

Autoimmune cardiac channelopathies and heart rhythm disorders: A contemporary review

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ABSTRACT

Cardiac arrhythmias still represent a major health problem worldwide, at least in part because the fundamental pathogenic mechanisms are not fully understood, thus affecting the efficacy of therapeutic measures. In fact, whereas cardiac arrhythmias are in most cases due to structural heart diseases, the underlying cause remains elusive in a significant number of patients despite intensive investigations even including postmortem examination and molecular autopsy. A large body of data progressively accumulated during the last decade provides strong evidence that autoimmune mechanisms may be involved in a significant number of such unexplained or poorly explained cardiac arrhythmias. Several proarrhythmic anti-cardiac ion channel autoantibodies have been discovered, in all cases able to directly interfere with the electrophysiologic properties of the heart but leading to different arrhythmic phenotypes, including long QT syndrome, short QT syndrome, and atrioventricular block. These autoantibodies, which may develop independent of a history of autoimmune diseases, could help explain a percentage of arrhythmic events of unknown origin, thereby opening new frontiers for diagnosis and treatment of heart rhythm disorders. Based on this evidence, the novel term *autoimmune cardiac channelopathies* was coined in 2017. Since then, the interest in the field of cardioimmunology has shown a tumultuous growth, so much so that the number of arrhythmogenic anti-ion channel autoantibodies reported has significantly increased, also in association with not previously described arrhythmic phenotypes, such as atrial fibrillation, Brugada syndrome, and ventricular fibrillation/cardiac arrest. Thus, an updated reassessment of this topic, also highlighting perspectives and unmet needs, has become necessary and represents the main objective of this review.

KEYWORDS Autoantibodies; Cardiac ion channels; Arrhythmias; Sudden cardiac death; Autoimmune disease

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Introduction

Cardiac arrhythmias are an important source of morbidity and mortality worldwide.¹ Specifically, atrial fibrillation (AF) represents a major cause of thromboembolic events and heart failure, and advanced atrioventricular block (AVB) is the most common indication for pacemaker implantation. Moreover, malignant ventricular arrhythmias (VAs) are recognized to be the leading mechanism for sudden cardiac death (SCD), accounting for ~5 million deaths every year worldwide.¹ Thus, cardiac arrhythmias currently represent a significant health problem, at least in part because the fundamental pathogenic mechanisms are not fully understood, thus limiting the efficacy of therapeutic measures.

Whereas cardiac arrhythmias are in most cases due to structural heart diseases,^{1,2} it is increasingly recognized that in a significant number of patients, the underlying cause remains elusive despite intensive investigations. This is true for a wide range of arrhythmias, including AF,³ AVB,^{3,4} idiopathic ventricular fibrillation (VF), and SCD.^{2,5} It is noteworthy that in up to 15% of patients presenting with cardiac arrest (CA)/SCD (30% in individuals <40 years), autopsy examination does not show any structural cardiac disease.² In this regard, inherited cardiac channelopathies, such as congenital long QT syndrome (LQTS) and Brugada syndrome (BrS), can account for a number of these events; however, in ~70% of cases, results of postmortem genetic testing by molecular autopsy turn out negative.²

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To date, a large body of data progressively accumulated during the last decade provides strong evidence that autoimmune mechanisms may be involved in a significant number of such unexplained or poorly explained cardiac arrhythmias.^{6–10} Specifically, several proarrhythmic anti-cardiac ion channel autoantibodies have been discovered, in all cases able to directly interfere with the electrophysiologic properties of the heart. In 2017, our group coined the novel term *autoimmune cardiac channelopathies*,⁷ adding a new classification to the acquired form of channelopathies from autoimmune origin. Since then, the interest in the field of cardioimmunology has shown a tumultuous growth,¹¹ so much so that the number of arrhythmogenic anti-ion channel autoantibodies reported has significantly increased, also in association with not previously described arrhythmic phenotypes, such as AF,¹² BrS,¹³ idiopathic VF,¹⁴ and unexplained CA.¹⁵ Thus, an updated reassessment of this topic has become necessary, representing the main objective of this contemporary review.

Classification of autoimmune cardiac channelopathies

We propose that arrhythmogenic autoimmune cardiac channelopathies can be classified according to 3 key criteria (Figure 1): the type of the targeted ion channel (ie, autoimmune calcium, potassium, and sodium channelopathies), the functional effect of the autoantibody on the target protein (ie, inhibiting and agonist-like arrhythmogenic autoantibodies), and the associated arrhythmic phenotype (ie, autoimmune tachyarrhythmias and bradyarrhythmias). As detailed in the following paragraphs, a peculiar behavior is shown by anti-Ro/SSA (Sjögren syndrome-related antigen A) antibodies, able to promote both tachyarrhythmias and bradyarrhythmias as a result of a multitarget inhibitory cross-reaction with different types of calcium and potassium channels in the heart.^{7,16}

As comprehensively described in the Supplemental Material (Data S1), these 3 classifications provide different points of view to better understand and to describe the multiple facets of this novel autoimmune mechanism for cardiac arrhythmias.

However, whereas the first 2 classifications are primarily focused on molecular and electrophysiologic aspects, more useful for basic science/translational studies, the third one is suitable for translation into the clinical setting. For this reason, it is the one primarily used in this review.

Tachyarrhythmias

Autoimmune cardiac channelopathies can promote several types of tachyarrhythmias, including VA and AF. VAs, which are the most severe,

potentially leading to CA and SCD, occur in the setting of 4 main electrocardiographic phenotypes: LQTS, short QT syndrome (SQTS), BrS, and short-coupled VF (SCVF).

Autoimmune LQTS

Three different anti-ion channel autoantibodies have currently been associated with the development of VA, also life-threatening, occurring in the presence of an electrocardiographic (or electrophysiologic) phenotype suggestive of LQTS. They are the anti-K_v11.1 and the anti-K_v1.4 inhibiting antibodies and the anti-Ca_v1.2 agonist-like antibody (Table 1). Whereas the association with LQTS and related VA is supported by a substantial number of experimental, clinical, and population studies for the first, the link is less robust in the other 2 cases as several basic and clinical aspects need further investigations (Tables 2 and 3; Figure 2).

Inhibiting anti-K_v11.1 (hERG) autoantibodies

The K_v11.1 channel, better known as human ether-à-go-go-related gene potassium channel (hERG), generates the rapid component of the delayed rectifier potassium current (I_{Kr}). It is well recognized that this channel plays a key role in determining ventricular action potential duration (APD) and is the target for most cases of drug-induced LQTS.¹⁷ Moreover, variants affecting the related encoding gene (*KCNH2*) represent the cause of the type 2 congenital LQTS.¹⁸

In 2015, we demonstrated that circulating anti-Ro/SSA 52-kDa antibodies in patients with connective tissue disease (CTD) presenting with LQTS cross-react with and inhibit hERG.¹⁹ (More details on molecular aspects and clinical significance of anti-Ro/SSA antibodies are in the Supplemental Material [Data S2]). Specifically, we provided evidence that sera, purified IgG, or affinity-purified anti-Ro/SSA 52-kDa autoantibodies from these patients were able to bind a specific 31-amino acid peptide sequence (GNMEQPHMDS-RIGWLHNLDQIGKPYNSSGL) on the extracellular loop of the pore-forming region of the channel (where significant homology with the Ro/SSA 52-kDa antigen exists), acutely inhibit I_{Kr} in a concentration-dependent manner, and prolong ventricular APD *in-vitro*.¹ These findings were supported and extended by Szendrey and coworkers,²⁰ who demonstrated that anti-Ro/SSA 52-kDa antibodies can also chronically inhibit I_{Kr} by a direct interaction with the hERG extracellular S5-pore linker as a result of an enhanced channel degradation by endocytosis. Moreover, guinea pig immunization with either the Ro 52-kDa antigen or the 31-amino acid hERG pore peptide led to a sharp prolongation of the heart rate-corrected QT interval (QTc) on the surface electrocardiogram and the APD at ventricular myocyte level,^{19,21} without any evidence of cardiac inflammation or fibrosis.²¹ In agreement with these mechanistic data, earlier clinical evidence demonstrated that in anti-Ro/SSA-positive CTD patients, the mean QTc was longer and the prevalence of QTc prolongation was higher compared with anti-Ro/SSA-negative CTD patients²² and associated with an increased incidence of complex VA.²³ As pointed out in a review²⁴ (and summarized

Abbreviations

AD:	autoimmune disease
anti-Ro/SSA:	anti-Ro/Sjögren syndrome-related antigen A
BrS:	Brugada syndrome
CA:	cardiac arrest
CTD:	connective tissue disease
LQTS:	long QT syndrome
SCVF:	short-coupled ventricular fibrillation
SQTS:	short QT syndrome
TdP:	torsades de pointes
VF:	ventricular fibrillation

with further updated data in [Supplemental Table 1](#)), consistent and similar findings were reported by >10 additional clinical studies performed in patients, adults and children, with different types of CTD. Moreover, preliminary data suggest that immunosuppressive therapy could reverse QTc prolongation in anti-Ro/SSA-positive CTD patients.^{25,26}

The clinical impact of these findings is significantly emphasized by accumulating data showing that circulating anti-Ro/SSA 52-kDa antibodies are associated with an increased risk for development of LQTS also in the absence of a manifest CTD (or other autoimmune disease [AD]), further pointing to a direct autoantibody-mediated interference on cardiac electrophysiology. The first evidence was provided by Cimaz and associates,²⁷ who demonstrated that the passive transplacental autoantibody passage from anti-Ro/SSA-positive CTD mothers to their unaffected newborns was frequently associated with transient but significant QTc prolongation, which disappeared within the first year of life concomitantly with maternal autoantibody clearance.²⁸ Later studies confirmed these findings, also reporting cases of newborns with anti-Ro/SSA-associated LQTS complicated by ventricular tachycardia (VT)/torsades de pointes (TdP) occurrence ([Supplemental Table 1](#)). Moreover, after the initial description by Nakamura and coworkers²⁹ of an otherwise healthy anti-Ro/SSA-positive woman who presented with recurring TdP episodes, we provided evidence that in a prospective cohort

of 25 consecutive adult patients with TdP, 60% of cases showed circulating anti-Ro/SSA 52-kDa antibodies, usually in the absence of a concomitant AD.³⁰ Again, sera and purified IgG from autoantibody-positive TdP patients (but not from those negative) were able to directly bind the 31-amino acid sequence on the hERG S5–S6 extracellular loop³⁰ and acutely and chronically inhibit I_{Kr} *in-vitro*.^{29,30} Such findings, combined with the evidence that anti-Ro/SSA antibodies can be found in a significant percentage of unselected individuals of the general population (up to ~3%–8%, depending on age),^{31,32} suggest that these autoantibodies may represent a hidden risk factor for LQTS and associated life-threatening VA in the general population. A strong support to this hypothesis has been provided by 2 large population studies.³³ The first, in a cohort of 7339 US veterans, showed that the presence of circulating anti-Ro/SSA antibodies ($n = 612$ [8.3%]), regardless of a CTD history, was independently associated with a 2 times increased risk of presenting with marked QTc prolongation >500 ms.³² In the second study, an Israeli nationwide cross-sectional investigation involving >100,000 participants, the authors provided evidence that anti-Ro/SSA-positive individuals showed higher rates of tachyarrhythmias, including a ~50% increased risk of paroxysmal VT (odds ratio, 1.49; 95% confidence interval, 1.10–2.01), compared with those testing negative, again independent of a concurrent diagnosis of AD.^{33,34}

