8

Mechanisms of Ca^{2+}–Triggered Arrhythmias

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1. Introduction

The first evidence that altered intracellular Ca^{2+} homeostasis is causally involved in ventricular tachyarrhythmias was revealed by investigations of the pathophysiology of digitalis intoxication (Ferrier et al., 1973; Rosen et al., 1973). More recently, spontaneous Ca^{2+} release from the sarcoplasmic reticulum (SR) through the cardiac ryanodine receptor (RyR2) has been found to play a fundamental role in the generation of lethal arrhythmias. Such arrhythmias occur in both acquired forms of cardiac diseases (e.g., heart failure, atrial fibrillation) and in a number of congenital arrhythmia syndromes associated with mutations of RyR2 or calsequestrin[1], such as cathecholaminergic polymorphic ventricular tachycardia (CPVT[2]). The currently incomplete understanding of the mechanism underlying disrupted Ca^{2+} regulation in arrhythmogenesis in heart failure has led scientists to the consideration that CPVT as a simplified human and experimental model may help to clarify the disruption of Ca^{2+} homeostasis as a substrate for triggered activity (Priori & Napolitano, 2005). Therefore, a better understanding of the similarities and differences between the mechanisms underlying triggered arrhythmias in acquired and inherited cardiac diseases, holds the promise to develop new specific diagnostic and therapeutic approaches for effective treatment of defective ion handling.

In this chapter, we will review common mechanisms that cause the susceptibility to, and initiation of, Ca^{2+}-dependent arrhythmias with a focus on increased SR Ca^{2+} release due to congenital or acquired RyR2 dysfunction and increased SR Ca^{2+} load. Finally, RyR2 stabilizers and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) inhibitors as novel therapeutic targets will be discussed.

2. Altered Ca^{2+} homeostasis is an arrhythmogenic substrate

In a normal cardiac myocyte, Ca^{2+} couples electrical activation (action potential) to mechanical activity (contraction and relaxation) through a process referred to as *excitation-contraction coupling*. The cardiac cycle begins with membrane depolarization, which activates L-type voltage-gated Ca^{2+} channels resulting in a Ca^{2+} influx. This small elevation of cytosolic [Ca^{2+}] binds to the RyR2. The RyR2 opens, resulting in a larger Ca^{2+} release from

[1] SR Ca^{2+} buffer protein
[2] Induced by emotional stress or physical activity in the absence of structural heart disease

the SR, a phenomenon termed *calcium-induced calcium release* (Endo, 1977). Using confocal microscopy with Ca^{2+}-sensitive dyes, the opening of individual RyR2 clusters can be visualized as brief increases of $[Ca^{2+}]_i$, called Ca^{2+} sparks (Cheng et al., 1993). SR Ca^{2+} release units are normally synchronized to release Ca^{2+} simultaneously. Ca^{2+} release from the SR is the major source of Ca^{2+} required for excitation-contraction coupling. The whole process of Ca^{2+} movement is characterized by a transient increase in intracellular $[Ca^{2+}]$ from 100 nM (resting or diastolic Ca^{2+}) to about 1 μM (systolic Ca^{2+}), which initiates the contraction (Bers, 2001). Relaxation is initiated by the termination of SR Ca^{2+} release, of which mechanisms are complex and rather controversial. These mechanisms include RyR2 adaptation, RyR2 inactivation, SR Ca^{2+} depletion and luminal regulation of the RyR2 (Stern & Cheng, 2004). Ca^{2+} then dissociates from troponin C and is recycled into the SR through phospholamban-regulated SR Ca^{2+}-ATPase (SERCA2a) and removed from the cells via the Na^+/Ca^{2+} exchanger across the sarcolemmal membrane (Bers, 2002). The orchestrated interplay between these Ca^{2+} fluxes within different compartments is a prerequisite for the maintenance of Ca^{2+} homeostasis and ultimately, the heart rhythm. However, spontaneous Ca^{2+} release from the SR (also called Ca^{2+} leak) between two consecutive Ca^{2+} cycles will alter Ca^{2+} homeostasis and generate an arrhythmogenic substrate, which will directly disturb the cardiac rhythm. Abnormal changes in intracellular Ca^{2+} handling may cause contractile dysfunction, subcellular Ca^{2+} alternans and oscillations of the myocyte membrane potential, such as early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). Both EADs and DADs may evoke a number of triggered arrhythmias (Figure 1) potentially causing sudden cardiac death.

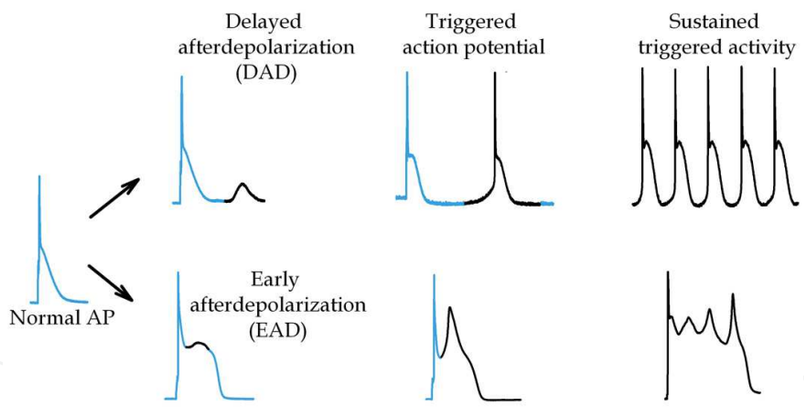

Fig. 1. Delayed (DAD) and early afterdepolarization (EAD) can evoke single or sustained trains of action potentials. Pro-arrhythmogenic and arrhythmic events are coloured black.

3. Triggered activity

The term *triggered activity* was coined to identify and differentiate pro-arrhythmic cellular events triggered by a preceding action potential from spontaneous depolarization of abnormal automaticity. Triggered activity is caused by membrane afterdepolarizations classified into (1) *early afterdepolarizations* (EADs) and (2) *delayed afterdepolarizations* (DADs) (Wit & Rosen, 1983). EADs are abnormal depolarizing oscillations of membrane potential that occur during the plateau or late repolarization of an action potential, while DADs are depolarizing membrane potential oscillations initiated after full repolarization of the

triggering action potential (Figure 1). When EAD and DAD reach thresholds of depolarizing currents, new triggering action potentials are generated that may elicit self-sustaining trains of triggered activity (Figure 1). Of the different cell types in the heart, Purkinje cells are particularly prone to initiating afterdepolarizations, suggesting that Ca^{2+}-dependent arrhythmic triggers may arise from the Purkinje fiber network (Boyden et al., 2000; Cerrone et al., 2007). This pro-arrhythmic behaviour is enhanced by disease-causing mutations in the RyR2 and greatly exacerbated by catecholaminergic stimulation (Kang et al., 2010).

