

Emerging Arrhythmic Risk of Autoimmune and Inflammatory Cardiac Channelopathies

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Cardiac arrhythmias are associated with high morbidity and mortality.¹ Specifically, malignant arrhythmias are a recognized leading cause of sudden cardiac death (SCD) in the Western countries. It has been estimated that every day >1000 SCDs occur in the United States.^{1,2} Although structural heart diseases, particularly coronary artery disease and heart failure,^{2,3} are the prevalent underlying causes of cardiac arrhythmias and SCD, structural alterations are not identified at the postmortem examination in 5% to 15% of patients, increasing up to 40% in subjects aged <40 years.^{1,2} The discovery that, in the absence of structural heart defects, mutations in the genes encoding for cardiac ion channels and/or associated regulatory proteins can promote arrhythmias led to the recognition of a new group of inherited arrhythmogenic diseases, accounting for a significant proportion of the unexplained cases.⁴ The term cardiac channelopathies has been used to designate a collection of genetically mediated syndromes, including long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS), idiopathic ventricular fibrillation (IVF), and progressive cardiac conduction disease.⁵ All these disorders are caused by the dysfunction (loss or gain of function) of specific cardiomyocyte ion channels, resulting in a disruption of the cardiac action

potential (AP).⁴ Such electrical abnormalities lead to an increased susceptibility to develop arrhythmias, syncope, seizures, or SCD, precipitated by episodes of polymorphic ventricular tachycardia (torsade de pointes [TdP]) or ventricular fibrillation (VF), typically in the presence of a structurally normal heart.⁴ Thus, although the term cardiac channelopathies does not per se imply a genetic origin, it currently coincides with that of inherited cardiac channelopathies.^{1,5}

Accumulating recent evidence demonstrated that factors other than genetic mutations can promote arrhythmias by causing a selective cardiac ion channel dysfunction in the absence of any structural heart defect. In addition to a well-recognized list of drugs directly interfering with cardiac ion channel function,⁶ immunologic and inflammatory factors can cause cardiac channelopathies.^{7,8} In fact, besides the established role of cardiac inflammation, often of autoimmune origin, in promoting arrhythmias in the presence of an autopsy/biopsy-proven inflammatory cell tissue infiltration,^{9–13} it is increasingly recognized that systemically released autoantibodies and cytokines can be per se arrhythmogenic, regardless of evident histologic changes in the heart.^{14–16} Several arrhythmogenic autoantibodies targeting calcium, potassium, or sodium channels in the heart have been identified, and the term autoimmune cardiac channelopathies has been proposed.⁷ Moreover, evidence exists that inflammatory cytokines, mainly tumor necrosis factor (TNF)- α , interleukin-1, and interleukin-6, can modulate expression and/or function of ion channels, both by directly acting on cardiomyocytes^{8,17} and/or inducing systemic effects (fever).¹⁷ A careful consideration of these, to date, largely overlooked factors is highly relevant because they are potentially involved in several unexplained arrhythmias/SCD that are negative for genetic factors.² In patients with unexplained cause of death after a comprehensive post-mortem genetic testing of blood/tissue samples (the so-called “molecular autopsy”), a genetic cause is demonstrated in no more than \approx 30% of cases.²

As such, a novel and more comprehensive classification of cardiac channelopathies is herein proposed, distinguishing the “classic” inherited forms, related to genetic mutations,

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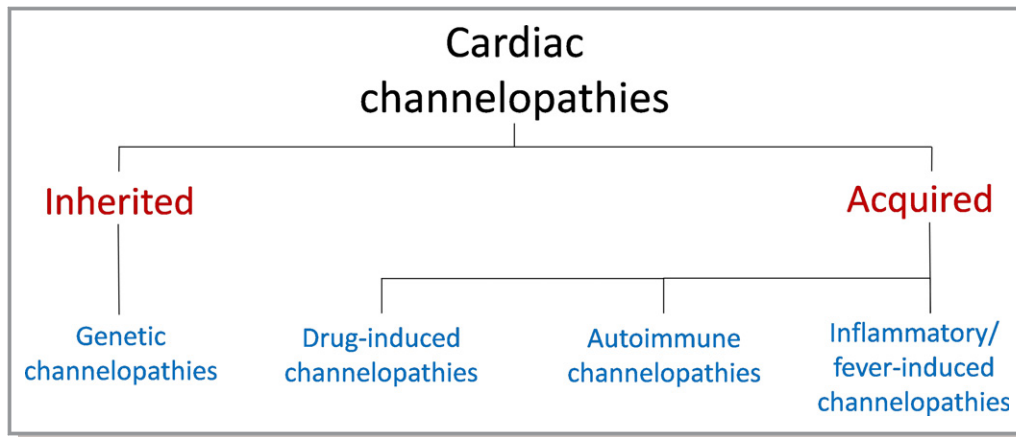


Figure 1. Classification of arrhythmogenic cardiac channelopathies. Besides the “classic” inherited forms of cardiac channelopathies related to genetic mutations, a wider spectrum of acquired forms includes not only drug-induced, but also autoimmune and inflammatory/fever-induced, cardiac channelopathies.

from the acquired forms, including drug-induced and more recently recognized autoimmune and inflammatory/fever-induced cardiac channelopathies (Figure 1). In this review, we focus on autoimmune and inflammatory/fever-induced channelopathies and their emerging impact on arrhythmic risk, providing both basic and clinical perspectives.

Clinical Syndromes

From a clinical point of view, cardiac channelopathies have been associated with ventricular arrhythmias (VAs), including ventricular tachyarrhythmias and VF, atrial fibrillation (AF), and bradyarrhythmias.

Tachyarrhythmias

Ventricular tachyarrhythmias and SCD

The most severe cardiac channelopathies are those increasing the propensity for VA and SCD. Among these, the 4 major syndromes are LQTS, SQTS, BrS, and CPVT. More recently recognized electrocardiographic phenotypes in this group are ERS and IVF. Because BrS and ERS share several clinical and pathophysiological aspects, including abnormal J-waves in the ECG, they are also collectively called “J-wave syndromes.”⁵

Long-QT Syndrome. LQTS is characterized by a prolonged heart rate–corrected QT interval (QTc) on the ECG, predisposing to life-threatening VA, particularly TdP.¹⁸ Although the cutoff value for QTc prolongation is traditionally set at 440 ms, it is currently recommended that only a QTc >99th percentile (ie, 470 ms for men and 480 ms for women) should be considered abnormally prolonged (and highly abnormal when >500 ms).¹⁸ The more the QTc prolongs,

the greater TdP risk, becoming high and extremely high when QTc >500 and >600 ms, respectively.^{18,19} It is noteworthy that QTc prolongation may not be always manifest in resting conditions, and it is unmasked only after provocative tests.⁵

The QT interval in the ECG is a surrogate measure of the average duration of the ventricular AP.²⁰ Whenever a channel dysfunction induces an increase in the inward Na⁺ or Ca⁺⁺ currents and/or a decrease in an outward K⁺ current, resulting in an inward shift in the balance of currents, the AP duration (APD) prolongs and, hence, the QT interval.^{19,21,22} Regardless of the specific channelopathy involved, ion channel dysfunctions resulting in APD prolongation will increase the susceptibility to develop oscillations at the plateau level (early afterdepolarizations).¹⁸ The early afterdepolarizations combined with differences in APD lengthening across the ventricular wall (transmural dispersion of depolarization) could trigger ectopic activity that can induce reentrant arrhythmias, particularly TdP.²¹ Although frequently self-terminating, TdP can degenerate into VF and SCD.^{18,19,22}

Such changes can result from a wide spectrum of cardiac channelopathies, both inherited and acquired, eventually emerging as LQTS.^{19,22} Genetic channelopathies are well recognized as mutations of 17 different genes that have been currently identified in clinically diagnosed LQTS.^{19,23} Mutations can involve genes encoding the channel-protein itself or ion channels’ regulatory proteins, resulting in loss of function of one of the K⁺ currents or gain of function of the Na⁺ or Ca⁺⁺ currents^{19,21} (Table 1). LQTS-causing mutations have a prevalence of ≈1:2000 in apparently healthy live births.⁵ LQT1 (*KCNQ1*, 30%–35%), LQT2 (*KCNH2*, 20%–25%), and LQT3 (*SCN5A*, 5%–10%) represent most of genotype-positive cases, whereas more recently discovered LQTSs collectively account for <5%.^{5,19}