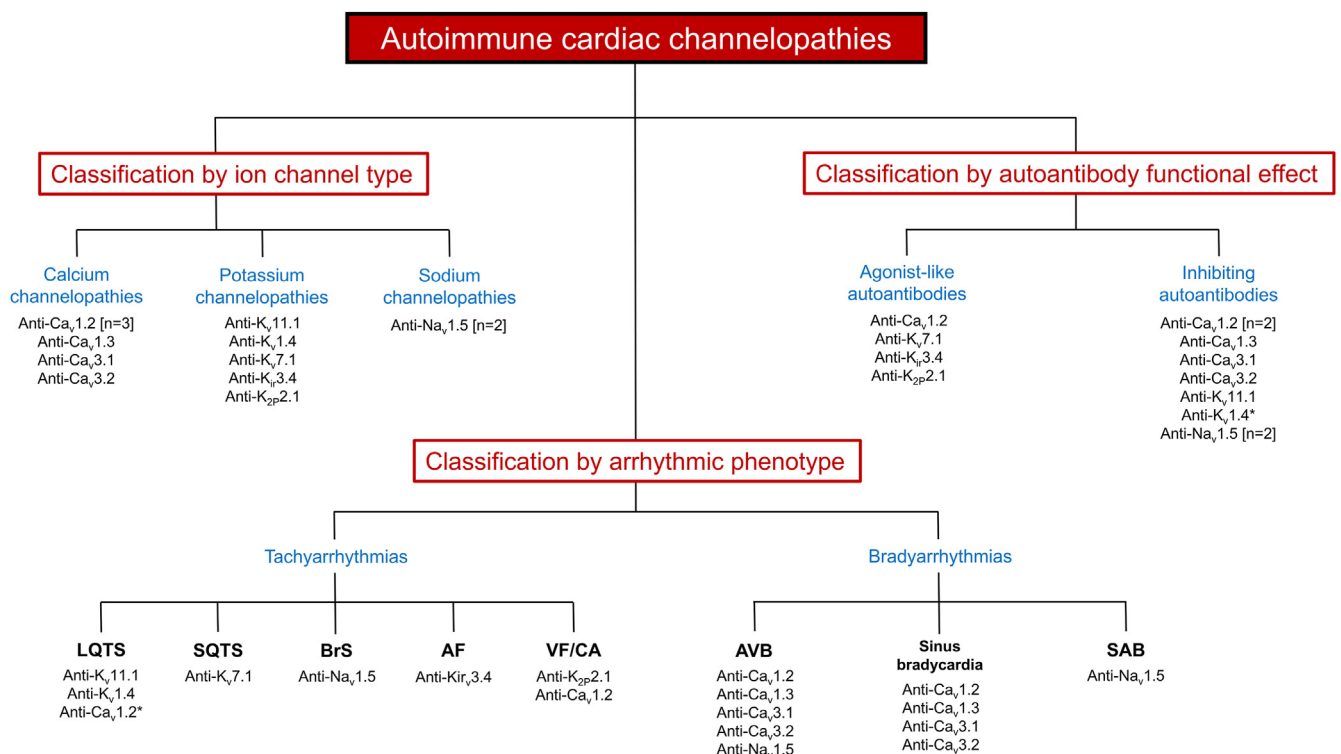


Figure 1

Classifications of autoimmune cardiac channelopathies. AF = atrial fibrillation; AVB = atrioventricular block; BrS = Brugada syndrome; CA = cardiac arrest; LQTS = long QT syndrome; SAB = sinoatrial block; SQTS = short QT syndrome; VF = ventricular fibrillation.

Table 1 Autoimmune cardiac channelopathies classified by arrhythmic phenotype

Clinical phenotype	ECG findings	Autoantibody type	Ion channel	Binding site	Targeted peptide	Effect on ion current	Effects on cell electrophysiology
Tachyarrhythmias	LQTS	Inhibiting* (anti-Ro/SSA)	K _v 11.1 (hERG)	Extracellular loop between S5–S6	GNMEQPHMDSRIGWLHNLGDQIGKPYNSSGL	I _{Kr} decrease	Ventricular cell APD prolongation
		Inhibiting	K _v 1.4	Intracellular N terminus	MPYGY	NA	NA
		Agonist-like	Ca _v 1.2	Intracellular N terminus of D1	VNENTRMYIPEENHQ	I _{CaL} increase	Ventricular cell APD prolongation, EADs occurrence
	SQTS	Agonist-like	K _v 7.1	Extracellular loop between S5–S6 of D1	AEKDAVNESGRVEFGSYADA	I _{Ks} increase	Ventricular cell APD shortening
	Brugada syndrome	Inhibiting	Na _v 1.5	Extracellular loops [†]	NA	I _{Na} decrease	NA
	Atrial fibrillation	Agonist-like	K _i 3.4	Extracellular loop between M1–M2	IETETTIGYGFRVITEKCPE	I _{KACh} increase	hiPSC-CMs APD shortening
		Agonist-like	K _{2P} 2.1 (TREK-1)	Extracellular loop between M1–M2	HSCVNSTELDELIQQIVAAI	I _{K2P} increase	hiPSC-CMs APD shortening
Bradyarrhythmias	VF/CA	Agonist-like	K _{2P} 2.1 (TREK-1)	Extracellular loop between M1–M2	HSCVNSTELDELIQQIVAAI	I _{K2P} increase	hiPSC-CMs APD shortening
		Inhibiting	Ca _v 1.2	Extracellular loop between S5–S6 of D3	DFDNVLAAMMALFTVSTFEG	I _{CaL} decrease	hiPSC-CMs APD shortening
		Inhibiting*	Ca _v 1.2	Extracellular loop between S5–S6 of D1	ELFMGKMKHTCYNQEGADV RQCQNGTVCKPGWDGPKHGI AEDDPSPCALETGHGRQCQN KGNVITYKDGEVDHPHIIQPR DFDNVLAAMMALFTVSTFEG	I _{CaL} decrease	Nodal cell AP inhibition
	AVB/sinus bradycardia	Inhibiting*	Ca _v 1.3	Extracellular loop between S5–S6 of D1	NA	I _{CaL} decrease	Nodal cell AP inhibition
		Inhibiting*	Ca _v 3.1	Extracellular loop between S5–S6 of D1	YNSSSNTTCVNWNQYYTNCS	I _{CaT} decrease	Nodal cell AP inhibition
		Inhibiting*	Ca _v 3.2	Extracellular loop between S5–S6 of D1	VGAARNACINWNQY	I _{CaT} decrease	Nodal cell AP inhibition
	AVB/SAB	Inhibiting	Na _v 1.5	Extracellular loop between S5–S6 of D1	GNLRHKCVRNFTELNGTNGSVEADGLWW	I _{Na} decrease	NA
		Inhibiting	Na _v 1.5	Extracellular loop between S5–S6 of D1	GNLRHKCVRNFTELNGTNGSVEADGLWW	I _{Na} decrease	NA

Anti-Ro/SSA = anti-Ro/Sjögren syndrome-related antigen A antibodies; AP = action potential; APD = action potential duration; AVB = atrioventricular block; CA = cardiac arrest; D1/D2/D3/D4 = domains 1/4; EADs = early afterdepolarizations; ECG = electrocardiogram; hERG = human ether-à-go-go-related gene potassium channel; hiPSC-CMs = human induced pluripotent stem cell-derived cardiomyocytes; I_{CaL} = L-type calcium channel current; I_{CaT} = T-type calcium current; I_{Na} = sodium channel current; I_{KACh} = acetylcholine-gated potassium channel current; I_{Kr} = rapid component of the delayed rectifier potassium channel current; I_{Ks} = slow component of the delayed rectifier potassium current; I_{K2P} = 2-pore domain potassium channel current; iCA = idiopathic cardiac arrest; LQTS = long QT syndrome; M1–M2: transmembrane segments 1–2; NA = datum not available; SAB = sinoatrial block; SCVF = short-coupled ventricular fibrillation; SQTS = short QT syndrome; S3–S4/S5–S6 = transmembrane segments 3–4/5–6; TREK-1 = TWIK-related potassium channel 1; VF = ventricular fibrillation.

*Anti-Ro/SSA antibody cross-reacting with the channel.

[†]Including extracellular loops between S5–S6 of D1, D2, D3, and D4 and between S3–S4 of D4.

Table 2 Key studies providing clinical support to the arrhythmogenicity of autoimmune cardiac channelopathies in adults

Author, year	Autoantibody	Study design	Study population	Main findings
Autoimmune long QT syndrome Lazzerini et al, 2004 ²²	Anti-K _v 11.1 (anti-Ro/SSA)	Cross-sectional	57 CTD patients (31 anti-Ro/SSA positive)	Mean QTc longer and prevalence of QTc prolongation >440 ms higher in autoAb-positive than in autoAb-negative patients (58% vs 0%)
Bourré-Tessier et al, 2011 ⁸⁹		Cross-sectional/ prospective	278 SLE patients (113 anti-Ro/SSA positive)	5 times higher risk of QTc prolongation in autoAb-positive vs autoAb-negative patients; association strongly persisted over time
Lazzerini et al, 2016 ³⁰		Cross-sectional	25 TdP patients	High prevalence of anti-Ro/SSA 52-kDa antibodies in unselected TdP patients (60%), independent of a history of AD
Lazzerini et al, 2021 ⁸³		Cross-sectional population based	7339 US veterans (612 anti-Ro/SSA positive)	QTc prolongation (>470 ms in men/>480 ms in women) in 10% of autoAb-positive vs 6.2% of autoAb-negative patients (marked QTc prolongation >500 ms, 3.1% vs 1.0%); autoAb positivity independently associated with a 2 times higher risk of marked QTc prolongation (>500 ms; OR, 2.27; 95% CI, 1.34–3.87)
Akuka et al, 2022 ³⁴		Cross-sectional population based	101,599 general population participants (11,525 anti-Ro/SSA positive)	AutoAb-positive participants showed a 50% increased risk of paroxysmal VT (OR, 1.49; 95% CI, 1.10–2.01) compared with autoAb-negative participants
Suzuki et al, 2005 ³⁵	Anti-K _v 1.4	Cross-sectional	61 MG patients (11 autoAb positive)	AutoAb-positive patients had increased incidence of QTc prolongation compared with autoAb-negative patients (36% vs 0%)
Suzuki et al, 2014 ³⁷		Cross-sectional	650 MG patients (70 autoAb positive)	High prevalence of QTc prolongation in autoAb-positive patients (14%); 20% of autoAb-positive patients with QTc prolongation showed TdP/SCD
Xiao et al, 2012 ⁴²	Anti-Ca _v 1.2	Prospective	80 DCM patients (39 autoAb positive)	8–10 times higher risk of VT/SCD in autoAb-positive vs autoAb-negative patients; autoAb positivity was the strongest independent predictor of SCD
Yu et al, 2014 ⁴¹		Prospective	2096 HF patients (841 with DCM [39 autoAb positive] and 1255 with ICM [51 autoAb positive])	Increased incidence of SCD in autoAb-positive patients; autoAb positivity independently associated with a 3 times higher risk of SCD
Autoimmune short QT syndrome Li et al, 2013 ⁴³	Anti-K _v 7.1	Cross-sectional	150 DCM patients (9 autoAb positive)	Significant QTc shortening in autoAb-positive patients
Autoimmune Brugada syndrome Tarantino et al, 2024 ¹³	Anti-Na _v 1.5	Case-control	50 BrS patients 50 controls without BrS	Higher prevalence of circulating of anti-Na _v 1.5 autoantibodies in BrS patients (90%) than in controls (6%), independent of genetic status
Autoimmune atrial fibrillation Maguy et al, 2023 ¹²	Anti-K _{ir} 3.4	Case-control/ prospective	51 patients with unexplained AF 37 healthy controls	16%–36% of AF patients presented with circulating autoAb compared with none of healthy controls

(continued)

Table 2 Continued

Author, year	Autoantibody	Study design	Study population	Main findings
Autoimmune ventricular fibrillation/cardiac arrest Li et al, 2024 ¹⁴	Anti-K ₂ P2.1	Case-control	33 IVF patients (14 SCVF, 19 u-IVF) 38 healthy controls	Higher prevalence of circulating of anti-K ₂ P2.1 autoantibodies in SCVF patients (50%) than in u-IVF patients (10%) and healthy controls (13%)
Maguy et al, 2020 ¹⁵	Anti-Ca _v 1.2	Cross-sectional	45 CA patients (23 idiopathic CA, 22 ICA) 29 healthy controls	Anti-Ca _v 1.2 autoAb was significantly upregulated in patients with idiopathic CA compared with ICA and healthy controls
Autoimmune atrioventricular block* Lazzerini et al, 2023 ¹⁶	Anti-Ca _v 1.2 (anti-Ro/SSA)	Cross-sectional	34 patients with isolated AVB of unknown origin	High prevalence of circulating anti-Ro/SSA 52-kDa antibodies in patients with isolated AVB of unknown origin (40%), independent of a history of AD Immunomodulating therapy improved/normalized AV conduction in patients with autoAb but not in those negative Anti-Ro/SSA positivity in 10% of patients implanted for isolated AVB of unknown origin
Villuendas et al, 2014 ⁷²		Retrospective population based	3586 patients with implanted PM	AutoAb-positive participants showed a 2 times higher risk of complete AVB (OR, 1.91; 95% CI, 1.40–2.60) compared with autoAb-negative participants
Akuka et al, 2022 ³⁴		Cross-sectional population based	101,599 general population participants (11,525 anti-Ro/SSA positive)	Anti-Ro/SSA positivity in 100% of athletes with advanced AVB
Lazzerini et al, 2024 ⁵⁹		Cross-sectional population based	2536 consecutive athletes <40 years who underwent annual medical screening	AutoAb-positive patients showed a 2.5 times higher risk of AVB (OR, 2.42; 95% CI, 1.18–5.43) compared with autoAb-negative patients
Hua et al, 2024 ⁵⁸		Retrospective observational	766 HF patients (70 anti-Ro/SSA positive)	Autoantibodies against Na _v 1.5 channel were detectable in pooled samples from AVB patients but not from healthy controls
Korkmaz et al, 2013 ⁶¹	Anti-Na _v 1.5	Cross-sectional	10 patients with isolated AVB 10 healthy controls	

AD = autoimmune disease; AF = atrial fibrillation; anti-Ro/SSA = anti-Ro/Sjögren syndrome–related antigen A; AVB = atrioventricular block; autoAb = autoantibody; BrS = Brugada syndrome; CA = cardiac arrest; CI = confidence interval; CTD = connective tissue disease; DCM = dilated cardiomyopathy; ICA = ischemic cardiac arrest; IVF = idiopathic ventricular fibrillation; HF = heart failure; ICM = ischemic cardiomyopathy; MG = myasthenia gravis; OR = odds ratio; PM = pacemaker; QTc = corrected QT interval; SCD = sudden cardiac death; SCVF = short-coupled ventricular fibrillation; SLE = systemic lupus erythematosus; TdP = torsades de pointes; u-IVF = undifferentiated IVF; VT = ventricular tachycardia.