3.1 Role of Ca^{2+} in EADs

Action potential prolongation and slowing of repolarization seem to be crucial determinants in the initiation and facilitation of EADs. Reactivation of the L-type Ca^{2+} channels at potentials within the "Ca^{2+} window current" (Hirano et al., 1992; January & Riddle, 1989), or and re-opening of Na^{+} channels (Boutjdir et al., 1994) have been proposed to underlie synchronous changes of $[Ca^{2+}]_i$ and upstroke of EADs. However, the concept that a change in membrane potential during an EAD primarily causes synchronous changes of $[Ca^{2+}]_i$ throughout the cardiac myocyte has been recently re-examined. Under β-adrenergic stimulation, spontaneous SR Ca^{2+} release in the form of propagating Ca^{2+} waves as a result of elevated SR Ca^{2+} content can also occur during the repolarizing phase of the action potential (Volders et al., 1997; Volders et al., 2000). This activates a Na^{+}/Ca^{2+} exchanger-dependent depolarizing current (NCX), which in an ischemic or failing heart triggers $[Ca^{2+}]_i$ alternans and concomitant sudden changes in action potential duration may give rise to EADs and trigger extrasystoles (Xie et al., 2009). EADs appear to depend on $[Ca^{2+}]_i$, NCX current (Patterson et al., 2006) and CaMKII (Anderson et al., 1998). Increased $[Ca^{2+}]_i$ further enhances L-type Ca^{2+} currents through the activation of CaMKII and is associated with transient inward currents carried by NCX.

More recently, another type of EADs associated with immediate recurrences of atrial fibrillation has been described (Burashnikov & Antzelevitch, 2006; Patterson et al., 2007). These EADs occur at potentials more negative than that of activation of L-type Ca^{2+} current, when the combination of short action potentials (parasympathetic stimulation) and increased SR Ca^{2+} load (sympathetic stimulation) were present. Triggered action potential generates a massive Ca^{2+} release of the Ca^{2+} accumulated in the SR during the pause that exceeds the duration of action potential. Because the action potential is short, the high $[Ca^{2+}]_i$ and the negative membrane potential generate NCX-mediated inward current that produces EADs. The most important hallmark of this type of triggered activity is that late phase 3 EADs are triggered by a massive but essentially *normal* SR Ca^{2+} release. This differs from other types of triggered activity, in which DADs and other EADs occur in conditions of *spontaneous* SR Ca^{2+} release. Normally, EADs occur under bradycardic conditions, whereas DADs are more likely to occur during tachycardia or rapid pacing (reviewed by Schotten et al., 2011).

3.2 Role of Ca^{2+} in DADs

DADs typically result from abnormal increase in $[Ca^{2+}]_i$ during diastole (Figure 2). The principal causes of elevated diastolic $[Ca^{2+}]_i$ and thus, cytosolic $[Ca^{2+}]$ oscillations are (1)

increased SR Ca^{2+} load, (2) *defective regulation of the RyR2-mediated Ca^{2+} release* or a combination of both. Both alterations increase the spontaneous RyR2 open probability and SR Ca^{2+} leak and cause sufficient cytosolic [Ca^{2+}] elevation associated with regenerative Ca^{2+} wave propagation. Ca^{2+} wave in turn may initiate a depolarizing Ca^{2+}-dependent inward current (I_{ti}). This transient current is largely carried by electrogenic NCX (>90% of I_{ti}) operating in its forward mode; NCX current depolarizes the sarcolemma and generates DADs by extruding 1 Ca^{2+} and taking up 3 Na^+. If the amplitude of a DAD reaches the threshold potential for voltage-gated Na^+ channels, a triggered action potential can result (Figure 1 and 2). This mechanism forms the basis for the typical rate and magnitude dependence of DADs: the faster is the triggering rhythm, the shorter is the interval of the triggered response and the faster are self-sustaining trains of DADs (Katra & Laurita, 2005). In other words, only spontaneous SR Ca^{2+} release events of sufficient magnitude and rate occurring at multiple sites synchronously within the cell will trigger DAD-mediated action potentials (Hoeker et al., 2009). The action potential initiation from a DAD is facilitated in cardiac myocytes from failing hearts, because of the increased expression of NCX and the reduction of repolarizing K^+ currents as a consequence of the electrophysiological remodelling (Tomaselli & Zipes, 2004). This implies that for any given rise in $[Ca^{2+}]_i$, the inward current carried by the NCX will be larger, and the reduction of outwardly directed K^+ currents will amplify the depolarizing effect of a given NCX current.

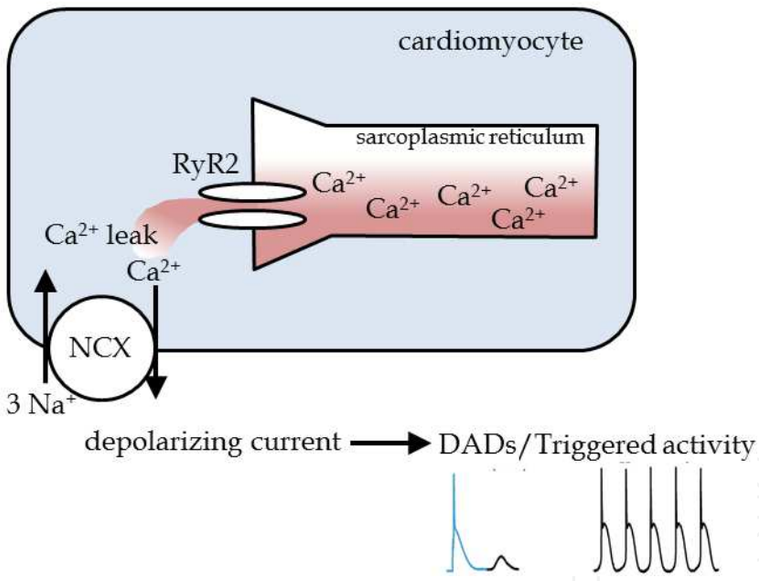

Fig. 2. Simplified electrophysiological mechanism underlying delayed afterdepolarization and triggered activity: spontaneous SR Ca^{2+} release ("Ca^{2+} leak") through dysfunctional RyR2 activates NCX exchange and causes membrane positive oscillations (DADs), which may escalate into triggered action potentials and sustained triggered activity (adapted from Kockskamper & Pieske, 2006).

