CONTEMPORARY REVIEW

Emerging Arrhythmic Risk of Autoimmune and Inflammatory Cardiac Channelopathies

Pietro Enea Lazzerini, MD; Pier Leopoldo Capecchi, MD;* Nabil El-Sherif, MD;* Franco Laghi-Pasini, MD;* Mohamed Boutjdir, PhD*

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 postmortem genetic testing of blood/tissue samples (the so-called “molecular autopsy”), a genetic cause is demonstrated in no more than ≈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,

---

From the Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy (P.E.L., P.L.C., F.L.-P.); Veterans Affairs New York Harbor Healthcare System, State University of New York Downstate Medical Center, New York, NY (N.E.-S., M.B.); and New York University School of Medicine, New York, NY (M.B.).

*Dr Capecchi, Dr El-Sherif, Dr Laghi-Pasini, and Dr Boutjdir contributed equally to this work.

Correspondence to: Pietro Enea Lazzerini, MD, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy. E-mail: lazzerini7@unisi.it

J Am Heart Assoc. 2018;7:e010595. DOI: 10.1161/JAHA.118.010595.

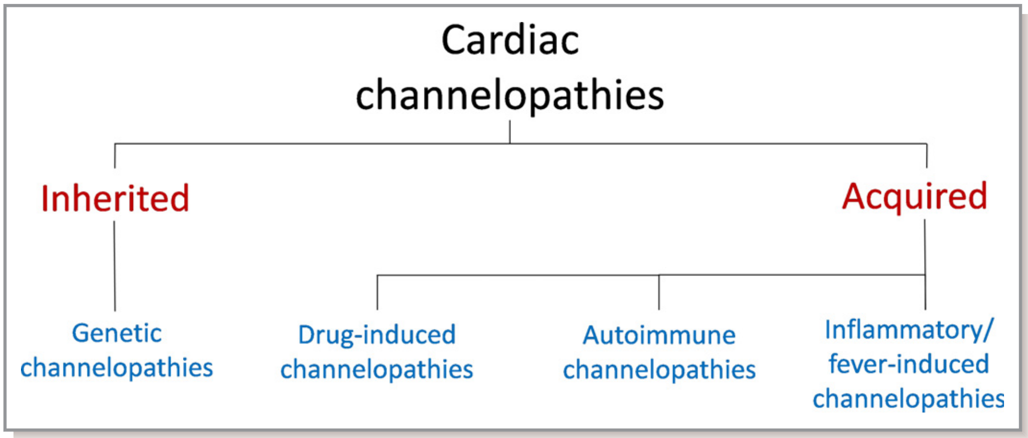

Figure 1. Classification of arrhythmogenic cardiac channelopathies. Besides the "classic" inherited forms of cardiac channelopathies related to genetic mutations, a wider spectrum of acquired forms includes not only drug-induced, but also autoimmune and inflammatory/fever-induced, cardiac channelopathies.

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, repectively.[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]

DOI: 10.1161/JAHA.118.010595

Table 1. Cardiac Channelopathies Associated With LQTS

Cardiac Channelopathies	Gene	Ion Channel/Regulatory Protein	Mechanism	Effect on Ion Current
Inherited forms				
Genetic				
LQT1	*KCNQ1*	K_v7.1	Loss-of-function mutation	I_{Ks} decrease
LQT2	*KCNH2*	hERG	Loss-of-function mutation	I_{Kr} decrease
LQT3	*SCN5A*	Na_v1.5	Gain-of-function mutation	I_{Na} increase
LQT4	*ANK2*	Ankyrin B	Loss-of-function mutation	I_{CaL} and I_{Na} increase
LQT5	*KCNE1*	Mink	Loss-of-function mutation	I_{Ks} decrease
LQT6	*KCNE2*	MiRP1	Loss-of-function mutation	I_{Kr} decrease
LQT7	*KCNJ2*	K_{ir}2.1	Loss-of-function mutation	I_{K1} decrease
LQT8	*CACNA1C*	Ca_v1.2	Gain-of-function mutation	I_{CaL} increase
LQT9	*CAV3*	Caveolin-3	Gain-of-function mutation	I_{Na} increase
LQT10	*SCN4B*	NavB4	Gain-of-function mutation	I_{Na} increase
LQT11	*AKAP9*	Yotiao	Loss-of-function mutation	I_{Ks} decrease
LQT12	*SNTA1*	α1 Syntrophin	Gain-of-function mutation	I_{Na} increase
LQT13	*KCNJ5*	K_{ir}3.4	Loss-of-function mutation	I_{KACH} decrease
LQT14	*CALM1*	Calmodulin-1	Loss-of-function mutation	I_{CaL} increase*
LQT15	*CALM2*	Calmodulin-2	Loss-of-function mutation	I_{CaL} increase*
LQT16	*CALM3*	Calmodulin-3	Loss-of-function mutation	I_{CaL} increase*
LQT17	*TRDN*	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_v1.4	Direct channel inhibition	I_{to} decrease*
Inflammatory				
TNF-α	···	hERG	Channel function inhibition	I_{Kr} decrease
	···	K_v7.1	Channel function inhibition[§]	I_{Ks} decrease
	···	K_v4.2/K_v4.3	Channel expression decrease	I_{to} decrease
Interleukin-1	···	Ca_v1.2	Channel function enhancement	I_{CaL} increase
	···	K_v4.2/K_v4.3	Channel function inhibition[§]	I_{to} decrease
Interleukin-6	···	Ca_v1.2	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 Ca^{2+} 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 al[40] 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 ≈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 protein[56] expression and/or alterations in channel-gating kinetics.[54] Reactive oxygen species production, nuclear factor-κB, and asphingomyelin 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 currents[21] (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 (≈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^+ current[64] (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	*KCNH2*	hERG	Gain-of-function mutation	I_{Kr} increase
SQT2	*KCNQ1*	$K_v7.1$	Gain-of-function mutation	I_{Ks} increase
SQT3	*KCNJ2*	$K_{ir}2.1$	Gain-of-function mutation	I_{K1} increase
SQT4	*CACNA1C*	$Ca_v1.2$	Loss-of-function mutation	I_{CaL} decrease
SQT5	*CACNB2*	$Ca_v\beta 2b$	Loss-of-function mutation	I_{CaL} decrease
SQT6	*CACNA2D1*	$Ca_v\alpha 2\delta$	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)	···	$K_{ir}6.2$	Direct channel activation	I_{KATP} increase
Levcromakalim (vasodilator)	···	$K_{ir}6.2$	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^+ current[21] (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 ≈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-α1 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	*SCN5A*	$Na_v1.5$	Loss-of-function mutation	I_{Na} decrease
BrS2	*GPD1L*	Glycerol-3-phosphate dehydrogenase 1-like	Loss-of-function mutation	I_{Na} decrease
BsS3	*CACNA1C*	$Ca_v1.2$	Loss-of-function mutation	I_{CaL} decrease
BsS4	*CACNB2*	$Ca_v\beta2b$	Loss-of-function mutation	I_{CaL} decrease
BrS5	*SCN1B*	$Na_v\beta1$	Loss-of-function mutation	I_{Na} decrease
BrS6	*KCNE3*	MiRP2	Gain-of-function mutation	I_{to} increase
BrS7	*SCN3B*	$Na_v\beta3$	Loss-of-function mutation	I_{Na} decrease
BrS8	*KCNJ8*	$K_{ir}6.1$	Gain-of-function mutation	I_{KATP} increase
BrS9	*CACNA2D1*	$Ca_v\alpha2\delta$	Loss-of-function mutation	I_{CaL} decrease
BrS10	*KCND3*	$K_v4.3$	Gain-of-function mutation	I_{to} increase
BrS11	*RANGRF*	MOG1	Loss-of-function mutation	I_{Na} decrease
BrS12	*SLMAP*	Sarcolemmal membrane-associated protein	Loss-of-function mutation	I_{Na} decrease
BrS13	*ABCC9*	SUR2A	Gain-of-function mutation	I_{KATP} increase
BrS14	*SCN2B*	$Na_v\beta2$	Loss-of-function mutation	I_{Na} decrease
BrS15	*PKP2*	Plakophillin-2	Loss-of-function mutation	I_{Na} decrease
BrS16	*FGF12*	FAHF1	Loss-of-function mutation	I_{Na} decrease
BrS17	*SCN10A*	$Na_v1.8$	Loss-of-function mutation	I_{Na} decrease
BsS18	*HEY2*	Hey2-encoded transcription factor	Gain-of-function mutation	I_{Na} increase
BrS19	*SEMA3A*	Semaphorin	Gain-of-function mutation	I_{to} increase
Acquired forms				
Drug induced*				
Antiarrhythmics (class IA-IC)	...	$Na_v1.5$	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	...	$Ca_v1.2$	Direct channel inhibition	I_{CaL} decrease
Fever induced				
Fever	...	$Na_v1.5$	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,