Table 1. Cardiac Channelopathies Associated With LQTS

Cardiac Channelopathies	Gene	Ion Channel/Regulatory Protein	Mechanism	Effect on Ion Current
Inherited forms				
Genetic				
LQT1	<i>KCNQ1</i>	K _v 7.1	Loss-of-function mutation	I _{Ks} decrease
LQT2	<i>KCNH2</i>	hERG	Loss-of-function mutation	I _{Kr} decrease
LQT3	<i>SCN5A</i>	Na _v 1.5	Gain-of-function mutation	I _{Na} increase
LQT4	<i>ANK2</i>	Ankyrin B	Loss-of-function mutation	I _{CaL} and I _{Na} increase
LQT5	<i>KCNE1</i>	Mink	Loss-of-function mutation	I _{Ks} decrease
LQT6	<i>KCNE2</i>	MiRP1	Loss-of-function mutation	I _{Kr} decrease
LQT7	<i>KCNJ2</i>	K _{ir} 2.1	Loss-of-function mutation	I _{K1} decrease
LQT8	<i>CACNA1C</i>	Ca _v 1.2	Gain-of-function mutation	I _{CaL} increase
LQT9	<i>CAV3</i>	Caveolin-3	Gain-of-function mutation	I _{Na} increase
LQT10	<i>SCN4B</i>	NavB4	Gain-of-function mutation	I _{Na} increase
LQT11	<i>AKAP9</i>	Yotiao	Loss-of-function mutation	I _{Ks} decrease
LQT12	<i>SNTA1</i>	α1 Syntrophin	Gain-of-function mutation	I _{Na} increase
LQT13	<i>KCNJ5</i>	K _{ir} 3.4	Loss-of-function mutation	I _{KACH} decrease
LQT14	<i>CALM1</i>	Calmodulin-1	Loss-of-function mutation	I _{CaL} increase*
LQT15	<i>CALM2</i>	Calmodulin-2	Loss-of-function mutation	I _{CaL} increase*
LQT16	<i>CALM3</i>	Calmodulin-3	Loss-of-function mutation	I _{CaL} increase*
LQT17	<i>TRDN</i>	Triadin	Loss-of-function mutation	I _{CaL} increase*
Acquired forms				
Drug induced[†]				
Antiarrhythmics (class IA-III)	...	hERG [‡]	Direct channel inhibition (and/or channel trafficking interference)	I _{Kr} decrease [‡]
Antimicrobials	...			
Antihistamines	...			
Psychoactive agents	...			
Motility and antiemetic drugs	...			
Anticancer drugs	...			
Immunosuppressants	...			
Autoimmune				
Anti-hERG antibodies (anti-Ro/SSA)	...	hERG	Direct channel inhibition	I _{Kr} decrease
Anti-Kv1.4 antibodies	...	K _v 1.4	Direct channel inhibition	I _{to} decrease*
Inflammatory				
TNF-α	...	hERG	Channel function inhibition	I _{Kr} decrease
	...	K _v 7.1	Channel function inhibition [§]	I _{Ks} decrease
	...	K _v 4.2/K _v 4.3	Channel expression decrease	I _{to} decrease
Interleukin-1	...	Ca _v 1.2	Channel function enhancement	I _{CaL} increase
	...	K _v 4.2/K _v 4.3	Channel function inhibition [§]	I _{to} decrease
Interleukin-6	...	Ca _v 1.2	Channel function enhancement	I _{CaL} increase

Anti-Ro/SSA indicates anti-Ro/Sjogren's syndrome-related antigen A; hERG, human ether-a-go-go-related gene K⁺-channel; I_{CaL}, L-type calcium current; I_{K1}, inward rectifier K⁺-current; I_{KACH}, acetylcholine-activated current; I_{Kr}, rapid component of the delayed rectifier potassium current; I_{Ks}, slow component of the delayed rectifier potassium current; I_{Na}, sodium current; I_{to}, transient outward potassium current; LQTS, long-QT syndrome; MiRP, MinK related protein 1; TNF-α, tumor necrosis factor-α.

*Proposed, because no direct evidence is currently available.

[†]A more comprehensive, detailed, and frequently updated list of QT-prolonging drugs is available at the website (<https://www.crediblemeds.org>).

[‡]Although hERG inhibition with I_{Kr} decrease is the mechanism involved in most cases, some drugs can inhibit other potassium currents (I_{to}, I_{Ks}, or I_{K1}) or augment sodium or calcium currents (I_{Na} or I_{CaL}).

[§]No data on channel expression are currently available.

Besides inherited forms, 3 types of acquired cardiac channelopathies associated with LQTS exist (ie drug induced,⁶ autoimmune,^{7,17,24} and inflammatory^{8,17,25}) (Table 1). However, these forms are, to date, largely overlooked or not classified as a channelopathy. For drugs, a wide range of structurally unrelated medications are known to cause acquired LQTS, mostly as the result of a direct human ether-a-go-go-related gene K⁺-channel (hERG) blockade.⁶ The long list of drugs primarily includes antiarrhythmics, antimicrobials, antihistamines, and psychoactive drugs (Table 1), and it is continuously increasing (<http://www.crediblemeds.org>).⁶ The other acquired forms of LQTS have received less attention, probably because they have been only recently characterized.^{7,17}

To date, 2 LQTS-induced autoimmune channelopathies have been identified, both associated with inhibiting autoantibodies cross-reacting with specific K⁺ channels (ie, hERG)^{26–28} and K_v1.4^{29,30}) (Table 1). Anti-Ro/SSA antibodies (including anti-Ro/SSA (anti-Ro/Sjogren's syndrome-related antigen A) 52-kD and anti-Ro/SSA 60-kD subtypes) can be the cause of a novel form of acquired LQTS via cross-reaction and blockade of the hERG-K⁺ channel (Table 1).^{7,26,31} Anti-Ro/SSA antibodies are reactive with the intracellular soluble ribonucleoproteins Ro/SSA antigen and are among the most frequently detected autoantibodies in several connective tissue diseases and in the general, otherwise healthy, population.^{31,32} Patients (and their newborns) with anti-Ro/SSA-positive connective tissue disease commonly show QTc prolongation, correlating with autoantibody levels (particularly anti-Ro/SSA 52-kD) and complex VA.^{31,33–37} Moreover, anti-Ro/SSA 52-kD antibodies significantly inhibit the rapid activating component of the delayed K⁺ currents (I_{Kr}), via a direct binding with the extracellular loop between segments S5 and S6 of the pore-forming hERG-channel subunit, where homology with the Ro/SSA 52-kD antigen is present.^{26–28} In addition, immunization of guinea pigs with a 31-amino acid peptide corresponding to a portion of this extracellular region of the hERG channel induced antibodies that inhibited I_{Kr} and caused APD and QTc prolongation, in the absence of any cardiac inflammation.¹⁶ Some authors did not find a significant (frequently near-significant) association between anti-Ro/SSA and QTc prolongation in patients with autoimmune diseases,^{38,39} and even in studies in which an association has been demonstrated, the rate of QTc prolongation varied significantly, from 10% to 60%.³⁷ Besides substantial differences in circulating levels of pathogenic anti-Ro/SSA 52-kD among the cohorts, recent evidence from simulation and clinical studies supports the hypothesis that a concomitant inhibitory effect of anti-Ro/SSA on L-type Ca²⁺ channels can partially counteract I_{Kr} inhibition-dependent prolongation of APD, and the resulting QTc duration on ECG.³¹ In particular, because I_{Kr} is activated after the peak of the T

wave, Tufan et al⁴⁰ demonstrated that the T_{peak}-T_{end} interval on ECG, a recognized independent predictor of SCD in the general population, is significantly prolonged in patients with anti-Ro/SSA 52-kD-positive connective tissue diseases, also in those patients in whom the QTc was found normal. Besides patients with connective tissue diseases, anti-Ro/SSA antibodies are also present in up to ≈3% of the general population,³² where they could significantly contribute to SCD risk.²⁸ Indeed, anti-Ro/SSA 52-kD antibodies exerting hERG-blocking properties were frequently found (60%) in unselected patients with TdP, mainly without manifest ADs.²⁸ However, no population data are currently available on the percentage of anti-Ro/SSA 52-kD carriers who actually manifest the channelopathy and/or develop arrhythmias.

Although less investigated, another form of LQTS-inducing autoimmune channelopathy may be related to anti-K_v1.4-K⁺ channel antibodies, detected in ≈10% to 20% of patients with myasthenia gravis.^{29,30} The K_v1.4 channel conducts a transient K⁺-outward current (I_{to}) chiefly determining the early repolarization phase of the AP.²⁰ Anti-K_v1.4-positive subjects frequently showed QTc prolongation (≈15%–35%)^{29,30} and significant mortality for lethal QT-associated arrhythmias (20% of cases).³⁰ Although pathophysiological studies are currently missing, LQTS seems to result from an autoantibody-dependent I_{to} inhibition, via direct channel binding (Table 1).^{7,29,30} Nevertheless, because signs of myocarditis are present in a fraction of anti-K_v1.4-positive patients with myasthenia gravis,^{29,30} it is possible that inflammatory mechanisms and structural heart changes may contribute to the pathogenesis of electric alterations.

Finally, agonist-like autoantibodies specifically interacting with the L-type Ca⁺⁺ channels were detected in ≈5% to 50% of patients with cardiomyopathies (both idiopathic dilated cardiomyopathy and ischemic cardiomyopathy) and were associated with an increased risk of life-threatening VA/SCD.^{41,42} Experimental studies suggest that these autoantibodies, by directly recognizing an intracellular sequence at the N-terminus of the Ca_v1.2 subunit, can increase L-type inward Ca⁺⁺ current (I_{CaL}), prolong APD, and result in early afterdepolarizations and VA.^{41,43} Although these data anticipate LQTS as the associated clinical phenotype, eventually promoting early afterdepolarization-induced VA and SCD, a specific investigation of QT-interval behavior in these patients is substantially missing, thus currently precluding this labelling.

