Calcium Handling Defects and Cardiac Arrhythmia Syndromes

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Calcium ions (Ca2+) play a major role in the cardiac excitation-contraction coupling. Intracellular Ca2+ concentration increases during systole and falls in diastole thereby determining cardiac contraction and relaxation. Normal cardiac function also requires perfect organization of the ion currents at the cellular level to drive action potentials and to maintain action potential propagation and electrical homogeneity at the tissue level. Any imbalance in Ca2+ homeostasis of a cardiac myocyte can lead to electrical disturbances. This review aims to discuss cardiac physiology and pathophysiology from the elementary membrane processes that can cause the electrical instability of the ventricular myocytes through intracellular Ca2+ handling maladies to inherited and acquired arrhythmias. Finally, the paper will discuss the current therapeutic approaches targeting cardiac arrhythmias.

Keywords: calcium signalling, cardiac arrhythmias, catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, atrial fibrillation, reentry, early afterdepolarization, delayed afterdepolarization

INTRODUCTION

Excitation-contraction coupling (E-C coupling) of the cardiac myocytes is a well studied phenomenon. We know that the calcium ion (Ca2+) plays a major role in controlling contraction and force, a feature that was originally described by Sidney Ringer more than a century ago (Ringer, 1883). Since this discovery, it has become clear that changes in intracellular Ca2+ concentration ([Ca2+]i) have a significant role in virtually all parts of the human body. Of particular importance is the fact, that within cardiac myocytes, [Ca2+]i changes must be tightly regulated, so that the heart can beat rhythmically. This means that during the cardiac systole, [Ca2+]i has to increase to certain levels to make contraction occur and must fall.

Abbreviations: AF, atrial fibrillation; AP, action potential; APD, action potential duration; AV, atrioventricular; BrS, Brugada syndrome; CaM, calmodulin; CaMKII, Ca2+/calmodulin-dependent protein kinase II; CICR, Ca2+-induced Ca2+ release; CPVT, catecholaminergic polymorphic ventricular tachycardia; CSQ2, calsequestrin 2; DAD, delayed afterdepolarization; EAD, early afterdepolarization; EC, excitation-contraction coupling; ERS, early repolarization syndrome; HF, heart failure; ICD, implantable cardiac defibrillator; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; NCX, sodium-calcium exchange; NFAT, nuclear factor of activated T-cells; PKA, protein kinase A; PLN, phospholamban; PMCA, plasma membrane Ca2+-ATPase; PVC, premature ventricular contraction; RSV, relative short term beat-to-beat variability of action potential duration; RyR, ryanodine receptor; SA, sinoatrial; SERCA, sarco/endoplasmic reticulum Ca2+-ATPase; SOCE, store overload-induced Ca2+ entry; SOICR, store overload-induced Ca2+ release; SQTS, short QT syndrome; SR, sarcoplasmic reticulum; SV, short term beat-to-beat variability of action potential duration; VF, ventricular fibrillation; VT, ventricular tachycardia.
in diastole, allowing the muscle to relax and prepare for the next cardiac cycle. E-C coupling has been reviewed in detail (Bers, 2002; Eisner et al., 2017), here we consider the elementary steps and the events that can lead to electrical disturbances (Figure 1).

The normal cardiac action potential (AP) originates in the sinoatrial node and propagates through the heart. In the ventricle the initial depolarization opens voltage-gated sodium channels leading to further depolarization which, in turn, opens the L-type Ca^{2+} channels, causing a large Ca^{2+}-influx (Figure 1A). Some Ca^{2+} can also enter via T-type Ca^{2+} channels and reverse mode Na^+/Ca^{2+} exchange (NCX) (Kohomoto et al., 1994; Sipido et al., 1997). This Ca^{2+} entry triggers a process known as calcium-induced calcium release (CICR), in which Ca^{2+} is released from the sarcoplasmic reticulum (SR) into the cytoplasm via ryanodine receptors (RyR), allowing Ca^{2+} to bind to the myofilament protein troponin C, activating the contractile machinery. Normal cardiac function also requires relaxation to occur; this results from a decrease of free cytoplasmic Ca^{2+} levels. Several Ca^{2+} transport pathways are involved in this process, as Ca^{2+} reuptake into the SR by the SR Ca^{2+}-ATPase (SERCA), Ca^{2+} extrusion by the sarcolemmal NCX and plasma membrane Ca^{2+}-ATPase (PMCA) (Figure 1B) (Bers, 2000). This normal cardiac function requires perfect coordination of the ion currents and intracellular processes, as any imbalance in Ca^{2+} homeostasis of a cardiac myocyte can lead to electrical disturbances (from cellular AP prolongation to complex arrhythmic storms) (Eisner et al., 2017; Eisner, 2018).

Here we review the role of Ca^{2+} in generating and maintaining cardiac arrhythmias from basic arrhythmia mechanisms to recent progresses in pharmacological challenges and possible future therapies.

**CALCIUM IN PATHOPHYSIOLOGY,**
**ARRHYTHMIA MECHANISMS**

Arrhythmia mechanisms have multiscale dynamics in the heart. The lower end is the molecular scale, originating from the stochastic behavior of ion channels, resulting from thermodynamic fluctuations (Qu and Weiss, 2015). Next is the cellular scale, with differences in the shape of the APs originating from distant parts of the myocardium (Figure 2A). Under some diseased conditions, several mechanisms can lead to electrical disturbances at the cellular level, including early or delayed afterdepolarizations (EAD or DAD, respectively) (Figures 3A–D). Whole-cell Ca^{2+} oscillations, developing into propagating Ca^{2+} waves arise when the molecular and cellular dynamics merge at the tissue and organ level. The lower and higher scales tend to have a bidirectional information flow. A good example is when EADs arising during an AP due to abnormal ion currents and Ca^{2+} dynamics, can bring an extra amount of Ca^{2+} into the cell due to L-type Ca^{2+} channel reopening and potentiate Ca^{2+} waves. These multiscale dynamics can lead to life threatening complex arrhythmias.

Normal cardiac automaticity originates in the sinoatrial (SA) node. If SA node impulse generation is impaired, atrioventricular node (AV node) and Purkinje fibers can show automatic activity. These secondary pacemakers are also called latent or subsidiary pacemakers (Antzelevitch and Burashnikov, 2011). SA node pacemaker activity depends on interactions of membrane potential and [Ca^{2+}], This “coupled-clock” pacemaker system

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**FIGURE 1 |** Schematic diagram of the cardiac excitation-contraction coupling. (A) Structures involved in Ca^{2+} transport in cardiac myocytes. Red trace shows a typical systolic Ca^{2+} transient. Briefly, during the Ca^{2+}-induced Ca^{2+} release process, Ca^{2+} entering the cell via L-type Ca^{2+} channels releases a larger amount of Ca^{2+} from the sarcoplasmic reticulum to activate the contractile machinery. Ca^{2+} extrusion requires NCX, PMCA, and SERCA. (B) Detailed section of the dyad showing the major proteins involved in Ca^{2+} cycling. Reproduced from Eisner et al. used with permission (Eisner et al., 2017). β-AR, β-adrenoceptor; NCX, Na^+/Ca^{2+} exchange; PMCA, plasma membrane Ca^{2+}-ATPase; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; CSQ, calsequestrin; PLN, phospholamban.
is produced by membrane proteins, driving the AP and the intracellular Ca²⁺ cycling molecules (Figure 4) (Maltsev et al., 2006; Lakatta, 2010; Joung et al., 2011).

The “membrane clock” implies sarcolemmal proteins, continuously driving the membrane potential to more positive or more negative values. The most important and well-known participant is the hyperpolarization-activated funny current (If), working mainly during early diastolic depolarization. The consequent depolarization opens Ca²⁺ channels (ICa,T and ICa,L) and the pacemaker (slow type) action potential occurs. As in the case of the working myocardium, K⁺ currents repolarize the membrane. In the last two decades it has become clear that spontaneous Ca²⁺ release in a cardiac cell is not always pathological. In the “calcium clock” mechanism, spontaneous SR Ca²⁺ release events, the Ca²⁺ sparks activate INCX and cause late diastolic membrane depolarization. Coupled clock pacemaker system comprises functional interactions between the membrane and calcium clock (Figure 4) (Vinogradova et al., 2006; Lakatta and DiFrancesco, 2009; Lakatta et al., 2010).

For physiological contraction and relaxation, not only pacemaker automaticity, but also the impulse conduction system needs to work properly. Spontaneous depolarization from the SA node propagates and depolarizes the distant parts of the cardiac muscle (Figure 2B), via the SA node, AV node, Bundle of His, Bundle branches, and Purkinje fibers pathway.

![Cellular physiological electrical activities](image1)

**FIGURE 2** | Cellular physiological electrical activities. (A) Transmural heterogeneity in the cardiac ventricular action potential, showing (from left to right) recordings from: subendocardium, midmyocardium, and subepicardium. Note the spike-and-dome action potential configuration in the subepicardium. END, subendocardial myocyte; MID, midmyocardial “M” myocyte; EPI, subepicardial myocyte. (B) Series of typical subepicardial ventricular action potentials at normal pacing activity.

![Cellular pathophysiological electrical activities](image2)

**FIGURE 3** | Cellular pathophysiological electrical activities. (A) Phase 2 early afterdepolarization (EAD), (B) Phase 3 EAD, (C) Late-phase 3 EAD, (D) Delayed afterdepolarization (DAD) manifesting triggered activity. Ca²⁺ has an important role in generating afterdepolarizations. Underlying mechanisms are described in the relevant sections. (E) Automaticity (spontaneous membrane potential oscillations) occurs if the membrane potential of the cells shift to more positive values causing abnormal activity. (F) Cardiac voltage alternans, manifesting a long-short-long-short pattern. (G) Short term beat-to-beat variability of the action potential duration. (a), (b), and (c) show different time points after interventions that increase action potential duration and beat-to-beat variability leading to EAD generation. Right panel of (G) shows action potential duration at 90% of the repolarization (APD₉₀) as a function of time.
Cardiac arrhythmia mechanisms can be divided into two main categories: abnormal impulse formation and abnormal impulse conduction. In general, these arrhythmic events occur when the electrical activity of the heart is slower or faster than normal and/or becomes irregular.

