) of Coxackie B3 virus [62], which is known as a common cause of myocarditis and anti-M7 Ab cross-react with sarcosine dehydrogenase from *Pseudomonas aeruginosa* [63].

2.5. Anti-beta 1-adrenergic receptor (anti-β1-AR) Ab

The contribution of anti-β1-AR Ab was demonstrated for myocarditis (33–96%), dilated cardiomyopathy (26–95%), ischemic cardiomyopathy (10–55%), Chagas' disease (30–98%), atrial fibrillation in Graves' disease (94%), peripartum cardiomyopathy (60–100%), primary ventricular tachycardia (about 50%), postural orthostatic tachycardia syndrome (POTS) (65–100%) and chronic fatigue syndrome (18%) [16,64–69]. Multivariate analysis further showed that the presence of anti-β1-AR Ab was an independent predictor of SCD in idiopathic dilated cardiomyopathy and chronic heart failure [70,71]. Autoimmune mechanism can also be proposed for cardiac-related adverse reactions following HPV vaccination [72]. Abnormal titer of anti-β1-AR Ab was identified in a case report of POTS following HPV vaccination [73]. Peptide matching analyses revealed pentapeptide sharing between β1-adrenergic receptor, β-adrenergic receptor kinase 1, β-adrenergic receptor kinase 2 and HPV L1s antigens (Table 1). From an immunological perspective, this overlap is relevant because pentapeptides are endowed with immunogenicity and antigenicity, according to the publicly available epitope database IEDB (Table 2). Orthostatic hypotension among middle-aged adults is associated with the development of atrial fibrillation, structural cardiac changes such as left ventricular hypertrophy as well as with the development of diastolic dysfunction, independently of traditional risk factors [74–76]. Orthostatic hypotension also increases the risk of incidental cardiovascular disease and all-cause mortality in population-based cohort studies [76]. Autoimmune mechanism has been suggested as a causal mechanism in both POTS and chronic fatigue syndrome [72]. POTS and orthostatic hypotension are both forms of orthostatic intolerance and orthostatic intolerance is a common dysfunction in chronic fatigue syndrome [77]. Whether POTS and chronic fatigue syndrome share detrimental effects on the myocardium with orthostatic hypotension, is to be studied. Prevalence of anti-β1-AR Ab in healthy individuals varies due to the techniques used, the incidence varies within 0–19% [16,65]. Anti-β1-AR Ab could interact with different domains of the beta1-adrenergic receptor but only those to the second loop of the receptor have sympathomimetic effects and cause left ventricular dilatation and dysfunction in immunized rats [78]. Similarly to β1-adrenergic receptor agonist isoprotenolol, anti-β1-AR Ab (through $G_{\alpha s}$ coupling to adenylate cyclase) activate cAMP (cyclic adenosine monophosphate)-dependent PKA (protein kinase A) [65]. PKA phosphorylates cardiac troponin I, L-type Ca^{2+} channel and activates Ca-ATPase 1 and 2 through phosphorylation of the phospholamban [79,80]. The effects are dual i.e. promoting both relaxation and contraction of cardiomyocytes.

Table 2
Epitopic sequences containing the pentapeptides shared with HPV L1s antigens.

IEDB ID	Epitopic sequence
13641	epeqve**LQPPP**qgg
58234	sgslgtls**SPSPS**av
112576	lfvtvvdttrstnmtlcasv**SKSAT**ytnsdykeymrhve
213306	kl**SPSPS**sr
223776	rer**SPSPS**f
438423	ka**SPSPS**lssy
452433	a**LQPPP**ap
459602	**SPSPS**pssl
471167	**SPSPSG**svl
480843	k**LQPPP**lgr
480844	k**LQPPP**vgr
485257	sas**SPSPS**f
505465	gka**SPSPS**l
506247	ivr**SKSAT**l
509963	lpy**SPSPS**l
556330	**SPSPS**srvtv
586208	**LQPPP**llql
586346	lsti**SKSAT**tv
588539	rks**SPSPSG**pk
588539	rks**SPSPSG**pk
588625	rl**SPSPS**dagr
605148	hri**SKSAT**r
633078	kellacshpf**SKSAT**e
649584	rv**LQPPP**eqenvqy
651631	v**LQPPP**eqenvqy
652690	yqa**SPSPS**pvgy
694210	ea**RKRAK**nkqlg
696465	**SPSPS**ppppprtptw

Data from ImmuneEpitopeDataBase (www.iedb.org). Shared sequences in capital letters.