DOI: 10.1161/JAHA.118.010595

vagotonic maneuvers, and electrolyte disturbances) and environmental (eg, drugs and toxic agents[66] [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	*RYR2*	Ryanodine receptor-2	Gain-of-function mutation	Diastolic Ca^{++} release
CPVT2	*CASQ2*	Calsequestrin-2	Loss-of-function mutation	Diastolic Ca^{++} release
CPVT3	*TECRL*	Trans-2,3-enoyl-CoA-reductase-like	Loss-of-function mutation	Diastolic Ca^{++} release
CPVT4	*CALM1*	Calmodulin-1	Loss-of-function mutation	Diastolic Ca^{++} release
CPVT5	*TRDN*	Triadin	Loss-of-function mutation	Diastolic Ca^{++} release
ERS				
Genetic				
ERS1	*KCNJ8*	$K_{ir}6.1$	Gain-of-function mutation	I_{KATP} increase
ERS2	*CACNA1C*	$Ca_v1.2$	Loss-of-function mutation	I_{CaL} decrease
ERS3	*CACNB2*	$Ca_v\beta 2b$	Loss-of-function mutation	I_{CaL} decrease
ERS4	*CACNA2D1*	$Ca_v\alpha 2\delta$	Loss-of-function mutation	I_{CaL} decrease
ERS5	*ABCC9*	SUR2A	Gain-of-function mutation	I_{KATP} increase
ERS6	*SCN5A*	$Na_v1.5$	Loss-of-function mutation	I_{Na} decrease
ERS7	*SCN10A*	$Na_v1.8$	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^+ channels[66] (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 inherited[95] 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 AF[95] (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			
KCNQ1	K_v7.1	Gain-of-function mutation	I_{Ks} increase
KCNE1	Mink	Gain-of-function mutation	I_{Ks} increase
KCNE2	MiRP1	Gain-of-function mutation	I_{Ks} increase
KCNE5	K_v7.1 (β subunit)	Gain-of-function mutation	I_{Ks} increase
KCNJ2	K_{ir}2.1 (β subunit)	Gain-of-function mutation	I_{K1} increase
KCNA5	K_v1.5	Gain-of-function mutation	I_{Kur} modulation
KCNH2	hERG	Gain-of-function mutation	I_{Kr} modulation
KCND3	K_v4.3	Gain-of-function mutation	I_{to} increase
KCNJ8	K_{ir}6.1	Gain-of-function mutation	I_{KATP} increase
KCNN3	KCa2.3	Gain-of-function mutation	SKCa modulation
HCN4	Hyperpolarization-activated cyclic nucleotide–gated potassium channel 4	Gain-of-function mutation	I_f modulation
ABCC9	SUR2A	Gain-of-function mutation	I_{KATP} decrease
Sodium channels			
SCN5A	Na_v1.5	Loss-of-function mutation	I_{Na} modulation
SCN1B	Na_vβ1	Loss-of-function mutation	I_{Na} decrease
SCN2B	Na_vβ2	Loss-of-function mutation	I_{Na} decrease
SCN3B	Na_vβ3	Loss-of-function mutation	I_{Na} decrease
SCN4B	Na_vβ4	Loss-of-function mutation	NC
SCN10A	Na_v1.8	Loss-of-function mutation	I_{Na} modulation
Calcium channels			
RYR2	Ryanodine receptor 2	Gain-of-function mutation	Diastolic Ca^{++} release
Gap-junction channels			
GJA1	Connexin 43	Loss-of-function mutation	Intercellular electrical coupling reduction
GJA5	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_v1.2	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 β3-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).