Inflammatory channelopathies are related to systemically or locally released inflammatory cytokines (mainly TNF-α, interleukin-1, and interleukin-6) able to directly affect the expression and/or function of several cardiac ion channels, resulting in a decrease of K⁺ currents (I_{Kr}, I_{to}, or the slow activating components of the delayed K⁺ current [I_{Ks}]) and/or

an increase of I_{CaL} (Table 1).^{8,17} Cardiac or systemic inflammation promotes QTc-interval prolongation via cytokine-mediated effects (Table 1), and this may increase SCD risk.^{8,17} This is supported by several studies in patients with inflammatory heart diseases, autoimmune inflammatory diseases, infections and apparently healthy subjects with low-grade chronic systemic inflammation.^{8,44–48} Thus, regardless of its origin, inflammation per se seems to represent a risk factor for LQTS and life-threatening VA. Accordingly, in unselected patients with TdP, C-reactive protein (CRP) and interleukin-6 levels are commonly increased, in $\approx 50\%$ of subjects associated with a definite inflammatory disease (infective/immune mediated/other).²⁵ Moreover, in patients with elevated CRP from different inflammatory conditions, QTc prolongation is common, and CRP reduction associates with a significant QTc shortening, also correlating with TNF- α /interleukin-6 decrease.^{25,49} QTc length and reversal of inflammation-driven QTc changes directly correlate with cytokine levels,^{25,44,49,50} suggesting direct functional effects on cardiac electrophysiological properties. Indeed, inflammatory cytokines prolong ventricular APD by inducing dysfunction of several cardiac ion channels, particularly K^+ channels (Table 1).^{8,17} TNF- α significantly reduces several K^+ currents, including I_{to} ,^{51–54} I_{Kr} ,^{55,56} I_{Ks} ,⁵⁶ and the ultrarapid activating component of the delayed K^+ currents,^{51,54} as a result of an inhibition of channel ($K_v4.2$, $K_v4.3$, or $K_v1.5$)^{51–54} or channel-interacting protein⁵⁶ expression and/or alterations in channel-gating kinetics.⁵⁴ Reactive oxygen species production, nuclear factor- κB , and sphingomyelin pathway activation seem to have an important role.^{53,55,56} Consistent APD-prolonging effects are also exerted by interleukin-1, by both reducing I_{to} ⁵⁷ and increasing I_{CaL} via a lipoxygenase pathway,⁵⁸ and interleukin-6, by phosphorylation of the 1829-serine residue of the $Ca_v1.2$ subunit, leading to I_{CaL} enhancement.⁵⁹

Evidence also exists that fever can trigger LQTS and related arrhythmias,^{60,61} particularly in preexisting I_{Kr} defects, either genetic or acquired,⁶⁰ by influencing temperature-sensitive biophysical properties of the hERG channel.⁶² Given the previously described K^+ current-inhibiting effects of cytokines during febrile inflammatory diseases, these molecules could synergistically work along with temperature in promoting LQTS-inducing channelopathies.

Short-QT Syndrome. SQTs is a clinical entity characterized by an abnormally abbreviated QTc associated with a high incidence of life-threatening VA and SCD, but also atrial arrhythmias, particularly AF.⁵ Although diagnostic QTc values are still debated, a cutoff of QTc < 360 ms is currently suggested.⁵ From an electrophysiological point of view, SQTs is associated with a heterogeneous APD abbreviation, mostly in the epicardium, leading to an increased transmural dispersion of repolarization that promotes reentrant

excitation.²¹ Dispersion of repolarization operating in both ventricular and atrial myocardium underlies the susceptibility of patients with SQTs to VA and AF.^{21,63}

Shortening of APD causing SQTs could result from any cardiac channelopathy leading to an increase in one of the repolarizing outward K^+ currents and/or a decrease in the inward Na^+ or Ca^{++} currents, resulting in an outward shift in the balance of currents²¹ (Table 2). Although inherited channelopathies are the most recognized, acquired channelopathies associated with SQTs have been recently described, including drug-induced and autoimmune forms^{7,64} (Table 2).

Genetic SQTs is extremely rare (< 200 cases worldwide),⁶³ with 6 identified causative genes. *SQT1*, *SQT2*, and *SQT3* are attributable to gain-of-function mutations of 3 different K^+ channel-encoding genes increasing repolarizing currents, whereas *SQT4*, *SQT5*, and *SQT6* are induced by loss-of-function mutations in genes encoding L-type Ca^{++} channel subunits, all decreasing the I_{CaL} -depolarizing current^{5,21,63} (Table 2). The recommendations on genetic SQTs diagnosis are based on QTc duration, personal/family history, and genetic testing,⁵ although the overall yield of genetic screening in patients with SQTs is still low ($\approx 15\%–20\%$).⁶³ Thus, although further causative genes are expected to be identified in the future,⁶³ a potential role for acquired channelopathies (Table 2) in several patients with SQTs should be considered.

Some drugs, including specific antiepileptic, antianginal, and vasodilator drugs (<http://www.crediblemeds.org>), can induce QTc shortening by directly interfering with specific cardiac ion channels, mainly decreasing the inward Na^+ current (I_{Na}) or increasing the acetylcholine-activated K^+ current⁶⁴ (Table 2). However, at present, there is little proof of QT-shortening drugs causing VF in humans in no more than rare isolated instances.⁶⁴

An autoimmune cardiac channelopathy leading to SQTs has recently been described in patients with dilated cardiomyopathy,⁶⁵ associated with $K_v7.1$ channel-targeting agonist-like autoantibodies increasing I_{Ks} ^{15,65} (Table 2). These autoantibodies, reacting with the S5 to S6 pore region, were demonstrated in patients with dilated cardiomyopathy with shortened QTc.⁶⁵ Although no direct data with purified autoantibodies are currently available, it is likely that anti- $K_v7.1$ antibodies enhance I_{Ks} by exerting an agonist-like effect on the channel. In fact, patient serum containing anti- $K_v7.1$ antibodies increased I_{Ks} density in human embryonic kidney 293 cells expressing *KCNQ1/KCNE1* genes, and APD was shortened as a result of an increase in I_{Ks} in cardiomyocytes isolated from rabbits immunized with the $K_v7.1$ channel pore-peptide.^{15,65} Moreover, immunized animals showed QTc shortening, reduced ventricular effective refractory periods, and markedly increased vulnerability to VA.¹⁵ Notably, these changes occurred in the presence of extensive antibody

Table 2. Cardiac Channelopathies Associated With SQTS

Cardiac Channelopathies	Gene	Ion Channel	Mechanism	Effect on Ion Current
Inherited forms				
Genetic				
SQT1	<i>KCNH2</i>	hERG	Gain-of-function mutation	I_{Kr} increase
SQT2	<i>KCNQ1</i>	$K_{v7.1}$	Gain-of-function mutation	I_{Ks} increase
SQT3	<i>KCNJ2</i>	$K_{ir2.1}$	Gain-of-function mutation	I_{K1} increase
SQT4	<i>CACNA1C</i>	$Ca_v1.2$	Loss-of-function mutation	I_{CaL} decrease
SQT5	<i>CACNB2</i>	$Ca_v\beta 2b$	Loss-of-function mutation	I_{CaL} decrease
SQT6	<i>CACNA2D1</i>	$Ca_v\alpha 2\delta$	Loss-of-function mutation	I_{CaL} decrease
Acquired forms				
Drug induced				
Rufinamide (antiepileptic)*	...	$Na_v1.5$	Direct channel inhibition	I_{Na} decrease
Lamotrigine (antiepileptic)*	...	$Na_v1.5$	Direct channel inhibition	I_{Na} decrease
		$Ca_v1.2$	Direct channel inhibition	I_{CaL} decrease
Nicorandil (antianginal)	...	$K_{ir6.2}$	Direct channel activation	I_{KATP} increase
Levcromakalim (vasodilator)	...	$K_{ir6.2}$	Direct channel activation	I_{KATP} increase
Autoimmune				
Anti- $K_{v7.1}$ antibodies	...	$K_{v7.1}$	Direct channel activation	I_{Ks} increase

hERG indicates human ether-a-go-go-related gene K^+ -channel; I_{CaL} , L-type calcium current; I_{K1} , inward rectifier K^+ -current; I_{KATP} , adenosine triphosphate-sensitive current; I_{Kr} , rapid component of the delayed rectifier potassium current; I_{Ks} , slow component of the delayed rectifier potassium current; I_{Na} , sodium current; SQTS, short-QT syndrome.

*Mechanisms of action of these drugs are proposed, because no direct evidence is currently available.

deposition within the myocardium, but without echocardiography modifications or histologic evidence of myocardial leukocyte infiltration or fibrosis.¹⁵

Brugada Syndrome. BrS is a channelopathy associated with a high incidence of SCD in a structurally normal heart, characterized by a peculiar ECG phenotype with accentuated J-waves leading to ST-segment elevation in right precordial leads.^{4,5,66} Three ECG patterns exist: type 1 (“coved type”), type 2 (“saddle-back type”), and type 3.²¹ The prevalence of BrS ranges from 5 to 20 cases/10 000 subjects worldwide, being particularly high in Asia. After car accidents, BrS is the leading cause of death in subjects aged <40 years, particularly men.^{4,5,67}

BrS is primarily recognized as a genetic channelopathy.²¹ To date, mutations in 19 genes have been identified, in all cases leading to an outward shift in the balance of currents during the AP early phases as a result of a decrease in the inward Na^+ or Ca^{++} currents or an increase in an outward K^+ current²¹ (Table 3). Mutations in the $Na_v1.5$ -encoding *SCN5A* gene account for >75% of BrS genotype-positive cases, although the yield of *SCN5A* testing for clinical cases is only \approx 25% to 30%.⁵ In the presence of the previously described changes in ion currents, particularly I_{Na} reduction, the net repolarizing effect of I_{to} during phase 1 is significantly

enhanced, thus reducing cell voltage to values below those required to activate L-type Ca^{++} channels. Such an effect, mainly evident in the subepicardial cells of the right ventricular outflow tract (RVOT), where I_{to} is prominent, reduces Ca^{++} -channel activation with a loss in the AP plateau. This accentuates the AP notch in the right ventricular epicardium relative to the endocardium, generating a transmural voltage gradient responsible for abnormal J-waves in the right precordial leads.^{21,67} Conduction of the AP dome from epicardial sites, where it is conserved, to sites where it is lost results in reentrant excitation (phase 2 reentry) and VT/VF.²¹ In this *repolarization hypothesis*, the evidence that an *SCN5A*-promoter polymorphism slowing cardiac conduction is common in Asians, and that men present a more prominent I_{to} current, may help explain racial and sexual differences.^{5,67} Besides repolarization abnormalities, many experimental data suggest that a slowed conduction in the RVOT is also involved in BrS-related ECG and arrhythmogenesis.⁶⁷ According to this *depolarization hypothesis*, the AP of the RVOT is delayed with respect to the AP of the right ventricle, and this potential gradient contributes to ST-segment elevation. The underlying mechanism seems to be a lower “conduction reserve” related to a particularly low RVOT expression of *SCN5A*, but also of connexin 43 (or gap junction- $\alpha 1$ protein) with abnormal gap-junctional