Abnormal Impulse Generation
Focal activity (enhanced or abnormal impulse generation) is an important arrhythmogenic mechanism and consists of abnormal automaticity and triggered activity.

Automaticity
In the normal human heart, the SA node generates the propagating APs and determine the heart rate. In the case of parasystole, when the primary pacemaker is bordered by ischemic, infarcted regions the impulse cannot leave the SA node. Under these conditions, parasystolic pacemakers can take over pacemaker activity and fire APs at a lower rate compared to that of the SA node (Gussak et al., 2003). The AV node produces a junctional rhythm of 40 to 60 bpm and Purkinje fibers of about 20 to 40 bpm (Tse, 2016). In diseased hearts (e.g. heart failure, HF) membrane potential of pacemaker cells can shift to more positive values and this depolarization causes abnormal automaticity. Enhanced activity (i.e. tachycardia) increases rate of AP discharge by three mechanisms: threshold potential shifts to more negative, maximum diastolic potential shifts to more positive, and the rate of phase 4 depolarization increases (Figure 3E) (Jalife et al., 2009).

Early Afterdepolarization
Aside from the abnormal automaticity, the most common causes of focal activity are the early and delayed afterdepolarizations (EAD and DAD, respectively). EADs occur before the terminal repolarization (phase 2 and phase 3 repolarization) of the AP, while DADs occur after the repolarization when membrane potential reaches the resting levels (Figure 5).

EADs usually occur when repolarization reserve is compromised, i.e. reduced outward currents (I_{K1}, I_{Kr}, I_{Kr}) and/or increased inward currents (I_{Na,w} window, I_{Ca,t}, I_{Ca,l}) (Damiano and Rosen, 1984; Sipido et al., 2007; Benitah et al., 2010; Horvath et al., 2015; Karagueuzian et al., 2017), that is, there is a change in the net membrane current during the plateau (Figure 5A). In most of the cases these conditions cause prolongation of the AP, allowing I_{Ca,l} to recover from inactivation (Chiamvimonvat et al., 2017) and as a positive feedback loop, triggering an AP (January and Riddle, 1989) (Figure 3A). Alternatively, at membrane potentials negative to the activation threshold for I_{Ca,L}, spontaneous Ca^{2+} release from the SR can activate I_{NCX} driving a depolarizing current by reactivating I_{Na} (Figure 3B) (Szabo et al., 1994). In addition, although EADs usually
occur when the AP duration (APD) is prolonged, some data suggests a novel mechanism, where even shortening of APD can be responsible for generation of EADs (late-phase 3 EAD) (Burashnikov and Antzelevitch, 2003). Late-phase 3 EADs occur particularly under elevated intracellular Ca2+ loading (i.e. large Ca2+ transient) and are considered as a hybrid between EAD and DAD (Figure 3C). At normal APD and at membrane potentials negative to the equilibrium of the INCX (and ICl(Ca)), these Ca2+-mediated currents are weakly inward. However, if APD is abbreviated, they become strongly inward, allowing an INCX-driven depolarizing current, when the shorter repolarization allows a stronger (and not spontaneous) Ca2+ release from the SR (Burashnikov and Antzelevitch, 2006). The EAD generated under these circumstances interrupts the final phase of the AP. A key difference compared to the previously described EADs (and DADs) is a non-spontaneous Ca2+ release in generating late-phase 3 EADs (Figure 5). Late-phase 3 EAD also has clinical relevance, as its appearance is immediately following termination of other tachyarrhythmias, such as atrial flutter and fibrillation or ventricular tachycardia and fibrillation (Burashnikov and Antzelevitch, 2006).

The contribution of spontaneous SR Ca2+ release and an inward I_{NCX} to the generation of EADs has been described (Priori and Corr, 1990; Volders et al., 1997). Furthermore, Volders et al. elegantly demonstrated in isoproterenol induced canine ventricular myocytes that early Ca2+ aftertransients and their aftercontractions precede the upstroke of the subsequent EAD so that they are a primary event inducing EADs (Volders et al., 1997). The time course of the EAD generation is characterized by a conditional phase (in other words, an initial delay in repolarization, defined by net membrane current) and the EAD upstroke. In this regard, a significant role of I_{NCX} has been suggested in the initial delay in repolarization, thus in the conditional phase (Volders et al., 2000).

In previous studies, distinct spatial features of afterdepolarization-associated Ca2+ transients had been shown; i.e., a heterogeneous pattern indicating focal, spontaneous SR Ca2+ release in DADs and a homogeneous pattern suggesting I_{Ca,L}-induced Ca2+ release in EADs (Miura et al., 1993; Miura et al., 1995; De Ferrari et al., 1995). However, it must be noted, under certain circumstances (adrenergic stimulation mediated sudden [Ca2+]i changes), Ca2+ release during an EAD is not governed by sarcolemmal Ca2+ influx, so that it is spontaneous, which resembles as a heterogeneous pattern, just like in the case of DADs (Volders et al., 1997).

In our previous work, EADs were evoked by Ik, blockade (dofetilide), activation of Na+ current (I_{Na,L}) (veratridine), and activation of I_{Ca,L} (BAY K8644) at slow pacing rates. Additional application of the Ca2+ chelator BAPTA-AM decreased [Ca2+]i as expected, but either reduced EAD frequency in the presence of dofetilide and veratridine or further increased EAD frequency in the presence of BAY K8644 (direct augmentation of the I_{Ca,L}).
brings extra Ca²⁺ inflow and is a substrate for increased EAD likelihood. Since BAPTA-AM decreased EAD frequency in the presence of veratridine, but failed to shorten APD, these results contradict the exclusive role of APD in EAD generation and indicate that an increase in [Ca²⁺]i is a significant factor not only for generating DADs, but for evoking EADs as well (Horvath et al., 2015). Moreover, in another set of experiments of Kistamas et al. H₂O₂ significantly increased APD and relative short term beat-to-beat variability (SV) (Kistamas et al., 2015a) and increased the occurrence of EADs on canine ventricular myocytes. Elevation of [Ca²⁺]i, in H₂O₂ was shown by others which can account for the increased SV and EAD incidence (Goldhaber, 1996; Xie et al., 2009; Szentandrassy et al., 2015; Kistamas et al., 2015). Furthermore, we also showed in guinea pig cardiomyocytes, that spontaneous Ca²⁺ release from the SR mediates (I_{Na,L}) induced EADs (Horvath et al., 2013). The two possible mechanisms proposed by Zaza et al. by which I_{Na,L} promotes EAD genesis are (1) the reactivation of I_{Ca,L} during the plateau phase of AP and (2) SR Ca²⁺ overload (Zaza et al., 2008). In our experiments the first EAD occurred at a membrane potential more positive than the window Ca²⁺ current voltage range, meaning that not the reactivation of I_{Ca,L} was responsible for the generation of EADs. In fact, several mechanisms were addressed, showing the SR load was key in formation of the EADs: (a) anemone toxin II (ATX-II) facilitates I_{Na,L} that caused elevated systolic Ca²⁺ transient and SR load, (b) the spontaneous Ca²⁺ wave precedes the first EAD, and (c) Ca²⁺ buffering with BAPTA in the patch pipette abolished EADs (Horvath et al., 2013).

Therefore, our recent knowledge about the factors involved in the development of EADs includes changes in [Ca²⁺], and the amplitude of Ca²⁺ transient, along with the APD and beat-to-beat variability of APD, AP morphology and plateau potential, net membrane current, and the actual availability of L-type Ca²⁺ channels. Regardless of the type of EAD mechanisms, if the depolarizing effect of the EAD on the membrane potential is sufficient to activate I_{Na,L} the result will be an abnormal impulse generation, triggered activity (Hoffman and Rosen, 1981).

EADs are more likely to develop in midmyocardial cells and Purkinje fibers than in subepi- or subendocardial cells. There is a difference in ion current composition (less I_{Ko}, more I_{Na,L} in midmyocardial cells), consequently these regions are more prone to AP prolongation (Liu and Antzelevitch, 1995; Zygmunt et al., 2001; Szabo et al., 2005). EADs are generally observed under conditions of ventricular hypertrophy and HF, injured cardiac tissue, or when the myocardium is exposed to catecholamines, hypoxia, acidosis, and pharmacologic agents (Roden, 2004; Roden, 2006). The clinical significance of EADs is clear, as they can either serve as the trigger or as the substrate for initiation and perpetuation of torsade de pointes arrhythmia (Volders et al., 2000). Being as a trigger, as EADs can cause new APs which will be reflected on the ECG as ectopic beats. EADs provide a substrate by causing electrical inhomogeneity in the surrounding tissues.

**Delayed Afterdepolarization**

DADs are the other common causes of focal activity and were originally described as oscillatory afterpotentials (Ferrier et al., 1973). They occur in diastole, after complete repolarization of the cell (Figure 5B). DADs can originate from intracellular Ca²⁺ overload that induces spontaneous SR Ca²⁺ release, resulting in a depolarizing current via forward mode I_{NCX} (Mechmann and Pott, 1986). Other nonselective Ca²⁺-sensitive cationic currents (I_{Ks}) and chloride current (I_{Cl(Ca)}) may also be involved in DAD generation (Asakura et al., 2014). These three depolarizing currents result in a transient inward current (I_i), which is responsible for the membrane depolarization (Figure 3D). Ca²⁺ overload of the cardiac myocytes can occur in several diseases and also in several experimental conditions, e.g. toxic levels of digitals (Ferrier et al., 1973; Saunders et al., 1973; Rosen et al., 1973), catecholamines (Wit and Cranefield, 1977; Rozanski and Lipsius, 1985; Priori and Corr, 1990), hypokalemia and hypercalcemia (Tse, 2016), hypertrophy, HF (Aronson, 1981; Vermeulen et al., 1994), and rapid heart rates. The amplitude of the generated DAD depends on the size of the Ca²⁺ transient and on the properties of I_{NCX} and the inward rectifier K⁺ current (I_{Ks}) (Pogwizd et al., 2001; Sung et al., 2006; Maruyama et al., 2010). Subthreshold DADs [appearing as the U wave on the electrocardiogram (ECG)] are small voltage deflections, which although unable to trigger a propagating action potential, may still cause dispersion of excitability, thereby promoting regional conduction block (Rosen et al., 1975; Surawicz, 1998; di Bernardo and Murray, 2002). However, if DADs reach the threshold potential for the opening of Na⁺ channels, a spontaneous AP emerges and can result in premature ventricular contraction (PVC). The clinical significance of DAD generation lies in triggered activity that contributes to arrhythmogenesis with catecholaminergic polymorphic ventricular tachycardia (CPVT), atrial fibrillation (AF), and HF. In CPVT and HF, intracellular Ca²⁺ load combines with RyR dysfunction (“leaky” RyR). Under circumstances when the SR becomes loaded (high Ca²⁺ load, fast heart rate, and/or increased adrenergic tone) and/or RyR becomes leaky, spontaneous Ca²⁺ release is favored.