*In adults.

Inhibiting anti-K_v1.4 autoantibodies

The K_v1.4 channel conducts the slow component of the transient potassium outward current ($I_{to,s}$), a main contributor to the action potential early phase 1 repolarization in ventricular myocytes.¹⁷

Whereas no forms of congenital LQTS due to variants in the encoding gene (*KCNA4*) have been described, evidence suggests that autoantibodies targeting the K_v1.4 channel may represent a cause of autoimmune LQTS and life-threatening arrhythmic events. Specifically, anti-K_v1.4 antibodies were reported in up to ~20% of cases in patients with myasthenia gravis.^{35–37} Studies demonstrated that 15%–35% of these patients show QTc prolongation, which can be complicated by TdP/SCD occurrences.³⁷ However, whereas 1 of these investigations involved a relatively large cohort of patients ($n = 650$), available data come from only a few studies, all performed by a single research group.^{35–37}

Although it has been demonstrated that these autoantibodies can directly bind the K_v1.4 channel by targeting a short amino acid sequence on the intracellular N terminus (MPYGY)³⁵ (Table 1), a finding suggesting that their QT-prolonging potential is related to an autoimmune-induced loss of function of the channel, mechanistic studies providing *in-vitro* evidence that anti-K_v1.4 antibodies inhibit $I_{to,s}$ and prolong ventricular APD are currently missing. Furthermore, given that in a percentage of anti-K_v1.4-positive patients, with or without myasthenia gravis, clinical and imaging features suggestive of myocarditis were demonstrated,^{35,37,38} it cannot be ruled out that the proarrhythmic changes associated with these autoantibodies may be due, at least in part, to indirect effects mediated by inflammatory mechanisms.³⁹

Agonist-like anti-Ca_v1.2 autoantibodies

The Ca_v1.2 protein is the dominant α_1 subunit isoform (α_{1C}) constituting L-type calcium channels in the heart, including ventricular myocytes. By generating the inward depolarizing calcium current I_{CaL} , Ca_v1.2 L-type channels are the key determinants of the ventricular action potential phase 2 plateau, in turn significantly affecting the overall APD in these cells, hence the QTc on the surface electrocardiogram.¹⁷

Arrhythmogenic agonist-like anti-Ca_v1.2 autoantibodies were first described in 2011 by Xiao and coworkers⁴⁰ in ~50% of 80 consecutive patients with idiopathic dilated cardiomyopathy (DCM). In these patients, the presence of circulating anti-Ca_v1.2 autoantibodies was found to be the strongest independent predictor for VT and SCD.⁴⁰ These findings were later confirmed and expanded by Yu and coworkers⁴¹ in a large cohort of >2000 patients with congestive heart failure, including 841 with DCM and 1255 with ischemic cardiomyopathy, in whom anti-Ca_v1.2 autoantibody positivity was associated with a ~3 times higher risk of SCD, after multivariate adjustment for a wide number of confounders.⁴¹

Based on these clinical data, Xiao and coworkers⁴² investigated *in-vitro* the basic mechanisms underlying the proarrhythmic activity of these autoantibodies. First, by a

combination of enzyme-linked immunosorbent assay (ELISA), immunofluorescence, and immunoblotting experiments, evidence was provided that anti-Ca_v1.2 autoantibodies can directly bind the cardiac myocyte sarcolemma as a result of a specific interaction with a 15-amino acid peptide sequence (VNENTRMYIPEENHQ; Table 1) localized at the intracellular N terminus of the domain 1 of the Ca_v1.2 protein.⁴² Then, by incubating *Xenopus* oocytes overexpressing the human Ca_v1.2 channel with affinity-purified anti-Ca_v1.2 autoantibodies from DCM patient sera, the authors reported a concentration-dependent acute increase of I_{CaL} (~20%–50%) as well as APD prolongation with early afterdepolarization occurrence in rat ventricular myocytes and enhanced propensity to VT development in Langendorff perfused hearts.⁴²

However, although these experimental data strongly suggest that the arrhythmogenic effects of agonist-like anti-Ca_v1.2 autoantibodies may develop in association with an electrocardiographic phenotype of LQTS, no clear evidence supports this assumption. In fact, whereas Yu and coworkers⁴¹ found that mean QTc value was numerically increased in anti-Ca_v1.2-positive DCM patients compared with patients without these autoantibodies (almost 20 ms), such a difference did not reach statistical significance. Thus, further studies are warranted to clearly define whether anti-Ca_v1.2 autoantibodies are a cause of autoimmune LQTS.

Autoimmune SQTS

Agonist-like anti-K_v7.1 autoantibodies accelerating ventricular repolarization and promoting VA have been identified in patients with DCM,⁴³ representing the first and to date the only example of autoimmune SQTS (Tables 2 and 3; Figure 3).

Agonist-like anti-K_v7.1 autoantibodies

The K_v7.1 channel, conducting the slow component of the delayed rectifier potassium current (I_{Ks}), is critically involved in regulating ventricular APD by fundamental contribution to the repolarization process.¹⁷ Accordingly, loss-of-function variant affecting the K_v7.1 encoding gene (*KCNQ1*) is the most common cause of congenital LQTS (type 1 LQTS), whereas gain-of-function variants are recognized to be responsible for a number of cases of congenital SQTS (type 2 SQTS).¹⁸

By studying 150 DCM patients, Li and colleagues⁴³ reported that ~5% of these patients showed significant QTc shortening in the presence of ELISA-detected circulating autoantibodies targeting an extracellular 20-amino acid sequence (AEKDAVNESGRVEFGSYADA; Table 1) of the pore-forming region of K_v1.7, between S5 and S6 transmembrane segments of domain 1. *In-vitro* incubation of HEK293 cells transiently expressing *KCNQ1/KCNE1* genes with sera from anti-K_v1.7 antibody-positive DCM patients was associated with an increase in I_{Ks} density, which was already evident after 1 hour and then further increased at 24 hours (up to 3 times increase).⁴³

The same group provided additional support and more detailed information for the underlying electrophysiologic mechanisms by vaccinating rabbits with the 20-amino acid

Table 3 Studies providing experimental support to the arrhythmogenicity of autoimmune cardiac channelopathies in adults

Author, year	Autoantibody	Animal models	Cell models	Main findings
Autoimmune long QT syndrome				
Nakamura et al, 2007 ²⁹	Anti-K _v 11.1 (anti-Ro/SSA)	-	HEK293 cells overexpressing the K _v 11.1 channel	Sera/purified IgGs from an anti-Ro/SSA–positive TdP patient directly bind to the K _v 11.1 protein and chronically inhibit I _{Kr}
Yue et al, 2015 ¹⁹		Guinea pig	HEK293 cells overexpressing the K _v 11.1 channel Guinea pig ventricular myocytes	Sera/purified IgGs/affinity-purified anti-Ro/SSA 52-kDa antibodies from anti-Ro/SSA–positive, but not negative, CTD patients with QTc prolongation directly bind to the K _v 11.1 protein, acutely inhibit I _{Kr} , and prolong ventricular APD; positive patients’ sera cross-react with a 31–amino acid peptide corresponding to the K _v 11.1 pore-forming region (S5–S6) Animals immunized with the Ro 52-kDa antigen develop QTc prolongation; animals’ sera acutely inhibit I _{Kr}
Lazzerini et al, 2016 ³⁰		-	HEK293 cells overexpressing the K _v 11.1 channel	Sera/purified IgGs from anti-Ro/SSA–positive, but not negative, TdP patients directly bind to the K _v 11.1 protein and acutely inhibit I _{Kr} ; positive patients’ sera cross-react with a 31–amino acid peptide corresponding to the K _v 11.1 pore-forming region (segments S5–S6)
Fabris et al, 2016 ²¹		Guinea pig	HEK293 cells overexpressing the K _v 11.1 channel Guinea pig ventricular myocytes	Animals immunized with the 31–amino acid peptide corresponding to the K _v 11.1 pore-forming region (S5–S6) recognized by anti-Ro/SSA 52-kDa antibodies develop QTc prolongation without any evidence of cardiac inflammation/fibrosis; animals’ sera acutely inhibit I _{Kr} and prolong ventricular APD
Szendrey et al, 2019 ²⁰		-	HEK293 cells overexpressing the K _v 11.1 channel Neonatal rat ventricular myocytes	Commercial anti-Ro/SSA 52-kDa antibodies directly bind to the K _v 11.1 protein at the extracellular S5-pore linker, chronically inhibit I _{Kr} , decrease channel expression with enhanced endocytic degradation, and prolong ventricular APD
Xiao et al, 2011 ⁴⁰	Anti-Ca _v 1.2	Langendorff isolated rat heart	Rat ventricular myocytes	Affinity-purified anti-Ca _v 1.2 autoantibodies from positive DCM patients prolong ventricular APD and induce EAD in ventricular myocytes and provoke VT in isolated hearts
Xiao et al, 2012 ⁴²		-	Human atrial myocytes <i>Xenopus</i> oocytes overexpressing the Ca _v 1.2 channel	Affinity-purified anti-Ca _v 1.2 autoantibodies from positive DCM patients directly bind to the Ca _v 1.2 channel on the myocyte and enhance I _{CaL}
Autoimmune short QT syndrome				
Li et al, 2013 ⁴³	Anti-K _v 7.1		HEK293 cells overexpressing the K _v 7.1 channel	Sera from anti-K _v 7.1 autoAb-positive DCM patients acutely enhance I _{Ks} , without any change in channel protein expression
Li et al, 2014 ⁴⁴		Rabbit	Rabbit ventricular myocytes	Animals immunized with a 20–amino acid peptide corresponding to the K _v 7.1 pore-forming region (S5–S6) develop QTc shortening, reduced ventricular effective refractory period, and increased propensity to VT induction, without any evidence of cardiac inflammation/fibrosis Ventricular myocytes from immunized rabbits show enhanced I _{Ks} and APD shortening
Maguy et al, 2020 ⁴⁵		Rabbit	Chinese hamster ovary cells overexpressing the K _v 7.1 channel	Affinity-purified anti-K _v 7.1 autoantibodies from animals immunized with a 20–amino acid peptide corresponding to the K _v 7.1 pore-forming region (S5–S6) enhance I _{Ks} . This effect is purely electrophysiologic, without any change in channel expression.