Table 3. Cardiac Channelopathies Associated With BrS

Cardiac Channelopathies	Gene	Ion Channel/Regulatory Protein	Mechanism	Effect on Ion Current
Inherited forms				
Genetic				
BrS1	<i>SCN5A</i>	Na _v 1.5	Loss-of-function mutation	I _{Na} decrease
BrS2	<i>GPD1L</i>	Glycerol-3-phosphate dehydrogenase 1-like	Loss-of-function mutation	I _{Na} decrease
BsS3	<i>CACNA1C</i>	Ca _v 1.2	Loss-of-function mutation	I _{CaL} decrease
BsS4	<i>CACNB2</i>	Ca _v β2b	Loss-of-function mutation	I _{CaL} decrease
BrS5	<i>SCN1B</i>	Na _v β1	Loss-of-function mutation	I _{Na} decrease
BrS6	<i>KCNE3</i>	MiRP2	Gain-of-function mutation	I _{to} increase
BrS7	<i>SCN3B</i>	Na _v β3	Loss-of-function mutation	I _{Na} decrease
BrS8	<i>KCNJ8</i>	K _{ir} 6.1	Gain-of-function mutation	I _{KATP} increase
BrS9	<i>CACNA2D1</i>	Ca _v α2δ	Loss-of-function mutation	I _{CaL} decrease
BrS10	<i>KCND3</i>	K _v 4.3	Gain-of-function mutation	I _{to} increase
BrS11	<i>RANGRF</i>	MOG1	Loss-of-function mutation	I _{Na} decrease
BrS12	<i>SLMAP</i>	Sarcolemmal membrane-associated protein	Loss-of-function mutation	I _{Na} decrease
BrS13	<i>ABCC9</i>	SUR2A	Gain-of-function mutation	I _{KATP} increase
BrS14	<i>SCN2B</i>	Na _v β2	Loss-of-function mutation	I _{Na} decrease
BrS15	<i>PKP2</i>	Plakophilin-2	Loss-of-function mutation	I _{Na} decrease
BrS16	<i>FGF12</i>	FAHF1	Loss-of-function mutation	I _{Na} decrease
BrS17	<i>SCN10A</i>	Na _v 1.8	Loss-of-function mutation	I _{Na} decrease
BsS18	<i>HEY2</i>	Hey2-encoded transcription factor	Gain-of-function mutation	I _{Na} increase
BrS19	<i>SEMA3A</i>	Semaphorin	Gain-of-function mutation	I _{to} increase
Acquired forms				
Drug induced*				
Antiarrhythmics (class IA-IC)	...	Na _v 1.5	Direct channel inhibition	I _{Na} decrease
Psychoactive agents [†]	...			
Anesthetics/analgesics [†]	...			
Antiepileptics	...			
Antihistamines [†]	...			
Potassium channel openers	...	K _{ir} 6.1/K _{ir} 6.2	Direct channel activation	I _{KATP} increase
Calcium channel blockers	...	Ca _v 1.2	Direct channel inhibition	I _{CaL} decrease
Fever induced				
Fever	...	Na _v 1.5	Channel biophysical properties modification	I _{Na} decrease

BrS indicates Brugada syndrome; FAHF1, fibroblast-growth factor homologous factor-1; I_{CaL}, L-type calcium current; I_{KATP}, adenosine triphosphate-sensitive current; I_{Na}, sodium current; I_{to}, transient outward potassium current; SUR2A, sulfonylurea receptor 2A.

*A more comprehensive, detailed, and frequently updated list of drugs is available at <https://www.brugadadrugs.org>.

[†]Some of the drugs included in these categories inhibit both sodium and calcium channels.

communication.⁶⁷ In addition, regulating effects on I_{Na} amplitude are recently documented as additional noncanonical functions of connexin 43.⁶⁸ Such an expression pattern, characteristic of the embryonic heart and physiologically retained in the adult RVOT, would be markedly accentuated in patients with BrS.⁶⁷ Accordingly, a genetically reduced

Na⁺-channel function unmasks slow conduction in RVOT.⁶⁷ Moreover, a recent postmortem study found that connexin 43 expression is reduced in RVOT of patients with BrS and correlated with abnormal APs.⁶⁹

The BrS-ECG phenotype is often concealed and unmasked by several acquired factors, both endogenous (eg, fever,

vagotonic maneuvers, and electrolyte disturbances) and environmental (eg, drugs and toxic agents⁶⁶ [http://www.brugadadrugs.org]). The role of class IC and IA antiarrhythmics and fever seems particularly important.^{5,66} Current recommendations require that the type 1 pattern, whether spontaneous or induced by Na⁺-channel blockers or fever, is present for the diagnosis of BrS. However, a provoked type 1 pattern alone is not sufficient without specific clinical or familial features.⁶⁶

Other acquired factors, partly overlapping those unmasking true genetic BrS (eg, electrolyte imbalances), can lead to a similar/identical ECG pattern in predisposed subjects, in the absence of any apparent genetic dysfunction.⁶⁶ Metabolic conditions, mechanical compression, myocardial ischemia and pulmonary embolism, and myocardial and pericardial diseases are included. These conditions, termed Brugada phenocopies, are thought to result from any acquired factor directly or indirectly increasing outward K⁺ currents and/or decreasing inward I_{Na} or I_{CaL}. However, the appropriateness of this terminology is highly debated, not only because the prerequisite of a genetic component is difficult to rule out,⁶⁶ but also because fever- or drug-induced type I pattern prevalence in the general population is relatively high, thus not being particularly specific.^{70–72} This could be related to genetic polymorphisms rather than disease-causing mutations,⁷⁰ as recognized for drug-induced LQTS.^{6,18} Thus, current experts' opinion is that, in the absence of further genetic or familial features, designating all these conditions as acquired forms of BrS may be more appropriate and better aligned with the terminology used for the LQTS.⁶⁶ Accordingly, drugs and fever are herein specifically recognized as inducers of BrS-associated acquired cardiac channelopathies (ie, potential causes of acquired BrS) (Table 3). Medications inducing BrS include class IA to IC antiarrhythmics and other Na⁺-channel blockers, such as psychoactive agents, anesthetics/analgesics, antiepileptics and antihistamines, as well as Ca⁺⁺-channel blockers and K⁺-channel openers.⁶

Fever is a well-recognized acquired factor unmasking BrS in predisposed subjects.⁶⁶ Although data on large populations are currently lacking, recent studies suggest that fever-induced BrS might have a higher than expected prevalence in the general population,^{70,72} also possibly associating with a significant risk of arrhythmic events.⁷³ Similarly to drug-induced BrS/LQTS, fever-induced BrS is probably an acquired channelopathy whose ECG/clinical consequences emerge only in the presence of a latent ion channel dysfunction.⁷⁰ Biophysical properties of the Na_v1.5 channel are significantly altered by high temperature, resulting in I_{Na} decrease.^{74,75} Thus, in febrile conditions, any subject with a preexisting Na⁺-channel impairment could develop an acquired BrS.⁶⁵ Independent of occult *SCN5A* disease-causing mutations, demonstrated in ≈15% to 25% of tested cases,⁷³ common *SCN5A*

polymorphisms may play an important predisposing role.⁷⁰ Besides genetics, also acquired factors, particularly drugs, may cause a latent ion channel dysfunction.^{70,76} The biophysical mechanisms in fever-induced BrS are supported by the evidence that warm water instillation into the epicardial space can mimic fever effect.⁷⁷ In addition, cytokines might intriguingly contribute to fever-induced BrS, possibly by decreasing cardiac connexin 43 expression.^{67,69} Indeed, increasing evidence points to systemic and/or cardiac inflammation as a novel factor potentially involved in BrS pathogenesis.^{78–80} Because the key mediators of the fever (ie, inflammatory cytokines) are also able to rapidly decrease ventricular expression of connexin 43^{81–83} and thereby the conduction reserve, it is possible to speculate that during febrile states not only high temperature but also the inflammatory process may per se promote acquired BrS via cytokine-mediated effects on gap-junction channels.

Catecholaminergic Polymorphic Ventricular Tachycardia.