Activated Ca-ATPase 1 and 2 cause Ca^{2+} flux from the cytoplasm to the endoplasmic reticulum. Phosphorylated cTnI is prevented from interacting with cTnT thus leading to a weaker Ca^{2+} binding. At the same time phosphorylation of L-type Ca channels and ryanodine receptor 2 lead to elevated Ca^{2+} flux in cytoplasm both from the extracellular matrix and the endoplasmic reticulum [79,80]. There are marked interspecies differences between the effects of anti-β1-Ab activation on the ion currents, and consequently – on the duration of the action potential. Prolongation of the action potential was reported in pig, rat and guinea pig cardiomyocytes, but an opposite effect was achieved in human, cat, rabbit and canine cardiomyocytes. It was shown in the latter case, that anti-β1-AR Ab activation amplifies L-type Ca^{2+} current (I_{Ca}), slow and rapid delayed rectifier K^+ current (I_{ks}, I_{kr}) which results in a decreased duration of the action potential and the elevation of the membrane potential during the plateau phase [81]. The suggested mechanism by which anti-β1-AR Ab lead to SCD is the electrical instability created by the increased beating frequency of the cardiac myocytes. [71] Besides the commonly known functional effects of anti-β1-AR Ab activation on cardiac contractility, anti-β1-AR Ab, like those towards other G-protein-coupled receptors, can transactivate receptor tyrosine kinases, to produce wider effects on the cellular growth and survival. Such components of tissue remodeling as hypertrophy, angiogenesis and fibrosis, accompanied by deep changes in cell metabolism are partially beneficial and potentially pathogenic: despite their participation in the initial adaptation to cardiac stress, being constantly engaged, they lead to a deterioration of the cardiac function. Four main groups of signaling pathways are known to be involved in myocardial hypertrophy 1) MAPK family (JNK, p38, ERK1/2) 2) gp130/JAK/STAT3 3) PI3K/AKT 4) Ca^{2+}/calmodulin [82,83]. It was shown that activation of anti-β1-AR Ab can couple the signal to all these pathways [84]. The cardiac hypertrophy results from the activation of c-Src (*via* complex of G-protein beta/gamma). One important target for c-Src is the extracellular regulated kinases 1 and 2 (Erk1/2), which is also activated by adenylate cyclase. However, the latter mechanism of

activation itself is not sufficient to induce hypertrophic remodeling [85]. Maturation and degranulation of cardiac mast cell are also intensified by anti-β1-AR Ab [16]. Cell-stimulating effects of anti-β1-AR Ab is coupled with cytotoxic ones: it is long known that continuing sympathetic stimulation can cause myocardial damage on a tissue level [86]. Sustained β-adrenergic receptor stimulation was shown to deliver a powerful cardiac apoptotic signal due to β1 and β2 adrenergic receptor coupling to the stimulatory G protein ($G_{\alpha s}$) [87]. It is mediated *via* a CaMKII, p38 MAPK and ATF6 pathways as well and causes decrease of autophagy [88].