4. The mechanism of triggered activity in situ

In conditions of increased spontaneous SR Ca^{2+} release, which may trigger DAD-evoked action potentials within a single myocyte, the presence of neighbouring cardiomyocytes *in*

situ act as a current sink, which inhibits DAD generation. To produce a triggered beat and overcome the current sink, spontaneous Ca^{2+} oscillations during diastole must occur in multiple neighbouring cells within a fairly narrow time scale. Whereas it is now well accepted that neighbouring cells are the source of spontaneous Ca^{2+} oscillations during diastole (Hoeker et al., 2009; Mulder et al., 1989), the mechanisms underlying triggered activity *in situ* remain elusive. It is unknown whether spontaneous Ca^{2+} oscillations originate from the extracellular space through L-type Ca^{2+} channels, or from SR via RyR2, or perhaps from other sources (e.g. myofilaments). The concept that neighbouring cells collectively share the same susceptibility for Ca^{2+} oscillations proved unlikely, for example, the Ca^{2+} handling properties required for the synchronization of triggered activity between cardiomyocytes vary both from apex to base and transmurally (Katra et al., 2004; Laurita et al., 2003; Prestle et al., 1999). Evidence is emerging that enhanced RyR2 open probability increases the amplitude and temporal synchronisation of spontaneous diastolic Ca^{2+} release, despite decreased cell-to-cell coupling and therefore, increased electrical membrane resistance (Plummer et al., 2011). Since these experiments were conducted on intact hearts, it remains unresolved whether the same mechanism underlies the propagation of triggered action potentials in, for example, non-ischemic failing hearts.

5. Ca^{2+}-induced arrhythmias in heart failure

Heart failure is associated with approximately 50% incidence of sudden cardiac death from ventricular fibrillation (Packer, 1985; Packer et al., 1999). A substantial body of evidence has accumulated demonstrating that *acquired* alterations in Ca^{2+} homeostasis lead to DADs in heart failure (reviewed by Pogwizd et al., 2001). Changes in Ca^{2+} handling, structural and electrophysiological remodelling are thought to account for abnormalities of excitation-contraction coupling and the susceptibility for cardiac arrhythmias, as well as to the reduced contractile force, prolongation of relaxation and the negative force-frequency relationship. The fundamental changes in Ca^{2+} handling that occur with heart failure are (1) increased NCX function resulting in increased removal of Ca^{2+} from the cytosol and larger depolarizing current and (2) the concurrently decreased inward rectifier K^+ current resulting in an even larger depolarisation; (3) reduced SR Ca^{2+} uptake due to decreased SERCA2a expression and reduced phosphorylation of phospholamban, (4) altered regulation of the RyR2 due to increased RyR2 phosphorylation associated with a decreased threshold for SR Ca^{2+} release (Trafford et al., 2000b) and (5) decreased β_1-adrenergic responsiveness, but increased β_2-adrenergic drive, which increases SR Ca^{2+} load (Desantiago et al., 2008). In heart failure, however, Ca^{2+} waves and DADs occur at reduced SR Ca^{2+} content. It is the adrenergic stimulation that is thought to increase SR Ca^{2+} load above the threshold required for triggered activity. Indeed, experimental findings from atrial and ventricular myocytes from failing hearts are consistent with enhanced SR Ca^{2+} loading associated with spontaneous SR Ca^{2+} release. The seemingly conflicting observation is that Ca^{2+}-dependent arrhythmias are more prevalent in heart failure due to enhanced diastolic SR Ca^{2+} release (Pogwizd et al., 2001), despite the decrease of SR Ca^{2+} content (Kubalova et al., 2005). To explain this dichotomy, Sobie et al. (2006) proposed an interesting hypothesis using a mathematical model based on the recent experimental findings. Their model predicts that (1) "rogue RyR2"[3] can operate almost invisibly to produce a fraction of the overall Ca^{2+} leak and (2) coupled gating between clustered RyR2s is disrupted in response to physiologic

[3] (unclustered) RyR2s in the SR membrane that are not part of RyR2 clusters

phosphorylation or excessive phosphorylation of RyR2s in disease states such as heart failure.

Defects in RyR2 regulation may also contribute to triggered activity and arrhythmogenesis in patients with atrial arrhythmias. Atrial fibrillation, the most common human cardiac arrhythmia, occurs in up to 30-40% of patients with heart failure (Cleland et al., 2003). Defects in Ca^{2+} release from the SR during diastole has been reported to be the mechanism underlying greater arrhythmogenic susceptibility in patients with atrial fibrillation (Hove-Madsen et al., 2004; Neef et al., 2010). Generation of transgenic mice harbouring a gain-of-function in the RyR2 has proven to be a valuable tool in unravelling molecular mechanisms causing atrial fibrillation. For instance, in $RyR2^{R176Q+/-}$ mice spontaneous atrial fibrillation was absent at rest but inducible by rapid atrial pacing, which also resulted in increased CaMKII phosphorylation of the RyR2 (Chelu et al., 2009). This implies that Ca^{2+} leak either through phosphorylated or defective RyR2 alone, might not be enough to produce atrial fibrillation. Both increased CaMKII activity and an arrhythmogenic substrate (e.g., RyR2 mutation) are elementary to produce atrial ectopy.

6. SR Ca^{2+} overload - a trigger for spontaneous SR Ca^{2+} release

The amount of Ca^{2+} within the SR is a critical regulator of contraction during normal excitation-contraction coupling. β-adrenergic stimulation, digitalis intoxication, rapid pacing and increased extracellular Ca^{2+} are conditions that increase inotropy by increasing SR Ca^{2+} content. When the amount of Ca^{2+} in the SR excessively increases, a phenomenon known as *SR Ca^{2+} overload* (Trafford et al., 1997; Trafford et al., 2001), a regenerative Ca^{2+} release and arrhythmia may occur. SR Ca^{2+} overload is a consequence of an imbalance between Ca^{2+} influx and efflux. This disequilibrium may evolve from (1) *the reduced Ca^{2+} efflux* (primarily due to increased NCX current in forward mode), (2) *increased SR Ca^{2+} uptake* (due to increased phosphorylation of phospholamban and/or SERCA2a expression), (3) *increased Ca^{2+} influx* across the sarcolemma (primarily due to increased L-type Ca^{2+} current), and (4) *altered SR Ca^{2+} buffering capacity* (due to a calsequestrin mutation). SR Ca^{2+} overload typically results in spontaneous SR Ca^{2+} release via RyR2. As opposed to the "silent" Ca^{2+} leak through rogue (or unclustered) RyR2 (Sobie et al., 2006), the diastolic Ca^{2+} leak via clustered RyR2 can be experimentally visualized as increased Ca^{2+} spark frequency, which, when high enough in a given volume of the cell, can initiate a Ca^{2+} wave. Once the Ca^{2+} wave has been initiated, the propagation of Ca^{2+} wave will largely depend on the amount of SR Ca^{2+} content. The greater the SR Ca^{2+} content, the more likely a Ca^{2+} wave is to propagate (Cheng et al., 1996) and trigger DAD. To distinguish spontaneous Ca^{2+} release due to the elevated SR Ca^{2+} load from depolarisation-initiated Ca^{2+} release, Wayne Chen's group coined the term *store overload-induced Ca^{2+} release* (SOICR) (Jiang et al., 2004). SOICR occurs when the threshold level for Ca^{2+} retention by RyR2 is exceeded. In addition to the SR Ca^{2+} content, the threshold is also determined by the properties of RyR2. For instance, the application of low dose caffeine, which increases the open probability of the RyR2 (Rousseau & Meissner, 1989), decreases the threshold and increases diastolic SR Ca^{2+} leak (Trafford et al., 2000b). On the other hand, tetracaine, which decreases RyR2 opening (Gyorke et al., 1997; Xu et al., 1993), increases threshold and decreases SR Ca^{2+} leak (Overend et al., 1997). Thus, modulation of RyR2 may have a significant impact on the properties of SOICR and therefore on the occurrence of DADs and triggered arrhythmias, while sustained impact on Ca^{2+}-