CPVT is a rare inherited channelopathy characterized by adrenergic-induced bidirectional or polymorphic VT or VF. Although the estimated prevalence is ≈0.1/10 000, the real frequency in the general population is unknown because the resting ECG is often unremarkable.^{5,84} Most patients experience arrhythmias before the age of 40 years, in one third of cases in individuals aged <10 years, and mortality is high in untreated subjects.⁷⁸ Typical presentations include either stress-induced syncope or cardiac arrest/SCD, as a result of polymorphic VA induced by adrenergic stimuli (exercise or emotions). The hallmark of CPVT is the so-called bidirectional VT, a peculiar polymorphic VT characterized by a 180° beat-to-beat rotation of the ectopic QRS complexes, highly specific but not always present.⁸⁴ Other common ECG findings comprise stress-induced supraventricular arrhythmias, including AF, as well as sinus bradycardia and prominent U waves in resting conditions.^{5,84}

Five different genes have been associated with CPVT encoding the ryanodine receptor-2 (RyR2), a Ca⁺⁺-release channel located in the sarcoplasmic reticulum (SR) membrane, or RyR2-regulatory protein, particularly calsequestrin-2 (CASQ2), calmodulin, triadin, and trans-2,2-enoyl-CoA reductase-like protein (Table 4).²³ CPVT1 (*RyR2*, 60%–65%) and CPVT2 (*CASQ2*, 3%–5%) alone explain about two thirds of genotype-positive patients.^{23,84} In all cases, mutations eventually result in an RyR2 malfunction leading to spontaneous Ca⁺⁺ leakage from SR in diastole, particularly during intense adrenergic activation (which physiologically increases Ca⁺⁺ release from the SR).²³ The subsequent Ca⁺⁺ overload is thought to cause delayed afterdepolarizations by activating the Na⁺/Ca⁺⁺ exchanger, which generates a Ca⁺⁺-dependent transient-inward depolarizing current, in turn triggering both ventricular and atrial tachyarrhythmias.^{4,21,23,84} An alternating

Table 4. Cardiac Channelopathies Associated With CPVT and ERS

Cardiac Channelopathies	Gene	Ion Channel/Regulatory Protein	Mechanism	Effect on Ion Current
CPVT				
Genetic				
CPVT1	<i>RYR2</i>	Ryanodine receptor-2	Gain-of-function mutation	Diastolic Ca ⁺⁺ release
CPVT2	<i>CASQ2</i>	Calsequestrin-2	Loss-of-function mutation	Diastolic Ca ⁺⁺ release
CPVT3	<i>TECLL</i>	Trans-2,3-enoyl-CoA-reductase-like	Loss-of-function mutation	Diastolic Ca ⁺⁺ release
CPVT4	<i>CALM1</i>	Calmodulin-1	Loss-of-function mutation	Diastolic Ca ⁺⁺ release
CPVT5	<i>TRDN</i>	Triadin	Loss-of-function mutation	Diastolic Ca ⁺⁺ release
ERS				
Genetic				
ERS1	<i>KCNJ8</i>	K _v 6.1	Gain-of-function mutation	I _{KATP} increase
ERS2	<i>CACNA1C</i>	Ca _v 1.2	Loss-of-function mutation	I _{CaL} decrease
ERS3	<i>CACNB2</i>	Ca _v β2b	Loss-of-function mutation	I _{CaL} decrease
ERS4	<i>CACNA2D1</i>	Ca _v α2δ	Loss-of-function mutation	I _{CaL} decrease
ERS5	<i>ABCC9</i>	SUR2A	Gain-of-function mutation	I _{KATP} increase
ERS6	<i>SCN5A</i>	Na _v 1.5	Loss-of-function mutation	I _{Na} decrease
ERS7	<i>SCN10A</i>	Na _v 1.8	Loss-of-function mutation	I _{Na} decrease

CPVT indicates catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; I_{CaL}, L-type calcium current; I_{KATP}, adenosine triphosphate-sensitive current; I_{Na}, sodium current; SUR2A, sulfonylurea receptor 2A.

activation of the Purkinje fibers in the 2 ventricles seems to be the electrophysiological mechanism responsible for bidirectional VT.^{21,84}

Besides genetic mutations responsible for CPVT, several acquired factors can induce bidirectional VT, including drugs, toxins, and inflammatory heart diseases.^{4,85} In particular, bidirectional VT is the prototypical arrhythmia during digitalis intoxication, although the underlying mechanism is indirect via inhibition of the Na⁺/K⁺-ATPase pump.⁴ Some CASQ2-affinity drugs, such as psychoactive agents (phenothiazines and tricyclic antidepressants) and cocaine, were shown to accumulate in the SR, leading to direct RyR2 dysfunction and Ca⁺⁺ leakage,^{86,87} similar to what was observed in all CPVT-related CASQ2 mutations. In addition, inflammatory cytokines can directly increase diastolic Ca⁺⁺ release and arrhythmia susceptibility, also regardless of structural alterations (eg, myocarditis). TNF-α and interleukin-1 were demonstrated to significantly enhance diastolic Ca⁺⁺ release by reducing expression and function of important SR Ca⁺⁺-handling proteins,^{88–90} including RyR2.⁹¹ Whether such drug- and inflammatory-induced channelopathies may represent novel potential forms of acquired CPVT is speculative at present.

Early Repolarization Syndrome. Early repolarization pattern (ERP) is a frequent ECG phenotype occurring in up to ≈10% of the general population, particularly men and athletes.^{63,66} Several studies suggest that ERP is familial,

thereby pointing to underlying genetic contributions.⁵ A recent expert consensus conference recommended that ERP is recognized in the presence of the following: (1) a J-wave, (2) a J-point elevation, and (3) a normal QRS duration.⁶⁶ ERP was considered benign until the 2000s, when both experimental and population-based clinical studies demonstrated that this pattern, particularly in the inferior and lateral leads, was associated with an increased incidence of VT/VF and SCD.^{5,63,66} Accordingly, ERS is now exclusively diagnosed in patients showing an ERP in the inferior and/or lateral leads, presenting with aborted cardiac arrest, documented VF, or polymorphic VT.^{5,66} The evidence that patients with ERP are more susceptible to VF during myocardial ischemia suggests that this pattern may represent a substrate increasing SCD risk in the presence of triggers.^{5,63}

The most accredited theory suggests that ECG features of ERS are secondary to repolarizing gradients across the ventricular wall.⁶³ Physiologically, epicardium has a higher I_{to}, particularly in the left ventricle inferior wall, responsible for a transmural voltage gradient. Conditions increasing outward K⁺ currents and/or decreasing inward I_{Na} or I_{CaL} may accentuate such a gradient, resulting in a prominent I_{to}-mediated phase 1 notch of the epicardial AP (responsible for J-wave and J-point elevation) and an increased vulnerability to VAs because of phase 2 reentry.²¹ In this context, further accentuation of I_{to} (eg, during myocardial ischemia) may precipitate VF.^{5,63,66}

ERS is considered an inherited channelopathy associated with genetic variants in 7 genes, leading to gain of function of the ATP-dependent K⁺ channel or loss of function of cardiac L-type Ca⁺⁺ or Na⁺ channels⁶⁶ (Table 4). Nevertheless, the lack of functional/biological validation of many of these mutations and the high prevalence of ERP in the general population support the current view that ERS has likely a polygenic basis, also being influenced by nongenetic factors.⁵ Several acquired factors are known to cause/modulate ERP, including acute myocardial injury or infarction, cardiac inflammatory diseases (possibly via cytokine-mediated effects),⁹² Takotsubo cardiomyopathy, left ventricular hypertrophy, high vagal tone, hypercalcemia, hyperpotassemia, and cocaine.⁶⁶ Although to date unproved, the possibility that some of these factors may act by inducing an acquired channelopathy is conceivable. Intriguingly, a potential role of inflammatory cytokines is suggested by a recent study that reported that among major league soccer players, subjects with ERP showed 3-fold higher circulating interleukin-6 levels than those without ERP.⁹²

Idiopathic Ventricular Fibrillation. IVF is a rare cause of sudden cardiac arrest identifying a VF of unknown origin despite extensive diagnostic testing.⁵ Thus, the diagnosis of IVF implies the exclusion of specific diseases, including structural heart diseases and primary arrhythmia syndromes, such as LQTS, SQTS, BrS, CPVT, and ERS.⁹³

Most of the currently recognized primary arrhythmia syndromes were initially labelled as IVF (eg, ERS), until recently regarded as a subentity of IVF. In all cases, the identification of a distinctive ECG phenotype and a separate genetic substrate led to reclassification of several patients, previously diagnosed as having IVF. As a result, IVF incidence is progressively declining.⁹³

Although pathogenic mechanisms remain largely unknown, recent data support a genetic substrate for IVF. Several causative mutations in 4 different genes (*DPP6*, *CALM1*, *RyR2*, and *IRX3*) responsible for changes in cardiac ion channels have been detected in patients with IVF, although it is not currently clear whether the disease is monogenic or polygenic.⁹³ Notably, most of these mutations have been demonstrated in a subgroup of patients characterized by short-coupled ventricular premature beats triggering TdP/immediate VF. By creating a repolarization gradient with the adjacent ventricular myocardium promoting phase 2 reentry, a selective I_{to} increase in Purkinje fibers may constitute the cellular mechanism for short-coupled ventricular premature beats triggering TdP/immediate VF. However, because no ECG phenotype can be detected, to date, short-coupled ventricular premature beats triggering TdP/immediate VF remain a subgroup of IVF.⁹³

An alternative hypothesis is that IVF is multifactorial, resulting from a combination of monogenic/polygenic

mutations and acquired abnormalities, either structural (minimal, subclinical alterations, currently undetectable with available diagnostic tools) or functional (eg, electrolyte disturbances or autonomic changes). Among the latter, it can be speculated that factors known to induce acquired cardiac channelopathies, but frequently unapparent, such as subclinical autoimmunity and inflammation,^{7,8} could also play a role in some patients.

Atrial Fibrillation

AF is the most common sustained arrhythmia in the general population.⁹⁴ Cardiac diseases, particularly coronary artery disease, valvular disease, and heart failure, represent definite risk factors for AF.⁹⁴ Cardiac channelopathies, both inherited⁹⁵ and acquired (inflammation-induced),⁹⁶ may generate an electric substrate for this arrhythmia, in the absence of structural heart defects.