Considering the mechanism of the spontaneous Ca²⁺ release, there are two main patterns. First, focal Ca²⁺ release, when Ca²⁺ signal acts locally (Lipp and Niggli, 1994) and secondly, when the released Ca²⁺ leaves its focus and propagates as a global Ca²⁺ wave through the myocyte (Takamatsu and Wier, 1990; Wier et al., 1987; Cheng et al., 1993).

Unlike the EADs, DADs are always generated at relatively rapid rates (Antzelevitch and Burashnikov, 2011). As mentioned earlier, late-phase 3 EADs are considered as a hybrid between EAD and DAD. A key difference is the time of the SR Ca²⁺ release during the AP (Figure 5). Ca²⁺ release occurs during diastole in the case of DAD, while late-phase 3 EAD is generated at the late repolarization of the AP (Fink and Noble, 2010).

**Beat-To-Beat Variability of Action Potential Duration**

Variations (physiological or pathological) in AP configuration can cause disturbances in Ca²⁺ signaling and the electrical properties of cardiac muscle. In our previous experiments, we determined the beat-to-beat variability of AP duration in isolated canine left ventricular myocytes in several experimental settings (Kistamas et al., 2015a; Kistamas et al., 2015b; Szentandrassy et al., 2015; Magyar et al., 2016), as recent studies suggest the short term beat-to-beat variability (SV) of APD as a novel method for predicting...
imminent cardiac arrhythmias (Thomsen et al., 2004; Abi-Gerges et al., 2010). Higher variability is considered to be arrhythmic by increasing dispersion of refractoriness (Figure 3G). We established the concept of relative short term beat-to-beat variability of APD (RSV) by normalizing the changes of short term variability of APD to the concomitant changes in APD [see (Nanasi et al., 2017) for review]. We summarized that RSV was decreased by ion currents involved in the negative feedback regulation of APD (ICa,L, IKS, and IKs), while it was increased by INa and Ito, and in general, increased if repolarization reserved was compromised. RSV was also increased at faster rates and at increased [Ca2+]i. Transient changes of [Ca2+]i due to Ca2+ released from the SR were the dominant contributor to this process (Kistamas et al., 2015b). High RSV at faster rates can also be explained by the elevated [Ca2+]i, as faster pacing increases ICa,L, ultimately overloading the cell with Ca2+ which, in turn, increases RSV.

Cardiac Alternans
A severe form of this beat-to-beat variation is cardiac alternans, where short and long AP duration alternate (Figure 3F). Pulse and T-wave alternans can be clinically observed and are considered to be a precursor for cardiac arrhythmias (Rosenbaum et al., 1994; Verrier et al., 2011). Cardiac alternans originates from instabilities of membrane voltage or of Ca2+ cycling. At the cellular level, alternans is manifested as beat-to-beat alternations in contraction amplitude (mechanical alternans), APD (electrical or APD alternans), and Ca2+ transient beat-to-beat alternations in contraction amplitude (mechanical alternans) at constant heart rate. However, because of the bidirectional information flow between membrane voltage and Ca2+ cycling, electrical alternans is always influenced by Ca2+ alternans, and vice versa (Weiss et al., 2006).

Two mechanisms have been described for Ca2+-driven alternans. One depends on the relationship between SR Ca2+ content and the amount of Ca2+ released from the SR (Eisner et al., 2000). If this relationship is steep then a small increase of SR Ca2+ content will produce a large increase of the amplitude of the Ca2+ transient resulting in increased Ca2+ influx via INCx and a decreased influx via ICa,L (Ca2+-dependent inactivation). The net result is a decrease of SR Ca2+ content. The next beat therefore arises from a depleted SR resulting in a smaller Ca2+ transient and decreased INCx, so that the cell will gain Ca2+ resulting in a larger SR content and Ca2+ transient for the third beat (Eisner et al., 2006). Later, it was shown that reduced SERCA pump activity is also needed for an alternating pattern to develop (Shiferaw et al., 2003; Qu et al., 2007; Xie et al., 2008; Li et al., 2009). Another mechanism for Ca2+-driven alternans has been proposed, when on every beat, the SR load is unchanged, however the released amount of Ca2+ is alternating beat-to-beat. This kind of alternans results from the refractoriness of the RyRs, without the need for SR Ca2+ content alternans (Picht et al., 2006; Shkryl et al., 2012).

Voltage-driven or electrical alternans is determined by APD restitution. Here, the shorter the preceding diastolic interval, the less the APD (Nolasco and Dahlen, 1968). The steeper this relationship, the more likely is alternans to occur. There may be several causes for this APD restitution. The rapid, pacing-induced electrical alternans occurs at fast heart rates (short diastolic intervals, where recovery of ICa,L is crucial, becoming a key factor in regulating the steepness of APD restitution (Mahajan et al., 2008). Another APD alternating mechanism is driven by INa at slow or normal heart rates and possibly accounts for T-wave alternans in patients with Brugada syndrome (Hopenfeld, 2006). The third type of electrical alternans is mediated by non-inactivating ICa,L with IKS at normal or slow rates and possibly cause T-wave alternans in LQTS patients (Wegener et al., 2008). Electrical, restitution-based alternans has been associated with the breakdown of reentry into ventricular fibrillation (VF). At the tissue level, if cellular alternanses in different regions of the ventricle occur in phase with each other (spatially concordant), T-wave alternanses is observed on the ECG. A more malignant form, the spatially discordant APD alternans, manifesting as QRS alternans on the ECG, causes large dispersion of refractoriness, a substrate for reentry. Spatially discordant alternans is a significant cause of wave break, a phenomenon that is essential to VF (Garfinkel, 2007). It has been shown, that interventions that lower the slope of the APD restitution curve can turn multiwave VF to single-wave monomorphic ventricular tachycardia (VT) (Garfinkel et al., 2000; Wu et al., 2002).

Abnormal Impulse Conduction
Abnormal impulse conduction, i.e. reentry, occurs when the AP fails to terminate and has the ability to re-excite tissue regions which have already recovered. This mechanism can be divided into two main types, one with an obstacle (circus type with anatomic or functional barrier) and the other without an obstacle (phase-2 reentry and reflection). The key difference is in refractoriness. Circus movement reentry travels around an anatomic or functional obstacle and all cells are recovered from inactivation, while cells involved in reflection or phase-2 reentry show large differences in recovery from refractoriness with no obstacle in the way of the reentrant wave. In addition, classic nomenclature distinguishes between microreentry and macroreentry, where the reentrant circuit does not or does appear on the surface ECG, respectively.

The myocardium works as a functional syncytium (Figure 6A). The elemental components of this system are the gap junctions. Gap junctions form channels (comprised of two neighboring connexons) between adjacent cardiomyocytes and allow the cardiac AP to propagate from cell to cell and thereby initiate contraction. However, gap junction channels are unevenly distributed within the cells, expressing a larger portion of connexons) between adjacent cardiomyocytes and allow the cardiac AP to propagate from cell to cell and thereby initiate contraction. However, gap junction channels are unevenly distributed within the cells, expressing a larger portion of connexons. This anisotropy allows a much larger obstacle (phase-2 reentry and reflection). The key difference is in refractoriness. Circus movement reentry travels around an anatomic or functional obstacle and all cells are recovered from inactivation, while cells involved in reflection or phase-2 reentry show large differences in recovery from refractoriness with no obstacle in the way of the reentrant wave. In addition, classic nomenclature distinguishes between microreentry and macroreentry, where the reentrant circuit does not or does appear on the surface ECG, respectively.

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Reentry was first described in 1906 by Mayer in rings of tissue cut from jellyfish (ring model) (Mayer, 1906). Later work by Mines showed that circus-type reentry can be initiated by electrical stimulation in cardiac muscle and was the first to define the concept of circus movement reentry around an anatomical obstacle (Figure 7A) (Mines, 1913; Mines, 1914).

The anatomical barrier can be a valve, vessel or scar. The possibility that circus-type reentry can form without an anatomical obstacle was proposed by Garrey (1914).

Initiation of reentry requires a trigger and a substrate. The trigger can be a premature contraction, while tissue substrate is the dispersion of refractoriness. On top of that, fundamental settings are needed for reentry excitation with anatomical obstacle: (1) the impulse initiating the circus movement must propagate in one direction (unidirectional block) and (2) the proportion of absolute and relative refractoriness in the tissue, that is, the reentrant circuit must be long enough to let all areas—within the circuit, distal from the stimulus—recover from refractory (excitable gap), so the circuit can return to its origin and continue as a new cycle (Figure 7A). Consequently, (3) the circulating movement would terminate in case of interruption of the reentrant circuit (Mines, 1913). These criteria proposed by Mines are still in use today. The above mentioned excitation is, in fact, a propagating wave. The length of this wave (wavelength) is determined by the distance between the wavefront (phase 0, AP depolarization) and waveback (phase 3, repolarization), that is, creating an arrhythmogenic excitation needs the special properties of refractoriness and conduction velocity (Weiss et al., 2000). If the above three criteria are not met, i.e. in sinus rhythm if the tissue around the anatomical obstacle is homogenous (and the impulse pathway is wide enough), the wavefront can simultaneously propagate in both pathways around the barrier. However, if the tissue is electrically heterogenous, due to dispersion of refractoriness, unidirectional conduction block can form caused by a PVC, i.e. initiating reentry (Figure 7B).