induced Ca^{2+} release is unlikely. Based on these observations, (Trafford et al., 2000b) proposed the *"SR Ca^{2+} auto-regulation" hypothesis,* which predicts that increased open probability of the RyR2 only transiently enhances spontaneous SR Ca^{2+} release, because of SR luminal Ca^{2+} regulation. Changes in RyR2 activity are compensated for by the SR Ca^{2+} content, implying that increased release reduces the steady-state SR Ca^{2+} content and consequently spontaneous Ca^{2+} release.

7. Arrhythmias triggered by dysfunctional SR Ca^{2+} handling

7.1 Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Abnormalities of intracellular Ca^{2+} regulation caused by dominant mutations in the RyR2 gene (Priori et al., 2001) and by recessive mutations in the calsequestrin gene (Lahat et al., 2001), encoding SR Ca^{2+} binding protein (calsequestrin 2), may account for malignant catecholamine-induced polymorphic ventricular arrhythmias (CPVT) (Priori et al., 2001; Swan et al., 1999). CPVT occurs suddenly and unexpectedly in young and otherwise healthy individuals under emotional stress or physical exercise (e.g. increased catecholaminergic stimulation). Known RyR2 and calsequestrin mutations account for approximately 50-60% and 1-2% of CPVT mutations, respectively (Cerrone et al., 2009). Causes for the remaining CPVT mutations have yet to be identified. Even prior to the linkage of RyR2 mutations and CPVT, the striking similarity between ECG patterns (bidirectional or polymorphic ventricular tachycardia) observed in CPVT patients and digitalis-induced arrhythmias in patients with digitalis-intoxication, led to the hypothesis that arrhythmias in CPVT were most likely initiated by SR Ca^{2+} overload and consequently by DADs and triggered activity (Leenhardt et al., 1995).

7.1.1 RyR2 mutations

Generation of genetically modified mouse models has advanced our understanding of mechanisms of both autosomal-dominant and recessive CPVT. The first CPVT transgenic mouse model with a gain-of-function defect in the RyR2 was generated by the Priori group (Cerrone et al., 2005). The introduction of the $RyR2^{R4496C+/-}$ mutation reliably reproduced the human phenotype. On exposure to isoproterenol (β-adrenergic agonist), this mouse model produced DADs and triggered activity underlying CPVT (Liu et al., 2006). Subsequent studies using other transgenic mouse models (Kannankeril et al., 2006; Lehnart et al., 2008; Uchinoumi et al., 2010) confirmed that RyR2 mutations modify intracellular Ca^{2+} regulation through an increased SR Ca^{2+} leak as a result of increased RyR2 open probability at resting conditions (Jiang et al., 2005). It is this increased SR Ca^{2+} leak that accounts for the increased propensity of DAD-mediated triggered activity. Lowered threshold due to the increased Ca^{2+} sensitivity to luminal and/or cytosolic Ca^{2+} has been attributed for the elevated propensity to arrhythmias in the $RyR2^{R4496C+/-}$ mutant (Fernandez-Velasco et al., 2009; Jiang et al., 2005). The decreased threshold may explain why mice expressing the RyR2 mutation are more likely to develop Ca^{2+} waves and DADs. However, neither mice nor patients with CPVT develop arrhythmias at rest. Faster heart rate and SR Ca^{2+} uptake during β-adrenergic stimulation is the physiological trigger, which increases SR Ca^{2+} load and subsequent Ca^{2+} waves followed by DAD-mediated triggered beats in ventricular cardiomyocytes harbouring RyR2 mutations (Kannankeril et al., 2006; Lehnart et al., 2008; Liu et al., 2006).

This raises the question as to why β-adrenergic stimulation is required to produce CPVT. β-adrenergic stimulation has been reported to produce Ca^{2+} waves by increasing the SR Ca^{2+} content and not by decreasing the threshold for SR Ca^{2+} release (Kashimura et al., 2010). β-adrenergic stimulation even increased the threshold for spontaneous SR Ca^{2+} release independent of SERCA2a activity in both wild-type and $RyR2^{R4496C+/-}$ cardiac myocytes, suggesting the reduced rather than increased arrhythmogenic potential for Ca^{2+}-dependent arrhythmias. This does not exclude the possibility that different RyR2 mutations respond differently to β-adrenergic stimulation, indicating diverse implications on the severity of the phenotype. For instance, it has been reported that the $RyR2^{R2474+/-}$ mutation renders the RyR2 more sensitive to adrenergic stimulation by destabilizing interdomain interaction within RyR2 (Uchinoumi et al., 2010). Such a defect could lower the SR Ca^{2+} threshold, so that enhanced SR Ca^{2+} uptake induced by β-adrenergic stimulation causes the level of free Ca^{2+} to overshoot its lowered SOICR threshold (Priori & Chen, 2011). Importantly, triggered activity in $RyR2^{R4496C+/-}$ cardiomyocytes does occur in the absence of β-adrenergic stimulation, if SR Ca^{2+} content is increased by ouabain, a cardiac glycoside with Na^+/K^+-ATPase inhibiting effect. Ouabain elevates cytosolic [Na^+] and thus, indirectly elevates SR Ca^{2+} load through the reverse mode of NCX and, in contrast to wild-type cardiac myocytes, massively increases the occurrence of DADs and triggered action potentials in $RyR2^{R4496C+/-}$ cardiomyocytes (Sedej et al., 2010). The finding that increased SR Ca^{2+} content (in the absence of catecholamines) suffices to induce arrhythmogenic events in mouse cardiomyocytes with a human CPVT mutation (Sedej et al., 2010), inspired Brette (2010) to give CPVT a new name: *Calcium* polymorphic ventricular tachycardia. Taken together, these findings highlight the importance of SR Ca^{2+} content in the CPVT arrhythmogenesis.