Autoimmune Brugada syndrome Tarantino et al, 2024 ¹³	Anti- $\text{Na}_v1.5$	Mouse	HEK293 cells overexpressing the $\text{Na}_v1.5$ channel hiPSC-derived cardiomyocytes	Plasma from anti- $\text{Na}_v1.5$ autoAb-positive BrS patients decreases I_{Na} density and promotes channel internalization. Wild-type mice injection with sera from BrS patients, but not from controls, reproduces typical Brugada-like ECG abnormalities along with malignant VA and SCD.
Pappone et al, 2024 ⁴⁹		Mouse	HEK293 cells overexpressing the $\text{Na}_v1.5$ channel	Plasma from anti- $\text{Na}_v1.5$ autoAb-positive breast cancer patients decreases I_{Na} density. Wild-type mice injection with sera from autoAb-positive, but not negative, patients reproduces typical Brugada-like ECG abnormalities along with malignant arrhythmias.
Autoimmune atrial fibrillation Maguy et al, 2023 ¹²	Anti- $\text{K}_{ir}3.4$	Mouse	hiPSC-derived atrial myocytes	Affinity-purified anti- $\text{K}_{ir}3.4$ autoantibodies from positive AF enhance I_{KAch} and shorten APD. Animals immunized with a 20-amino acid peptide corresponding to the $\text{K}_{ir}3.4$ pore-forming region (M1–M2) show significant shortening of the AERP and a higher propensity for development of pacing-induced AF compared with sham-immunized control animals, without any appreciable structural or functional heart change.
Autoimmune ventricular fibrillation/cardiac arrest Li et al, 2024 ¹⁴	Anti- $\text{K}_{2P}2.1$		HEK293 cells overexpressing the $\text{K}_{2P}2.1$ channel hiPSC cardiomyocytes	Purified IgGs from pooled plasma samples of anti- $\text{K}_{2P}2.1$ autoAb-positive SCVP patients enhance I_{K2P} and shorten APD
Maguy et al, 2020 ¹⁵	Anti- $\text{Ca}_v1.2$		hiPSC-derived ventricular myocytes	Purified IgGs from pooled plasma samples of anti- $\text{Ca}_v1.2$ autoAb-positive idiopathic CA patients inhibit I_{CaL} , shorten APD, and induce alternans
Autoimmune atrioventricular block* Lazzerini et al, 2023 ¹⁶	Anti- $\text{Ca}_v1.2$ (anti-Ro/SSA)		HEK293 cells overexpressing the $\text{Ca}_v1.2$ channel	Purified IgGs from anti-Ro/SSA-positive, but not negative, AVB patients acutely inhibit I_{CaL} and chronically downregulate $\text{Ca}_v1.2$ protein expression; positive patients' sera cross-react with 5 peptides corresponding to the $\text{Ca}_v1.2$ pore-forming region (S5–S6)
Korkmaz et al, 2013 ⁶¹	Anti- $\text{Na}_v1.5$	Rat	Adult rat ventricular myocytes	Animals immunized with a 28-amino acid peptide corresponding to the $\text{Na}_v1.5$ pore-forming region (S5–S6) develop PR interval prolongation and recurrent episodes of third-degree AVB (and SA block) in the presence of a significant reduction of $\text{Na}_v1.5$ mRNA and protein expression in the myocardium but without any evidence of cardiac inflammation/fibrosis. Pooled serum samples from patients with idiopathic AVB, but not from healthy controls, found that in these participants, but not in healthy control sera, autoantibodies against different consensus motifs of the $\text{Na}_v1.5$ channel were detectable, including the S5–S6 peptide sequence. Sera from AVB patients or immunized rats inhibit I_{Na} .

AERP = atrial effective refractory period; AF = atrial fibrillation; anti-Ro/SSA = anti-Ro/Sjögren syndrome-related antigen A; AVB = atrioventricular block; autoAb = autoantibody; BrS = Brugada syndrome; CA = cardiac arrest; CTD = connective tissue disease; DCM = dilated cardiomyopathy; EAD = early afterdepolarization; ECG = electrocardiogram; HEK293 = human embryonic kidney 293 cells; hiPSC = human induced pluripotent stem cell; I_{CaL} = L-type calcium channel current; I_{Na} = sodium channel current; I_{KAch} = acetylcholine-gated potassium channel current; I_{Kr} = rapid component of the delayed rectifier potassium channel current; I_{Ks} = slow component of the delayed rectifier potassium current; I_{K2P} = 2-pore domain potassium channel current; IgG = immunoglobulin G; QTc = corrected QT interval; S5–S6: transmembrane segments 5–6; SA = sinoatrial; SCD = sudden cardiac death; SCVP = short-coupled ventricular fibrillation; TdP = torsades de pointes; VA = ventricular arrhythmia; VT = ventricular tachycardia.

*In adults.

target peptide.⁴⁴ Three weeks after immunization, animals developed high titers of anti-K_v7.1 autoantibodies along with significant QTc shortening as well as reduced ventricular effective refractory period and increased propensity to VT induction during the *in-vivo* electrophysiologic study. Moreover, ventricular myocytes isolated from immunized rabbits showed augmented I_{Ks} density and APD shortening, in the absence of any inflammatory or fibrotic change of the heart.⁴⁴ These findings were replicated and further refined by using affinity-purified anti-K_v7.1 antibodies from vaccinated animals in *in-vitro* cellular models. Specifically, evidence was also provided that the agonist-like effect of these autoantibodies on I_{Ks} is concentration dependent and solely electrophysiologic, as demonstrated by their ability to shift the voltage dependence of activation and slow current deactivation (with increased open time probability of the channel), without any measurable enhancement of K_v7.1 mRNA or protein expression.⁴⁵ Of note, the authors additionally demonstrated that agonist-like anti-K_v7.1 antibodies (polyclonal/monoclonal) were able to reverse APD prolongation and to suppress early afterdepolarization occurrence in *in-vitro* models of both LQTS type 2⁴⁵ and LQTS type 3,⁴⁶ intriguingly pointing to K_v7.1 peptide vaccination as a novel promising therapeutic approach for patients with congenital LQTS refractory to conventional treatments.⁴⁷

Overall, although these experimental studies provide strong evidence supporting the arrhythmogenicity of anti-K_v7.1 autoantibodies by inducing an autoimmune SQTS, their clinical relevance remains substantially unexplored. Specific investigations are needed to better clarify the prevalence of these autoantibodies in patients with unexplained or poorly explained SQTS, also beyond a concomitant DCM diagnosis, and their impact in terms of VA and SCD occurrence.

Autoimmune BrS

BrS is currently considered an inherited channelopathy, mostly due to loss-of-function mutations of the *SCN5A* gene encoding the Na_v1.5 channel. However, no more than 20%–30% of BrS patients are *SCN5A* genotype positive, and mutations of other less recognized genes account for only a small increase in this percentage.¹⁸

Surprisingly, recent studies provided evidence that circulating anti-ion channel autoantibodies can be found in most patients with BrS, primarily arrhythmogenic anti-Na_v1.5 autoantibodies inhibiting channel function, thereby pointing to autoimmunity as a novel and important pathogenic mechanism operating in a large proportion of BrS cases (Tables 2 and 3; Figure 4).^{13,48,49} Furthermore, these findings will have an impact on the diagnosis of BrS, which is now primarily clinical and genetic based, to also include an autoimmune antibody-based testing.

Inhibiting anti-Na_v1.5 autoantibodies

The Na_v1.5 channel mediates the inward sodium current (I_{Na}), which represents the key depolarizing current in ventricular myocytes.¹⁷ A decrease of I_{Na} density in these cells, specif-

ically in those of the right ventricular outflow tract where Na_v1.5 channel expression is constitutively low,⁵⁰ is recognized to be a crucial electrophysiologic alteration for the pathogenesis of BrS, whether the *repolarization* or *depolarization* hypothesis of the disease is considered.⁸

In a study published in 2024, Tarantino and colleagues¹³ unexpectedly provided evidence that 90% of 50 BrS patients (vs 6% of 50 controls; diagnostic area under the curve of 0.92, with 94% specificity and 90% sensitivity; negative predictive value of 90.4%, positive predictive value of 93.8%) presented with circulating anti-Na_v1.5 autoantibodies, first detected by western blotting and then confirmed in their binding specificity by immunoprecipitation and immunofluorescence. By using a microarray-based epitope mapping method, the authors demonstrated that plasma samples cross-reacted with the extracellular loops throughout domains 1–4 of the Na_v1.5 channel (including extracellular loops between S5–S5 of domains 1–4 and between S3–S4 of domain 4), although the specific peptide sequences involved were not identified. Moreover, patch-clamp experiments showed that 1-hour incubation of Na_v1.5-expressing HEK293 cells with 5% plasma from autoantibody-positive BrS patients resulted in a significant 40% decrease of I_{Na} density. Such effect, which was prevented by plasma IgG depletion, was at least in part due to an autoantibody-triggered internalization of the Na_v1.5 channel, as demonstrated by a biotinylation *in-vitro* assay. Similarly, human induced pluripotent stem cell-derived (hiPSC) cardiomyocytes after 1-hour incubation with BrS patient plasma demonstrated a 50% decrease in I_{Na} density compared with untreated cardiomyocytes. Interestingly, BrS patients' plasma did not alter either L- or T-type calcium currents, indicating specificity for Na_v1.5 channel. More important, injection of wild-type mice with sera from BrS patients (n = 4), but not from controls (n = 3), was able to rapidly (minutes) reproduce typical Brugada-like ST-segment electrocardiographic abnormalities complicated with malignant VA and SCD.¹³ Although these impressive results require confirmation through independent studies using larger sample sizes, it is not unusual to observe fast electrophysiologic response (minutes) from hearts exposed to autoantibodies.^{51–53} Moreover, transcriptome analysis of peripheral blood mononuclear cells from BrS patients remarkably revealed significant upregulation in immune signaling pathways. The authors also reported that presence of anti-Na_v1.5 autoantibodies was independent of *SCN5A* mutation status, age, sex, or electrocardiographic pattern of the patients; they concluded that anti-Na_v1.5 autoantibodies could be a useful noninvasive biomarker for BrS and went further to call for a reevaluation of the pathophysiologic process of BrS, now implicating an immune-mediated mechanism.

Interestingly, the same group demonstrated that anti-Na_v1.5 autoantibodies with similar *in-vitro* electrophysiologic properties and *in-vivo* arrhythmogenic potential can be found in a high percentage of women with metastatic breast cancer, a disease increasingly recognized to be burdened by a significant risk of SCD, not fully explained by cardiotoxic anticancer therapies.⁴⁹ Because Na_v1.5 channels are overexpressed in