The heritability of AF is supported by many studies in the general population and twins, and a family history of AF is associated with a 2-fold risk.⁹⁵ Moreover, patients with some specific genetic channelopathies, particularly LQTS, SQTS, BrS, and CPVT, are at increased risk of AF.⁵ Accordingly, several gain-of-function or loss-of-function mutations in many genes encoding for cardiac ion channels have been described in patients with early-onset lone AF or families with autosomal dominant AF⁹⁵ (Table 5). These variants, mainly involving K⁺- or Na⁺-channel subunits or gap-junction proteins (connexin 40 or connexin 43), can either shorten or prolong atrial APD and impaired cell-cell coupling, leading to intra-atrial conduction heterogeneity.⁹⁵ These changes putatively create a substrate for reentry or increase susceptibility to early and/or delayed afterdepolarizations, both able to promote AF.⁹⁵ However, although these variants have strong effects and a clear phenotype, they are rare, thereby accounting only for a small proportion of AF (familial monogenic forms). Thus, several genome-wide association studies have been performed to identify common genetic variants or single-nucleotide polymorphisms.⁹⁵ Altogether, genome-wide association studies led to the identification of >30 AF-associated loci, mostly involving regulatory sequences presumed to influence gene expression. Some of these variants are close to ion channels or related proteins known to regulate the atrial APD (*KCNN3*, *HCN4*, and *Ca_v1.2*), thereby putatively acting via channelopathy-mediated mechanisms.⁹⁵

In most cases, AF may result from a complex combination of genetic and acquired risk factors.⁹⁴ In particular, a key role for inflammation, either cardiac or systemic, in the pathophysiology of AF is largely supported.⁹⁶ Several studies associate CRP and inflammatory cytokine levels (mainly TNF- α and interleukins 1, 2, and 6) with the presence/outcome of AF.⁹⁶ Although sustained inflammation is associated with atrial structural remodeling, several data indicate that

Table 5. Cardiac Channelopathies Associated With AF

Gene/Acquired Factor	Ion Channel	Mechanism	Effect on Ion Current
Inherited forms			
Genetic			
Potassium channels			
<i>KCNQ1</i>	K _v 7.1	Gain-of-function mutation	I _{Ks} increase
<i>KCNE1</i>	Mink	Gain-of-function mutation	I _{Ks} increase
<i>KCNE2</i>	MiRP1	Gain-of-function mutation	I _{Ks} increase
<i>KCNE5</i>	K _v 7.1 (β subunit)	Gain-of-function mutation	I _{Ks} increase
<i>KCNJ2</i>	K _{ir} 2.1 (β subunit)	Gain-of-function mutation	I _{K1} increase
<i>KCNA5</i>	K _v 1.5	Gain-of-function mutation	I _{Kur} modulation
<i>KCNH2</i>	hERG	Gain-of-function mutation	I _{Kr} modulation
<i>KCND3</i>	K _v 4.3	Gain-of-function mutation	I _{to} increase
<i>KCNJ8</i>	K _{ir} 6.1	Gain-of-function mutation	I _{KATP} increase
<i>KCNN3</i>	KCa2.3	Gain-of-function mutation	SKCa modulation
<i>HCN4</i>	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	Gain-of-function mutation	I _f modulation
<i>ABCC9</i>	SUR2A	Gain-of-function mutation	I _{KATP} decrease
Sodium channels			
<i>SCN5A</i>	Na _v 1.5	Loss-of-function mutation	I _{Na} modulation
<i>SCN1B</i>	Na _v β1	Loss-of-function mutation	I _{Na} decrease
<i>SCN2B</i>	Na _v β2	Loss-of-function mutation	I _{Na} decrease
<i>SCN3B</i>	Na _v β3	Loss-of-function mutation	I _{Na} decrease
<i>SCN4B</i>	Na _v β4	Loss-of-function mutation	NC
<i>SCN10A</i>	Na _v 1.8	Loss-of-function mutation	I _{Na} modulation
Calcium channels			
<i>RYR2</i>	Ryanodine receptor 2	Gain-of-function mutation	Diastolic Ca ⁺⁺ release
Gap-junction channels			
<i>GJA1</i>	Connexin 43	Loss-of-function mutation	Intercellular electrical coupling reduction
<i>GJA5</i>	Connexin 40	Loss-of-function mutation	Intercellular electrical coupling impairment
Acquired forms			
Inflammatory			
TNF-α	Connexin 40	Channel expression decrease	Intercellular electrical coupling reduction
	Connexin 43	Channel redistribution	Intercellular electrical coupling impairment
	Ryanodine receptor 2	Channel function increase	Diastolic Ca ⁺⁺ release
Interleukin-1	Ca _v 1.2	Channel expression decrease	I _{CaL} decrease

AF indicates atrial fibrillation; I_{CaL}, L-type calcium current; I_{K1}, inward rectifier K⁺-current; I_{KATP}, adenosine triphosphate-sensitive current; I_{Ks}, slow component of the delayed rectifier potassium current; I_{Kur}, ultrarapid component of the delayed rectifier potassium current; I_{Na}, sodium current; I_{to}, transient outward potassium current; I_f, funny current; MiRP, MinK related protein 1; NC, not characterized; SKCa, small-conductance calcium-activated potassium channels; SUR2A, sulfonylurea receptor 2A; TNF-α, tumor necrosis factor-α.

inflammatory cytokines can also directly induce significant changes in the electrical properties of the atrium, already in the short-term, thereby independent of any structural alteration.^{8,96} In fact, mounting evidence points to TNF-α and interleukin-1 as mediators of acquired atrial channelopathies, leading to an increased susceptibility to AF

(Table 5). Specifically, these cytokines are able to enhance propensity to delayed afterdepolarizations promoting ectopic activity^{97,98} and to slow atrial conduction, creating a vulnerable substrate for reentry.^{99–101} TNF-α and interleukin-1 significantly increase spontaneous diastolic SR Ca⁺⁺ leak in cardiomyocytes by impairing RyR2 or related SR Ca⁺⁺-

handling proteins.^{88–91} In atrial myocytes, TNF- α seems to act^{97,98} via a reactive oxygen species pathway, increasing Ca⁺⁺/calmodulin-dependent protein-kinase II-dependent RyR2 phosphorylation.⁹⁸ TNF- α can also induce gap-junction channel dysfunction via impaired atrial connexin 40 and connexin 43 expression and/or distribution,^{99–101} thus favoring a slow and heterogeneous conduction in the atria. Similar effects on Ca⁺⁺ handling^{89–91} and connexins^{81–83} can also be induced in ventricles by interleukin-1. In addition, by inducing an L-type Ca⁺⁺ channelopathy, interleukin-1 can shorten the atrial effective refractory period, thereby creating a further substrate for reentry.¹⁰¹ Other cytokine-induced channelopathies in atrial cardiomyocytes involve (T)-type Ca⁺⁺ channel (TNF- α -mediated Ca_v3.1/Ca_v3.2 downregulation with transient inward Ca⁺⁺-current (I_{CaT}) decrease)¹⁰² and Na⁺ channel (interleukin-2-mediated cardiac Na⁺-channel β 3-subunit upregulation with I_{Na} increase),¹⁰³ although mechanistic links with AF are merely speculative.

Bradyarrhythmias

Bradyarrhythmias, including sinoatrial (SA) node dysfunction and AV-conduction defects, frequently occur in the clinical practice.¹⁰⁴ Characteristic ECG findings include persistent sinus bradycardia, SA block, sick-sinus syndrome, prolonged P-wave duration, AV block, and QRS widening with axis deviation.⁵ Bradyarrhythmias may be either physiological (ie, in athletes) or pathological.¹⁰⁴ Although structural cardiac diseases eventually leading to sclerosis of the conduction system account for most of the latter forms, bradyarrhythmias may also occur in a structurally normal heart as a result of inherited or acquired cardiac channelopathies.^{5,7,105} Several ion channels critically involved in pace-making cells' automaticity and/or AP propagation throughout the conduction system may be affected (ie T- and L-type Ca⁺⁺ channels, Na⁺ channel, hyperpolarization-activated cyclic nucleotide-gated channels [HCN4], transient receptor-potential cation-channel subfamily melastatine member-4 [TRPM4] channel, and gap-junction channels^{5,105,106}) (Table 6).

Among genetic forms, loss-of-function variants of the Na_v1.5-channel cause most of familial cases of isolated progressive cardiac conduction disease.⁵ Also gain-of-function or loss-of function mutations in the *TRPM4* gene may be commonly involved (10%–25%).^{5,105} Conversely, loss-of-function mutations in genes encoding for L-type Ca⁺⁺ channel (Ca_v1.3), Na⁺-channel β -subunit, or gap-junction-forming connexins are described as single case reports^{5,105,107} (Table 6). For hereditary SA node dysfunction, several mutations in both *HCN4* and *SCN5A* genes have been identified, although relative proportions are still unknown^{5,105} (Table 6).

Medications¹⁰⁴ and autoimmune reactions⁷ represent the best-recognized acquired factors responsible for

channelopathy-induced bradyarrhythmias. Drugs include molecules directly inhibiting Na⁺ and/or Ca⁺⁺ channels, or the HCN4 channel^{106,108} (Table 6). However, with few exceptions (lithium and phenytoin), most involved drugs are antiarrhythmics purposely used to reduce heart automaticity/dromotropism (Ca⁺⁺-channel blockers and ivabradine) or widely known to exert negative effects on such parameters (class I antiarrhythmics and amiodarone). Thus, in these cases, bradyarrhythmias are well-expected adverse events.