The leading circle model was described by Allessie et al., as “the head of the circulating wavefront is continuously biting in its own tail of refractoriness” (Allessie et al., 1977). The main differences compared to the ring model are (1) the length of the circuit is determined by conduction velocity, stimulating efficacy, and refractory period not by an anatomic obstacle, (2) while the length of the circuit is not fixed, it can be altered by changes in electrophysiological properties of the tissue. (3) There is no excitible gap in the leading circle model and (4) a shortcut of the circuit is possible and finally (5) revolution time is inversely related to conduction velocity (Figure 7B) (Allessie et al., 1977).

Spiral waves and rotors can be induced in small two-dimensional pieces of cardiac muscle, without an anatomical barrier, and can drift through the tissue (Pertsov et al., 1993). Scroll waves are the three-dimensional forms of spiral waves. Spiral waves can develop both in homogenous and heterogenous tissues and either in stable or in an unstable form (Ikeda et al.,

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**Reentry Without Anatomical Obstacle (Functional Block)**

In the cases, when there is no anatomical barrier present, functional reentry can still form, maintained only by the electrical properties (dispersion of refractoriness) of the tissue. The best known examples are the leading circle, spiral wave, and figure-of-eight reentry (Figure 7B).

**Reentry With Anatomical Obstacle (Ring Model)**

Reentry was first described in 1906 by Mayer in rings of tissue cut from jellyfish (ring model) (Mayer, 1906). Later work by Mines showed that circus-type reentry can be initiated by electrical stimulation in cardiac muscle and was the first to define the concept of circus movement reentry around an anatomical obstacle (Figure 7A) (Mines, 1913; Mines, 1914).
The former might result in monomorphic VT, while the latter can cause polymorphic VT or torsade de pointes (Figure 7B) (Gray et al., 1995).

Figure-of-8 type reentry was first demonstrated by el-Sherif et al. In this case the reentrant wavefront reaches a functional conduction block surrounded by regions of reduced excitability. As conduction is not favored through such tissue, the wavefront drives clockwise and counterclockwise around the two arcs of functional block and beyond the barriers of low excitability the two separated waves can collide. If the conduction is slow enough and the intermediate area can be activated, reentry can form (Figure 7B) (el-Sherif et al., 1985; Lazzara, 1988).

Phase-2 Reentry

In the previous reentrant mechanisms, the trigger and the substrate originated from different etiologies, while in the case of phase-2 reentry, trigger and substrate are from the same source. Phase-2 reentry occurs in ischemia (Lukas and Antzelevitch, 1996), Brugada syndrome (Brugada and Brugada, 1992) or under conditions of higher pacing rates and higher extracellular Ca\(^{2+}\) concentration (Di Diego and Antzelevitch, 1994). It is caused by severe spatial dispersion of repolarization, that is, spike-and-dome configuration of AP morphology is lost at one site (predominantly at the epicardial region), while preserved at another site and is responsible for the transition to VT and VF. APs without the dome (short APD, early repolarization) can therefore be reexcited and reentry can be initiated (Antzelevitch, 2007). Loss of dome can be explained by a stronger transient outward current (I_{to}) current, and overall by the competitive behavior between INa and I_{to} (Greenstein et al., 2000; Szabo et al., 2005; Dong et al., 2010). If the actual membrane potential value is more negative than the activation threshold for the ICa,L then the AP dome vanishes. Cantalapiedra et al. showed in a simplified ionic and in a realistic cardiac model, that the origin of reexcitation is based on the presence of slow Ca\(^{2+}\) pulse, produced by the slow inward Ca\(^{2+}\) current (I_{si}), so that the slow pulse propagates to the regions of short APs until it triggers a fast pulse (Cantalapiedra et al., 2010). Interestingly, the same research group argued that conditions (e.g. drugs) increasing the ICa,L, to recover the dome or to prevent the loss of dome, increases dispersion of repolarization, however, also increasing the probability of reexcitation, through the stabilizing effect of the Ca\(^{2+}\) conductance (ICa,L) on the slow Ca\(^{2+}\) pulse (Cantalapiedra et al., 2009).

Reflection

Reflection is another example of non-circus movement reentry, with a one-dimensional behavior and can be the cause of PVCs or even lethal arrhythmias (Wit et al., 1972; Rosenthal, 1988; Van Hemel et al., 1988). Reflection describes reentry in a linear bundle of a conductive tissue. A stimulus from the proximal region travels through an inexorable gap and elicits an AP at the distal end. Slow electrotonic currents (inexcitable region can only transmit electrotonic currents) generated by this AP can then propagate in the retrograde direction and reenter and reexcite the proximal elements (Antzelevitch et al., 1980). There must be
an adequate conduction delay to let reflection happen (proximal end can recover from refractoriness), depending on the pacing interval and stimulus strength. It was also shown that neither EADs nor automaticity was required for reflection (Cabo and Barr, 1992; Kandel and Roth, 2015).

**Biexcitability**

A novel wave dynamic, termed biexcitability has been described in recent studies (Chang et al., 2012). In pacemaker regions \( I_{Ca,L} \) causes the activation, while in working muscle cells, the upstroke of the AP is driven by \( I_{Na} \) and \( I_{Ca,L} \). During biexcitability both form of activation can coexist at the same tissue. Under certain conditions, like long QT syndrome, repolarization reserve is compromised, APD prolongs, and EADs can occur. Consequently, there can be a situation where the cells develop two stable membrane potential values (~80 mV and ~50 mV) and switches between them (Gadsby and Cranefield, 1977), resulting in a Na+- and Ca2+-mediated (fast) or a Ca2+-mediated (slow) propagating wavefront. This bi-stable behavior might serve as an explanation for the two different possible outcomes of torsade de pointes. According to Chang et al., in cases where the Ca2+-mediated slow spiral wave is terminated, leads to termination of the torsade de points, while if the tissue is sufficiently heterogenous, Na+ and Ca2+-mediated fast spiral waves degeneratetorsade de pointes to VF (Chang et al., 2012; Chang et al., 2013).

DADs can induce focal VT by DAD-mediated triggered activity or initiate reentry. Moreover, unstable Ca2+ signaling can dynamically serve as a substrate for reentry, by promoting dispersion of excitability or promoting dispersion of refractoriness (Weiss et al., 2015). In those tissue regions, where subthreshold DADs do not trigger a propagating AP, the resultant small membrane depolarization can still be sufficient to depress excitability by inactivating the fast voltage gated Na+ channels. This condition can lead to reentry, as the inactivated Na+ channels form a regional conduction block for impulses generated by suprathreshold DADs (Rosen et al., 1975; Liu et al., 2015). In the latter case, DAD-mediated triggered activity at fast rates can promote Ca2+ transient alternans, which in turn causes APD alternans, thereby increasing the dispersion of refractoriness (Sato et al., 2006; Weiss et al., 2006). As previously mentioned, subthreshold EADs can also enhance the dispersion of refractoriness, also creating a reentry substrate.

For more detailed reviews on conduction disorders, see Qu and Weiss (2015) and Antzelevitch and Burashnikov (2011).

The following sections will provide further insights into intracellular Ca2+ handling maladies in the most prevalent inherited and acquired arrhythmia syndromes, caused by channelopathies and defects in Ca2+ handling genes. Ca2+ handling defects also have an arrhythmogenic role in diseases, such as heart failure and cardiomyopathies, however they are beyond the scope of the present review [see recent reviews (Coppini et al., 2018; Johnson and Antoons, 2018; Denham et al., 2018)].

**INHERITED SYNDROMES**

**Catecholaminergic Polymorphic Ventricular Tachycardia**

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a severe arrhythmogenic disorder, manifesting as a bidirectional or polymorphic VT, mainly in young patients with structurally healthy hearts after exercise or acute emotional stress (Reid et al., 1975). As heart rate increases as a result of exercise or emotional stress, the ectopic ventricular trigger increases in complexity, such that VT turns into VF and may lead to syncope or sudden cardiac death (Counsel, 1978; Leenhardt et al., 1995).

The main criteria for CPVT diagnosis are as follows: structurally normal heart (and normal coronary arteries in individuals above 40 years of age), normal QT interval, and adrenergically induced bidirectional or polymorphic VT (Venetucci et al., 2012). CPVT is also diagnosed in patients who carry a pathogenic mutation and in family members of a CPVT index case, fulfilling the above mentioned criteria (Priori et al., 2013). There are also nonspecific features, therefore not diagnostic criteria, including a prominent U wave on the ECG accompanied by sinus bradycardia (Postma et al., 2005).

In CPVT, arrhythmias are induced by Ca2+ release from the SR leading to a DAD. The fundamental feature of this process is the Ca2+ release unit (Ca2+ sparks), where the spontaneous Ca2+ release occurs. If sufficient number of release units are activated, a Ca2+ wave is born, which depends on the SR Ca2+ content and the SR Ca2+ threshold (Lukyanenko et al., 1999; Venetucci et al., 2007). Interventions that alter RyR opening will affect SR Ca2+ threshold. For example, caffeine increases the open probability of RyR, therefore it is easy to elicit spontaneous Ca2+ release (Trafford et al., 2000), on the other hand tetracaine has an opposite effect, by reducing RyR opening, SR Ca2+ release threshold is higher (Overend et al., 1997; Venetucci et al., 2006).