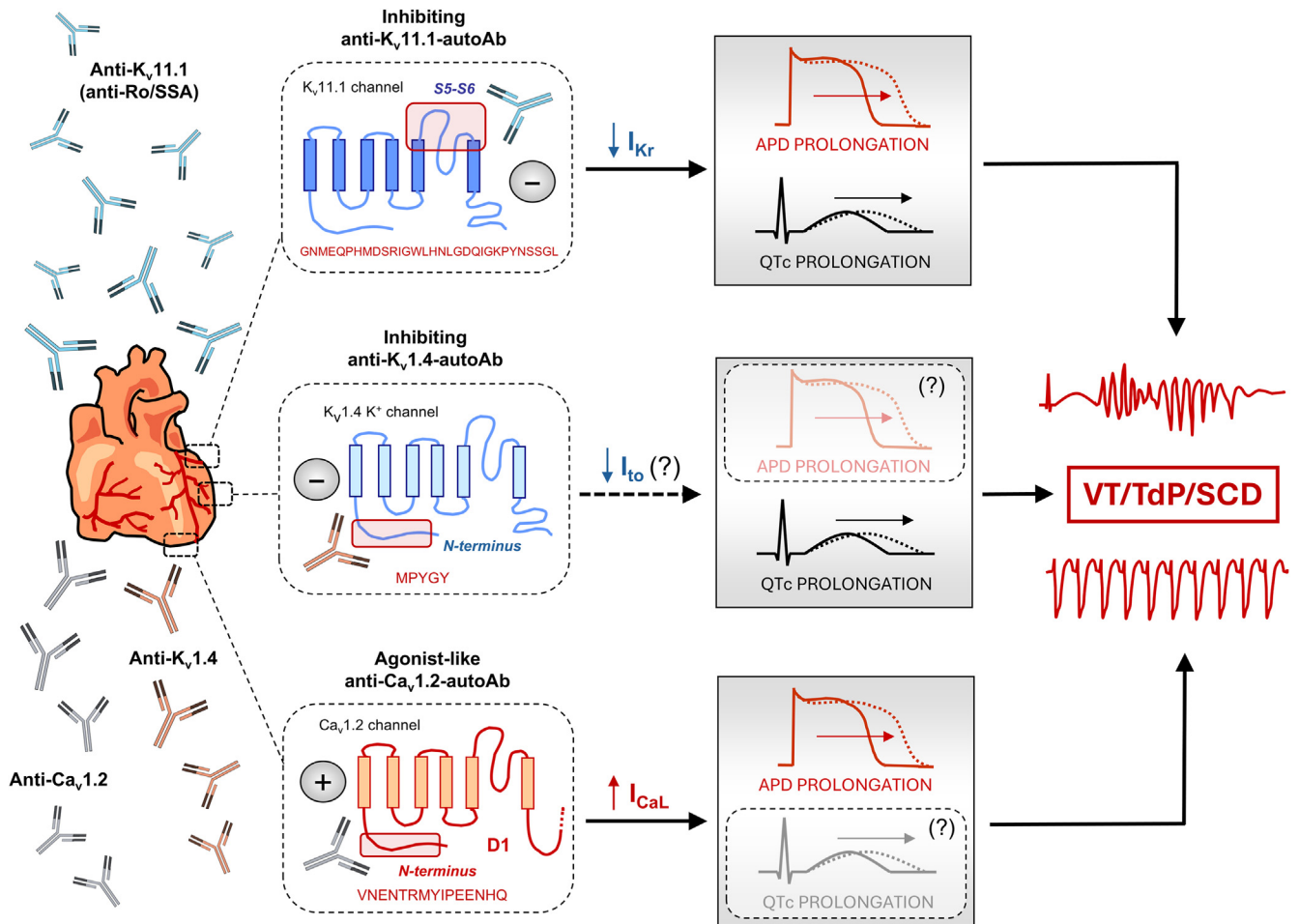


Figure 2

Autoimmune long QT syndrome: molecular bases and electrophysiologic mechanisms. Three different anti-ion channel autoantibodies can be responsible for an electrocardiographic or electrophysiologic phenotype suggestive of long QT syndrome, that is, the inhibiting anti-K_v11.1 and anti-K_v1.4 autoantibodies and the agonist-like anti-Ca_v1.2 autoantibody. See text and tables for more details. APD = action potential duration; autoAb = autoantibody; D1 = domain 1; I_{CaL} = L-type calcium channel current; I_{Kr} = rapid component of the delayed rectifier potassium channel current; I_{Ks} = slow component of the delayed rectifier potassium current; QTc = heart rate-corrected QT interval; S5-S6: transmembrane segments 5-6; SCD = sudden cardiac death; TdP = torsades de pointes; VT = ventricular tachycardia. The red squares indicate the portion of the channel where the target peptide sequences (reported in red block letters) are located. The red arrow pointing up indicates increase; blue arrows pointing down indicate decrease. The black dotted arrows and question marks indicate alterations that are likely but still not proven.

metastatic breast cancer, in which they promote cell invasiveness, the authors hypothesized that these findings may be the expression of off-target effects of an immune response primarily directed against cancer.⁴⁹ Although intriguing, the impact should be taken with caution as the paper is currently still in a preprint stage and not peer reviewed yet. If confirmed, autoimmune interference in cardiac ion channel function may further expand the spectrum of clinical conditions linked to unexplained arrhythmic risk.

Although these data provide initial but sound evidence supporting the hypothesis that in a significant proportion of patients, BrS results from an autoimmune sodium channelopathy, confirmatory studies are needed. In addition, further investigation is warranted to define the actual clinical impact of these autoantibodies on the risk of arrhythmic events as well as the exact peptide sequences targeted on the channel,

fundamental for development of specific diagnostic methods for wide use in the clinic.

The reason that anti-Na_v1.5 autoantibodies, like SCN5A variants in BrS, primarily affect the right ventricular outflow tract remains unclear. They likely inhibit Na_v1.5 channels throughout the heart, but the clinical impact may be limited elsewhere because of higher channel expression or compensatory mechanisms.

Anti-connexin43 autoantibodies

In the ventricle, connexin43 represents the principal pore-forming subunit constituting gap junctions, intercellular ion channels regulating impulse conduction through electrical coupling of adjacent cardiomyocytes.¹⁷ Increasing evidence points to reduced conduction reserve in left ventricular outflow tract due to defective function of connexin43 gap

junctions as an important additional mechanism in the pathogenesis of BrS.⁸

By studying 18 BrS patients, Chatterjee and associates⁴⁸ found that elevated levels of circulating anti-connexin43 autoantibodies were detectable in all cases, associated with abnormal connexin43 expression and aggregate formation in the myocardium. However, because no experimental data supporting a direct electrophysiologic and arrhythmogenic impact of these autoantibodies were provided, it is not currently possible to discriminate whether anti-connexin43 autoantibodies play a mechanistic role in BrS or merely represent a marker of a disease-intrinsic cell injury leading to abnormal antigen exposure to the immune system.⁴⁸

Autoimmune AF

AF is the most common arrhythmia worldwide, usually representing a consequence of structural heart diseases or systemic disorders.¹ However, in up to 3% of patients, corresponding to an estimated high number of ~1.5 million people globally,³ AF cause remains elusive despite intensive investigation. A study found the presence of arrhythmogenic anti-K_{ir}3.4 autoantibodies in patients with unexplained AF, providing a substantial albeit early support to the view that in the growing family of autoimmune cardiac channelopathy-associated arrhythmias, AF could also be listed (Tables 2 and 3; Figure 5).¹²

Agonist-like anti-K_{ir}3.4 autoantibodies

The inwardly rectifying potassium channel subunit 3.4 (K_{ir}3.4) is selectively expressed in atrial myocardium, where, in association with K_{ir}3.1 subunit, forms the acetylcholine-gated K_{ACh} channel, which underlies the I_{K_{ACh}} current and plays an increasingly recognized role in AF pathogenesis.¹⁷

Maguy and coworkers¹² used a high-throughput microarray-based technology to study a total of 51 patients with unexplained AF (including 14 with no AF at baseline who had unexplained AF during follow-up) and demonstrated that 16%–36% of these patients presented with circulating autoantibodies specifically reacting with a peptide sequence (IETETIGYGFRVITEKCP) located in an extracellular site close to the pore domain between M1 and M2 transmembrane segments of the K_{ir}3.4 channel (Table 1).¹² This autoantibody was then purified by affinity chromatography and electrophysiologically characterized on hiPSC atrial myocytes, where it enhanced I_{K_{ACh}} and shortened APD, alterations that can promote the well-known multiple-circuit reentry mechanism underlying AF occurrence (Table 1).¹²

To further substantiate the clinical relevance of these findings, the authors established an animal model by immunizing mice with the targeted peptide, in all cases generating high titers of anti-K_{ir}3.4 autoantibodies without any appreciable structural or functional heart change. Whereas none of the immunized mice spontaneously presented with AF, during intracardiac electrophysiologic study, they showed a significant shortening of the atrial effective refractory period and a

higher propensity to development of AF on rapid atrial pacing compared with sham-immunized control animals.¹²

Although needing clinical confirmation in larger studies, this work provides considerable evidence that unexplained AF may be linked, at least in a percentage of cases, to a channelopathy of autoimmune origin. In these patients, a personalized treatment approach, radically different from that commonly adopted for traditional AF, might be necessary.

Autoimmune VF

VF is the common end point underlying a significant number of CAs, in turn accounting for ~1000 deaths daily worldwide.¹ Although most VFs and CAs are the result of cardiac structural diseases, particularly ischemic heart disease and heart failure, in 5%–10% of these patients, the cause remains unidentified even after an accurate diagnostic workup including advanced imaging (autopsy in SCD) and specific testing for genetic channelopathies.²

The recent discovery of arrhythmogenic anti-ion channel autoantibodies in 2 subsets of these patients, specifically agonist-like anti-K_{2P}2.1 autoantibodies in SCVF (a peculiar form of VF thought to account for 7%–14% of apparently unexplained CA)¹⁴ and inhibiting anti-Ca_v1.2 autoantibodies in idiopathic CA,¹⁵ strongly suggests that a significant percentage of VF/CA of unknown origin may be driven at least in part by autoimmune mechanisms (Tables 2 and 3; Figure 6).

Agonist-like anti-K_{2P}2.1 (TREK-1) autoantibodies

The K_{2P}2.1 channel, also named TREK-1 (TWIK-related potassium channel 1), belongs to the 2-pore domain potassium channel family and is principally expressed in ventricles.⁵⁴ This channel, which contributes to resting membrane potential stabilization by generating the outward potassium current I_{K_{2P}}, is increasingly recognized to play a significant role in the pathogenesis of VA.⁵⁴

In a single-center case-control study, Li and coworkers¹⁴ prospectively enrolled 33 patients with idiopathic VF, including 14 with SCVF and 19 with undifferentiated idiopathic VF, in all cases testing negative for genetic channelopathies. Peptide microarray assay screening of plasma samples revealed the presence of circulating anti-TREK-1 autoantibodies targeting the HSCVNSTELDELIOQIVAAI sequence of the cap domain (Table 1), close to the selectivity filter of the channel, in 50% of SCVF patients (vs 10% in undifferentiated idiopathic VF and 12% in healthy controls). Patch-clamp experiments, performed by incubating HEK293 cells stably expressing the human TREK-1 channel with purified anti-TREK-1 autoantibodies from SCVF patients, demonstrated a 5-fold increase of I_{K_{2P}}. Of note, such an agonist-like effect was significantly reversed (40%) by quinidine, the only oral antiarrhythmic drug known to be effective in SCVF. Moreover, electrophysiologic characterization of hiPSC cardiomyocytes showed that anti-TREK-1 autoantibody exposure was associated with a dose-dependent APD shortening, again reversed on quinidine incubation¹⁴ (Table 1). Whereas functional and

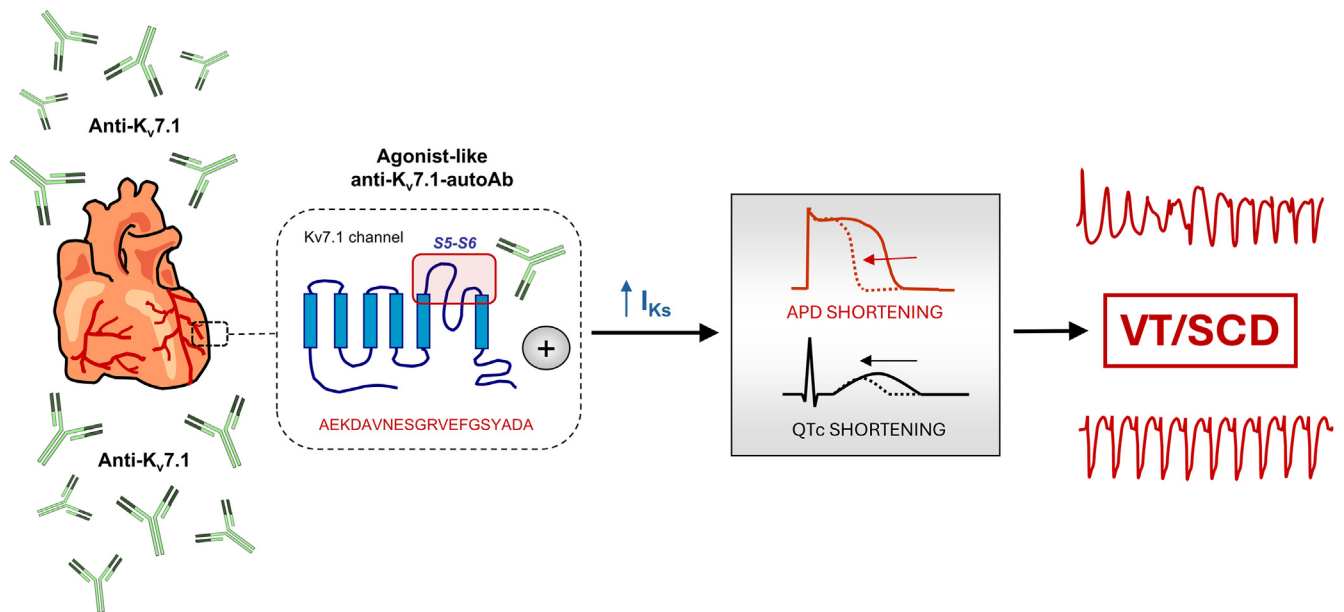


Figure 3

Autoimmune short QT syndrome: molecular bases and electrophysiologic mechanisms. Agonist-like anti-Kv7.1 autoantibodies accelerating ventricular repolarization and shortening action potential duration (APD) can be cause of autoimmune short QT syndrome. See text and tables for more details. autoAb = autoantibody; I_{Ks} = slow component of the delayed rectifier potassium current; QTc = heart rate–corrected QT interval; S5–S6 = transmembrane segments 5–6; SCD = sudden cardiac death; VT = ventricular tachycardia. The red square indicates the portion of the channel where the target peptide sequence (reported in red block letters) is located. The blue arrow pointing up indicates increase.