7.1.2 Calsequestrin 2 mutations

The recessive forms of CPVT due to the calsequestrin gene mutation (casq) are found in approximately 1-2% of CPVT patients (Cerrone et al., 2009). Calsequestrin is an intra-SR Ca^{2+} binding protein, which plays a pivotal role in regulating SR Ca^{2+} release by (1) increasing the SR luminal total Ca^{2+} content through its low Ca^{2+} binding affinity, (2) buffering free Ca^{2+} levels in the SR lumen, and (3) regulating SR Ca^{2+} release either through the direct (MacLennan & Chen, 2009) or indirect interaction with RyR2 (calsequestrin-triadin-junction complex) (Gyorke & Terentyev, 2008; Qin et al., 2008). Reduced levels of calsequestrin may result in rapid recovery of SR free Ca^{2+} after each Ca^{2+} release and a potentially higher level of SR free Ca^{2+} during a sudden increase in SR Ca^{2+} loading (e.g., β-adrenergic stimulation). The common hallmark of all calsequestrin-associated CPVT mutations is decreased luminal Ca^{2+} binding and Ca^{2+} buffering resulting in increased luminal free Ca^{2+}, which exceeds the normal threshold for SOICR. In turn, this increases the propensity for SR Ca^{2+} release from the overloaded SR and evokes DADs and triggered activity. Studies on $casq^{-/-}$ null mice and humans showed that calsequestrin is not critical for normal RyR2 regulation under resting conditions, since excitation-contraction coupling appeared normal and arrhythmias were not observed under basal conditions. However, the administration of isoproterenol increased the SR Ca^{2+} leak, which was proportional to the calsequestrin loss, indicating that calsequestrin's primary role is a "molecular brake" that prevents spontaneous Ca^{2+} release at high SR Ca^{2+} load (Chopra et al., 2007). Taken together, calsequestrin-induced CPVT and RyR2-mediated CPVT share a common causal arrhythmogenic mechanism involving disruption of Ca^{2+} homeostasis.

8. Molecular mechanisms underlying increased SR Ca^{2+} leak

At present many aspects of the molecular mechanisms by which RyR2 mutations alter the physiological RyR2 properties in acquired (e.g. heart failure) and congenital triggered arrhythmias (e.g. CPVT) remain controversial. However, an increase in Ca^{2+} leak from the SR via RyR2 is the unifying phenomenon for heart failure and CPVT. The concept that arrhythmias occur due to increased Ca^{2+} sensitivity (and thus, lower threshold) of the RyR2 at luminal or cytosolic sites has emerged.

8.1 Increased sensitivity of RyR2 to luminal or cytosolic Ca^{2+} activation

Spontaneous SR Ca^{2+} release occurs when the SR Ca^{2+} content reaches threshold (Dibb et al., 2007), suggesting that luminal Ca^{2+} concentration affects RyR2 opening and modulates the amount of Ca^{2+} released from the SR during SR Ca^{2+} overload. Indeed, increasing luminal Ca^{2+} elevates RyR2 open probability and increases RyR2 sensitivity to Ca^{2+} leading to spontaneous SR Ca^{2+} release (SOICR) (Fernandez-Velasco et al., 2009; Jiang et al., 2004; Jiang et al., 2005). SR Ca^{2+} release increases in nonlinear accelerating fashion with increasing SR luminal Ca^{2+} concentration (Trafford et al., 2000a). This nonlinear relationship implies that SR Ca^{2+} release is not passively driven by a Ca^{2+} concentration gradient and raises the question, whether other mechanisms beside the luminal SR Ca^{2+} concentration may also trigger RyR2 activity.

Numerous CPVT-linked RyR2 mutations expressed in heterologous cells as well as native cardiomyocytes preferentially sensitize the RyR2 to luminal Ca^{2+} activation (Jiang et al., 2004; Jiang et al., 2005; Jones et al., 2008). Consequently, the threshold luminal Ca^{2+} level required for triggering SOICR is reduced and susceptibility for SOICR increased. However, few RyR2 mutations affects both the response of the RyR2 to cytosolic and luminal Ca^{2+} concentration (Fernandez-Velasco et al., 2009; Jiang et al., 2004; Jones et al., 2008). Despite the increased sensitivity to both cytosolic and luminal Ca^{2+} concentration, Ca^{2+}-induced Ca^{2+} release in cardiomyocytes harbouring CPVT RyR2 mutations is at resting conditions little, if at all, affected (Mohamed et al., 2007). This can be explained by the "SR Ca^{2+} auto-regulation" hypothesis (Trafford et al., 2000a). SR Ca^{2+} content counterbalances defective luminal or cytosolic Ca^{2+} activation of the RyR2. For instance, increased SR Ca^{2+} release due to enhanced luminal or cytosolic Ca^{2+} activation will lead to reduced SR Ca^{2+} load, which will counteract increased Ca^{2+} release propensity from the SR (auto-regulation). Altered Ca^{2+} activation of RyR2 will have only a transient effect on Ca^{2+}-induced Ca^{2+} release under resting conditions and lead to a new steady-state within few heartbeats. In conditions above the critical SR Ca^{2+} load (e.g., emotional stress, physical exercise, β-adrenergic stimulation in heart failure), the "SR Ca^{2+} auto-regulation" fails to prevent cardiomyocytes from SOICR, the trigger of DADs and triggered arrhythmias. Taken together, it is the increase in SR Ca^{2+} content what renders the SR Ca^{2+} leak uncontrolled.

To explain lower threshold for SOICR release, two mechanisms have been proposed and they will be presented below: (1) excessive RyR2 phosphorylation linked with the FKBP12.6 dissociation from the RyR2 complex and (2) weaker interdomain interactions within RyR2.

8.1.1 FKBP12.6 unbinding hypothesis (increased RyR2 phosphorylation)

RyR2 forms a macromolecular complex with numerous proteins on the SR luminal side (e.g., triadin, junctin, calsequestrin) as well as the cytosolic side (e.g., calmodulin, FKBP12.6), just to name a few. In addition, two main kinases are also part of the RyR2 complex involved in RyR2 phosphorylation: protein kinase A (PKA), activated by β-adrenergic stimulation, and CaMKII, activated by increased cytosolic Ca^{2+} turnover (e.g. increased heart rate). These proteins provide different regulatory modalities to control RyR2 open probability. Disruption of critical protein-protein interactions within the RyR2 macromolecular complex may alter the sensitivity of the RyR2 to Ca^{2+} activation. For instance, stabilization of the RyR2 is thought to depend on the 12.6. kDa FK506-binding protein (FKBP12.6 or calstabin 2). This protein prevents aberrant activation of the RyR2 during the diastole. The dissociation of FKBP12.6 from RyR2 as a result of a RyR2 mutation or phosphorylation of RyR2 by PKA during β-adrenergic stimulation has been shown to increase the sensitivity of the RyR2 to cytosolic Ca^{2+} activation (Lehnart et al., 2008; Marx et al., 2000; Wehrens et al., 2003). In other words, RyR2 mutations or the "hyperadrenergic" state as often seen in heart failure make the RyR2 channel leaky and increase the susceptibility for the initiation and propagation of Ca^{2+} waves. These findings led to the paradigm that impaired binding of FKBP12.6 to RyR2 is a common final pathway for arrhythmogenesis in CPVT and heart failure (Wehrens et al., 2003). However, other studies failed to reproduce these findings. Furthermore, in later studies the same CPVT RyR2 mutations showed either no effect on FKBP12.6 binding (George et al., 2003; Jiang et al., 2005; Liu et al., 2006) or even increased binding affinity of FKBP12.6 for the RyR2 (Tiso et al., 2002). Recent evidence even suggests that PKA is not involved in the dissociation of FKBP12.6 from RyR2, thus questioning the causality between RyR2 phosphorylation and FKBP12.6 dissociation (Guo et al., 2010).