2.5.1. Anti-muscarinic 2-acetylcholine receptor (anti-M_2AchR) Ab

AAb against other receptors can also modulate myocardial properties. The titer of anti-M_2AchR Ab in healthy individuals was determined 0–17% in several studies [16,89]. Abnormal titers of anti-M2R Ab have been identified in patients with dilated cardiomyopathy (in 15–51% patients), ischemic cardiomyopathy (50–62%), Chagas' disease (27–99%), peripartum cardiomyopathy (46%) and atrial fibrillation (both idiopathic and combined with Graves' disease - 23 and 88% correspondingly) [16,89]. In another study, using a cut-off level of 101.83 ng/mL, anti-M_2AchR Ab levels predicted the presence of idiopathic paroxysmal atrial fibrillation with a sensitivity of 94.68% and specificity of 81.33% [90]. Hou et al. showed in small samples a prevalence of anti-M_2AchR Ab in 53% patients with ischemic heart disease and chronic heart failure, in 56% patients with dilated cardiomyopathy and chronic heart failure and in 56% patients with hypertensive heart disease and chronic heart failure [91]. The prevalence results differ among authors due to the inclusion criteria for patients with dilated cardiomyopathy and Chagas' disease. Anti-M_2AchR Ab from sera of patients with dilated cardiomyopathy exerted a negative chronotropic effect both *in vitro* (in rat cardiomyocytes assay) [92] and *in vivo* experiment on rat [93]. Consistently with these results, immunization of mice with the N terminus part of the second loop of muscarinic 2-acetylcholine receptor lead to an increased degree of bradycardia following carbachol administration [94]. Anti-M_2AchR Ab were reported in several case reports of patients who developed POTS after HPV vaccinations [95,96]. Pentapeptide sharing was revealed between muscarinic 2-acetylcholine receptor and HPV L1s antigen (Table 1). Analysis of the publicly available epitope database IEDB shows immunological potential of the peptide sharing (Table 2). The effects of anti-M_2AchR Ab interaction with the muscarinic 2-acetylcholine receptor include inhibition of L-type calcium current as well as increase of outward acetylcholine-regulated potassium current ($I_{K,Ach}$) that causes hyperpolarization and shortening of the action potential duration [92]. However, it should be mentioned, that anti-M_2AchR Ab from human patients with Chagas' disease cause a blockage of the cardiac parasympathetic modulation by desensitization of the receptor. It means that anti-M_2AchR Ab from sera of patients with different disease differ in their functional activity. Hence extrapolation of the results for the effects of the AAb in individuals with a particular nosological form to the AAb against the same receptor/enzyme in individuals with other nosological forms is questionable [97,98]. In line with a receptor desensitization in animal studies, anti-M_2AchR Ab were associated with a poor response to digoxin treatment (which can function as vagal stimulation) in chronic heart failure patients [91].

2.6. Anti-alpha 1-adrenegic receptor (anti-α1-AR Ab)

In patients with hypertension, the titers of the agonistic AAb to the α1-adrenergic receptor were increased (25% compared with 5% in normotensives) [99], and the functional autoimmune epitope was mapped to the second extracellular loop of the receptor [100]. These Ab, in addition to their vascular action, also recognize myocardial α1-adrenergic receptor and therefore may contribute to a hypertrophic remodeling of the heart. There are three subtypes of α1-adrenergic receptor: A, B and D, but anti-α1-AR Ab specifically targets the isoform A. Pentapeptide sharing was revealed between α-1A adrenergic receptor and HPV L1s antigen (Table 1). Analysis of the publicly available epitope database IEDB shows immunological potential of the peptide sharing (Table 2). Rats immunized with a peptide corresponding to the second extracellular loop of the α1-AR produced Ab and developed cardiac hypertrophy, signs of cardiomyocyte remodeling (including such molecular markers as increased c-jun and matrix metalloproteinase-2 mRNA expression), but no increase in blood pressure [101]. Other effects of the anti-α1-AR Ab include diastolic dysfunction independent of hypertension and greater sensitivity to angiotensin II [102]. These Abs acutely stimulate L-type Ca^{2+} current, cause an increased Ca_i^{2+} in isolated adult rat cardiomyocytes and exert a positive chronotropic action in spontaneously contracting neonatal cardiomyocytes [103]. Protein kinase C and ERK1/2 are the established mediators of the α1-adrenergic receptor signaling in numerous cell types [104]. They recently have been identified by Wenzel et al. [105] to be also targets for agonistic AAbs to the α1-adrenergic receptor isolated from patients with refractory hypertension. This fact helps to explain the contribution of anti-α1-AR Ab to cardiac hypertrophy.

2.7. Anti-beta3-adrenegic receptor (anti-β3-AR) Ab

27–41% of patients with heart failure are positive for anti-β3-AR Ab (compared to 11% of healthy individuals) [106,107]. These Abs could improve *in vivo* cardiac function according to echocardiographic parameters and reduce the serum levels of N-terminal pro-brain natriuretic peptide in rats with heart failure. They also exhibited negative chronotropic and inotropic effects accompanied by a decreased intracellular Ca^{2+} transient and membrane L-type Ca^{2+} current in cardiomyocytes [107]. However, *ex vivo* study of cardiac function has revealed both systolic and diastolic dysfunction in β3 immunized rats, similarly to the β1 immunized rats [108]. Therefore, the cardioprotective role of anti-β3-AR Ab has not been completely proven yet.