Medications[104] and autoimmune reactions[7] 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 ≈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 ≈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 bradyarrhythmias[7] (Table 6). Korkmaz et al[14] 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				
SCN5A	Na$_v$1.5	Loss-of-function mutation	I$_{Na}$ decrease	SSS, SAN exit block, AVB, PCCD
TRPM4	TRPM4	Loss-of-function mutation/ gain-of-function mutation	Nonselective cation current changes	Sinus bradycardia, PFHB I, PCCD
HCN4	Hyperpolarization-activated cyclic nucleotide–gated potassium channel 4	Loss-of-function mutation	I$_f$ decrease	Sinus bradycardia
CACNA1D	Ca$_v$1.3	Loss-of-function mutation	I$_{CaL}$ decrease	Sinus bradycardia, AVB
SCN1B	Na$_v\beta$1	Loss-of-function mutation	I$_{Na}$ decrease	Sinus bradycardia, AVB
GJA5	Connexin 40	Loss-of-function mutation	Intercellular electrical coupling reduction	PFHB I
GJC1	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$_v$1.5 pore-peptide sequence. In this model, appearance of high titers of anti-Na$_v$1.5 autoantibodies was associated with conduction disturbances, in the absence of any functional heart alteration or signs of myocardial inflammation or fibrosis at the histologic examination.[14] Electrophysiological and biochemical characterization of sera from Na$_v$1.5-immunized rats confirmed that anti-Na$_v$1.5 autoantibodies can significantly reduce I$_{Na}$ density, at least in part by downregulating Na$_v$1.5 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 autoantibodies[7] 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 al[116] 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

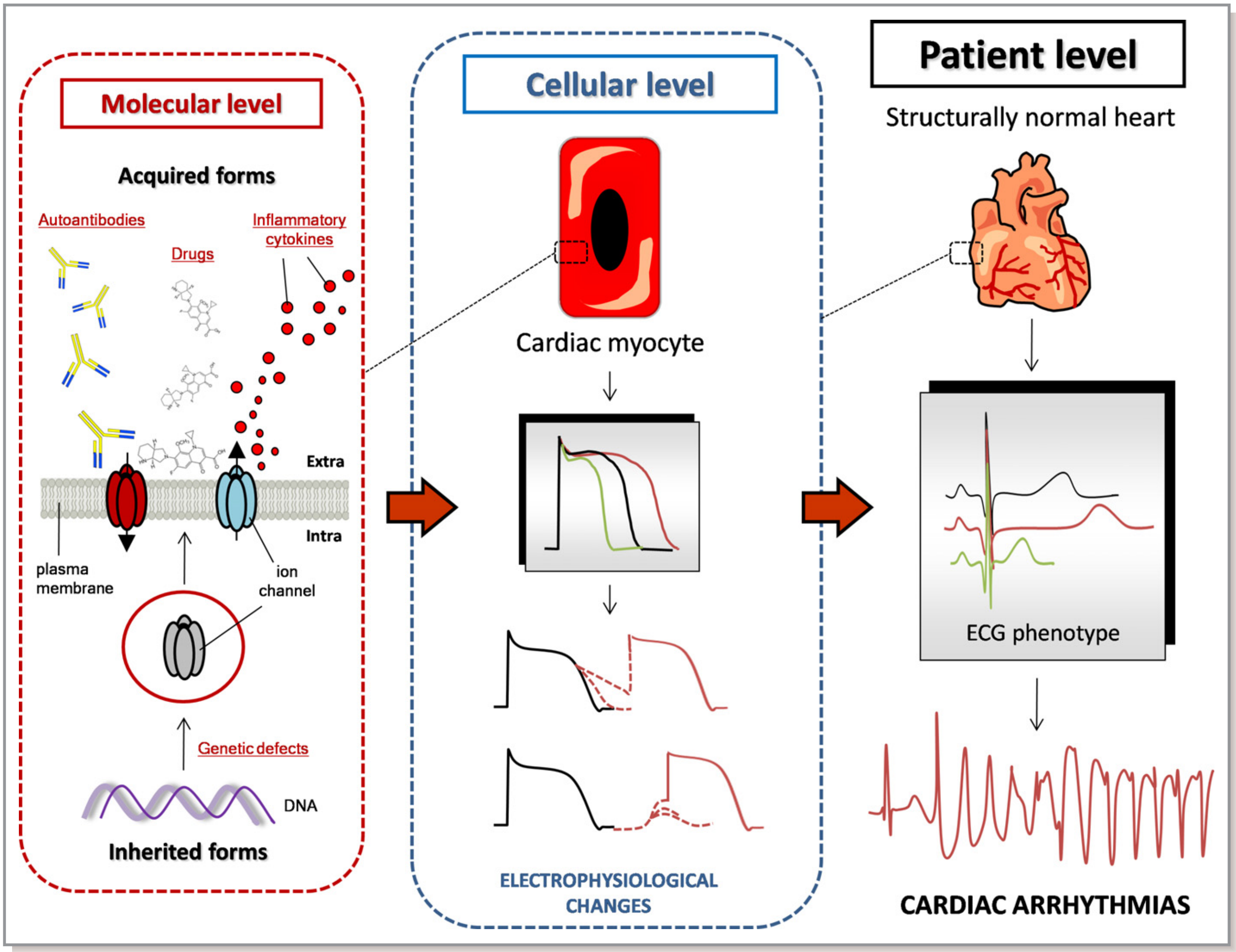

Figure 2. Cardiac channelopathies and arrhythmias: from the channel to the patient. In a structurally normal heart, both inherited (genetic defects) and acquired (drugs, autoantibodies, and inflammation/fever) factors can induce cardiac ion channel dysfunction, responsible for electrophysiological changes 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 block[127] 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 TdP[28] 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 pigs[16] 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.

Sources of Funding

This work has received funding from “Fondo Aree Sottoutilizzate-Salute ToRSADE project” (FAS-Salute 2014, Regione Toscana) and a Merit Review grant I01 BX002137 from Biomedical Laboratory Research and Development Service of Veterans Affairs Office of Research and Development (Boutjdir).

Disclosures

None.