8.1.2 Domain unzipping hypothesis (weaker interdomain interaction)

Proper folding of the RyR2 relies on intimate intermolecular interaction between RyR2 domains. These domain interactions are believed to stabilize and maintain the closed state of the RyR2 channel (Ikemoto & Yamamoto, 2000), suggesting a close mechanistic similarity between PKA-mediated FKBP12.6 dissociation and domain-domain interaction within the RyR2 channel (Ikemoto & Yamamoto, 2002). For example, defective RyR2 interdomain interactions (also called domain unzipping) between the N-terminal domain and central domain in the context of RyR2 mutations weaken this interaction and destabilize the closed state of the RyR2 (Ikemoto & Yamamoto, 2000; Tateishi et al., 2009). Weakening of these interdomain interactions occurs transiently on a beat-to-beat basis during excitation-contraction coupling, but permanently in both CPVT-associated RyR2 mutations and in pacing-induced failing hearts (Oda et al., 2005). Destabilisation of the zipped state may alter the sensitivity of RyR2 to luminal or cytosolic Ca^{2+} and contribute to abnormal SR Ca^{2+} leak. Although the majority of the reported CPVT mutation sites are within the N-terminal and central domain, it is possible that "domain unzipping" also affects less conserved regions of RyR2 mutations associated with CPVT. It has been demonstrated that, depending on the location of the RyR2 mutation, a distinct pattern of conformational instability in Ca^{2+} handling and interdomain interaction is introduced. This suggests that the mutational locus may be an important mechanistic determinant of Ca^{2+} release channel dysfunction in arrhythmia and sudden cardiac death (George et al., 2006).

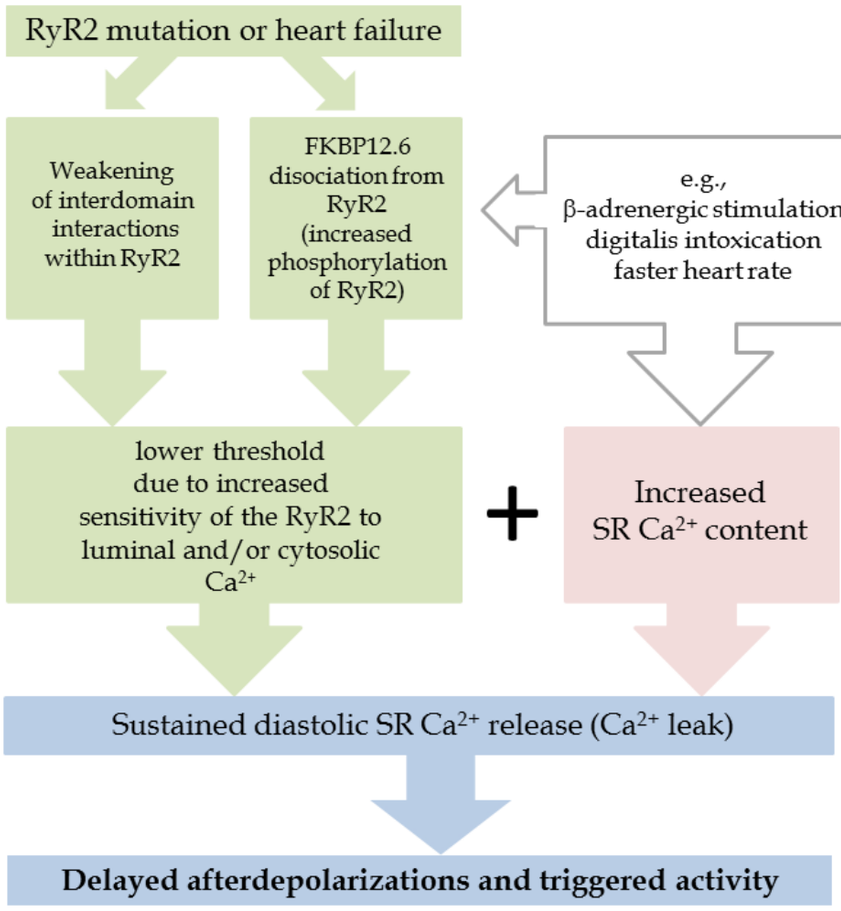

Fig. 3. Hypothetical mechanisms of acquired (e.g. heart failure) and inherited RyR2 dysfunction (e.g. CPVT): (1) *domain unzipping* and (2) *FKBP12.6 unbinding* due to enhanced RyR2 phosphorylation. Both RyR2 aberrations increase the sensitivity of the RyR2 and lower the threshold for SR Ca^{2+} release. The maintenance of increased SR Ca^{2+} load during, for example, β-adrenergic stimulation is considered a major determinant for the sustained spontaneous Ca^{2+} release from the SR and arrhythmogenesis. If SR Ca^{2+} content is normal, a transient diastolic SR Ca^{2+} release will occur.

9. Normalizing RyR2 function prevents triggered arrhythmias

After the discovery that mutations in the RyR2 gene underlie Ca^{2+} homeostasis disturbances associated with CPVT (Laitinen et al., 2001; Priori et al., 2001), important insights into novel and specifically tailored therapies that may target the common pathway underlying CPVT and heart failure have emerged. Recent studies suggest the usage of therapeutic approaches that should combine two actions: (1) *suppression of SR Ca^{2+} overload* and (2) *stabilization of the RyR2 dysfunction* by reducing the RyR2 open probability and thence, increasing the SR threshold. Such therapeutic actions might together effectively prevent RyR2-mediated SR Ca^{2+} leak in CPVT carriers, whereas RyR2 stabilization alone might be sufficient in heart failure patients. A novel class of drugs - RyR2 stabilisers - that has attracted much attention in the past few years and will remain the subject of intensive investigations include K201, dantrolene and flecainide.