2.8. Anti-beta2-adrenegic receptor (anti-β2-AR) Ab

Human anti-β2-AR Ab were also shown to counteract the hypershrinking, necrosis, apoptosis and heart dysfunction caused by human anti-β1-AR Ab both *in vitro* (neonatal rat cardiomyocytes) and *in vivo* mice model of heart failure induced by passive immunization with β1-Ab. However, anti-β2-AR Ab can also inhibit the activity of adenylate cyclase. A decrease of intracellular cAMP and Ca^{2+} can inhibit the contraction of cardiomyocytes and be ultimately detrimental for cardiac function in heart failure. Thus, anti-β2-AR Ab activate the β2-AR/G_i pathway and exhibit a “bidirectional” effect on cardiac function in heart failure [109]. This bidirectional effect might be the cause, why use of β_1-selective antagonist can have detrimental effects in some patients with heart failure [110]. Data from immunization experiments with the second extracellular loop of the β_2-adrenoceptor are not available and the prevalence of β_2-adrenoceptor Ab in different heart diseases is poorly understood. Their presence was proven in Chagas' disease and heart failure [109,111]. In Chagas' disease human anti β2-AR Ab display positive inotropic and chronotropic effects on isolated rat cardiomyocytes depending on complement, calcium and leukotrienes [112,113].

2.8.1. Anti-angiotensin II type 1 receptor (anti-AT_1R) Ab

According to several studies, Ab directed against the second extracellular loop of the angiotensin II type 1 receptor are prevalent in over 95% of patients with pregnancy-associated hypertension [114]. *In vivo* administration of anti-AT_1R Ab isolated from preeclamptic humans to pregnant mice was shown to induce hypertension in those animals [115]. Anti-AT_1R Ab have also been identified in a subset of individuals with essential hypertension (27–69% compared to 7–23% in healthy controls) [116,117] and in 70% of patients with POTS [118]. Angiotensin II acting on the angiotensin II type 1 receptor on cardiomyocytes

was shown to have no effects on heart function but aggravate cardiac hypertrophy, macrophages infiltration, cell death and expression of NAPH oxidase 2 and TGF beta [119]. Dechend et al. showed that anti-AT_1R Ab cause activation of NAPH oxidase in vascular smooth muscle cells [120]. The ability of anti-AT_1R Ab-positive IgG of patients with systemic scleroderma to induce proinflammatory and profibrotic events was also proved *in vitro* [121]. The role of these Ab in myocardial inflammation, fibrosis and hypertrophy can be suggested, however, it is to be explored.

2.9. Anti-adenine nucleotide transporter (anti-ANT) Ab

Anti-ANT Ab were found in 57–91% of myocarditis/dilated cardiomyopathy sera and in neither controls with ischemic heart disease, nor in healthy individuals. Experimentally induced affinity-purified anti-ANT Ab cross-linked to calcium channel complex of rat cardiac myocytes, induced enhancement of transmembrane Ca^{2+} current and produced Ca-dependent cell lysis in the absence of complement [55]. However, Ab-dependent cell lysis has not been reported using the AAb from sera of patients. The ability of sera of patients to inhibit adenine nucleotide exchange *in vitro* was registered in 90% of patients with dilated cardiomyopathy and ejection fraction < 40% and in 40% of patients with dilated cardiomyopathy and ejection fraction > 40%, but only in 2% of controls. Anti-ANT Ab alter the function of the enzyme *in vivo* (according to measurements of the cytosolic and mitochondrial adenine nucleotide concentrations in immunized animals with high titers of the Ab) [122]. Later, Kuhl et al. have identified two proteins on the cell surface of cardiac myocytes that anti-ANT Ab bind to and that may serve as receptors for receptor-mediated endocytosis, thus enabling their penetration into the cell [123]. Finally, the effect of Ab mediated block of transporter on cardiac function *in vivo* was demonstrated [124]. The external heart work of immunized guinea pigs was seen to be reduced in close relation to the decrease in cytosolic-mitochondrial difference of the phosphorylation potential of ATP. The authors conclude that Ab-mediated carrier dysfunction through creating the observed imbalance in myocardial energy metabolism is responsible for the impairment of cardiac function [124].