References

1. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2017. Available at: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000548. Accessed October 3, 2018.
2. Semsarian C, Ingles J. Molecular autopsy in victims of inherited arrhythmias. *J Arrhythm*. 2016;32:359–365.
3. El-Sherif N, Boutjdir M, Turitto G. Sudden cardiac death in ischemic heart disease: pathophysiology and risk stratification. *Card Electrophysiol Clin*. 2017;9:681–691.
4. Cerrone M, Priori SG. Genetics of sudden death: focus on inherited channelopathies. *Eur Heart J*. 2011;32:2109–2118.
5. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963.
6. Turker I, Ai T, Itoh H, Horie M. Drug-induced fatal arrhythmias: acquired long QT and Brugada syndromes. *Pharmacol Ther*. 2017;176:48–59.
7. Lazzerini PE, Capecchi PL, Laghi-Pasini F, Boutjdir M. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. *Nat Rev Cardiol*. 2017;14:521–535.
8. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. *Eur Heart J*. 2017;38:1717–1727.
9. Isber N, Restivo M, Gough WB, Yang H, el-Sherif N. Circus movement atrial flutter in the canine sterile pericarditis model: cryothermal termination from the epicardial site of the slow zone of the reentrant circuit. *Circulation*. 1993;87:1649–1660.
10. Ryu K, Li L, Khrestian CM, Matsumoto N, Sahadevan J, Ruehr ML, Van Wagoner DR, Efimov IR, Waldo AL. Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. *Am J Physiol Heart Circ Physiol*. 2007;293:H1231–H1241.
11. Sadrpour SA, Srinivasan D, Bhimani AA, Lee S, Ryu K, Cakulev I, Khrestian CM, Markowitz AH, Waldo AL, Sahadevan J. Insights into new-onset atrial fibrillation following open heart surgery and implications for type II atrial flutter. *Europace*. 2015;17:1834–1839.
12. Lazzerini PE, Capecchi PL, Guideri F, Acampa M, Galeazzi M, Laghi Pasini F. Connective tissue diseases and cardiac rhythm disorders: an overview. *Autoimmun Rev*. 2006;5:306–313.
13. Lazzerini PE, Capecchi PL, Guideri F, Acampa M, Selvi E, Bisogno S, Galeazzi M, Laghi-Pasini F. Autoantibody-mediated cardiac arrhythmias: mechanisms and clinical implications. *Basic Res Cardiol*. 2008;103:1–11.
14. Korkmaz S, Zitron E, Bangert A, Seyler C, Li S, Hegedüs P, Scherer D, Li J, Fink T, Schweizer PA, Giannitsis E, Karck M, Szabó G, Katus HA, Kaya Z. Provocation of an autoimmune response to cardiac voltage-gated sodium channel NaV1.5 induces cardiac conduction defects in rats. *J Am Coll Cardiol*. 2013;62:340–349.
15. Li J, Maguy A, Duverger JE, Vigneault P, Comtois P, Shi Y, Tardif JC, Thomas D, Nattel S. Induced KCNQ1 autoimmunity accelerates cardiac repolarization in rabbits: potential significance in arrhythmogenesis and antiarrhythmic therapy. *Heart Rhythm*. 2014;11:2092–2100.

16. Fabris F, Yue Y, Qu Y, Chahine M, Sobie E, Lee P, Wieczorek R, Jiang XC, Capecchi PL, Laghi-Pasini F, Lazzerini PE, Boutjdir M. Induction of autoimmune response to the extracellular loop of the HERG channel pore induces QTc prolongation in guinea-pigs. *J Physiol*. 2016;594:6175–6187.

17. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Long QT syndrome: an emerging role for inflammation and immunity. *Front Cardiovasc Med*. 2015;2:26.

18. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular Nursing; American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2010;55:934–947.

19. El-Sherif N, Turitto G, Boutjdir M. Congenital long QT syndrome and torsade de pointes. *Ann Noninvasive Electrocardiol*. 2017;22:e12481.

20. Grant AO. Cardiac ion channels. *Circ Arrhythm Electrophysiol*. 2009;2:185–194.

21. Obeyesekere MN, Antzelevitch C, Krahn AD. Management of ventricular arrhythmias in suspected channelopathies. *Circ Arrhythm Electrophysiol*. 2015;8:221–231.

22. El-Sherif N, Turitto G, Boutjdir M. Acquired long QT syndrome and torsade de pointes. *Pacing Clin Electrophysiol*. 2018;41:414–421.

23. Landstrom AP, Dobrev D, Wehrens XHT. Calcium signaling and cardiac arrhythmias. *Circ Res*. 2017;120:1969–1993.

24. Lee HC, Huang KT, Wang XL, Shen WK. Autoantibodies and cardiac arrhythmias. *Heart Rhythm*. 2011;8:1788–1795.

25. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, Morozzi G, Lorenzini S, Simpatico A, Selvi E, Bacarelli MR, Finizola F, Vanni F, Lazaro D, Aromolaran A, El Sherif N, Boutjdir M, Capecchi PL. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. *Heart*. 2017;103:1821–1829.

26. Nakamura K, Katayama Y, Kusano KF, Haraoka K, Tani Y, Nagase S, Morita H, Miura D, Fujimoto Y, Furukawa T, Ueda K, Aizawa Y, Kimura A, Kurachi Y, Ohe T. Anti-KCNH2 antibody-induced long QT syndrome: novel acquired form of long QT syndrome. *J Am Coll Cardiol*. 2007;50:1808–1809.

27. Yue Y, Castrichini M, Srivastava U, Fabris F, Shah K, Li Z, Qu Y, El-Sherif N, Zhou Z, January C, Hussain MM, Jiang XC, Sobie EA, Wahren-Herlenius M, Chahine M, Capecchi PL, Laghi-Pasini F, Lazzerini PE, Boutjdir M. Pathogenesis of the novel autoimmune-associated long-QT syndrome. *Circulation*. 2015;132:230–240.

28. Lazzerini PE, Yue Y, Srivastava U, Fabris F, Capecchi PL, Bertolozzi I, Bacarelli MR, Morozzi G, Acampa M, Natale M, El-Sherif N, Galeazzi M, Laghi-Pasini F, Boutjdir M. Arrhythmogenicity of anti-Ro/SSA antibodies in patients with torsades de pointes. *Circ Arrhythm Electrophysiol*. 2016;9:e003419.

29. Suzuki S, Satoh T, Yasuoka H, Hamaguchi Y, Tanaka K, Kawakami Y, Suzuki N, Kuwana M. Novel autoantibodies to a voltage-gated potassium channel Kv1.4 in a severe form of myasthenia gravis. *J Neuroimmunol*. 2005;170:141–149.

30. Suzuki S, Baba A, Kaida K, Utsugisawa K, Kita Y, Tsugawa J, Ogawa G, Nagane Y, Kuwana M, Suzuki N. Cardiac involvements in myasthenia gravis associated with anti-Kv1.4 antibodies. *Eur J Neurol*. 2014;21:223–230.

31. Boutjdir M, Lazzerini PE, Capecchi PL, Laghi-Pasini F, El-Sherif N. Potassium channel block and novel autoimmune-associated long QT syndrome. *Card Electrophysiol Clin*. 2016;8:373–384.

32. Hayashi N, Koshiba M, Nishimura K, Sugiyama D, Nakamura T, Morinobu S, Kawano S, Kumagai S. Prevalence of disease-specific antinuclear antibodies in general population: estimates from annual physical examinations of residents of a small town over a 5-year period. *Mod Rheumatol*. 2008;18:153–160.

33. Lazzerini PE, Acampa M, Guideri F, Capecchi PL, Campanella V, Morozzi G, Galeazzi M, Marcolongo R, Laghi-Pasini F. Prolongation of the corrected QT interval in adult patients with anti-Ro/SSA-positive connective tissue diseases. *Arthritis Rheum*. 2004;50:1248–1252.