Autoimmune forms are related to autoantibodies specifically targeting either Ca⁺⁺ or Na⁺ channels in the heart conduction tissue^{7,14,109} (Table 6). Currently, the largest evidence is for anti-Ro/SSA antibodies, which can induce conduction disturbances and SA node dysfunction by directly inhibiting both L- and T-type channels.¹⁰⁹ Anti-Ro/SSA antibodies play a key role in the pathogenesis of autoimmune-associated congenital heart block, a conduction disturbance affecting fetal AV and SA nodes, in a structurally normal heart, because of the transplacental passage of anti-Ro/SSA antibodies.¹¹⁰ It develops in \approx 2% to 5% of offspring from anti-Ro/SSA-positive mothers and consists of different degrees of AV block and sinus bradycardia, the third-degree AV block being associated with high mortality.¹¹⁰ Anti-Ro/SSA antibodies, particularly anti-Ro/SSA 52-kD, can induce conduction defects in the fetal heart as a result of a direct cross-reaction with L- and T-type Ca⁺⁺-channel α -subunits (Ca_v1.2 and Ca_v1.3, and Ca_v3.1 and Ca_v3.2, respectively), via inhibitory effects on I_{CaL} and I_{CaT}.^{7,111} Moreover, the specific autoantibody-binding site in both channel types has been identified and is localized on the extracellular loop of domain I pore-forming segments S5 to S6.^{7,112} After a short-term phase with purely functional and reversible effects, long-term antibody exposure can induce Ca⁺⁺-channel internalization, apoptosis, and cell death, eventually resulting in inflammation, fibrosis, and calcification of the conduction system (irreversible third-degree AV block).^{7,109} Also, the adult conduction system may be a target for anti-Ro/SSA antibodies, although more rarely and less severely.^{7,113} Age-related differences in cardiomyocyte Ca⁺⁺-channel expression and Ca⁺⁺ handling might account for a purely electrophysiological effect with reversible AV blocks.^{7,109} However, preliminary retrospective data suggest that \approx 20% of all cases of isolated third-degree AV block of unknown origin in adults may be anti-Ro/SSA associated.¹¹³

In addition, recent evidence demonstrated that in a fraction of patients with idiopathic AV blocks, a Na_v1.5-channel autoimmune channelopathy represents the likely mechanism of bradyarrhythmias⁷ (Table 6). Korkmaz et al¹⁴ provided evidence that anti-Na_v1.5 autoantibodies inhibit channel function, leading to a significant decrease of I_{Na} current by recognizing a site on the third extracellular pore region (S5–S6) of Na_v1.5. These findings, obtained by using

Table 6. Cardiac Channelopathies Associated With Bradyarrhythmias

Gene/Acquired Factor	Ion Channel	Mechanism	Effect on Ion Current	Clinical Phenotype
Inherited forms				
Genetic				
<i>SCN5A</i>	Na _v 1.5	Loss-of-function mutation	I _{Na} decrease	SSS, SAN exit block, AVB, PCCD
<i>TRPM4</i>	TRPM4	Loss-of-function mutation/ gain-of-function mutation	Nonselective cation current changes	Sinus bradycardia, PFHB I, PCCD
<i>HCN4</i>	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	Loss-of-function mutation	I _f decrease	Sinus bradycardia
<i>CACNA1D</i>	Ca _v 1.3	Loss-of-function mutation	I _{CaL} decrease	Sinus bradycardia, AVB
<i>SCN1B</i>	Na _v β1	Loss-of-function mutation	I _{Na} decrease	Sinus bradycardia, AVB
<i>GJA5</i>	Connexin 40	Loss-of-function mutation	Intercellular electrical coupling reduction	PFHB I
<i>GJC1</i>	Connexin 45	Loss-of-function mutation	Intercellular electrical coupling impairment	PCCD
Acquired forms				
Drug induced				
Antiarrhythmics (class I)	Na _v 1.5	Direct channel inhibition	I _{Na} decrease	Sinus bradycardia, AVB
Amiodarone	Ca _v 1.2	Direct channel inhibition	I _{CaL} decrease	Sinus bradycardia AVB
	Na _v 1.5	Direct channel inhibition	I _{Na} decrease	
Calcium channel blockers	Ca _v 1.2	Direct channel inhibition	I _{CaL} decrease	Sinus bradycardia, AVB
Ivabradine	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	Direct channel inhibition	I _f decrease	Sinus bradycardia
Lithium	Na _v 1.5	Direct channel inhibition	I _{Na} decrease	Sinus bradycardia, AVB
Phenytoin	Na _v 1.5	Direct channel inhibition	I _{Na} decrease	Sinus bradycardia, AVB
Autoimmune				
Anti-L-type calcium channel antibodies (anti-Ro/SSA)	Ca _v 1.2/Ca _v 1.3	Direct channel inhibition	I _{CaL} decrease	Sinus bradycardia, AVB
Anti-T-type calcium channel antibodies (anti-Ro/SSA)	Ca _v 3.1/Ca _v 3.2	Direct channel inhibition	I _{CaT} decrease	Sinus bradycardia, AVB
Anti-sodium channel antibodies	Na _v 1.5	Direct channel inhibition/ channel expression reduction	I _{Na} decrease	Sinus bradycardia, AVB

Anti-Ro/SSA indicates anti-Ro/Sjogren's syndrome-related antigen A; AVB, AV block; I_{CaL}, L-type calcium current; I_{CaT}, T-type calcium current; I_f, funny current; PCCD, progressive cardiac conduction disease; PFHB I, progressive familial heart block I; SAN, sinoatrial node; SSS, sick sinus syndrome; TRPM4, transient receptor-potential cation-channel subfamily-melastatine member-4.

patients' sera, were confirmed and expanded in rats immunized with the corresponding Na_v1.5 pore-peptide sequence. In this model, appearance of high titers of anti-Na_v1.5 autoantibodies was associated with conduction disturbances, in the absence of any functional heart alteration or signs of myocardial inflammation or fibrosis at the histologic examination.¹⁴ Electrophysiological and biochemical characterization of sera from Na_v1.5-immunized rats confirmed that anti-Na_v1.5 autoantibodies can significantly reduce I_{Na} density, at least in part by downregulating Na_v1.5 protein expression.¹⁴

The "Multihit Theory": Concept and Clinical Impact

A single channelopathy per se is not able in most cases to induce symptoms, and rarely even the related clinical phenotype. This is well demonstrated for inherited forms, particularly LQTS, BrS, and CPVT, where provocative tests can unmask latent genetic defects.⁵ Consistent data are also available for drug-induced, autoimmune, and inflammatory/fever-induced channelopathies. Indeed, only a small

proportion of the large number of exposed subjects develops drug-induced LQTS/BrS and related arrhythmias, despite the resulting channel dysfunction.⁶ Similarly, high temperature,^{60,62} cytokines,^{8,17} and anti-ion channel autoantibodies⁷ induce cardiac channelopathies; however fever-, inflammatory-, and autoimmune-induced phenotypes and arrhythmias occur only in a fraction of the subjects at risk. Such evidence strongly suggests that multiple often-redundant ion channel mechanisms are implicated in preserving normal AP genesis and conduction, thus rendering the clinical phenotype unapparent despite subtle channel dysfunction. This view is well represented by the “repolarization reserve” theory, first proposed by Roden to explain drug-induced LQTS/TdP risk,¹¹⁴ and now widely recognized. Therefore, >1 single component needs to be impaired for ECG/clinical symptoms to emerge, and the number of required “hits” will depend on the functional impact of each single offending factor.¹¹⁴ In a single patient, multiple QT-prolonging factors are concomitantly required to significantly disrupt repolarization. Besides specific inherited or acquired channelopathies, other physiological (eg, age, sex, common polymorphisms, autonomic changes, and exercise) or pathological conditions, either functional (electrolyte imbalances) or structural (heart disease), may be superimposed in an intricate and often unpredictable scenario. Accordingly, patients developing marked QTc prolongation and TdP concomitantly present multiple risk factors.¹⁸ On 40 consecutive unselected patients with TdP, on average >4 factors per subject were detectable (electrolyte imbalances, cardiac and extracardiac diseases, drugs, anti-Ro/SSA antibodies, and inflammation), with a high prevalence of acquired channelopathies.²⁵ Additionally, subclinical inherited channelopathies and common polymorphisms are frequently found in patients developing TdP.¹⁸

Beyond LQTS, such a multihit theory could be more generally applied to all arrhythmogenic phenotypes. BrS is often latent, emerging only in the presence of other concomitant factors, including acquired channelopathies (ie, drugs or fever), autonomic changes, electrolyte disturbances, or structural heart disease, cooperating to unmask genetic predisposition and increase risk for fatal arrhythmia.⁶⁶ By demonstrating that multiple risk factors are frequently concomitant in patients with BrS, the group of Viskin suggested to extend the concept of repolarization and/or conduction reserves to this condition.^{70,76} Similar considerations could also be applied to ERS, where acquired factors can trigger phenotype development and arrhythmias,^{63,66} as well as AF,¹¹⁵ and possibly bradyarrhythmias. Notably, Otway et al¹¹⁶ demonstrated that in a family with a missense *KCNQ1* variant leading to I_{Ks} gain of function, AF was only present in those individuals who were both genotype positive and who had long-standing hypertension and atrial dilation, thus stressing the concept that interactions with a

concomitant structural heart disease are crucial to promote AF development in patients with inherited (and acquired) channelopathies. Moreover, genetic differences in the conduction reserve depend on cardiomyocyte L-type Ca^{++} -channel expression and significantly affect the risk of anti-Ro/SSA-associated bradyarrhythmias.¹¹⁷ This is likely why only a fraction of autoantibody-positive subjects show conduction disturbances.^{7,109} Altogether, an integrated view of all components, inherited and acquired, as well as functional and structural factors is crucial to estimate the actual arrhythmic risk in the single patient with suspected or proven channelopathy. Indeed, avoidance of potentially harmful drugs and lifestyle habits (ie, excessive alcohol intake, cocaine use, competitive/strenuous exercise, and stressful environments), together with management of electrolyte imbalances and fever (antipyretics), are already considered as class I recommendations, particularly in LQTS, BrS, and CPVT.^{1,5}