2.9.1. Other antimitochondrial antibodies (AMA)

The ability to inhibit *in vitro* activity of the other mitochondrial enzyme – pyruvate dehydrogenase – was shown for anti-M2 Ab [125]. Interestingly, it was revealed in one study among patients who underwent AMA-M2 screening following the detection of elevated hepato-biliary enzymes, that prevalence of supraventricular arrhythmias in AMA-M2-positive individuals was higher than that in AMA-M2 negative ones. The anti-M2 Ab was an independent risk factor for supraventricular arrhythmias in patients with elevated hepato-biliary enzymes (odds ratio 3.52, $p = .011$) [126]. Presumably, AMA-M2 are able to inhibit the activity of pyruvate dehydrogenase also *in vivo*, thus altering energy metabolism. The role of mitochondria for electrical functioning of the heart and in particular the arrythmogenic effect of the metabolic inhibition were described. [127,128]. In another study 8 out of 13 patients with inflammatory myopathies associated with anti-mitochondrial antibodies displayed various patterns of arrhythmia and 6 out of 13 demonstrated decreased ejection fraction (< 50%) [129].

2.10. Anti-Na/K-ATPase Ab

Anti-sarcolemmal Na/K-ATPase Ab also have an ability to inhibit target enzyme. Baba et al. showed that 26% of patients with dilated cardiomyopathy are positive for these Ab (compared to 2% in control group), and that ventricular tachycardia and SCD was independently predicted by the presence of Ab, as well as poor systolic function. The authors hypothesize that the reduction of Na/K–ATPase activity leads to an abnormal intracellular Ca^{2+} handling and delayed after-depolarizations *via* reverse-mode operation of the Na/Ca^{2+} exchanger resulting from increased intracellular Na concentration [130]. Further, it has been shown that immunization of rabbits with sarcolemmal Na/K–ATPase results in myocardial hypertrophy due to left ventricular pressure overload and myocardial fibrosis [131]. Coexistence of gastropathies and cardiac arrhythmias has been noticed by clinicians long ago. Na/K–ATPase and H/K–ATPase of gastric acidic pump have common epitopes. Human gastric parietal cells and cardiomyocytes share the 35 kDa glycoprotein, and infection with Helicobacter pylori is able to induce cross-reacting AAb towards parietal cells and cardiomyocytes, implicated both in gastropathy and atrial fibrillation mechanisms [132].

2.10.1. Anti-cardiac Ca^{2+} channels Ab

Activating Ab against cardiac Ca^{2+} channels were detected in 5–49% patients with dilated cardiomyopathy and in 4% patients with ischemic cardiomyopathy *versus* 1–6% in controls [133–135]. These Ab enhanced calcium current on Xenopus oocytes expressing human $Ca_V1.2$ subunit of calcium channel and induced ventricular arrhythmic potential in Langendorff isolated rat heart model. They also caused early after depolarization and prolonged the plateau of action in rat ventricular myocytes [133,134]. These effects were prevented by pre-incubation with either the L-type Ca^{2+} channel antagonist nifedipine or with high concentrations of the L-type Ca^{2+} channel antigenic peptide. Activating anti-cardiac Ca^{2+} channels Ab were shown to be independent predictors of ventricular tachycardia (in patients with dilated cardiomyopathy) and SCD (in patients with dilated cardiomyopathy and ischemic cardiomyopathy) [133,135]. Loss-of-function mutation in CACNA1C gene, which encodes $Ca_V1.2$, represents one form of long QT syndrome [71].

