Chapter 29
RyR2 in Cardiac Disorders

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Abstract Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by the occurrence of adrenergically induced polymorphic ventricular arrhythmias. Mutations in the cardiac ryanodine receptor (*RYR2*) underlie the majority of CPVT cases and show an autosomal dominant inheritance pattern. Mutations in *RYR2* and other genes involved in CPVT cause spontaneous diastolic calcium release from the sarcoplasmatic reticulum (SR), which eventually lead to triggered arrhythmias. CPVT is usually diagnosed by use of exercise testing. β-blockers are the mainstay of drug therapy in CPVT, whereas flecainide and left cardiac sympathetic denervation can be added or performed in patients with significant ventricular arrhythmias or arrhythmic events on β-blocker therapy.

29.1 Introduction

In cardiac muscle, excitation–contraction coupling is initiated by a small influx of external calcium through the voltage-dependent L-type calcium channels into the cytosol during an action potential (Fabiato 1983). This calcium triggers the opening of the cardiac ryanodine receptor (RyR2), which regulates a large calcium release from intracellular calcium stores to the cytoplasm, ultimately leading to contraction. Mutations in the gene encoding RyR2 (OMIM #180902) have been associated with an autosomal dominant form of catecholaminergic polymorphic ventricular tachycardia (CPVT) (Priori et al. 2001), an inherited arrhythmia syndrome characterized by adrenergically induced ventricular arrhythmias including ventricular fibrillation (VF) (Leenhardt et al. 1995). Ventricular arrhythmias or

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symptoms typically occur during physical or emotional stress in patients with CPVT. The exact prevalence of CPVT is unknown but is estimated to be 1 in 10,000.

The first case report on CPVT dates from 1960, describing three sisters out of five siblings who suffered from frequent attacks of multifocal ventricular extrasystoles without any structural cardiac abnormalities (Berg KJ 1960). This case was followed by another case report in 1975 (Reid et al. 1975), and two series published by Coumel and coworkers from Paris (Coumel et al. 1978; Leenhardt et al. 1995). The link between mutations in *RYR2* and CPVT was discovered in 2001 (Laitinen et al. 2003; Priori et al. 2001). In the past decade, much has been learned about *RYR2* mutations and CPVT across the full spectrum from bench to bedside. This knowledge is also relevant, because proarrhythmic mechanisms similar to CPVT are believed to play a role in atrial fibrillation (AF) (Voigt et al. 2012) and ventricular arrhythmias in heart failure (George 2008).

29.2 Catecholaminergic Polymorphic Ventricular Tachycardia

29.2.1 The Cardiac RYR2

There are three isoforms of RyRs: RyR1 is mainly expressed in skeletal muscle, *RYR2* in cardiac muscle, and *RYR3* in the brain. RyR2 is located in the membrane of the (SR) of cardiomyocytes and is a homotetramer (Fig. 29.1). Each monomer consists of a large cytosolic domain and a smaller transmembrane domain. The channel pore is encompassed by four polypeptides, forming a tetramer. RyR2 is, among others, associated with FKBP12.6, protein kinase A, calcium/calmodulin-dependent kinase II (CaMKII), and calmodulin (CALM) at the N-terminal cytoplasmic domain (Priori and Chen 2011), and calsequestrin (CASQ2), junctin (ASPH), and triadin (TRDN) at the C-terminus (Faggioni et al. 2012).

29.2.1.1 *RYR2* Mutations

The gene encoding the 4967-amino acid RyR2 channel is located on the long arm of chromosome 1 (1q42-43) and contains 105 exons, making it one of the largest genes in the human genome. Mutations in *RYR2* are identified in approximately 60 % of patients with a definite clinical diagnosis of CPVT (Medeiros-Domingo et al. 2009). To date, over 130 unique disease-causing mutations have been identified in *RYR2* (Medeiros-Domingo et al. 2009). These include almost exclusively missense mutations and approximately 20 % of *RYR2* mutations are de novo (Medeiros-Domingo et al. 2009). Mutations in *RYR2* have a propensity to be clustered in three known hotspots: the N-terminal domain (codons 44–466), the