9.1 K201 (or JTV-519)

K201 is the 1, 4-benzothiazepine derivative that was initially developed to prevent Ca^{2+} overload-induced myocardial infarction and sudden cardiac cell death (Kaneko et al., 1997). As shown in Table 1, K201 has been reported to have various actions at multiple sites in the cardiomyocyte, including non-specific multi-ion channel blocking effect (Kimura et al., 1999; Nakaya et al., 2000) and inhibition of SERCA (Loughrey et al., 2007). Most important is the finding that K201 stabilizes RyR2 and suppresses SR Ca^{2+} leak by increasing the binding affinity for the FKBP12.6 to RyR2 (Wehrens et al., 2004). Recent studies, however, demonstrated that FKBP12.6 may not be involved in regulation of Ca^{2+} release from the SR, since loss of FKBP12.6 failed to increase RyR2-mediated spontaneous Ca^{2+} release and stress-induced ventricular arrhythmias (Guo et al., 2010; Xiao et al., 2007). K201 binds to the central region of RyR2 (Yamamoto et al., 2008), thereby inducing a rapid conformational change in RyR2 correcting defective channel gating of RyR2 independent of RyR2 phosphorylation (Yano et al., 2003). The closed state of RyR2 prevents SR Ca^{2+} leak and propagation of spontaneous Ca^{2+} waves independent of FKBP12.6 association (Hunt et al., 2007; Yamamoto et al., 2008). K201 effects are dose-dependent and concentrations up to 1 μM ensure RyR2-mediated action (Table 1). K201 prevented ventricular arrhythmias in FKBP12.6-deficient mice (Wehrens et al., 2004), but failed to prevent DADs and ventricular tachycardia induced by isoproterenol and caffeine in a CPVT mouse model carrying a human $RyR2^{R4496C+/-}$ mutation (Liu et al., 2006). On the other hand, pre-treatment with K201 massively reduced triggered activity evoked by ouabain-induced SR Ca^{2+} overload in the $RyR2^{R4496C+/-}$ cardiomyocytes (Sedej et al., 2010). Taken together, it is still unclear whether K201 exerts its antiarrhythmic effects specifically through stabilization of the RyR2 or through synergistic inhibitory actions on sarcolemmal ion currents or by any other additional action(s). Nevertheless, K201 appears a suitable prototype for development of compounds that more specifically target RyR2, such as S107, a more specific RyR2 stabilizer (Lehnart et al., 2008).

9.2 Dantrolene

Emerging evidence suggests that defective interdomain interactions within RyR2 play a key role in abnormal channel gating of RyR2 in failing hearts and RyR2 mutations (Kobayashi et al., 2009; Oda et al., 2005). Therefore, correction of the defective interdomain interaction may represent a new therapeutic strategy against heart failure and possibly cardiac arrhythmia. Dantrolene has been primarily used to treat acute malignant hyperthermia by targeting skeletal muscle RyR1. Recently, dantrolene has been also found to bind to domain 601-620 of RyR2 and reduce abnormal SR Ca^{2+} leak by correcting defective interdomain interaction within RyR2 in pacing-induced heart failure. As a result, DADs and Ca^{2+} spark frequency are reduced (Kobayashi et al., 2005; Kobayashi et al., 2009). Pre-treatment with dantrolene prevents both ventricular arrhythmia induced by either epinephrine or exercise in $RyR2^{R2474S+/-}$ knock-in mouse model for human CPVT (Kobayashi et al., 2010). Dantrolene also improves contractile function in dogs after pacing-induced heart failure (Kobayashi et al., 2009). Importantly, dantrolene has no appreciable effect on normal SR and cardiac function, indicating that dantrolene may be effective for stabilizing RyR2 merely in the unzipped state.

K201 concentration/ duration of intervention	Animal model,origin of cells	In vivo effect	In vitro effect	References
1-10 μM acute	Guinea-pig, Ventricle	no data	Frequency and voltage-dependent inhibition of Na^+, Ca^{2+}, K^+ currents, reduced action potential duration	(Kimura et al., 1999; Kiriyama et al., 2000)
1 μM acute	Guinea-pig, Atrium	inhibition of atrial fibrillation	Inhibition of the muscarinic acetylcholine-receptor operated K current, delayed rectifier K^+ current, prolonged action potential duration	(Nakaya et al., 2000)
1 and 3 μM (2-3 min)	Rabbit, Ventricle	no data	inhibition of RyR2 and SERCA reduced diastolic Ca^{2+} release, reduction of Ca^{2+} wave velocity and frequency, unchanged SR Ca^{2+} content and L-type Ca^{2+}-current, K201 effect FKBP12.6-independent	(Loughrey et al., 2007)
0.5 mg/kg/h (1 week) 1 μM (2h pre-incubation)	Mouse, $FKBP12.6^{+/-}$ Ventricle	No exercise-induced ventricular tachycardia & sudden death	reduced inward transient current (I_{ti}), K201 effect FKBP12.6-dependent	(Lehnart et al., 2006; Wehrens et al., 2004)
0.5 mg/kg/h (1 week) 1 μM and 10 μM (acute)	Mouse, $RyR2^{R4496C+/-}$ Ventricle	CPVT	isoproterenol-induced triggered activity	(Liu et al., 2006)
1 μM (1h pre-incubation)	Mouse, $RyR2^{R4496C+/-}$ Ventricle	no data	reduced ouabain-evoked triggered activity (DAD and triggered AP frequency)	(Sedej et al., 2010)
1-10 μM	Rat, Ventricle HEK-293 cells	no data	no SR Ca^{2+} leak, K201 effect FKBP12.6-independent	(Hunt et al., 2007)
0.5 mg/kg/h (1, 4 weeks) 1 μM (acute)	Dog, HF model, SR vesicles	no data	no SR Ca^{2+} leak, normal PKA phosphorylation, K201 effect FKBP12.6-dependent	(Kohno et al., 2003)
0.3 μM	Dog, HF model, SR vesicles and ventricle	no data	no SR Ca^{2+} leak, reduced Ca^{2+} spark frequency (RyR2 mutations mimicked using synthetic peptides)	(Tateishi et al., 2009)
1 μM	Dog, MI model, Purkinje cells	no data	reduced micro Ca^{2+} waves	(Boyden et al., 2004)
0.5 mg/kg/h (4 weeks)	Dog, HF model, SR vesicles	no data	no SR Ca^{2+} leak, normal PKA phosphorylation, K201 effect FKBP12.6-dependent	(Yano et al., 2003)

Abbreviations: HEK-293= human embryonic kidney cell line 293, HF= heart failure, PKA= protein kinase A, RV= right ventricle, SR= sarcoplasmic reticulum, MI= myocardial infarction