mapping studies suggest that SCVF originates from Purkinje fibers, this initial trigger eventually causes SCVF in the ventricle.⁵⁵ Moreover, it has been demonstrated that both the ventricle and Purkinje fibers express TREK-1 channels.⁵⁶ Although the electrophysiologic consequences of anti-TREK-1 antibodies on the His-Purkinje system were not investigated in this study, the authors concluded that in SCVF patients, an autoantibody-induced gain of function of the $K_{2p2.1}$ channel may shorten the ventricular refractory period, providing the predisposing substrate for VF occurrence.¹⁴

Inhibiting anti- $Ca_v1.2$ autoantibodies

A similar high-throughput peptide-based screening approach was used by the same group to identify potentially relevant anti-ion channel autoantibodies in a more general cohort of 23 survivors of unexplained CA resulting from shockable rhythm, that is, patients with documented pulseless VT or VF in whom structural heart disease, including coronary heart disease, and primary electric disorders were excluded (idiopathic CA).¹⁵ By comparing reactivity of plasma samples from these patients with that of 22 patients with ischemic CA (and 29 matched healthy controls), Maguy and coworkers¹⁵ provided evidence that increased levels of a single autoantibody recognizing a peptide sequence (DFDNVLAAMMALFTVSTFEG) on the third S5–S6 extracellular loop domain 3 of $Ca_v1.2$ channel pore-forming region were selectively associated with idiopathic CA. Prompted by these findings, the autoantibody was purified from patients' samples and its arrhythmogenic potential tested *in-vitro* on hiPSC ventricular myocytes. The authors demonstrated that anti- $Ca_v1.2$ autoantibodies were able both to reduce APD at 90% repolarization (2.8 times)

and to decrease I_{CaL} (2 times) in these cells, effects that were abolished in the presence of a peptide corresponding to the extracellular target sequence. Noteworthy, autoantibody incubation induced 1 episode of alternans, a characteristic substrate for tachyarrhythmias, further supporting the pathogenic relevance of these electrophysiologic changes.¹⁵

Overall, these data substantiate the hypothesis that a fraction of apparently idiopathic VF/CA is rather of autoimmune origin, due to specific anti-ion channel autoantibodies interfering with the electrical stability of the ventricular myocardium. Whether VF always arises as such or represents, at least in a number of cases, a degeneration of a prior specific life-threatening VA (eg, an autoimmune LQTS-induced TdP) is not currently known but possibly suggested by some findings of the Maguy study^{15,57} in which patients with CA due to pulseless VT were also included.

Bradyarrhythmias

Autoimmune cardiac channelopathies can lead to bradyarrhythmias, even severe and life-threatening.^{7,8,10} Although the largest evidence refers to AVB, accumulating evidence indicates that anti-ion channel autoantibodies may also induce sinoatrial dysfunction and intraventricular conduction disturbances.^{7,8,10,58} Specifically, it is well recognized that inhibiting autoantibodies against L- and T-type calcium channels play an important pathogenic role in autoimmune congenital heart block in newborns.^{7,8,10} In addition, several studies in recent years provided evidence that also in adults, a significant number of unexplained bradyarrhythmias have an autoimmune origin related to circulating autoantibodies targeting and inhibiting L-type calcium or sodium channels (Tables 2 and 3).^{16,59–61}

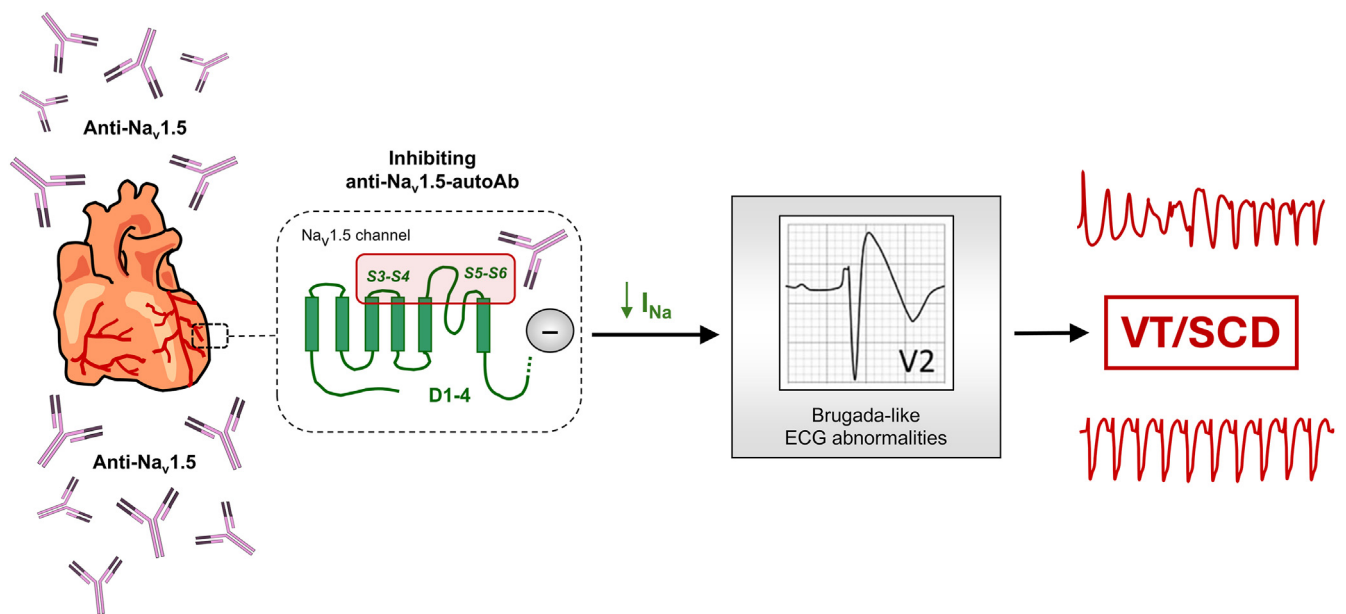


Figure 4

Autoimmune Brugada syndrome: molecular bases and electrophysiologic mechanisms. Inhibiting anti- $\text{Na}_v1.5$ autoantibodies can be cause of autoimmune Brugada syndrome. See text and tables for more details. autoAb = autoantibody; ECG = electrocardiogram; I_{Na} = sodium channel current; S3–S4/S5–S6 = transmembrane segments 3–4/5–6; SCD = sudden cardiac death; VT = ventricular tachycardia. The red square indicates the portion of the channel where the target peptide sequence (reported in red block letters) is located. The green arrow pointing down indicates decrease.

Autoimmune AVB in newborns

Autoimmune congenital heart block has been the first to be described and, so far, remains the most established form of autoimmune-mediated arrhythmia.^{7,62} This condition, representing the most common cause of severe atrioventricular (AV) dysfunction in newborns with a structurally normal heart, occurs in 2%–5% of children of anti-Ro/SSA-positive mothers (particularly those anti-Ro/SSA 52-kDa positive and regardless of manifest AD) because of fetal conduction system damage due to the transplacental passage of these autoantibodies from the mother to the fetus.⁶² Specifically, a large body of evidence indicates that autoimmune congenital heart block is an autoimmune cardiac channelopathy provoked by an inhibitory cross-reaction between anti-Ro/SSA 52-kDa antibodies and specific binding sites of calcium channels, both L-type ($\text{Ca}_v1.2$, $\text{Ca}_v1.3$) and T-type ($\text{Ca}_v3.1$, $\text{Ca}_v3.2$), in the fetal heart.^{63–65} (Table 1). In the early phases of disease, conduction disturbances consist of sinus bradycardia and lower degrees of AVB due to a purely electrophysiologic interference that is potentially reversible after maternal immunomodulating treatment. Later on, chronic autoantibody binding can promote calcium channel internalization and cell injury, leading first to inflammatory damage and then, if the process is not stopped at this stage, to irreversible complete AVB due to fibrosis and calcification of the conduction tissue.^{7,62,66}

Because no substantial advancements have been made in the last few years regarding basic mechanisms and clinical management of autoimmune congenital heart block, a detailed description of this complex condition is beyond the

specific objective of this contemporary review. We therefore refer readers to some excellent papers that recently reviewed this topic.^{10,66–68}

Autoimmune AVB in adults

Isolated AVB of unknown origin, that is, in the absence of any structural heart disease or other well-defined causes of AVB, accounts for ~50% of cases of pacemaker implantation in adults aged <50 years.⁴ Recent data suggest that in up to half of these patients, the AVB is the result of an autoimmune cardiac channelopathy due to blocking autoantibodies against $\text{Ca}_v1.2$ or $\text{Na}_v1.5$ channels (Tables 2 and 3; Figure 7).^{16,59–61}

Inhibiting anti- $\text{Ca}_v1.2$ autoantibodies

By generating I_{CaL} , $\text{Ca}_v1.2$ is one of the most important channels promoting electric conduction through the AV node. Accordingly, well-known conditions leading to delayed AV conduction, such as aging and intensive training, are associated with reduced $\text{Ca}_v1.2$ expression and I_{CaL} density in nodal cells.^{69,70} Moreover, it has been demonstrated that targeted $\text{Ca}_v1.2$ loss in adult mice causes AVB.⁷¹

Although the adult AV node is traditionally considered resistant to anti-Ro/SSA antibodies because of an inherently high calcium channel reserve,⁶³ in the last few years, some translational and population-based studies provided evidence that these autoantibodies are causally involved in several cases of isolated AVB in adults,^{16,34,59} through inhibiting effects on $\text{Ca}_v1.2$ channel function.^{16,59,60}

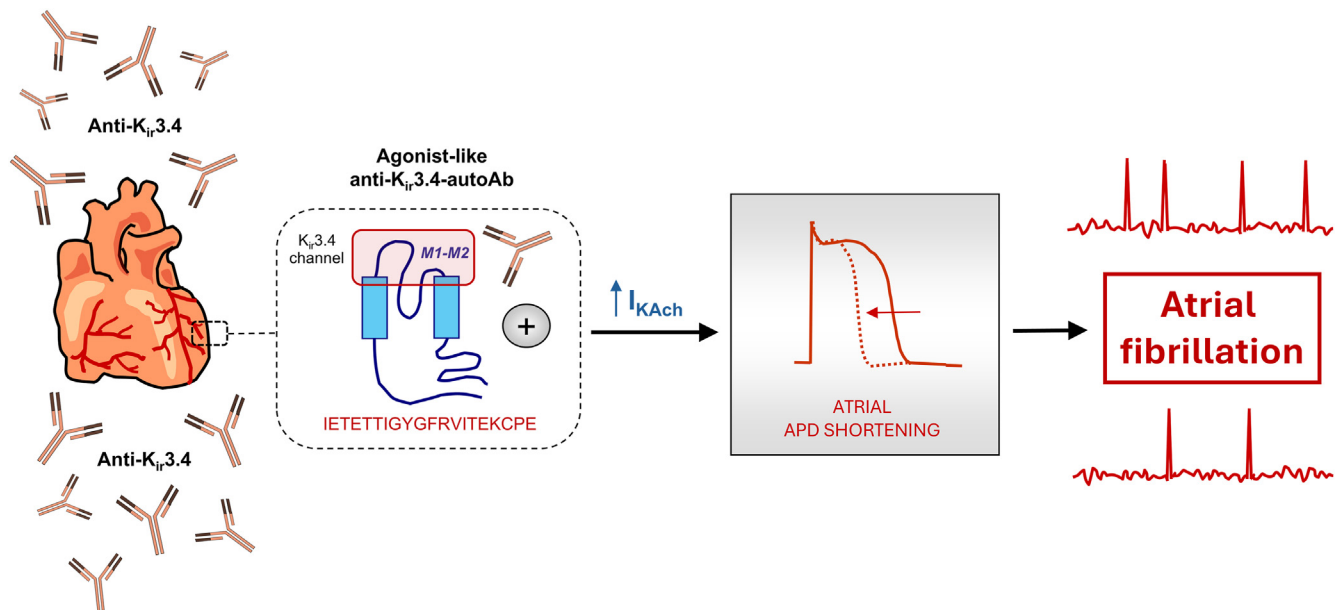


Figure 5

Autoimmune atrial fibrillation: molecular bases and electrophysiologic mechanisms. Agonist-like anti-Kir3.4 autoantibodies shortening atrial action potential duration (APD) can be cause of autoimmune atrial fibrillation. See text and tables for more details. autoAb = autoantibody; I_{KACh} = acetylcholine-gated potassium channel current; M1-M2 = transmembrane segments 1–2. The red square indicates the portion of the channel where the target peptide sequence (reported in red block letters) is located. The blue arrow pointing up indicates increase.