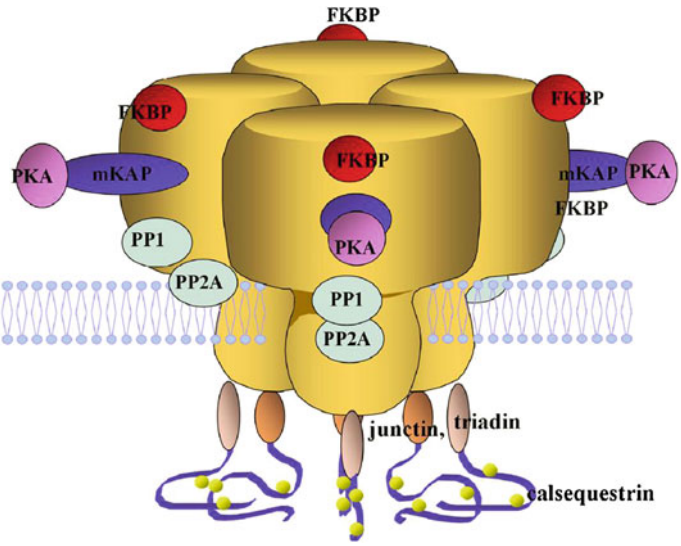

Fig. 29.1 Schematic illustration of the *RYR2* macromolecular complex. Calmodulin (CALM), FKBP12.6 (calstabin 2), protein kinase A (PKA), phosphatase 1 (PP1), and phosphatase 2A (PP2A) bind to the cytoplasmic region of *RYR2*; junctin and triadin anchor calsequestrin to *RYR2* and bind to the intraluminal portion of *RYR2* (Reproduced with permission from Yano et al. 2005. Pharmacol Ther 107(3):377–391)

central domain (codons 2246–2534), and the C-terminal channel forming domain (codons 3778–4959) (Medeiros-Domingo et al. 2009; Priori and Chen 2011).

Mutations in *RYR2* have also been identified with more complex phenotypes than classic CPVT. In two separate families with a large genomic deletion in *RYR2*, involving exon 3, sinoatrial node and atrioventricular node dysfunction, atrial fibrillation, atrial standstill, and left ventricular dysfunction and dilatation were identified in addition to the classic CPVT phenotype (Bhuiyan et al. 2007). In addition, fibrofatty myocardial replacement in the right ventricle and intracellular calcium deposits have been identified in patients carrying a *RYR2* mutation (Tiso et al. 2001).

29.2.2 Pathological Background

29.2.2.1 Excitation–Contraction Coupling

Calcium-induced calcium release (CICR) plays an important role in cardiac excitation–contraction coupling. CICR is initiated by a small influx of external calcium through the voltage-dependent L-type calcium channels into the cytosol during the plateau phase of the action potential (Fabiato 1983). The entered