34. Cimaz R, Stramba-Badiale M, Brucato A, Catelli L, Panzeri P, Meroni PL. QT interval prolongation in asymptomatic anti-SSA/Ro-positive infants without congenital heart block. *Arthritis Rheum*. 2000;43:1049–1053.

35. Lazzerini PE, Capecchi PL, Guideri F, Bellisai F, Selvi E, Acampa M, Costa A, Maggio R, Garcia-Gonzalez E, Bisogno S, Morozzi G, Galeazzi M, Laghi-Pasini F. Comparison of frequency of complex ventricular arrhythmias in patients with positive versus negative anti-Ro/SSA and connective tissue disease. *Am J Cardiol*. 2007;100:1029–1034.

36. Bourré-Tessier J, Clarke AE, Huynh T, Bernatsky S, Joseph L, Belisle P, Pineau CA. Prolonged corrected QT interval in anti-Ro/SSA-positive adults with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2011;63:1031–1037.

37. Lazzerini PE, Capecchi PL, Acampa M, Morozzi G, Bellisai F, Bacarelli MR, Dragoni S, Fineschi I, Simpatico A, Galeazzi M, Laghi-Pasini F. Anti-Ro/SSA-associated corrected QT interval prolongation in adults: the role of antibody level and specificity. *Arthritis Care Res (Hoboken)*. 2011;63:1463–1470.

38. Gordon PA, Rosenthal E, Khamashta MA, Hughes GR. Absence of conduction defects in the electrocardiograms [correction of echocardiograms] of mothers with children with congenital complete heart block. *J Rheumatol*. 2001;28:366–369.

39. Bourré-Tessier J, Urowitz MB, Clarke AE, Bernatsky S, Krantz MJ, Huynh T, Joseph L, Belisle P, Bae SC, Hanly JG, Wallace DJ, Gordon C, Isenberg D, Rahman A, Gladman DD, Fortin PR, Merrill JT, Romero-Diaz J, Sanchez-Guerrero J, Fessler B, Alarcón GS, Steinsson K, Bruce IN, Ginzler E, Dooley MA, Nived O, Sturfelt G, Kalunian K, Ramos-Casals M, Petri M, Zoma A, Pineau CA. Electrocardiographic findings in systemic lupus erythematosus: data from an international inception cohort. *Arthritis Care Res (Hoboken)*. 2015;67:128–135.

40. Tufan AN, Sag S, Oksuz MF, Ermurat S, Coskun BN, Gullulu M, Budak F, Baran I, Pehlivan Y, Dalkilic E. Prolonged T_{peak}-T_{end} interval in anti-Ro52 antibody-positive connective tissue diseases. *Rheumatol Int*. 2017;37:67–73.

41. Xiao H, Wang M, Du Y, Yuan J, Cheng X, Chen Z, Zou A, Wei F, Zhao G, Liao YH. Arrhythmogenic autoantibodies against calcium channel lead to sudden death in idiopathic dilated cardiomyopathy. *Eur J Heart Fail*. 2011;13:264–270.

42. Yu H, Pei J, Liu X, Chen J, Li X, Zhang Y, Li N, Wang Z, Zhang P, Cao K, Pu J. Calcium channel autoantibodies predicted sudden cardiac death and all-cause mortality in patients with ischemic and nonischemic chronic heart failure. *Dis Markers*. 2014;2014:796075.

43. Xiao H, Wang M, Du Y, Yuan J, Zhao G, Tu D, Liao YH. Agonist-like autoantibodies against calcium channel in patients with dilated cardiomyopathy. *Heart Vessels*. 2012;27:486–492.

44. Medenwald D, Kors JA, Loppnow H, Thiery J, Kluttig A, Nuding S, Tiller D, Greiser KH, Werdan K, Haerting J. Inflammation and prolonged QT time: results from the cardiovascular disease, living and ageing in Halle (CARLA) study. *PLoS One*. 2014;9:e95994.

45. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. 2002;105:2595–2599.

46. Ukena C, Mahfoud F, Kindermann I, Kandolf R, Kindermann M, Böhm M. Prognostic electrocardiographic parameters in patients with suspected myocarditis. *Eur J Heart Fail*. 2011;13:398–405.

47. Pisoni CN, Reina S, Arakaki D, Eimon A, Carrizo C, Borda E. Elevated IL-1β levels in anti-Ro/SSA connective tissue diseases patients with prolonged corrected QTc interval. *Clin Exp Rheumatol*. 2015;33:715–720.

48. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, Kovacs RJ. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*. 2013;6:479–487.

49. Lazzerini PE, Acampa M, Capecchi PL, Fineschi I, Selvi E, Moscadelli V, Zimbone S, Gentile D, Galeazzi M, Laghi-Pasini F. Antiarrhythmic potential of anticytokine therapy in rheumatoid arthritis: tocilizumab reduces corrected QT interval by controlling systemic inflammation. *Arthritis Care Res (Hoboken)*. 2015;67:332–339.

50. Adlan AM, Panoulas VF, Smith JP, Fisher JP, Kitas GD. Association between corrected QT interval and inflammatory cytokines in rheumatoid arthritis. *J Rheumatol*. 2015;42:421–428.

51. Petkova-Kirova PS, Gursoy E, Mehdi H, McTiernan CF, London B, Salama G. Electrical remodeling of cardiac myocytes from mice with heart failure due to the overexpression of tumor necrosis factor-alpha. *Am J Physiol Heart Circ Physiol*. 2006;290:H2098–H2107.

52. Kawada H, Niwano S, Niwano H, Yumoto Y, Wakisaka Y, Yuge M, Kawahara K, Izumi T. Tumor necrosis factor-alpha downregulates the voltage gated outward K$^+$ current in cultured neonatal rat cardiomyocytes: a possible cause of electrical remodeling in diseased hearts. *Circ J*. 2006;70:605–609.

53. Fernández-Velasco M, Ruiz-Hurtado G, Hurtado O, Moro MA, Delgado C. TNF-alpha downregulates transient outward potassium current in rat ventricular myocytes through iNOS overexpression and oxidant species generation. *Am J Physiol Heart Circ Physiol*. 2007;293:H238–H245.

54. Grandy SA, Fiset C. Ventricular K$^+$ currents are reduced in mice with elevated levels of serum TNFalpha. *J Mol Cell Cardiol*. 2009;47:238–246.

55. Wang J, Wang H, Zhang Y, Gao H, Nattel S, Wang Z. Impairment of HERG K(+) channel function by tumor necrosis factor-alpha: role of reactive oxygen species as a mediator. *J Biol Chem*. 2004;279:13289–13292.