In the previous sections we detailed the normal Ca2+ cycling and consequences of elevated [Ca2+]i. Briefly, the main arrhythmogenic mechanism in CPVT is due to SR Ca2+ release increasing cytoplasmic Ca2+ levels, NCX exchanges Ca2+ with Na+, thereby generating \( I_{Na} \). \( I_{Na} \) produces DADs and if DADs reach the activation threshold of Na+ channels, an elicited AP causes triggered activity, which in turn can lead to an extrasystolic heartbeat. Mutations in CPVT have been shown to alter RyR function and increase the occurrence of spontaneous Ca2+ release events after sympathetic stimulation (Liu et al., 2006). β-adrenergic activation increases SR Ca2+ content, while the same process enhances RyR phosphorylation by Ca2+/calmodulin-dependent protein kinase II (CaMII) and protein kinase A (PKA) (Kashimura et al., 2010; Liu et al., 2011a; Venetucci et al., 2012). In addition to the phosphorylation by PKA, CaMII-mediated phosphorylation increases the \( I_{Ca,L} \) and SERCA (by removing the inhibitory effect of phospholamban on SERCA) and activates RyR. Simultaneous activation of \( I_{Ca,L} \), SERCA (increases SR Ca2+ content), and RyR therefore increases the possibility of spontaneous Ca2+ release (Maier and Bers, 2007; Hegyi et al., 2019). Experimental data confirmed that higher RyR Ca2+ sensitivity alone is not sufficient to elicit...
spontaneous Ca\(^{2+}\) release and that inhibition of CaMKII in a CPVT mouse model prevents arrhythmias (Venetucci et al., 2001). The structure of this intra-SR Ca\(^{2+}\) buffer changes Ca\(^{2+}\) concentration. At low SR Ca\(^{2+}\) concentrations (<0.6 mmol/L) CSQ2 is a monomer, which is converted to a dimer (0.6–3 mmol/L) or polymer (>3 mmol/L) at higher Ca\(^{2+}\) concentrations (Mitchell et al., 1988; Wang et al., 1998). It has been shown that, in the absence of functional CSQ2, RyR channels open spontaneously, without the need for L-type Ca\(^{2+}\) current mediated trigger (Knollmann et al., 2006) and that mutation of CSQ2 destabilizes Ca\(^{2+}\) storing capacity of the SR, which in turn alters the Ca\(^{2+}\) sensitivity of RyR (Viatchenko-Karpinski et al., 2004). In all CSQ2 mutations (missense, deleterious, nonsense), level of CSQ2 protein is reduced or absent, perhaps because it is more susceptible to degradation (Rizzi et al., 2008; Faggioni et al., 2012). Impaired polymerization (Bal et al., 2010), reduced RyR binding and modulation (Houle et al., 2004; Terent’ev et al., 2006) are generally associated with lower SR Ca\(^{2+}\) content, higher [Ca\(^{2+}\)]i, and Ca\(^{2+}\) leak through RyR, these effects

| Syndrome/Phenotype | Genes | Genetic Locus | Functional effect | Protein | Ref | Syndrome overlap |
|--------------------|-------|---------------|------------------|---------|-----|-----------------|
| CPVT-1             | RYR2  | 1q43          | GoF              | ryanodine receptor 2 | [Laitinen et al., 2001; Priori et al., 2001] | LQTS-14 |
| CPVT-2             | CASQ2 | 1p13.1        | GoF              | calsequestrin 2     | [Lahat et al., 2001] | |
| CPVT-4             | CALM1 | 14q31–q32     | LoF              | calmodulin 1        | [Nyegaard et al., 2012; Sondergaard et al., 2015; Sondergaard et al., 2017] | |
| CPVT-5             | TRDN  | 6q22.31       | LoF              | triadin              | [Chopra et al., 2009] | LOTS-17 |
| LOTS-4             | ANK2  | 4q25–q26      | LoF              | ankyrin B             | [Bhuyan et al., 2013; Mohler et al., 2003] | |
| LOTS-8             | CACNA1C| 12p13.33      | GoF              | α\(_{1C}\) subunit of LTCC | [Splawski et al., 2004; Thiel et al., 2006; Boczek et al., 2015; Landstrom et al., 2016] | |
| (Timothy syndrome) |       |               |                  |                     |                  | |
| LOTS-14            | CALM1 | 14q32.11      | GoF/LoF          | calmodulin 1        | [Shamgar et al., 2006; Gray and Behr, 2018; Jensen et al., 2018; Wren et al., 2019] | |
| LOTS-15            | CALM2 | 2p21          | LoF              | calmodulin 2        | [Shamgar et al., 2006; Gray and Behr, 2018; Jensen et al., 2018; Wren et al., 2019] | |
| LOTS-16            | CALM3 | 19q13.32      | LoF              | calmodulin 3        | [Shamgar et al., 2006; Gray and Behr, 2018; Jensen et al., 2018; Wren et al., 2019] | |
| LOTS-17            | TRDN  | 6q22.31       | LoF              | triadin              | [Attmann et al., 2015] | |
| (Triadin Knockout Syndrome) |       |               |                  |                     |                  | CPVT-5 |
| BrS-3              | CACNA1C| 12p13.33      | LoF              | α\(_{1C}\) subunit of LTCC | [Schwartz et al., 1995; Rosero et al., 1997] | SOTS-4, ERS/IVF |
| BrS-4              | CACNB2 | 10p12.33–p12.31| LoF | β\(_{2}\) subunit of LTCC | [Schwartz et al., 1995; Rosero et al., 1997] | SOTS-5, ERS/IVF |
| BrS-11             | CACNA2D1| 7q21.11       | LoF              | α\(_{2B}\) subunit of LTCC | [Schwartz et al., 1995; Rosero et al., 1997] | SOTS-6, ERS/IVF |
| BrS-15             | TRMP4 | 19q13.33      | GoF/LoF          | potential melastatin 4 | [Liu et al., 2013] | |
| SOTS-4             | CACNA1C| 12p13.33      | LoF              | α\(_{1C}\) subunit of LTCC | (Antzelevitch et al., 2007; Bjørregaard et al., 2010) | |
| SOTS-5             | CACNB2 | 10p12.33–p12.31| LoF | β\(_{2}\) subunit of LTCC | (Antzelevitch et al., 2007; Bjørregaard et al., 2010) | |
| SOTS-6             | CACNA2D1| 7q21.11       | LoF              | α\(_{2B}\) subunit of LTCC | (Antzelevitch et al., 2007; Bjørregaard et al., 2010) | |
| ERS/IVF            | CACNA1C| 12p13.33      | LoF              | α\(_{1C}\) subunit of LTCC | (Priori et al., 2013) | |
|                   | CACNB2 | 10p12.33–p12.31| LoF | β\(_{2}\) subunit of LTCC | (Priori et al., 2013) | |
|                   | CACNA2D1| 7q21.11       | LoF              | α\(_{2B}\) subunit of LTCC | (Priori et al., 2013) | |

CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; BrS, Brugada syndrome; SQTS, short QT syndrome; ERS, early repolarization syndrome; IVF, idiopathic ventricular fibrillation; LTCC, L-type Ca\(^{2+}\) channel; GoF, gain-of-function; LoF, loss-of-function.
can be augmented by β-stimulation (Song et al., 2007). An interesting feature of CSQ2 protein reduction is a subsequent reduction in triadin and junctin levels. Denegri et al. showed in CSQ2 knock-out animal model that viral gene transfer for in vivo replacement of CSQ2 restored normal CSQ2 levels along with triadin and junctin, and ultimately prevented arrhythmias (Denegri et al., 2012).

Other, less frequent gene mutations have also been described, such as autosomal recessive forms of CPVT, the CPVT-3 and CPVT-5, while CPVT-4 is an autosomal dominant form of the inherited syndrome. CPVT-3 subtype is related to the gene encoding trans-2,3-enoyl-CoA reductase-like protein (TECRL) and is first seen at an early age with high likelihood of infant sudden cardiac death (Bhuiyan et al., 2007). When CPVT-3 is studied in induced pluripotent stem cell-derived cardiomyocytes (iPSC-CM) slower Ca2+ reuptake, slower Ca2+ transient upstroke velocity, and increased APD has been observed, along with norepinephrine-induced DADs, which could be eliminated by flecainide (see below) (Devala et al., 2016). Mutations in CALM1-encoded calmodulin (CaM) cause the CPVT-4 subtype. In vitro experiments showed that this gene anomaly in the C domain compromises Ca2+ binding to CaM and impairs interaction between RyR and its CaM-binding domain, leading to an increased open state of RyR (Nyegaard et al., 2012; Søndergaard et al., 2015; Søndergaard et al., 2017). TRDN-encoded triadin mutation results in CPVT-5 subtype, which may cause diastolic Ca2+ leak and Ca2+ overload. Electron microscopy experiments uncovered fragmentation and reduced contact at the dyadic cleft, thus possibly lacking the negative feedback of SR Ca2+ release on the L-type Ca2+ channels, so SR Ca2+ overload may arise from the uncontrolled Ca2+ influx (Chopra et al., 2009).

A possible loss-of-function RyR mutation has also been proposed in a case classified as idiopathic VF, where a reduced SR Ca2+ sensitivity was shown (Jiang et al., 2007). Moreover, exercise induced bidirectional VT has been reported in types of long QT syndromes (LQTS-4 and LQTS-7) (Table 1) (Mohler et al., 2004; Vega et al., 2009).

Because of the hiding nature of the disease, it is difficult to diagnose CPVT, as patients have normal heart structure and show no symptoms before syncope or sudden cardiac death. However, if diagnosed, there are several therapeutic approaches to CPVT.

Generally speaking, life-long administration of β-blockers is the first choice as treatment. Studies showed that nadolol was clinically effective and a useful prophylactic (Priori et al., 2013). In countries, where nadolol is not available, propranolol was also shown to be effective (Hayashi et al., 2009). Carvedilol has been shown to inhibit store overload-induced Ca2+ release (SOICR) and is the only β-blocker to have RyR inhibitory action, albeit it is a less potent β-blocker after all (Zhou et al., 2011). Patients with CPVT are recommended to remove the triggers, in other words to limit or avoid any vigorous physical activities and stressful environments (Priori et al., 2013). In some patients (lacking long-term studies yet) β-blocker and non-dihydropyridine Ca2+-channel blocker (verapamil) combination therapy was shown to be beneficial (Swan et al., 2005; Rosso et al., 2007).