2.10.2. Anti-Ro/SSA Ab

Anti-Ro/SSA Ab is a well-known reason for autoimmune congenital heart block (ACHB) if passively transferred from pregnant mothers with Sjogren's syndrome and systemic lupus erythematosus to their fetuses [136]. Several groups demonstrated deposition of anti-Ro/SSA in the cardiac tissue of fetuses who died from ACHB [137,138]. Clinical symptoms of ACHB included atrioventricular (AV) block of various degree and sinus bradycardia, but few other effects were described as well, like endocardial fibroelastosis, valvular insufficiency, and/or dilated cardiomyopathy, significantly reducing cardiac function and requiring transplant [139]. In prospective study of pregnancies in anti-Ro/SSA positive women the risk of ACHB was estimated to be 2–5% with no previously affected child and 15–20% with a previously affected one [140]. The current opinion is that these Ab are necessary but not sufficient to cause the disease. Adult hearts are less prone to be affected by anti-Ro/SSA Ab due to several reasons [141], but the incidence of anti-Ro/SSA Ab-associated AV block in adults is probably higher than recognized because these patients (and their mothers) are frequently asymptomatic for autoimmune disease [142]. Retrospective studies on large populations suggest that anti-Ro/SSA Ab might underlie at least 10% of all cases of isolated third-degree AV blocks of unknown origin in young adults [143]. This data are very important since the acquired form the AV block (unlike congenital one) is characterized by a good response to immunosuppressive therapy [142]. Direct and indirect evidence of anti-Ro/SSA Ab role in ACHB were also obtained in animal studies: first-degree AV block has been reported in 9–45% of pups born to females immunized with Ro52 p200-epitope. Animal models have yielded a higher rate of first-degree AV block in newborn pups (47–100%) as well as the presence of sinus bradycardia. These models were based both on transfer of anti-Ro/SSA Ab purified from mothers of children with ACHB and transfer of monoclonal Ab targeting the p200 epitope of Ro52. However, immunization induce a variable repertoire of Ab, hence the precise specificity in the pathogenic Ab is important [144]. Well-known mechanism of rhythm disturbance caused by anti-Ro/SSA is inhibition of I_{CaL} and I_{CaT} in the heart conduction system and sinus node respectively due to cross-reactivity of

the Ab with L-type and T-type Ca channels [144]. It was demonstrated by perfusion with IgG Ab containing anti-Ro/SSA Ab from mothers, whose children develop ACHB, but not with IgG Ab from mothers with healthy children, that these Ab have an immediate effect on heart electrophysiological properties. In the first case bradycardia associated with 2:1 second-degree AV block arose within 5 min which progressed to third-degree AV block after 15 min [145]. Their long-term effects include internalization and degradation of calcium channels, insufficient excitation-contraction coupling, impaired calcium homeostasis and eventually apoptotic cell death as well as induction of inflammation that ends in fibrosis of the conduction system [144]. Cross-reactivity of anti-Ro/SSA Ab with hERG1 K^+ channels with inhibitory effect on their function constitutes a novel form of acquired long QT syndrome of autoimmune origin [146,147]. Mutations in the KCNH2 gene, encoding hERG1, account for nearly 1/3 of cases of congenital long QT syndrome [148] and novel acquired form seems to be a new example of autoimmune phenocopy for a genetic disease. Since both genetic defects and dysregulating effects of AAb can interfere with function of complex proteins, the existence of autoimmune phenocopies for monogenic genetic disorders seems to be a general pathologic phenomenon. There are a few examples from various groups of diseases (immune bullose dermatoses, secondary autoimmune cardiomyopathies) etc. [149]. The drugs that prolongate QT have their effect due to block of hERG1 channel [150]. Both genetic and acquired QT prolongation often leads to early after-depolarization and if it progresses to a critical threshold in a large area of the myocardium, it can result in an ectopic beat. In the presence of an exaggerated heterogeneity of action potential duration across the myocardium, the ectopic beat can induce reentrant excitation and *torsades de pointes*. Long QT due to any reason predispose patient to a life-threatening ventricular arrhythmia and SCD. Indeed, in a prospective cohort of 25 patients who experienced *torsades de pointes* independently of ongoing therapies and concomitant diseases, circulating anti-Ro/SSA-52kD Ab were frequently detected (60% of cases), mostly in patients with no history of an autoimmune disease [151]. However, since Ca and K channels are known to have different effects on QT duration, cross-reactivity of anti-Ro/SSA Ab leads *in vivo* to complex effect, in some studies without statistically significant QT prolongation. Interestingly, causal relationship between QT-prolongation and anti-Ro/SSA is more controversial in newborns/fetuses than in adults. In fact, differently from the conduction system susceptibility, it is possible that ventricular repolarization may be more vulnerable to the effect of anti-Ro/SSA Ab in adults rather than in fetuses/newborns [141]. The reason for this phenomenon is to be elucidated.