56. Hatada K, Washizuka T, Horie M, Watanabe H, Yamashita F, Chinushi M, Aizawa Y. Tumor necrosis factor-alpha inhibits the cardiac delayed rectifier K

current via the asphingomyelin pathway. *Biochem Biophys Res Commun*. 2006;344:189–193.

57. Monnerat G, Alarcón ML, Vasconcellos LR, Hochman-Mendez C, Brasil G, Bassani RA, Casis O, Malan D, Travassos LH, Sepúlveda M, Burgos JI, Vila-Petroff M, Dutra FF, Bozza MT, Paiva CN, Carvalho AB, Bonomo A, Fleischmann BK, de Carvalho AC, Medei E. Macrophage-dependent IL-1β production induces cardiac arrhythmias in diabetic mice. *Nat Commun*. 2016;7:13344.
58. Li YH, Rozanski GJ. Effects of human recombinant interleukin-1 on electrical properties of guinea pig ventricular cells. *Cardiovasc Res*. 1993;27:525–530.
59. Hagiwara Y, Miyoshi S, Fukuda K, Nishiyama N, Ikegami Y, Tanimoto K, Murata M, Takahashi E, Shimoda K, Hirano T, Mitamura H, Ogawa S. SHP2-mediated signaling cascade through gp130 is essential for LIF-dependent I CaL, [Ca2+]i transient, and APD increase in cardiomyocytes. *J Mol Cell Cardiol*. 2007;43:710–716.
60. Burashnikov A, Shimizu W, Antzelevitch C. Fever accentuates transmural dispersion of repolarization and facilitates development of early afterdepolarizations and torsade de pointes under long-QT conditions. *Circ Arrhythm Electrophysiol*. 2008;1:202–208.
61. Amin AS, Herfst LJ, Delisle BP, Klemens CA, Rook MB, Bezzina CR, Underkofler HA, Holzem KM, Ruijter JM, Tan HL, January CT, Wilde AA. Fever-induced QTc prolongation and ventricular arrhythmias in individuals with type 2 congenital long QT syndrome. *J Clin Invest*. 2008;118:2552–2561.
62. Zhao Y, Wang T, Guo J, Yang T, Li W, Koichopolos J, Lamothe SM, Kang Y, Ma A, Zhang S. Febrile temperature facilitates hERG/IKr degradation through an altered K(+) dependence. *Heart Rhythm*. 2016;13:2004–2011.
63. Mazzanti A, Underwood K, Nevelev D, Kofman S, Priori SG. The new kids on the block of arrhythmogenic disorders: short QT syndrome and early repolarization. *J Cardiovasc Electrophysiol*. 2017;28:1226–1236.
64. Shah RR. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. *Br J Pharmacol*. 2010;159:58–69.
65. Li J, Seyler C, Wiedmann F, Schmidt C, Schweizer PA, Becker R, Katus HA, Thomas D. Anti-KCNQ1 K$^+$ channel autoantibodies increase IKs current and are associated with QT interval shortening in dilated cardiomyopathy. *Cardiovasc Res*. 2013;98:496–503.
66. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AAM. J-wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Europace*. 2017;19:665–694.
67. Sieira J, Dendramis G, Brugada P. Pathogenesis and management of Brugada syndrome. *Nat Rev Cardiol*. 2016;13:744–756.
68. Leo-Macias A, Agullo-Pascual E, Delmar M. The cardiac connexome: non-canonical functions of connexin43 and their role in cardiac arrhythmias. *Semin Cell Dev Biol*. 2016;50:13–21.
69. Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, Makita N, Kowase S, Boonmee N, Vitayakritsirikul V, Ratanarapee S, Sharma S, van der Wal AC, Christiansen M, Tan HL, Wilde AA, Nogami A, Sheppard MN, Veerakul G, Behr ER. Fibrosis, connexin-43, and conduction abnormalities in the Brugada syndrome. *J Am Coll Cardiol*. 2015;66:1976–1986.
70. Adler A, Topaz G, Heller K, Zeltser D, Ohayon T, Rozovski U, Halkin A, Rosso R, Ben-Shachar S, Antzelevitch C, Viskin S. Fever-induced Brugada pattern: how common is it and what does it mean? *Heart Rhythm*. 2013;10:1375–1382.
71. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, Aydin M, Pfeiffer R, Burashnikov E, Wu Y, Antzelevitch C. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. *Heart Rhythm*. 2015;12:1584–1594.
72. Rattanawong P, Vutthikraivit W, Charoensri A, Jongraksak T, Prombandankul A, Kanjanahattakij N, Rungaramsin S, Wisaratapong T, Ngarmukos T. Fever-induced Brugada syndrome is more common than previously suspected: a cross-sectional study from an endemic area. *Ann Noninvasive Electrocardiol*. 2016;21:136–141.
73. Mizusawa Y, Morita H, Adler A, Havakuk O, Thollet A, Maury P, Wang DW, Hong K, Gandjbakhch E, Sacher F, Hu D, Amin AS, Lahrouchi N, Tan HL, Antzelevitch C, Probst V, Viskin S, Wilde AA. Prognostic significance of fever-induced Brugada syndrome. *Heart Rhythm*. 2016;13:1515–1520.
74. Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, Brugada J, Brugada R, Antzelevitch C. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. *Circ Res*. 1999;85:803–809.
75. Keller DI, Rougier JS, Kucera JP, Benammar N, Fressart V, Guicheney P, Madle A, Fromer M, Schläpfer J, Abriel H. Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. *Cardiovasc Res*. 2005;67:510–519.