Table 1. K201 effects on triggered activity in different animal models

9.3 Flecainide

In analogy with the local anaesthetic-tetracaine, flecainide is effective in suppressing spontaneous SR Ca^{2+} release by directly inhibiting RyR2 activity in mice and in humans with calsequestrin-associated CPVT (Watanabe et al., 2009) and murine Purkinje cells harbouring $RyR2^{R4496C+/-}$ mutation (Kang et al., 2010). This effect has been attributed to the reduced duration of channel openings without affecting closed channel duration and net spark-mediated Ca^{2+} leak (Hilliard et al., 2010). Thus, flecainide directly targets the molecular defect responsible for arrhythmogenic Ca^{2+} waves that trigger exercise- and catecholamine-induced polymorphic ventricular arrhythmias. In combination with flecainide's Na^{+}-channel inhibition, which reduces the rate of triggered activity, flecainide seems to be a safe and effective therapy in the majority of CPVT patients who suffer from exercise-induced ventricular arrhythmias (van der Werf et al., 2011). Given the rare onset of CPVT episodes and different causality of fatal arrhythmias (exercise-independent), further long-term follow-up clinical studies are required to justify the use of flecainide in preventing fatal arrhythmias in CPVT patients. Collectively, blocking the RyR2 open state has emerged as a new promising therapeutic strategy to prevent Ca^{2+} wave propagation during diastole.

9.4 CaMKII inhibition

In heart failure, the expression and activity of CaMKII are increased (Hoch et al., 1999; Kirchhefer et al., 1999). Chronic activation of CaMKII phosphorylates common Ca^{2+} regulatory proteins with PKA, including L-type voltage-gated Ca^{2+} channels, phospholamban and RyR2 (Ji et al., 2003). The increased L-type Ca^{2+} current may facilitate Ca^{2+} window currents (Dzhura et al., 2000) and trigger EADs, whereas CaMKII phosphorylation of RyR2 increases the sensitivity to Ca^{2+}-dependent activation and the frequency of Ca^{2+} sparks (Guo et al., 2006). Such effects may enhance diastolic SR Ca^{2+} release and trigger DADs, despite reduced SR Ca^{2+} content (Chelu et al., 2009; Maier et al., 2003; Wu et al., 2002). A CaMKII inhibitor, KN-93, effectively blocks both EADs (Anderson et al., 1998) and DADs resulting from enhanced diastolic SR Ca^{2+} leak and Ca^{2+} waves in an arrhythmogenic rabbit model of non-ischemic heart failure (Ai et al., 2005; Curran et al., 2010).

CaMKII activation and Ca^{2+} handling abnormalities have been reported to play a major role in the vicious cycle of arrhythmogenesis promotion and mechanical dysfunction that characterizes electrical storm[4] . Infusion of a calmodulin antagonist W-7 to a rabbit model of electrical storm reduces CaMKII hyperphosphorylation, suppresses ventricular tachycardia or fibrillation, and rescues left ventricular dysfunction (Tsuji et al., 2011).

CaMKII activity also increases during exercise in healthy individuals and may play a role in CPVT (Kemi et al., 2005; Rose & Hargreaves, 2003). Genetic overexpression of CaMKII in a CPVT mouse model with a gain-of-function RyR2 mutation (R4496C) causes increased diastolic SR Ca^{2+} leak, DADs and fatal ventricular arrhythmias (Dybkova et al., 2011), whereas acute CaMKII inhibition in the same CPVT mouse model prevents arrhythmias (Liu et al., 2011). Acute CaMKII inhibition has also been proven to be beneficial in treating atrial arrhythmias induced by rapid pacing in CPVT mice with another RyR2 mutation (R176Q). These mice showed increased susceptibility to atrial fibrillation induction due to CaMKII-mediated increase in RyR2-dependent Ca^{2+} leak (Chelu et al., 2009). Consistent with

[4] defined as 3 or more episodes of ventricular tachycardia or fibrillation in a 24-hour period

these findings, CaMKII inhibition completely reverses the effects of overexpressed miR-1[5] (also in the presence of β-adrenergic activation), a small muscle-specific noncoding microRNA, which increases the diastolic SR Ca^{2+} leak and reduces SR Ca^{2+} content (Terentyev et al., 2009).

It is important to distinguish the specificity of the CaMKII-dependent targets contributing to arrhythmias from other CaMKII-dependent physiological pathways. However, it is becoming increasingly clear that CaMKII inhibitors reduce RyR2 sensitivity to Ca^{2+} and thereby, restore the threshold for spontaneous SR Ca^{2+} release to a normal or even higher level. Taken together, confirming these findings with pharmacologic targeting of RyR2 in conjunction with selected CaMKII signalling might be a promising target for the treatment of cardiac arrhythmias, such as heart failure, CPVT and electrical storms.

10. Conclusion

Since the discovery that mutations in the RyR2 gene underlie Ca^{2+} homeostasis disturbances associated with CPVT, important new insights have been obtained into the molecular mechanisms underlying Ca^{2+}-triggered atrial and ventricular arrhythmias. Increased sensitivity of the RyR2 and lowered threshold for the spontaneous SR Ca^{2+} leak have emerged as causal arrhythmogenic mechanisms linking acquired and congenital arrhythmias in patients with heart failure and CPVT, respectively. The emerging evidence that inhibition of CaMKII reduces RyR2 sensitivity to Ca^{2+} and restores the threshold for spontaneous SR Ca^{2+} release has paved the way to move from bench to bedside. Selected targeting of RyR2 in conjunction with CaMKII signalling might be a promising target for the treatment of Ca^{2+}-triggered arrhythmias.

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12. References

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[5] miR-1 is upregulated in heart failure (Thum et al., 2007)

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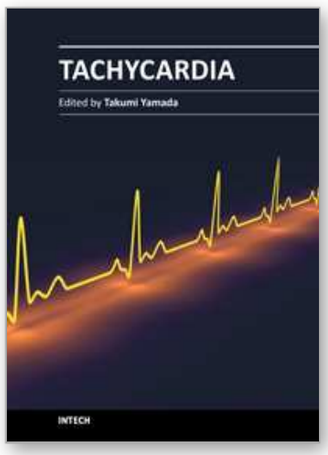

Tachycardia
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Heart rates are normally controlled by a natural pacemaker, the sinus node, and normal heart rhythm is called sinus rhythm. Tachycardia is defined as a faster heart rhythm than normal sinus rhythm. Tachycardias can cause symptoms such as palpitations, chest pain, shortness of breath and fatigue, which reduce the quality of life. Fast tachycardias can cause hemodynamic collapse and sudden cardiac death. The causes, mechanisms, and origins of tachycardias are various. The diagnosis of tachycardias is made by electrocardiograms and electrophysiological testing. Tachycardias can be managed and treated by pharmacological and non-pharmacological approaches. This book covers these concerns from basic and clinical points of view and will lead to a further understanding and improvement in the clinical outcomes of tachycardias.

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