2.10.3. Anti-potassium voltage-gated channel subfamily Q member 1 (KCNQ1) Ab

Ab against KCNQ1 K^+ channel demonstrate agonist-like activity associated with a shortened QT [152]. That can be considered an autoimmune form of type 2 congenital short QT syndrome, caused by gain-of-function mutation in KCNQ1 gene. The prevalence of anti-KCNQ1 Ab is unknown. In the only one study on their prevalence 9 out of 150 patients with dilated cardiomyopathy were positive for these Ab [152]. Congenital form of short QT syndrome predisposes to developing life-threatening ventricular tachyarrhythmias, the arrhythmogenic effect of the acquired one was shown in immunized rabbits [153]. But AAb pathogenic in one case, may be beneficial in other one, which was shown in a well-recognized rabbit model of human long QT syndrome induced by infusion with methoxamine and dofetilide. In this model corrected QT prolongation was less severe in KCNQ1 channel peptide-immunized animals, compared with a control group (18% *versus* 73% increase upon drug challenge). The authors speculated that KCNQ1 vaccination might be useful for the treatment of a congenital long QT syndrome [153].

2.10.4. Anti-K_v1.4 K^+ channel Ab

Abs against the K_v1.4 K^+ channels were detected in sera of 10–18% patients in myasthenia gravis [154–156]. Myocarditis and QT-prolongation were determined respectively in 11–27% and 36% anti-K_v1.4 K^+ Ab positive patients [154,156]. Heart muscle function in *ex vivo* chick embryos, according to ultrasound echocardiography, was significantly suppressed by additing sera with anti-K_v1.4 K^+ Ab from patients with myasthenia gravis compared with sera without these Ab from patients with the same disease [156]. No studies on the mechanism of anti-K_v1.4 K^+ Ab action are currently available. In some anti-K_v1.4 K^+ Ab positive patients clinical and instrumental signs of structural heart damage (myocarditis) are present. Considering the difference of clinical manifestation in patients with these Abs from ones with Abs against other K channels one can suggest both cytotoxic effects and inhibition of ion current through K_v1.4 K^+ channel [140].

2.10.5. Anti-Na_v1.5 channel Ab

The data on the prevalence of anti-Na_v1.5 Ab in heart diseases are limited. In a single study 10 out of 10 patients with idiopathic AV block II-III degrees were positive for these Ab compared to none in control group. It is in accordance with the following results:

1) All rats immunized with a peptide corresponding to the extra-cellular region of the Na_v1.5 channel showed repeated and prolonged episodes of intermittent third-degree AV and SA blocks.
2) I_{Na} density was reduced in ventricular cardiomyocytes incubated with sera both from immunized rats and anti- Na_v1.5 Ab positive patients, compared with sera from healthy individuals [157].

In addition, loss-of-function mutation in SCN5A gene, which encode Na_v1.5 channel, represents one form of long QT syndrome [71].

3. Conclusion

The research of cardiotropic Abs and their biological effects has a long history and was continued in epoch of molecular and cellular biomedicine. The aim of this review was to identify the role of AAb in heart diseases, drawing on revised Witebsky-Rose criteria. These criteria include:

1) Direct proof (reproduction of the disease or its major pathological manifestation in experimental animals following passive transfer of the autoreactive cells/AAb or in humans *via in utero* materno-fetal transfer).
2) Indirect proof (reproduction of the essential features of the disease by immunization of the laboratory animals with the target autoantigen).
3) Circumstantial evidence (association with other autoimmune disease in the same individual or in the same family, lymphocytic infiltration in a target organ, statistical association with a particular MHC haplotype or aberrant expression of MHC class II on the affected organ, favorable response to immunosuppression) [158].

However, it ought not to be forgotten, that according to a novel concept AAb are not exclusively linked with the triggering of autoimmunity [159]. At least autoantibodies targeting G protein-coupled receptors in healthy donors were shown to provide homeostatic functions and form network signatures [159]. Further studying of AAb networks in healthy individuals and in both autoimmune and non-autoimmune cardiovascular diseases may contribute to the development of screening for SCD [71] and new therapeutic strategies in cardiology.

Source funding

This work is supported by the grant of the Government of the Russian Federation for the state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

Conflict of interest

YS is appearing in vaccine compensation court, Washington DC. USA.

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