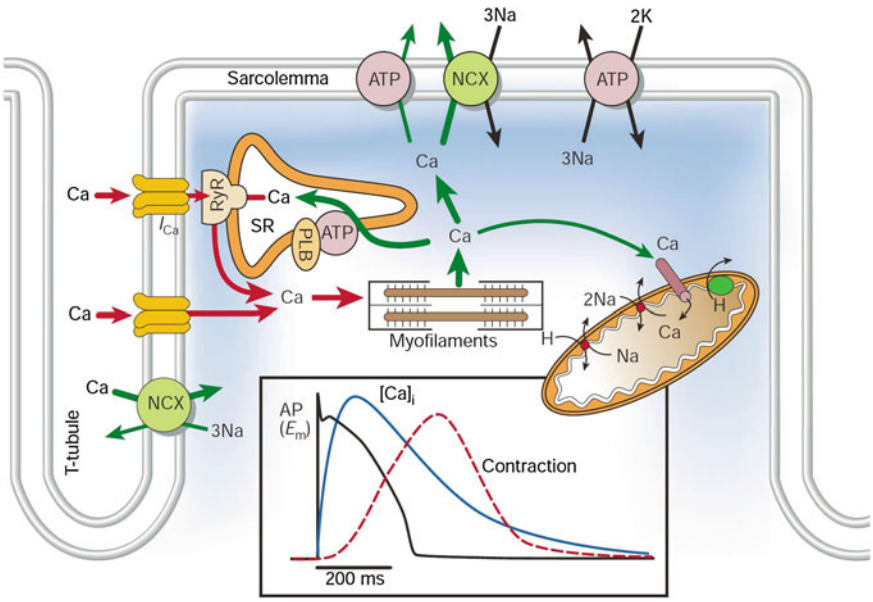

Fig. 29.2 Calcium transport in ventricular myocytes. Inset shows the time course of an action potential, calcium transient, and contraction measured in a rabbit ventricular myocyte. NCX, sodium/calcium exchanger; ATP, ATPase; PLB, phospholamban; SR, sarcoplasmic reticulum. Reproduced with permission from Bers 2002. Nature. 415, (6868):198–205

calcium triggers subsequent calcium release from the SR, the main intracellular calcium storage of the cardiac myocyte, through activation of the cytosolic calcium sensor of RyR2. Calcium then binds to troponin C and eventually results in myocardial contraction. During relaxation, the bulk of the released calcium is transferred back into the SR by sarcoplasmatic reticulum calcium adenosine triphosphate (SERCA). The remainder is removed from the cytosol by the sodium/calcium exchanger (NCX) (Fig. 29.2).

RyR2 activity is regulated by several signaling pathways (Priori and Chen 2011). Under adrenergic stimulation, β-adrenergic receptors stimulate adenylyl cyclase to produce cAMP, which in turn activates protein kinase A (PKA) as well as other mediators. PKA phosphorylates RyR2 and other central proteins related to excitation–contraction coupling, such as phospholamban and the L-type calcium channels. The overall result is CICR gain of function in response to adrenergic activation.

29.2.2.2 Pathophysiology of CPVT Related to Mutations in RYR2

RYR2 mutations result in inappropriate calcium leakage from the SR, which leads to elevated calcium concentrations in the cytoplasm (Fatima et al. 2011; Suetomi et al. 2011). This activates the electrogenic NCX. As NCX exchanges one calcium

ion outward for three sodium ions inward, there is a net inward electrical current (named transient inward current; I_{Na}), generating delayed after potentials (DADs). If this depolarization wave amplitude reaches the threshold potential, full depolarization and triggered arrhythmias may occur. Adrenergic stimulation increases spontaneous calcium leak (Cerrone et al. 2007).

Several mechanisms by which *RYR2* mutations lead to aberrant diastolic calcium release have been hypothesized: a reduced binding affinity of the channel-stabilizing protein calstabin 2 (FKBP12.6) (Wehrens et al. 2004), destabilization of the closed state of the channel by mediation of defective interdomain interaction (Suetomi et al. 2011), and store overload induced calcium release, in which calcium accumulates in the SR (Jiang et al. 2004). Several mouse studies suggest that the His-Purkinje system is the critical contributor to, i.e., the origin of ventricular arrhythmias in CPVT (Cerrone et al. 2007; Herron et al. 2010; Kang et al. 2010).

29.2.2.3 Other CPVT Types

CASQ2 is the main calcium buffering protein in the SR. Mutations in *CASQ2* (OMIM #114251) probably cause CPVT by a loss of Ca buffering (Viatchenko-Karpinski et al. 2004). In addition, loss of CASQ2 may lead to a reduced direct inhibitory effect on RyR2. Finally, CASQ2 loss may lead to a reduction of the CASQ2 binding proteins TRDN and ASPH and remodeling of SR structure. Mutations in *TRDN* (OMIM #603283) could cause CPVT by an impaired FKBP12.6-*RYR2* interaction or a reduction of CASQ2 (Roux-Buisson et al. 2012). Finally, mutations in *CALM* may cause CPVT through a dominant-negative effect on the RyR2 channel complex, leading to inappropriate calcium leakage from the SR (Nyegaard et al. 2012).