Flecainide administration has been suggested on top of β-blockers to prevent arrhythmias, in CPVT patients refractory to β-blockers alone (Biernacka and Hofman, 2011; Pott et al., 2011; van der Werf et al., 2011). Flecainide is a Na+-channel blocker drug, specifically a Class Ic antiarrhythmic agent. Several studies, including three retrospective cohorts in human patients with CPVT (Liu et al., 2011; Radwanski et al., 2016; Kamankeril et al., 2017) have shown the effectiveness of flecainide but there is still debate around the mechanism by which it exerts its antiarrhythmic effect. Watanabe et al. concluded that the most important effect of flecainide was blocking the RyR along with the Na+-channel blockade (Watanabe et al., 2009). They hypothesized that blocking RyR reduces the spontaneous Ca2+ release events and therefore DADs, while Na+-channel blockade prevents the possibility of triggered activity from any residual DADs (Hilliard et al., 2010). Of the Class Ic antiarrhythmic drugs, only flecainide and propafenone was shown to inhibit RyR activity (Hwang et al., 2011). On the other hand, Liu et al. showed in an animal model of CPVT that although flecainide prevents VT and triggered activity, spontaneous Ca2+ release and DADs were still detectable in single myocytes. They concluded that the antiarrhythmic effect of flecainide results from its Na+-channel blocker effect rather than via RyR inhibition (Liu et al., 2011b; Bannister et al., 2015). These conflicting results raise the question whether the different effects seen in the previous studies are dependent of a specific genetic mutation. In a recent study, isolated myocytes from Casq2−/− and RyR2R4496C+/− mice were compared (Hwang et al., 2019). It was found that the former produces a stronger proarrhythmic response upon isoproterenol stimulation, but flecainide prevented arrhythmias in both cases. Also independent from the underlying mutation, effect of flecainide decreased at high Ca2+ load. An additional drug has also been tested both in vitro and in vivo. 1,4-benzothiazepine derivative K201 (JTV519) was shown to prevent arrhythmias in mouse models by reducing RyR opening, SERCA activity and ICa,L (Lehnart et al., 2004; Loughrey et al., 2007).

The latest guidelines recommend implantable cardiac defibrillator (ICD) implantation in patients with diagnosis of CPVT who experience VT, syncope, or cardiac arrest despite the optimal medical treatment (Priori et al., 2013). However, the use of ICDs without concomitant use of β-blockers is dangerous because of the possibility of shock-related electrical storms in these patients (Mohamed et al., 2006; Pflaumer and Davis, 2012). Selective left cardiac sympathetic denervation (LCSD) can be a useful therapeutic method and may be considered in patients with uncontrollable arrhythmias (patients with contraindications to β-blockers; when ICD cannot be implanted; or when recurrent VTs manifest in patients with ICD and β-blockers treatment) (Priori et al., 2013). Pulmonary vein isolation (catheter ablation) was reported to be efficient in some patients with CPVT and AF (Sumimoto et al., 2010), while the possibility of gene therapy was suggested after successful adenoviral vector infection (CASQ2 gene) in R3Q knock-in mutant mouse with dysfunctional CSQ2 (Denegri et al., 2014). Family screening of first degree relatives
Prolongation of APD can happen in an inhomogenous pattern, congenital LQTS cases (El-Sherif et al., 2017). Current (LQTS-3). LQTS-1 decreased outward currents (LQTS1-2) and increased inward points towards compromised repolarization reserve with consequential reduction in IKs (Splawski et al., 1997); LQTS-6, a loss-of-function mutation of the KCNE1-encoded minK mutation, an anomaly, causing LQTS-12 by enhancing Na+ current (Nav1.5) (SNTA1-encoded channelopathy). LQTS is characterized by a prolonged QT interval on frontal ECG (Sanguinetti et al., 1996; Barhanin et al., 1996) while LQTS-2 is also a loss-of-function mutation, but of the KCNH2 channel gene (K,11.1), encoding IKs (Sanguinetti et al., 1995). LQTS-3 is an inherited gain-of-function mutation of SCN5A Na+ channel (Na,1.5) encoding IKs (Wang et al., 1995). All three mutations play key role in determining the length of AP and all of them points towards compromised repolarization reserve with decreased outward currents (LQTS1-2) and increased inward current (LQTS-3). LQTS-1–3 account for ~75–85% of the congenital LQTS cases (El-Shrief et al., 2017).

The above mentioned conditions are illustrated in the cases of LQTS-1, LQTS-2, and LQTS-3. LQTS-1 is caused by the loss-of-function mutation of the KCNQ1 gene (K,7.1) that encodes IKs (Sanguinetti et al., 1996; Barhanin et al., 1996) while LQTS-2 is also a loss-of-function mutation, but of the KCNH2 channel gene (K,11.1), encoding IKs (Sanguinetti et al., 1995). LQTS-3 is an inherited gain-of-function mutation of SCN5A Na+ channel (Na,1.5) encoding IKs (Wang et al., 1995). All three mutations play key role in determining the length of AP and all of them points towards compromised repolarization reserve with decreased outward currents (LQTS1-2) and increased inward current (LQTS-3). LQTS-1–3 account for ~75–85% of the congenital LQTS cases (El-Shrief et al., 2017).

Mutations of several other genes have been described in LQTS patients. Mutations of structural and channel interacting proteins result in: LQTS-4, a loss-of-function mutation of ANK2-encoded ankyrin B and leads to Ca2+ overload, QT prolongation, sinus bradycardia, AF, and CPVT (Bhuiyan et al., 2013; Mohler et al., 2003); LQTS-5, a loss-of-function mutation of the KCNE1-encoded minK mutation, consequential reduction in IKs (Splawski et al., 1997); LQTS-6, a loss-of-function mutation of the KCNE2-encoded MiRP1, causing a faster inactivation time course for IKr, enhanced ICa,L, and reduced ICa,L (Liu et al., 2014); LQTS-9, CALM3-encoded Caveolin 3, causing an enhanced ICa,L; and LQTS-11, a mutant AKT kinase anchoring protein (AKAP9-Yotiao) results in an abnormal response upon β-stimulation, as mutation reduces interaction between AKAP9 and K,QT1 channel α subunit (KCNQ1, IKs) leading to dysfunctional response to CAMP and a prolonged APD (QT) (Chen et al., 2007).

LQTS-9 and LQTS-10 (gain-of-function mutation in SCN4B-encoded Na+ channel Na,b4 β-subunit) together resemble the LQTS-3 phenotype as QT prolongation is achieved by increased Na+ current (Medeiros-Domingo et al., 2007). Mutation of SNTA1-encoded α-1-syntrophin is a gain-of-function gene anomaly, causing LQTS-12 by enhancing Na+ current (Na,1.5) (Wu et al., 2008). LQTS-7 and LQTS-13 are affecting repolarizing K+ currents and channels. LQTS-7 or Andersen-Tawil type 1 syndrome is caused by the loss-of-function mutation of the KCN2-encoded KQ,2.1 inward rectifier K+ channel, responsible for IK1, and as IK1 is an important player in terminal repolarization, reduction of KQ,2.1 function prolongs QT interval (Plaster et al., 2001). In LQTS-13, a loss-of-function mutation on KCNJ5-encoded KQ,3.4 causes loss of acetylcholine activated, G-protein-gated K+ (IKAcH) channel function. IKAcH is formed by KQ,3.1 and KQ,3.4. Mutation in KQ,3.4 function disrupts membrane targeting and stability, i.e. reduced membrane expression has been suggested as the cause of LQTS-13 (Yang et al., 2010).

Although most of the LQTS mutant genes are related to K+ and Na+ channels (i.e. LQTS-1–3 being ~75–85% of total congenital LQTS), there are several Ca2+-signaling proteins that are linked to the occurrence of long QT intervals, typically causing LQTS-8, LQTS-14, LQTS-15, LQTS-16, and LQTS-17 (Table 1).

LQTS-8 is a gain-of-function mutation of the CACNA1C-encoded α1C subunit of L-type Ca2+ channel (Ca,1.2) and is generally associated with Timothy syndrome. Timothy syndrome is a rare (less than 30 patients reported worldwide), but severe multisystem disorder, involving QT prolongation, syndactyly, congenital heart defects, cardiomyopathies, bradyarrhythmia (caused by AV block rather than sinus bradycardia), and autism (Splawski et al., 2004). LQTS-8 mutation of the Ca,1.2 leads to (1) a significant reduction in voltage-dependent inactivation of ICa,L, (2) enhanced ICa,L, (3) decreased current density with enhanced window current, and (4) a steeper APD restitution curve (Thiel et al., 2008; Boczek et al., 2015; Landstrom et al., 2016). A lesser inactivation of the steady-state current and/or increased peak current means a higher Ca2+ influx, which can in turn prolong APD, therefore QT interval. A steeper APD restitution curve is proarrhythmic, being a substrate for alternans, as detailed in previous chapters. The mutation can also cause T-wave alternans on the ECG by increasing the dispersion of repolarization (Zhu and Clancy, 2007). In iPSC cells of a Timothy syndrome patient, a cyclin-dependent kinase inhibitor, roscovitine was found to shorten APD by partially recovering inactivation of the mutant channel (yarotskyy et al., 2010; Yazawa et al., 2011). If Timothy syndrome/LQTS-8 is diagnosed, because of the high mortality, ICD implantation is the first choice. ICD is often supplemented with β-blockers, relying on the fact that they are generally effective in LQTS patients. Also, verapamil (Jacobs et al., 2006), mexiletine (Krause et al., 2011), and ranolazine (Shah et al., 2012) have been shown to shorten APD by affecting ICa,L and reducing the risk of arrhythmias.