76. Konigstein M, Rosso R, Topaz G, Postema PG, Friedensohn L, Heller K, Zeltser D, Belhassen B, Adler A, Viskin S. Drug-induced Brugada syndrome: clinical characteristics and risk factors. *Heart Rhythm*. 2016;13:1083–1087.
77. Chung FP, Raharjo SB, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chao TF, Liao JN, Lin CY, Chang YT, Hung Y, Te A, Yamada S, Tasaka H, Wang CT, Chen SA. A novel method to enhance phenotype, epicardial functional substrates, and ventricular tachyarrhythmias in Brugada syndrome. *Heart Rhythm*. 2017;14:508–517.
78. Frustaci A, Priori SG, Pieroni M, Chimenti C, Napolitano C, Rivolta I, Sanna T, Bellocci F, Russo MA. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation*. 2005;112:3680–3687.
79. Bonny A, Tonet J, Márquez MF, De Sisti A, Temfemo A, Himbert C, Gueffaf F, Larrazet F, Ditah I, Frank R, Hidden-Lucet F, Fontaine G. C-reactive protein levels in the Brugada syndrome. *Cardiol Res Pract*. 2011;2011:341521.
80. Li A, Tung R, Shivkumar K, Bradfield JS. Brugada syndrome-malignant phenotype associated with acute cardiac inflammation? *HeartRhythm Case Rep*. 2017;3:384–388.
81. Baum JR, Long B, Cabo C, Duffy HS. Myofibroblasts cause heterogeneous Cx43 reduction and are unlikely to be coupled to myocytes in the healing canine infarct. *Am J Physiol Heart Circ Physiol*. 2012;302:H790–H800.
82. Fernandez-Cobo M, Gingalewski C, Drujan D, De Maio A. Downregulation of connexin 43 gene expression in rat heart during inflammation: the role of tumour necrosis factor. *Cytokine*. 1999;11:216–224.
83. De Jesus NM, Wang L, Lai J, Rigor RR, Francis Stuart SD, Bers DM, Lindsey ML, Ripplinger CM. Antiarrhythmic effects of interleukin 1 inhibition after myocardial infarction. *Heart Rhythm*. 2017;14:727–736.
84. Imberti JF, Underwood K, Mazzanti A, Priori SG. Clinical challenges in catecholaminergic polymorphic ventricular tachycardia. *Heart Lung Circ*. 2016;25:777–783.
85. Berte B, Eyskens B, Meyfroidt G, Willems R. Bidirectional ventricular tachycardia in fulminant myocarditis. *Europace*. 2008;10:767–768.
86. Kim E, Tam M, Siems WF, Kang C. Effects of drugs with muscle-related side effects and affinity for calsequestrin on the calcium regulatory function of sarcoplasmic reticulum microsomes. *Mol Pharmacol*. 2005;68:1708–1715.
87. Sanchez EJ, Hayes RP, Barr JT, Lewis KM, Webb BN, Subramanian AK, Nissen MS, Jones JP, Shelden EA, Sorg BA, Fill M, Schenk JO, Kang C. Potential role of cardiac calsequestrin in the lethal arrhythmic effects of cocaine. *Drug Alcohol Depend*. 2013;133:344–351.
88. London B, Baker LC, Lee JS, Shusterman V, Choi BR, Kubota T, McTiernan CF, Feldman AM, Salama G. Calcium-dependent arrhythmias in transgenic mice with heart failure. *Am J Physiol Heart Circ Physiol*. 2003;284:H431–H441.
89. Duncan DJ, Yang Z, Hopkins PM, Steele DS, Harrison SM. TNF-alpha and IL-1beta increase Ca^{2+} leak from the sarcoplasmic reticulum and susceptibility to arrhythmia in rat ventricular myocytes. *Cell Calcium*. 2010;47:378–386.
90. Francis Stuart SD, De Jesus NM, Lindsey ML, Ripplinger CM. The crossroads of inflammation, fibrosis, and arrhythmia following myocardial infarction. *J Mol Cell Cardiol*. 2016;91:114–122.
91. Thaik CM, Calderone A, Takahashi N, Colucci WS. Interleukin-1 beta modulates the growth and phenotype of neonatal rat cardiac myocytes. *J Clin Invest*. 1995;96:1093–1099.
92. Stumpf C, Simon M, Wilhelm M, Zimmermann S, Rost C, Achenbach S, Brem MH. Left atrial remodeling, early repolarization pattern, and inflammatory cytokines in professional soccer players. *J Cardiol*. 2016;68:64–70.
93. Visser M, van der Heijden JF, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic ventricular fibrillation: the struggle for definition, diagnosis, and follow-up. *Circ Arrhythm Electrophysiol*. 2016;9:e003817.
94. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
95. Hucker WJ, Saini H, Lubitz SA, Ellinor PT. Atrial fibrillation genetics: is there a practical clinical value now or in the future? *Can J Cardiol*. 2016;32:1300–1305.
96. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol*. 2015;12:230–243.
97. Saba S, Janczewski AM, Baker LC, Shusterman V, Gursoy EC, Feldman AM, Salama G, McTiernan CF, London B. Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-{alpha}. *Am J Physiol Heart Circ Physiol*. 2005;289:H1456–H1467.
98. Zuo S, Li LL, Ruan YF, Jiang L, Li X, Li SN, Wen SN, Bai R, Liu N, Du X, Dong JZ, Ma CS. Acute administration of tumour necrosis factor-α induces spontaneous calcium release via the reactive oxygen species pathway in atrial