However, because of the conventional wisdom that cardiac channelopathies are synonymous of inherited cardiac channelopathies, genetic testing is presently the core diagnostic approach to subjects with arrhythmogenic ECG phenotypes and/or life-threatening arrhythmias/cardiac arrest in a structurally normal heart. Beyond genetic forms, acquired channelopathies should be equally considered and carefully addressed, particularly in subjects without family history. Although recognition requires different levels of complexity, depending on the factors involved, awareness is the key element. Drug involvement may be relatively easily identifiable, provided that the updated lists of medications implicated in the different phenotypes are regularly consulted. Similar considerations apply to fever- and inflammatory-induced channelopathies. Indeed, a febrile/inflammatory process is often clinically evident, whereas subclinical inflammation may be revealed by routine markers, particularly CRP, as a reflection of circulating cytokines.⁸

The diagnosis of an autoimmune channelopathy may be more difficult, because pathogenic anti-ion channel autoantibodies can also be present in apparently healthy subjects, regardless of any manifestation of AD.⁷ Thus, a concealed autoimmune channelopathy may be implicated in cases of unexplained arrhythmias/SCD, and only specific autoantibody testing can reveal an underlying autoimmune origin.⁷ In particular, patients who should be tested include those presenting with rhythm disturbances/aborted cardiac arrest in the absence of any recognized causative factor, despite intensive investigation (including genetic testing), but also possibly several subjects with structural heart disease or inherited channelopathies not responding to conventional treatments. These subjects, particularly the last category, should be also tested for increased inflammation markers

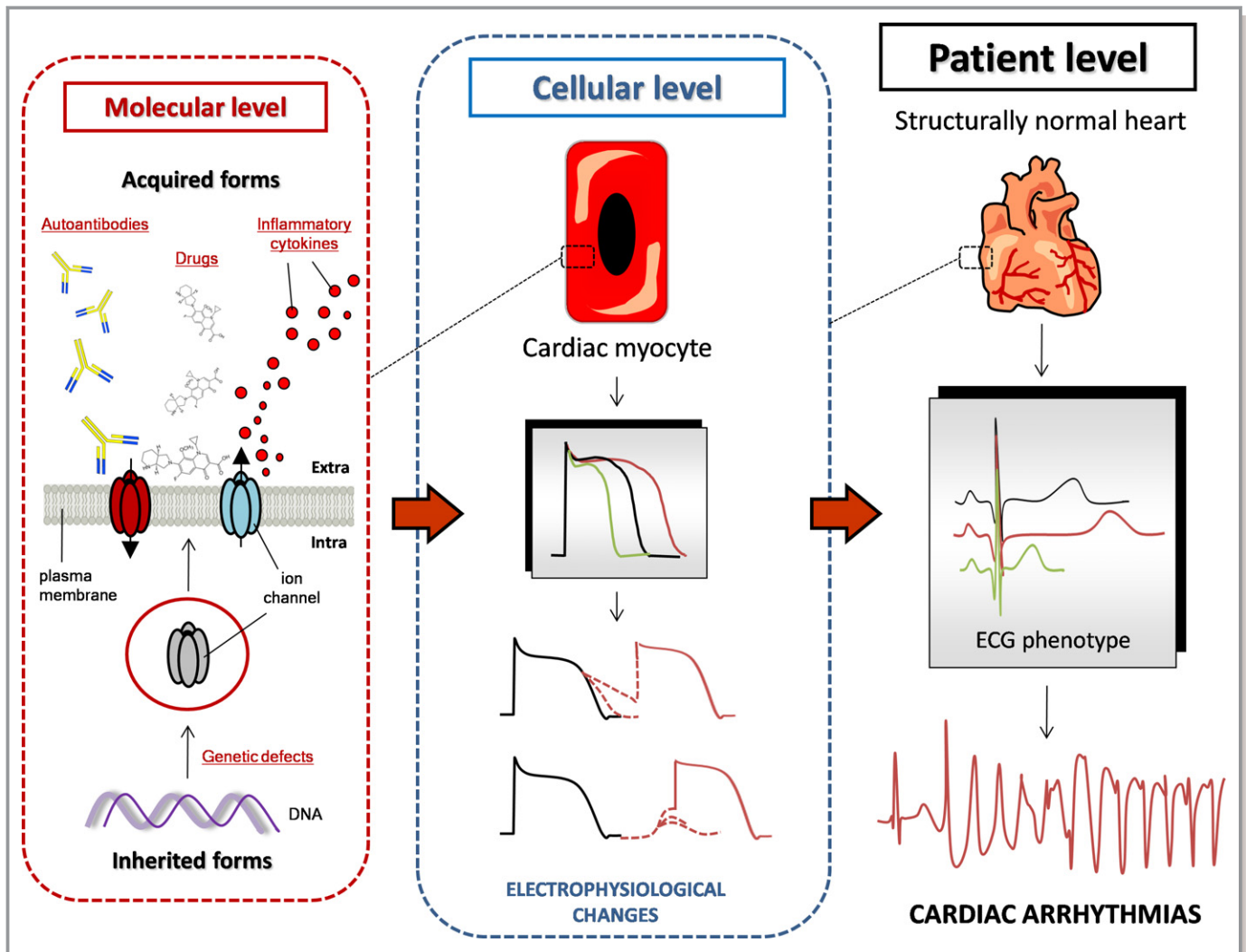


Figure 2. Cardiac channelopathies and arrhythmias: from the channel to the patient. In a structurally normal heart, both inherited (genetic defects) and acquired (drugs, autoantibodies, and inflammation/fever) factors can induce cardiac ion channel dysfunction, responsible for electrophysiological changes leading to specific electrocardiographic phenotypes and cardiac arrhythmias.

because an inflammatory process, also transient and/or subclinical, may play an important contributing role in triggering or enhancing electric instability in patients already predisposed to arrhythmias. Indeed, acute inflammatory illnesses are increasingly recognized as possible precipitant factors of malignant arrhythmias/electrical storms in subjects with congenital LQTS,^{61,118–120} and signs of subclinical immune-inflammatory activation have been demonstrated in patients with cardiomyopathies^{121–123} or inherited LQTS/CPVT who underwent left cardiac sympathetic denervation for intractable arrhythmias.¹²⁴ Unfortunately, although CRP and anti-Ro/SSA antibody testing is largely available in the clinical practice (Western blot technique is recommended for detecting arrhythmogenic anti-Ro/SSA subtypes),^{7,28,37} other specific anti-ion channel autoantibodies are currently tested in only few reference centers worldwide.^{14,30,41,65}

Perspectives and Conclusions

Among acquired channelopathies, autoimmune and inflammatory channelopathies have long been neglected but now represent an increasingly recognized mechanism for cardiac arrhythmias. These mechanisms may have a causal role in arrhythmias and SCD in apparently healthy individuals,^{7,8,14,45,113,125,126} as well as being actively involved in enhancing electrical instability in genetically predisposed patients.^{17,78–80,124} The identification of such mechanisms as a causal factor for arrhythmias might open novel targeted therapeutic avenues for the immune-inflammatory system, including anti-inflammatory and immunomodulating drugs, plasmapheresis, and immunoadsorption, which may effectively reduce arrhythmic risk.^{7,8} This view is supported by some studies in patients with autoimmune-associated congenital heart block¹²⁷ or inflammation-driven AF forms^{128,129} and in

case reports showing the reversal effects of immunosuppressive therapy in anti-Ro/SSA-associated LQTS and AV block in adults.^{125,126,130} In addition, the evidence that autoantibodies induce channelopathies by directly cross-reacting with specific amino acid sequences on ion channel proteins suggests an innovative therapeutic approach based on the use of short decoy peptides (peptide-based therapy) distracting the pathogenic antibodies from channel binding sites.⁷ Experimental studies using sera from anti-Ro/SSA-positive subjects with TdP²⁸ or affinity-purified anti-L-type Ca⁺⁺-channel autoantibodies from patients with dilated cardiomyopathy^{41,43} may help demonstrate that competing peptides can effectively counteract autoantibody-channel interaction, and may prevent abnormal electrophysiological effects and VA.

Besides inducing arrhythmogenic channelopathies, anti-ion channel antibodies obtained via peptide vaccination might in the future be used as antiarrhythmic therapy in some patients with inherited channelopathies. For example, K_v7.1-channel vaccination has been proposed as a therapeutic option in patients with congenital LQTS resistant to conventional treatments.^{15,65} Although speculative, the evidence that hERG-channel peptide immunization can generate antibodies inhibiting I_{Kr} and slowing of ventricular repolarization in guinea pigs¹⁶ suggests a potential therapeutic role using hERG-channel peptide vaccination in selected patients with congenital SQTs.

In conclusion, although molecular targets and mechanisms responsible for arrhythmogenic cardiac channelopathies may be different, the final common outcome is the development of an ion channel dysfunction leading to an increased vulnerability to cardiac arrhythmias (Figure 2). Because the concomitant presence of multiple, synergistically cooperating determinants is frequent in the clinical setting, an integrated approach of all potential components in inherited and acquired cardiac channelopathies, including autoimmune and inflammatory/fever-induced forms, may be crucial in clinical practice to comprehensively assess and manage the actual arrhythmic risk in the individual patient.

In fact, although the clinical impact of autoimmune and inflammatory/fever-induced channelopathies on the arrhythmic risk in the general population is not clearly defined, because large prevalence studies are currently lacking, present evidence already suggests that the cardiologist should consider an “internist” holistic view of the patient, and what is currently considered the narrow domain of the cardiac electrophysiologist now should become the interest of the well-informed general practitioner.

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None.

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