LQTS-14–16 are newly described subtypes of LQT syndrome, caused by mutations in the genes coding the ubiquitous Ca2+ sensor and binder, calmodulin (CaM). Mutations in CALM1-encoding CaM1, CALM2-encoding CaM2, and CALM3-encoding CaM3 are responsible for producing LQTS-14, LQTS-15, and LQTS-16, respectively. Patients diagnosed with these conditions are usually young and have a high rate of cardiac arrest with severe QT prolongation (Gray and Behr, 2016). CaM
is important in the inactivation of Na⁺ channels, Ca²⁺-dependent inactivation of I_{Ca,L} and also important in the trafficking, assembly, and gating of the I_{Ca}, channel, KCNQ1 (Shamgar et al., 2006). Gene anomalies, affecting CaM, and therefore, Ca²⁺ binding and/or enhancing I_{Ca,L} can lead to severe APD prolongation. To date, over 20 mutations have been reported in the disease group of calmodulinopathies (Jensen et al., 2018; Wren et al., 2019) associated with LQTS, CPVT, and idiopathic VF. LQTS mutations, e.g. CaM-D130G, CaM-D96V, CaM-N98S, and CaM-F142L are all having impaired Ca²⁺ binding properties at the EF hand domains (Crotti et al., 2013). In CaM-D130G, CaM-D96V, and CaM-N98S mutations impaired CaM-dependent inhibition of RyR was reported, thereby increasing SR Ca²⁺ release due to an increased open state of RyR (Sondergaard et al., 2017; Jensen et al., 2018). Unexpectedly, an LQTS-associated CaM mutation, CaM-F142L did not diminish, but, increased the CaM-dependent RyR gating inhibition and caused faster RyR closing at high [Ca²⁺]i (Sondergaard et al., 2017). The authors proposed that the mutation displayed both gain-of-function and loss-of-function properties. In the process of gain-of-function, F142L mutation increases the interactions between the C-domain of CaM and the CaM binding domain of RyR, therefore enhancing RyR inhibition. On the other hand, the loss-of-function effect impairs the ability of the C-domain of CaM to bind free Ca²⁺, i.e. decreases RyR inhibition. However, at high [Ca²⁺]i, C-domain of CaM saturates allowing the increased RyR inhibitory effect to be the dominant one (Sondergaard et al., 2017). One might assume an overlap between LQTS and CPVT as diminished inhibitory effect on RyR gating is generally associated with CPVT. In mutant guinea pig cells, it was shown that decreased inhibition of RyR gating with impaired CaM effect on the CaM-dependent inactivation of I_{Ca,L} (i.e. increased I_{Ca,L}) may contribute to APD prolongation and that LQTS associated CaM mutations can lead to electrical alternans, a pathological feature of LQTS (Limpiitikul et al., 2014).

Recently a novel mutation, LQTS-17 has been proposed, however, the nomenclature is still indistinct. Some reviews refer to LQTS-17 as a mutation in TRDN-encoded triadin, which has also been linked to CPVT-5 (Landstrom et al., 2017). However, Altmann et al., originally identified the autosomal recessive homozygous or compound heterozygous frameshift loss-of-function mutations in TRDN, proposed the term Triadin Knockout Syndrome (TKOS) or TRDN-mediated autosomal-recessive LQTS, rather than LQTS-17 (Altmann et al., 2015). As in the previous case, here is also the possibility of an overlap with CPVT, as QT prolongation and disease appearance at young age is accompanied by arrhythmias that occur during exercise. The possible cellular mechanism includes reduced negative feedback on I_{Ca,L} (i.e. increased I_{Ca,L}), increased spontaneous Ca²⁺ release via RyR, and promotion of SR Ca²⁺ loading by NCX. It is not clear yet, whether the arrhythmogenic feature is mediated by DAD or EAD, but in a TRDN-null mice model, nifedipine aborted SR Ca²⁺ overload and spontaneous Ca²⁺ release (Chopra et al., 2009).

Most although of the LQTSs are inherited in an autosomal dominant form, there is a relatively rare, autosomal recessive inherited form, causing the Jervell and Lange-Nielsen syndrome (KCNIQ1 or KCNE1, leading to reduced I_{Na}). LQTS-related arrhythmias can be triggered by either slow or fast heart rate or by sinus pauses, therefore the relation between the LQTSs and the sinoatrial node is an interesting topic; for details, see the mini-review from Wilders and Verkerk (2018). For a detailed summary chart about LQTSs with the genetic loci, see a recent review of Landstrom et al. (Landstrom et al., 2017).

Pharmacological management of congenital LQTS starts with the administration of β-blockers, irrespective of the genotype (Moss et al., 2000). In one study, propranolol was shown to be the most effective β-blocker (Na⁺ channel blockade with limited effects on K⁺ channels) (Chockalingam et al., 2012). It should be noted that care is required with the use of β-blockers at low heart rate in LQTS-3 since bradycardia-dependent arrhythmias occur more often in these patients (El-Sherif et al., 2017). It was shown in LQTS-2 patients that besides β-blockers, application of mexiteline may also have positive effects (Kim et al., 2010; Ildarova et al., 2012). As an add-on therapy, in the case of LQTS-3 patients mexiteline (Schwartz et al., 1995), lidocaine, tocainide (Rosero et al., 1997), flecainide (Moss et al., 2005), phenytoin (Vukmir and Stein, 1991), or ranolazine (Moss et al., 2008) can be useful (Priori et al., 2013). In LQTS where mutations cause reduction in K⁺ currents, drugs that enhance K⁺ currents, nicorandil (Shimizu et al., 1998) or RPR26043 (Kang et al., 2005) were shown to be effective. ICD implantation is recommended for survivors of cardiac arrest or with recurrent syncope while on β-blocker (Priori et al., 2013). Left cardiac sympathetic denervation (LCSD) can also be performed on high-risk patients (arrhythmic events even in the presence of β-blocker/ICD). In addition to drugs or surgical procedures, lifestyle changes, such as avoidance of drugs that lengthen QT interval, identification and correction of electrolyte abnormalities, avoidance of strenuous exercise (especially swimming in LQTS-1 patients) and abrupt loud noises (LTQS-2) are recommended for patients (Priori et al., 2013).

**Brugada Syndrome**

Brugada syndrome (BrS) is characterized by ST elevation in V1-V3 ECG leads and is associated with elevated risk of polymorphic VT, VF, and sudden cardiac death (Brugada and Brugada, 1992). Two hypotheses have been proposed to describe the mechanism behind BrS and how ST segment elevation is linked to VT/VF. (Ringer, 1883) In the repolarization hypothesis, the loss of spike-and-dome AP morphology (heterogenous shortening of AP due to predominance of I_{Na} over I_{Na} and I_{Ca,L}) is suggested in the epicardium of the right ventricular outflow tract, causing an enhanced transmural dispersion of repolarization, i.e. ST elevation (Yan and Antzelevitch, 1999). The arrhythmogenic mechanism is delivered by phase-2 reentry, when the produced extrasystole can occur on the preceding T wave (R-on-T phenomenon), finally initiating VT/VF. (Bers, 2002) The depolarization theory proposes a slowed conduction and delayed activation mechanism in the right ventricular outflow tract as a substrate for reentry (Meregalli et al., 2005).
To date, 23 gene (gain-of-function and also loss-of-function) mutations have been described generating BrS-1–BrS-23 (Gray and Behr, 2016). The most common subtype is BrS-1, mutation affects the SCN5A-encoded α-subunit of the Na⁺ channel (Na⁺,1.5) and is accountable for about one third of all BrS (Antzelevitch et al., 2005). Genes, governing Ca²⁺-signaling molecules are also affected in BrS and causing 10–15% of cases (Burashnikov et al., 2010) (Table 1). Loss-of-function mutation of the CACNA1C-encoded α₁C-subunit (Ca₂⁺,1.2α1; BrS-3), the CACNB2-encoded β₂-subunit (Ca₂⁺,β2; BrS-4), and the CACNA2D1-encoded α₂δ₁-subunit (Ca₂⁺,α2δ1; BrS-11) of the L-type Ca²⁺ channel (governing I_Ca,L) have been described with a concomitant reduction of I_Ca,L (Antzelevitch et al., 2007). Patients harboring these Ca²⁺-related mutations showed BrS like ECG but with shorter than normal QT intervals. Recently, a new Ca²⁺-related mutation has been linked to BrS, accounting for about 6% of the cases. Mutation of the TRPM4-encoded Ca²⁺ activated non-selective cation channel transient receptor potential melastatin 4 (TRPM4; BrS-15) can either be gain-of-function or loss-of-function (Liu et al., 2013). TRPM4-mediated current increases APD in atrial muscle and isolated myocytes (Simard et al., 2013), possibly by promoting the plateau (as it is more likely to activate when Ca²⁺ is elevated). Therefore, TRPM4 mutation may change the AP dome and be arrhythmogenic. TRPM4 may also slow down conduction by altering the availability of Na⁺ channels (Liu et al., 2013).

There have been pharmacological attempts to manage BrS (isoproterenol, quinidine, procainamide, propafenone, pilsicainide, flecainide), some of them were effective in preventing recurrent episodes of VF or electrical storms, but did not reduce the overall risk of VF (Brugada et al., 2000; Shimizu et al., 2000; Morita et al., 2003; Belhassen et al., 2004; Ohgo et al., 2007). Guidelines are also recommending lifestyle changes (omit drugs that aggravate ST elevation, avoid alcohol and immediate treatment if fevered) and implantation of ICD (Priori et al., 2013).

**Short QT Syndrome**

Short QT syndrome (SQTS) is a rare inherited syndrome characterized by QT intervals essentially shorter than 360 ms and by an increased incidence of VT/VF mainly in youngsters (Bjerregaard et al., 2010). There are eight different gene mutations, of which three affect I_Ca,L (Table 1). Loss-of-function mutation of the CACNA1C-encoded α₁C-subunit (Ca₂⁺,1.2α1; SQTS-4), the CACNB2-encoded β₂-subunit (Ca₂⁺,β2; SQTS-5), and the CACNA2D1-encoded α₂δ₁-subunit (Ca₂⁺,α2δ1; SQTS-6) of the L-type Ca²⁺ channel, similar to the BrS-3, BrS-4, and BrS-11 phenotype. These mutations decrease I_Ca,L (alter current density and activation/inactivation kinetics), cause heterogenous shortening of APD and QT interval, therefore increases dispersion of repolarization (Antzelevitch et al., 2007). Transmural dispersion of repolarization (shortening effect is more pronounced in the epicardium compared to endocardium and midmyocardium) finally serves as a substrate for reentry. These mutations combined with the mutation of SCN5A-encoded α-subunit of the Na⁺ channel (Na⁺,1.5) causes an overlapping phenotype of SQTS and BrS.