myocytes. *Europace*. 2017. Available at: https://academic.oup.com/europace/article-abstract/20/8/1367/4555382?redirectedFrom=fulltext. Accessed October 3, 2018.

99. Sawaya SE, Rajawat YS, Rami TG, Szalai G, Price RL, Sivasubramanian N, Mann DL, Khoury DS. Downregulation of connexin40 and increased prevalence of atrial arrhythmias in transgenic mice with cardiac-restricted overexpression of tumor necrosis factor. *Am J Physiol Heart Circ Physiol*. 2007;292:H1561–H1567.
100. Liew R, Khairunnisa K, Gu Y, Tee N, Yin NO, Naylynn TM, Moe KT. Role of tumor necrosis factor-α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. *Circ J*. 2013;77:1171–1179.
101. Sun Z, Zhou D, Xie X, Wang S, Wang Z, Zhao W, Xu H, Zheng L. Cross-talk between macrophages and atrial myocytes in atrial fibrillation. *Basic Res Cardiol*. 2016;111:63.
102. Rao F, Xue YM, Wei W, Yang H, Liu FZ, Chen SX, Kuang SJ, Zhu JN, Wu SL, Deng CY. Role of tumour necrosis factor-a in the regulation of T-type calcium channel current in HL-1 cells. *Clin Exp Pharmacol Physiol*. 2016;43:706–711.
103. Zhao Y, Sun Q, Zeng Z, Li Q, Zhou S, Zhou M, Xue Y, Cheng X, Xia Y, Wang Q, Tu X. Regulation of SCN3B/scn3b by interleukin 2 (IL-2): IL-2 modulates SCN3B/scn3b transcript expression and increases sodium current in myocardial cells. *BMC Cardiovasc Disord*. 2016;16:1.
104. Mangrum JM, DiMarco JP. The evaluation and management of bradycardia. *N Engl J Med*. 2000;342:703–709.
105. Rezazadeh S, Duff HJ. Genetic determinants of hereditary bradyarrhythmias: a contemporary review of a diverse group of disorders. *Can J Cardiol*. 2017;33:758–767.
106. Dobrzynski H, Anderson RH, Atkinson A, Borbas Z, D'Souza A, Fraser JF, Inada S, Logantha SJ, Monfredi O, Morris GM, Moorman AF, Nikolaidou T, Schneider H, Szuts V, Temple IP, Yanni J, Boyett MR. Structure, function and clinical relevance of the cardiac conduction system, including the atrioventricular ring and outflow tract tissues. *Pharmacol Ther*. 2013;139:260–288.
107. Delmar M, Makita N. Cardiac connexins, mutations and arrhythmias. *Curr Opin Cardiol*. 2012;27:236–241.
108. Osmonov D, Erdinler I, Ozcan KS, Altay S, Turkkan C, Yildirim E, Hasdemir H, Alper AT, Cakmak N, Satilmis S, Gurkan K. Management of patients with drug-induced atrioventricular block. *Pacing Clin Electrophysiol*. 2012;35:804–810.
109. Karnabi E, Boutjdir M. Role of calcium channels in congenital heart block. *Scand J Immunol*. 2010;72:226–234.
110. Brito-Zerón P, Izmirly PM, Ramos-Casals M, Buyon JP, Khamashta MA. The clinical spectrum of autoimmune congenital heart block. *Nat Rev Rheumatol*. 2015;11:301–312.
111. Xiao GQ, Hu K, Boutjdir M. Direct inhibition of expressed cardiac L- and T-type calcium channels by IgG from mothers whose children have congenital heart block. *Circulation*. 2001;103:1599–1604.
112. Karnabi E, Qu Y, Wadgaonkar R, Mancarella S, Yue Y, Chahine M, Clancy RM, Buyon JP, Boutjdir M. Congenital heart block: identification of autoantibody binding site on the extracellular loop (domain I, S5-S6) of alpha(1D) L-type Ca channel. *J Autoimmun*. 2010;34:80–86.
113. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Isolated atrioventricular block of unknown origin in adults and anti-Ro/SSA antibodies: clinical evidence, putative mechanisms, and therapeutic implications. *Heart Rhythm*. 2015;12:449–454.
114. Roden DM. Repolarization reserve: a moving target. *Circulation*. 2008;118:981–982.
115. Otway R, Vandenberg JI, Fatkin D. Atrial fibrillation: a new cardiac channelopathy. *Heart Lung Circ*. 2007;16:356–360.
116. Otway R, Vandenberg JI, Guo G, Varghese A, Castro ML, Liu J, Zhao J, Bursill JA, Wyse KR, Crotty H, Baddeley O, Walker B, Kuchar D, Thorburn C, Fatkin D. Stretch-sensitive KCNQ1 mutation A link between genetic and environmental factors in the pathogenesis of atrial fibrillation? *J Am Coll Cardiol*. 2007;49:578–586.
117. Karnabi E, Qu Y, Mancarella S, Boutjdir M. Rescue and worsening of congenital heart block-associated electrocardiographic abnormalities in two transgenic mice. *J Cardiovasc Electrophysiol*. 2011;22:922–930.
118. Silva Marques J, Veiga A, Nóbrega J, Correia MJ, de Sousa J. Electrical storm induced by H1N1 A influenza infection. *Europace*. 2010;12:294–295.
119. Lim SM, Pak HN, Lee MH, Kim SS, Joung B. Fever-induced QTc prolongation and ventricular fibrillation in a healthy young man. *Yonsei Med J*. 2011;52:1025–1027.
120. Amin AS, Klemens CA, Verkerk AO, Meregalli PG, Asghari-Roodsari A, de Bakker JM, January CT, Wilde AA, Tan HL. Fever-triggered ventricular arrhythmias in Brugada syndrome and type 2 long-QT syndrome. *Neth Heart J*. 2010;18:165–169.
121. Streitner F, Kuschyk J, Veltmann C, Brueckmann M, Streitner I, Brade J, Neumaier M, Bertsch T, Schumacher B, Borggrefe M, Wolpert C. Prospective study of interleukin-6 and the risk of malignant ventricular tachyarrhythmia in ICD-recipients: a pilot study. *Cytokine*. 2007;40:30–34.
122. Wu KC, Gerstenblith G, Guallar E, Marine JE, Dalal D, Cheng A, Marbán E, Lima JA, Tomaselli GF, Weiss RG. Combined cardiac magnetic resonance imaging and C-reactive protein levels identify a cohort at low risk for defibrillator firings and death. *Circ Cardiovasc Imaging*. 2012;5:178–186.
123. Ajijola OA, Hoover DB, Simerly TM, Brown TC, Yanagawa J, Biniwale RM, Lee JM, Sadeghi A, Khanlou N, Ardell JL, Shivkumar K. Inflammation, oxidative stress, and glial cell activation characterize stellate ganglia from humans with electrical storm. *JCI Insight*. 2017;2:94715.
124. Rizzo S, Basso C, Troost D, Aronica E, Frigo AC, Driessen AH, Thiene G, Wilde AA, van der Wal AC. T-cell-mediated inflammatory activity in the stellate ganglia of patients with ion-channel disease and severe ventricular arrhythmias. *Circ Arrhythm Electrophysiol*. 2014;7:224–229.
125. Santos-Pardo I, Martínez-Morillo M, Villuendas R, Bayes-Genis A. Anti-Ro antibodies and reversible atrioventricular block. *N Engl J Med*. 2013;368:2335–2337.
126. Lazzerini PE, Brucato A, Capecchi PL, Baldi L, Bacarelli MR, Nucci C, Moscadelli V, Morozzi G, Boutjdir M, Laghi-Pasini F. Isolated atrioventricular block of unknown origin in the adult and autoimmunity: diagnostic and therapeutic considerations exemplified by 3 anti-Ro/SSA-associated cases. *HeartRhythm Case Rep*. 2015;1:293–299.
127. Saxena A, Izmirly PM, Mendez B, Buyon JP, Friedman DM. Prevention and treatment in utero of autoimmune-associated congenital heart block. *Cardiol Rev*. 2014;22:263–267.
128. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. *Circulation*. 2009;119:1853–1866.
129. Salih M, Smer A, Charnigo R, Ayan M, Darrat YH, Traina M, Morales GX, DiBiase L, Natale A, Elayi CS. Colchicine for prevention of post-cardiac procedure atrial fibrillation: meta-analysis of randomized controlled trials. *Int J Cardiol*. 2017;243:258–262.
130. Saribayev M, Tufan F, Oz F, Erer B, Ozpolat T, Ozturk GB, Akin S, Saka B, Erten N, Tascioglu C, Karan A. Corticosteroid treatment normalizes QTc prolongation and improves heart block in an elderly patient with anti-Ro-positive systemic lupus erythematosus. *Aging Clin Exp Res*. 2014;26:337–339.

Key Words: antibody • arrhythmia (mechanisms) • inflammation • ion channel