By prospectively enrolling 34 consecutive patients with AVB of unknown origin diagnosed between 18 and 65 years of age, we found that circulating anti-Ro/SSA 52-kDa antibodies were present in ~40% of patients, independent of a history of AD.¹⁶ *In-vitro* treatment of $Ca_v1.2$ -transfected HEK293 cells with purified IgG from anti-Ro/SSA-positive but not negative AVB patients acutely (10 minutes) reduced I_{CaL} density and chronically (24 hours) downregulated $Ca_v1.2$ protein expression. Moreover, ELISA experiments demonstrated high reactivity when anti-Ro/SSA-positive sera were incubated with 5 peptides corresponding to the $Ca_v1.2$ pore extracellular loop between S5 and S6 in domains 1 and 3, specifically selected for their linear homology with the Ro 52-kDa protein, in turn strongly correlated with the extent of $Ca_v1.2$ inhibition, both as current density and protein expression¹⁶ (Table 1). Noteworthy and intriguingly, 1 of these peptides (DFDNVLAAMMALFTVSTFEG) was the same recognized by the inhibiting anti- $Ca_v1.2$ autoantibodies found by Maguy and colleagues in patients with idiopathic CA.^{15,57} Furthermore, a short course of corticosteroids at immunosuppressive doses (steroid test) was effective in inducing rapid improvement/normalization (hours-days) of AV conduction in anti-Ro/SSA-positive patients but not in those negative.¹⁶ Based on these findings, in some patients, an immunomodulatory regimen was maintained for a longer time, and in all cases, regardless of the specific drugs used to taper corticosteroids (azathioprine, high-dose immunoglobulins, hydroxychloroquine), the improvement persisted over time.¹⁶ In particular, in 1 patient with high-grade AVB at baseline, long-lasting hydroxychloroquine monotherapy was able to keep a persistent asymptomatic first-degree AVB (follow-up >3 years), demonstrating to be a safe and effective pacemaker-sparing intervention.^{16,60}

Some population studies provided strong support to these data, emphasizing their clinical and epidemiologic relevance.^{34,59,72} In fact, after a seminal report based on a historical Spanish cohort of 3586 pacemaker patients that found anti-Ro/SSA positivity in ~10% of patients implanted for AVB of unknown origin,⁷² 2 large cross-sectional studies investigated the impact of anti-Ro/SSA antibodies on the risk of AVB in the general population.^{34,59} In the first one, Akuka and coworkers³⁴ conducted a nationwide retrospective analysis involving data from >100,000 participants, including 11,525 with circulating anti-Ro/SSA antibodies. The authors found that positive individuals had a risk of presenting with AVB, either complete or incomplete, twice the control group. Of note, also the prevalence of intraventricular conduction disturbances (left and right bundle branch block, left bundle hemiblock) was up to 80% higher in anti-Ro/SSA-positive than in negative participants. Multivariate logistic regression analysis confirmed these findings, also demonstrating that the association between anti-Ro/SSA positivity and conduction disturbances was independent of a wide number of confounders, including structural heart disease and history of AD.³⁴ The second population study, which enrolled 2536 consecutive athletes <40 years old without prior cardiac disease or heart interventions who underwent annual medical screening, reported an overall prevalence of advanced AVB in ~0.1% of participants. In 100% of these cases, anti-Ro/SSA antibodies were detected. Moreover, IgG purified from anti-Ro/SSA-positive but not negative AVB inhibited both I_{CaL} and $Ca_v1.2$ expression *in-vitro*.⁵⁹

Overall, these data suggest that anti-Ro/SSA antibodies cross-reacting with and inhibiting $Ca_v1.2$ channels represent an epidemiologically relevant and potentially reversible cause of isolated AVB in adults. This view is further supported by a

retrospective observational cohort study conducted on 766 patients with heart failure, in whom the presence of anti-Ro/SSA antibodies (9.1% of cases) was independently associated with a higher risk of AVB (2.5-fold) and left and right bundle branch block (3-fold), again irrespective of a CTD history.⁵⁸ These new data are important as they intriguingly indicate that the arrhythmogenic activity of these autoantibodies is relevant even in the presence of a concomitant structural heart disease, likely adding an electrophysiologic component to the background tissue injury-driven conduction delay (multi-hit theory).⁸ Further studies are warranted to explore clinical implications and therapeutic potential of such findings.

Inhibiting anti- $\text{Na}_v1.5$ autoantibodies

$\text{Na}_v1.5$ channels, conducting the inward sodium current I_{Na} , are increasingly recognized to have a central role in AV conduction because of their critical localization in the pathways leading to the open node, that is, the inferior nodal extension and the transitional zone.⁷³ Since the channel density in these areas is lower than in the working myocardium, it may account for the peculiar vulnerability of AV conduction to conditions impairing sodium channel function. Accordingly, loss-of-function mutations of the $\text{Na}_v1.5$ encoding gene *SCN5A* represent the most common inherited cause of progressive cardiac conduction disease.¹⁸

Korkmaz and associates⁶¹ were the first and to date the only investigators to provide clear evidence that inhibiting anti- $\text{Na}_v1.5$ autoantibodies can represent, beyond anti-Ro/SSA antibodies, another potential cause of isolated AVB in adults. By immunizing rats with a peptide sequence (GNLRHKCVRNFTLNSTNGSVEADGLVW; Table 1) corresponding to the extracellular loop of the $\text{Na}_v1.5$ channel between the S5–S6 segments of the first domain, the authors found that high-titer anti- $\text{Na}_v1.5$ antibody development was associated with significant PR interval prolongation compared with control animals. Moreover, all immunized rats but not controls showed repeated prolonged episodes of third-degree AVB (and sinoatrial block) during Holter electrocardiography monitoring. These alterations occurred in the presence of a significant reduction of $\text{Na}_v1.5$ mRNA and protein expression in the myocardium, but without any inflammatory or fibrotic reaction on histologic examination.⁶¹ To support the clinical relevance of these findings, the authors analyzed by ELISA pooled serum samples from 10 patients with idiopathic AVB and found that in these patients but not in healthy control sera, autoantibodies against different consensus motifs of the $\text{Na}_v1.5$ channel were detectable, including the peptide sequence of the S5–S6 extracellular loop. Finally, incubation with sera either from these patients or from immunized rats significantly and specifically reduced I_{Na} in adult rat ventricular myocytes in culture.⁶¹

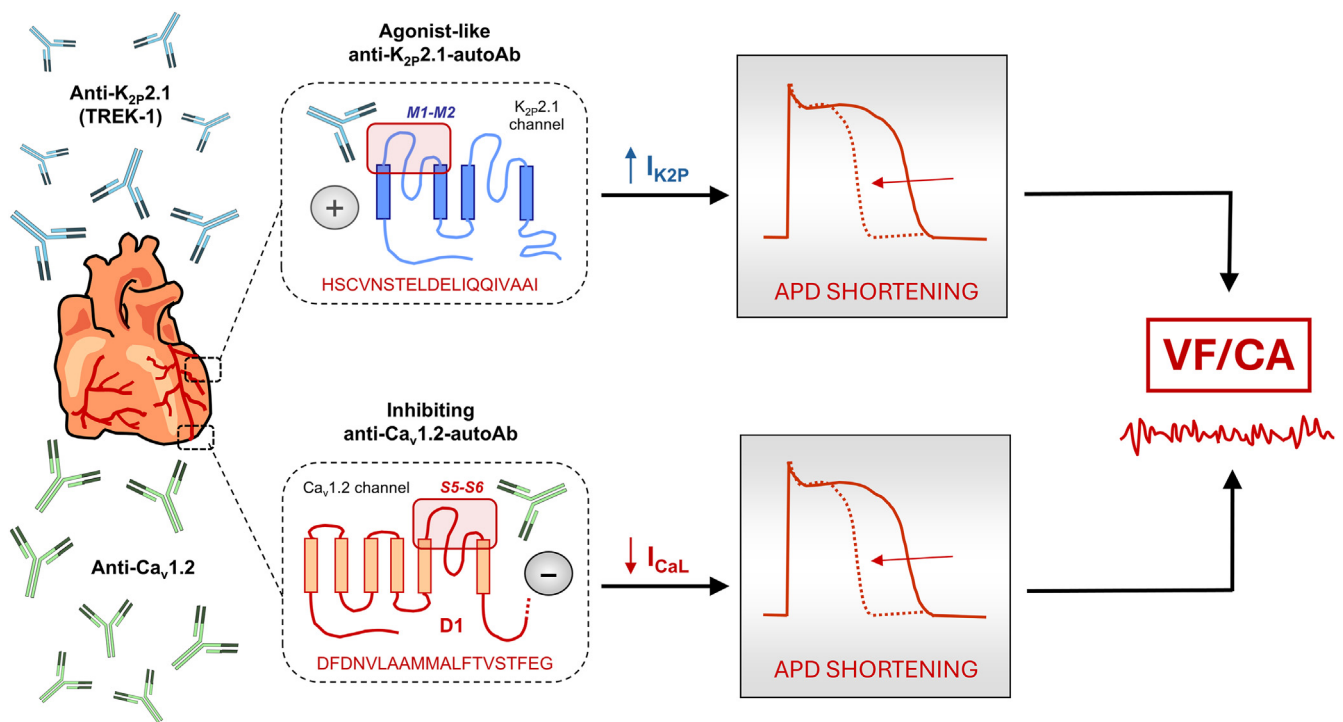


Figure 6

Autoimmune ventricular fibrillation: molecular bases and electrophysiologic mechanisms. Agonist-like anti-K_{2p2.1} autoantibodies and inhibiting anti-Ca_v1.2 autoantibodies shortening ventricular action potential duration (APD) can be cause of autoimmune ventricular fibrillation (VF)/cardiac arrest (CA). See text and tables for more details. autoAb = autoantibody; D1 = domain 1; I_{CaL} = L-type calcium channel current; I_{K2P} = 2-pore domain potassium channel current; M1–M2: transmembrane segments 1–2; S5–S6: transmembrane segments 5–6; TREK-1: TWIK-related potassium channel 1. The red squares indicate the portion of the channel where the target peptide sequences (reported in red block letters) are located. The blue arrow pointing up indicates increase; the red arrow pointing down indicates decrease.