**Early Repolarization Syndrome and Idiopathic Ventricular Fibrillation**

Early repolarization syndrome (ERS) is characterized by J-point and ST segment elevation in two or more contiguous leads on ECG (Boineau, 2007). The early repolarization pattern (in the inferior and/or lateral precordial leads) had been considered harmless, but it has recently been associated with idiopathic ventricular fibrillation (IVF) (Rosso et al., 2008). ERS now is diagnosed in IVF survival patients, without other causes of cardiac arrest (channelopathies; structural or non-structural heart diseases, e.g. BrS; metabolic; toxicological; respiratory; and infectious) (Haissaguerre et al., 2008). Seven gene mutations were shown, to date, including loss-of-function mutations of CACNA1C, CACNB2, and CACNA2D1, as seen in BrS or SQTS (Table 1). L-type channel mutations account for 16% of cases (Burashnikov et al., 2010). CaM-F90L mutation was proposed to be linked to IVF phenotype, where the authors speculated that CaM mutations could be arrhythmogenic by altering Ca²⁺ binding and/or binding of target proteins, thus generating a rather insensitive CaM and that the gene anomaly is more pronounced in the Purkinje system (Marsman et al., 2014). Recently, a novel single point mutation in RyR2 (RyR2-H29D) has been linked to IVF phenotype (Cheung et al., 2015). RyR2-H29D mutation was shown to be associated with short-coupled premature ventricular contractions, initiating polymorphic VT. This mutation caused diastolic Ca²⁺ leak at rest by higher open probability and higher frequency of opening of RyR at low diastolic Ca²⁺ levels in a non-PKA phosphorylated state, unlike the typical CPVT-related RyR mutations. Therefore, RyR dysfunction caused by RyR2-H29D mutation may play a role in short-coupled polymorphic VT.

J-point elevation associated malignant arrhythmias have recently been proposed with a new classification, as J-wave syndrome (Antzelevitch and Yan, 2010).

**ACQUIRED SYNDROMES**

**Acquired Long QT Syndrome**

In addition to the congenital form, LQTS can also be acquired. The prevalence of acquired LQTS is greater than that of congenital forms (El-Sherif et al., 2019). It is generally caused by adverse, unwanted drug effects and/or electrolyte abnormalities and may predispose to the prolongation of the APD/QT interval, increase in dispersion of refractoriness and to a higher risk for generating EADs, being the substrates for VTs, especially for torsade de pointes VT (El-Sherif and Turitto, 1999).

The above mentioned effects are often seen for the hERG-encoded (human ether-à-go-go-related gene or KCNH2) Kᵥ11.1 channel, responsible for IKr while effects on enhanced INa,L has also been reported (Yang et al., 2014). The role of dispersion of repolarization in generating tachyarrhythmias (and the role as a preclinical proarrhythmia marker) is further supported by a series of experiments, where DL-sotalol and amiodarone were compared (Milberg et al., 2004). It was shown, that both hERG-blockers increased QT interval, however only DL-sotalol increased transmural dispersion of refractoriness, EADs and
torsade de pointes (and caused triangulation of the AP), while amiodarone caused phase-2 prolongation of the AP without triangulation, which is otherwise considered proarrhythmic.

Several other causes of acquired LQTS have been described, including electrolyte disorders (El-Sherif and Turitto, 2011), such as hypokalemia, hypomagnesemia or hypocalcemia, hypothyroidism, hypothermia, but also antidepressant and antipsychotic treatments (Sicouri and Antzelevitch, 2018), female gender, and autoimmune and inflammatory diseases (Laizzerini et al., 2015; Boutjdir et al., 2016). Hypocalcemia causes QT prolongation via phase-2 prolongation of AP (Eryol et al., 2003), also longer and late Ca\(^{2+}\) influx (due to reduced Ca\(^{2+}\)-dependent inactivation of I\(_{\text{Ca,L}}\)) can favor the formation of EADs.

### Atrial Fibrillation

The most prevalent cardiac arrhythmia is atrial fibrillation (AF) and this can be classified as paroxysmal (spontaneously self-terminates into sinus rhythm in less than 7 days), persistent (lasts for more than 7 days), long-lasting persistent (AF lasts for more than a year) or permanent AF (without active rhythm control) (Kirchhof et al., 2016). AF is multifactorial. Basic arrhythmogenic mechanisms include Ca\(^{2+}\) handling defects such as triggered activity (DAD, late-phase 3 EAD), conduction block (reentry), and Ca\(^{2+}\)-driven cardiac alternans and altered Ca\(^{2+}\) buffering (Nattel and Dobrev, 2016). DAD-mediated triggered arrhythmias are underlined by Ca\(^{2+}\) handling instability in AF, namely RyR dysfunction (increased phosphorylation and open probability), increased SERCA function, increased diastolic SR Ca\(^{2+}\) leak and spontaneous SR Ca\(^{2+}\) release, increase in Ca\(^{2+}\) sparks and waves, enhanced CaMKII function (with subsequent RyR hyperphosphorylation), or reduced I\(_{\text{Ca,L}}\) (Sood et al., 2008; Neef et al., 2010; Shan et al., 2012; Voigt et al., 2012). Involvement of late-phase 3 EAD has also been shown (Burashnikov and Antzelevitch, 2006). As in most of the AF models APD is abbreviated, this observation can be somewhat surprising, since EADs generally occur at a prolonged APD. However, as we previously described, late-phase 3 EADs occur at shorter APD and at elevated Ca\(^{2+}\) loading conditions (such as rapid atrial pacing). These ectopic activities can serve as a trigger for reentry which is considered to be the main arrhythmogenic mechanism in AF. Also, I\(_{\text{Ca,L}}\) reduction in AF causes APD shortening and promotes reentrant activity (Heijman et al., 2014). Reduction of I\(_{\text{Ca,L}}\) might be governed by reduction of protein and mRNA levels of the channel (alpha subunit) after rapid pacing. This transcriptional downregulation of Ca\(^{2+}\) channel has been proposed to be mediated by activation of calcineurin by Ca\(^{2+}\)/CaM, which in turn, regulates nuclear translocation of NFAT (Qi et al., 2008).

A novel, interesting theory has been proposed, namely, Ca\(^{2+}\) signaling silencing, as an antiarrhythmic adaptive mechanism in AF (Greiser et al., 2014). The key observation was, that sustained high atrial pacing may not lead to Ca\(^{2+}\) instability, suggesting a role of accompanying cardiovascular diseases (e.g. HF) rather than “lone AF” itself in those cases when unstable Ca\(^{2+}\) signaling occurs in AF. Ca\(^{2+}\) signaling silencing process includes the failure of centripetal intracellular Ca\(^{2+}\) signal propagation (also unchanged level of Ca\(^{2+}\) sparks and decreased amplitude of the systolic Ca\(^{2+}\) transient), remodeling of the RyR complex (reduced protein expression and CaMKII-mediated phosphorylation), and lower Na\(^{+}\) concentration (consequential reduction in Ca\(^{2+}\) load) (Greiser, 2017). The decreased propagation was associated with an increase of cytoplasmic buffer power possibly due to increased Ca\(^{2+}\) sensitivity of myofilaments resulting from decreased phosphorylation of troponin I (Greiser et al., 2014). The authors concluded that the Ca\(^{2+}\) signaling phenotype in AF patients is a net result of factors that stabilize (i.e. Ca\(^{2+}\) signaling silencing) or destabilize it (arrhythmogenic Ca\(^{2+}\) instability). Therefore, future therapeutic approaches should identify the substrate (arrhythmia enhancing abnormalities or arrhythmia suppressing Ca\(^{2+}\) signaling silencing) and tailor therapies for individual AF patients (Kirchhof et al., 2016; Schotten et al., 2016; Greiser, 2017).

For an excess review about the role of Ca\(^{2+}\) in the pathophysiology of AF see the review of Denham et al. (2018).

### CONCLUSIONS

In summary, we have reviewed the roles of Ca\(^{2+}\) in cardiac E-C-coupling focusing on those defects which lead to cardiac arrhythmias in inherited and acquired syndromes. In the last few decades there have been great advances in the understanding of these arrhythmias, however, there is still a need for more work investigating the physiology and pathophysiology of Ca\(^{2+}\) related events. Designing drugs to treat a specific disease type has never been simple; it is enough to think of the early disappointing attempts to block the Na\(^{+}\) or K\(^{+}\) channels (CAST and SWORD trials, respectively). Multiple characteristics of novel therapeutic approaches have to be determined and to be considered as a complex, systems problem.

Along with the generally used β-blockers, newly developed selective drugs without proarrhythmic side effects are necessary. While implantable cardiac defibrillators provide longer life expectancy, they cannot prevent the onset of cardiac events. An additional helpful tool would be reliable and effective risk stratification and clinical guidance for all of the syndromes discussed. It should not be overlooked that in the future other genetic mutations may be discovered requiring novel biological therapies. Because of the diversity of inherited and acquired mutations individually tailored therapeutic approaches (gene-specific or mutation-specific pharmacological and/or gene therapy) will be required.

To gain a better understanding of the role of Ca\(^{2+}\) in the cardiac arrhythmias data from basic science should meet the clinical practice; translational aspects must be key in all fields of science.
AUTHOR CONTRIBUTIONS

KK conceived the review and drafted the manuscript. KK, RV, BH, TB, PN, and DE revised the manuscript critically for important intellectual content. DE contributed to the critical review of the literature, editing of the manuscript text and review of the figures. All authors approved the final version of the manuscript submitted.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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