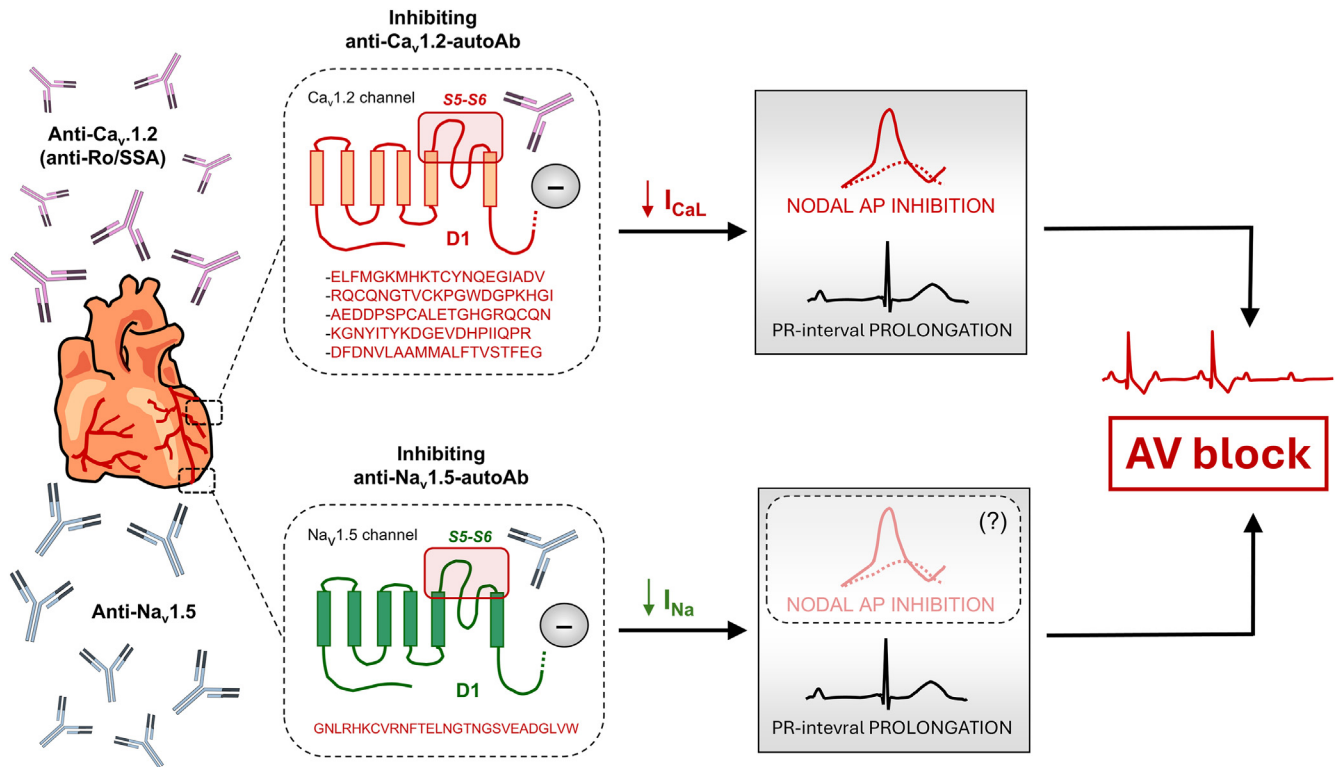


Figure 7

Autoimmune atrioventricular block: molecular bases and electrophysiologic mechanisms. Inhibiting anti- $\text{Ca}_v1.2$ autoantibodies and anti- $\text{Na}_v1.5$ autoantibodies can be cause of autoimmune atrioventricular (AV) block. See text and tables for more details. AP = action potential; autoAb = autoantibody; D1 = domain 1; I_{CaL} = L-type calcium channel current; I_{Kr} = rapid component of the delayed rectifier potassium channel current; I_{Na} = sodium channel current; S5–S6 = transmembrane segments 5–6. The red squares indicate the portion of the channel where the target peptide sequences (reported in red block letters) are located. The red and green arrows pointing down indicate decrease. The question mark indicates alterations that are likely but still not proven.

The “multi-hit” theory

A single cardiac channelopathy alone cannot in most cases produce symptoms and rarely even the related clinical phenotype.⁸ This is well proven for inherited forms, particularly LQTS and BrS, for which provocative tests can reveal latent genetic defects.¹⁸ Indeed, Goldenberg and colleagues⁷⁴ provided evidence that of 1861 patients with genotype-positive LQTS, QTc interval was normal in more than half of cases, even including ~25% of patients with values ≤ 440 ms. These patients still presented in follow-up with a 10 times higher risk of aborted CA and SCD compared with genotype-negative family members, suggesting that an underlying channelopathy, although not clinically evident, can predispose to life-threatening arrhythmic events, probably when other concomitant QT-prolonging risk factors are present.

Such evidence strongly suggests that numerous, often redundant ion channel mechanisms are involved in keeping normal action potential genesis and conduction, thus rendering the phenotype not clinically evident despite the underlying channel dysfunction. This concept is well exemplified by the “repolarization reserve” theory, first proposed by Roden⁷⁵ to explain drug-induced LQTS/TdP risk and now widely accepted. Hence, more than 1 single contributor needs to be impaired for electrocardiographic or clinical symptoms to appear, and the number of needed “hits” will depend on

the functional effect of each single offending factor.⁷⁵ In a single patient, multiple QT-prolonging factors need to be concurrently present to significantly disturb repolarization, so much as to precipitate TdP development. Case in point, in a cohort of 66 consecutive patients who had TdP, many concomitant acquired QT-prolonging risk factors were demonstrable, on average >5 per patient.⁷⁶

Beyond LQTS, such a multi-hit theory could be more generally applied to all arrhythmogenic phenotypes. For example, BrS is often silent, emerging only when other concomitant factors occur, primarily fever or drugs but also autonomic fluctuations, electrolyte imbalances, or structural cardiac disease, synergistically acting to reveal genetic predisposition and increasing the risk for life-threatening arrhythmias.^{77–79} In agreement with these considerations, the group of Viskin has proposed to extend the concept of repolarization or conduction reserves also to BrS.^{78,79} Thus, also for BrS, the presence of a genetic mutation, although pathogenic, should not be considered alone as causal but only able to increase the likelihood for development of disease.

The same considerations can be applied to autoimmune cardiac channelopathies. In fact, although experimental studies clearly demonstrated that anti-ion channel autoantibodies do induce ion channel dysfunction, autoimmune-induced phenotypes and arrhythmias occur in only a fraction of the autoantibody-positive patients at risk.⁷ In this

perspective, anti-ion channel autoantibodies (eg, anti- $\text{Na}_v1.5$ in BrS or anti- $\text{K}_v11.1$ in LQTS), like genetic mutations, are potentially causal but usually not sufficient alone to produce the disease.

Limitations and unanswered questions

This topic being a recent and evolving field, there is a general paucity of studies reproducing the findings reported by others. In fact, except for anti-Ro/SSA-associated forms, in most of the other autoimmune cardiac channelopathies, independent studies replicating the original observations are to date substantially missing (Supplemental Table 2). This gap, which is mostly due to the fact that many of these channelopathies have been described for the first time only recently (5 new forms in the last 5 years),^{12–15,80} may represent a potential limitation that needs to be highlighted for a more cautious and balanced view of the topic.

Another important aspect precluding a deeper understanding of this field is that several general questions still remain unanswered. Where do the different autoantibodies come from? Why are they generated? Are they released because the patients have some kind of disease or are they causal to the disease? It is recognized that autoimmunity occurs when the immune response is triggered as a result of not only non-self foreign but also self antigens. The resulting autoantibodies can be pathogenic, like those covered in this review, but may also be beneficial for disease diagnosis, prognosis, and treatment.⁸¹ The exact mechanisms are not fully understood, but several factors can contribute to development of autoantibodies. These include but are not limited to genetic or environmental factors, for example, gene variants that increase susceptibility to ADs, abnormal surface exposure of otherwise intracellular antigens, molecular mimicry, inflammation/infection, and hormonal causes often in women who are disproportionately affected by AD.⁸¹ In this regard, it is intriguing to hypothesize that also aberrant functioning ion channels, such as sodium channels encoded by the mutated *SCN5A* gene in BrS patients, might promote autoantigen formation, in turn triggering development of autoantibodies. However, the evidence provided by Tarantino and colleagues¹³ that anti- $\text{Na}_v1.5$ channel autoantibodies are found both in patients with *SCN5A* mutations and in those without apparently argues against this hypothesis.

Perspectives and unmet needs

Arrhythmias associated with autoimmune cardiac channelopathies develop in most cases in the absence of a concomitant definite AD. In these patients, “the heart rhythm disturbance itself is the AD.” This is an important concept because it implies that physicians must consider an underlying autoimmune mechanism independent of the presence or not of such a clinical feature. The approach should be in some way like that currently adopted for inherited cardiac channelopathies, that is, the patient is tested when an apparently unexplained arrhythmia/proarrhythmic electrocardiographic phenotype is present, regardless of other concomitant clinical

features suggesting a genetic disease.¹⁸ Likewise, the possibility of an underlying autoimmune cardiac channelopathy should be considered in all patients with heart rhythm disturbances of unknown origin as only specific testing can demonstrate the presence of arrhythmogenic anti-ion channel autoantibodies. Whereas adding this novel perspective to current management of patients with arrhythmias could lead to an adequate diagnosis in a nonnegligible number of cases labeled idiopathic, the challenge is that the laboratory diagnosis of autoimmune cardiac channelopathy is not accessible to all in daily practice. In fact, anti-ion channel autoantibody testing is currently available in only a few centers, almost exclusively for research purposes and usually restricted, depending on the institution, to 1 specific type alone. Presently, the only one commercially available and reliable is the anti-Ro/SSA testing, based on 3 main methods—fluoroenzyme immunoassay, line blot immunoassay, and immune western blotting—the last being the most specific and sensitive for detecting arrhythmogenic autoantibodies (Supplemental Table 3).^{30,80,82,83} In this perspective, it will be fundamental to develop a diagnostic system suitable for easy and widespread clinical use, ideally an immune-enzymatic method using the specific peptide sequences recognized on ion channels as revealing antigens, through which to test simultaneously the patient’s serum for several different autoantibodies, in turn selected on the basis of the arrhythmic phenotype present. This diagnostic system should meet the World Health Organization’s ASSURED criteria (affordable, sensitive, specific, user-friendly, rapid, equipment-free, delivered) for the ideal test that can be used at all levels of the global health care system, including the developing world.⁸⁴ Currently, diagnosis of autoimmune cardiac channelopathies falls short of ideal standards, but raising health care providers’ awareness of their clinical significance will drive interest in developing multi-autoantibody detection tools. In contrast, and because there are already platforms available for the simultaneous detection of other autoantibodies (>120 purified antigens are offered by several commercial sources; <https://www.genecopoeia.com/product/omicsarray-antigen-microarrays/>; <https://microarray.creative-proteomics.com/antigen-microarray-services.htm>) based on protein microarray permitting powerful detection of autoantibodies associated with many ADs, the development and application of similar technologies for the detection of autoantibodies responsible for cardiac channelopathies are readily available for exploration and applicability.⁸⁵

Another key point is the treatment of the underlying autoimmune cardiac channelopathies. In fact, the evidence that anti-ion channel autoantibodies exert their proarrhythmic effects by directly interfering with cardiac electrophysiology, in most cases in the absence of any inflammatory or fibrotic change in the heart, strongly suggests that therapeutic interventions aimed at inhibiting the production of autoantibodies or their interaction with ion channels can be effective for treating these conditions. For the first objective, administration of immunomodulatory agents seems to be, at least theoretically, the best option. Indeed, corticosteroids, azathioprine, high-

dose immunoglobulins, and hydroxychloroquine demonstrated their efficacy in reversing anti-Ro/SSA-associated AVB and LQTS in several adult patients along with the disappearance of autoantibody positivity.^{16,25,86–88} However, confirmatory data from clinical trials are currently not available. In addition, studies testing the effectiveness of this approach in other autoimmune cardiac channelopathy-associated arrhythmias are to date missing.

Regarding the second objective, the evidence that the specific sequence recognized by the autoantibody is known in most cases makes it reasonable to consider the development of a therapeutic competition strategy based on specifically designed decoy peptides. In this way, by providing a “false” target mimicking the epitopes on the channel protein, autoantibodies would be distracted and neutralized, thus preventing their binding to ion channels and subsequently the related proarrhythmic consequences. In agreement with this premise, *in-vitro* experiments demonstrated the effectiveness of these peptides in inhibiting autoantibody-channel interaction or electrophysiologic changes when sera or affinity-purified autoantibodies from patients with autoimmune cardiac channelopathy-associated arrhythmias were used, specifically samples from patients with TdP and inhibiting anti-K_v11.1 autoantibodies,³⁰ VT and agonist-like anti-Ca_v1.2 autoantibodies,^{40,42} or idiopathic CA and inhibiting anti-Ca_v1.2 autoantibodies.¹⁵ These findings, although preliminary, are promising and intriguing as they could open, in perspective, an innovative therapeutic approach to these conditions, much more targeted and potentially free of the systemic adverse effects observed with immunosuppressants and immunomodulatory drugs.

Conclusion

Autoimmune cardiac channelopathies are ever more recognized as a novel and epidemiologically important cause of a wide spectrum of cardiac arrhythmias. Whereas it is expected that this arrhythmogenic mechanism may be primarily involved in unexplained or poorly explained heart rhythm disorders occurring in young people with a structurally normal heart, recent data intriguingly suggest that anti-ion channel autoantibodies might contribute to arrhythmia development also in patients older or with known cardiac disease^{16,58,60} by adding additional “hits” of electrophysiologic origin (thereby potentially reversible) to classic arrhythmogenic risk factors.

This field, unexpectedly and tumultuously grown in the last few years, urgently requires greater and more generalized awareness. In fact, the new concept of autoimmune cardiac channelopathies should enter the knowledge background of the clinical cardiac electrophysiologist and cardiologist as well as that of the basic/translational scientists involved in the arena of cardioimmunology. Only in this way can the current gaps in diagnosis and treatment be filled, allowing this new pathologic entity to be fully included in the daily practice management of patients with cardiac arrhythmias.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2025.03.1879>.

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