29.2.3 Clinical Characteristics of CPVT

29.2.3.1 Clinical Presentation

The classic CPVT patient is a child experiencing emotion or exercise-induced syncope, aborted cardiac arrest or sudden cardiac death (SCD) with a family history of similar events in young relatives. In some cases, children are initially diagnosed with epilepsy, because CPVT-related syncope may be accompanied by convulsive movements and urinary or fecal incontinence, and CPVT may be diagnosed during follow-up when symptoms persist despite antiepileptic drug therapy. However, CPVT patients with a more benign course and a debut of symptoms during adulthood are increasingly being identified (Sy et al. 2011). Conversely, *RYR2* mutations have been identified in victims of SIDS, suggesting a wide range of phenotype severity among patients carrying a *RYR2* mutation (Tester et al. 2004).

29.2.3.2 Electrophysiological Characteristics

Resting 12-lead electrocardiograms of CPVT patients are normal, including a normal corrected QT-interval. However, sinus bradycardia (Leenhardt et al. 1995; Postma et al. 2005) and prominent U-waves (Leenhardt et al. 1995; Viitasalo et al. 2008) may be present. In a series containing 116 relatives carrying a mutation in *RYR2*, which were identified by predictive genetic testing of the mutation identified in the proband, sinus bradycardia was observed in 19 % (van der Werf et al. 2012a). In addition, other supraventricular dysrhythmias were present in 16 %, and mainly included intermittent ectopic atrial rhythm identified by Holter monitoring. In one study including eight CPVT patients in whom electrophysiological study was performed, evidence of sinus node dysfunction was demonstrated in four (Sumitomo et al. 2007). Indeed, a recent study found that increased diastolic calcium release through mutant *RYR2* led to a decrease in sino-atrial node automaticity by a reduced L-type calcium channel current and SR calcium depletion during diastole (Neco et al. 2012).

During exercise testing, a characteristic increase in severity of polymorphic ventricular arrhythmias is often observed, starting with isolated ventricular premature beats (VPB), followed by bigeminal VPBs, couplets, and eventually runs of multiple VPBs (Fig. 29.3). In the minority of patients, bidirectional ventricular tachycardia (VT) can be observed: a hallmark of CPVT defined as VT with a beat-to-beat alternating QRS axis (Sy et al. 2011). When exercise testing is ended, ventricular arrhythmias rapidly recede in most patients, and the reverse heart rate–dependent sequence can sometimes be observed during recovery. VPBs usually occur at a heart rate of 110–130 beats per min. and, in the absence of therapeutic interventions, the ventricular arrhythmia threshold heart rate is remarkably reproducible in an individual patient. VPBs with a left bundle branch block morphology and inferior axis and a right bundle block morphology and superior axis are predominant (Sumitomo et al. 2003; Sy et al. 2011). The occurrence of exercise-induced supraventricular tachyarrhyhmias in CPVT patients has been reported, but is not commonly observed (see above) (van der Werf et al. 2012a).

29.2.3.3 Genotype-Phenotype Correlations

Among patients with a mutation in *RYR2*, approximately 50 % display phenotypic features of CPVT at the first cardiological examination (van der Werf et al. 2012a). This number increases to over 60 % when mutation-carriers are repeatedly being examined during follow-up (van der Werf et al. 2012a).

Hitherto, *RYR2* mutation-carriers with a CPVT phenotype might have an increased risk of arrhythmic events as compared with mutation-carriers without a CPVT phenotype (so-called silent mutation-carriers), but this has not convincingly been shown (Hayashi et al. 2012; van der Werf et al. 2012a). An association between the presence of a CPVT phenotype among *RYR2* mutation-carriers and risk of arrhythmic events is, however, expected in future studies with larger

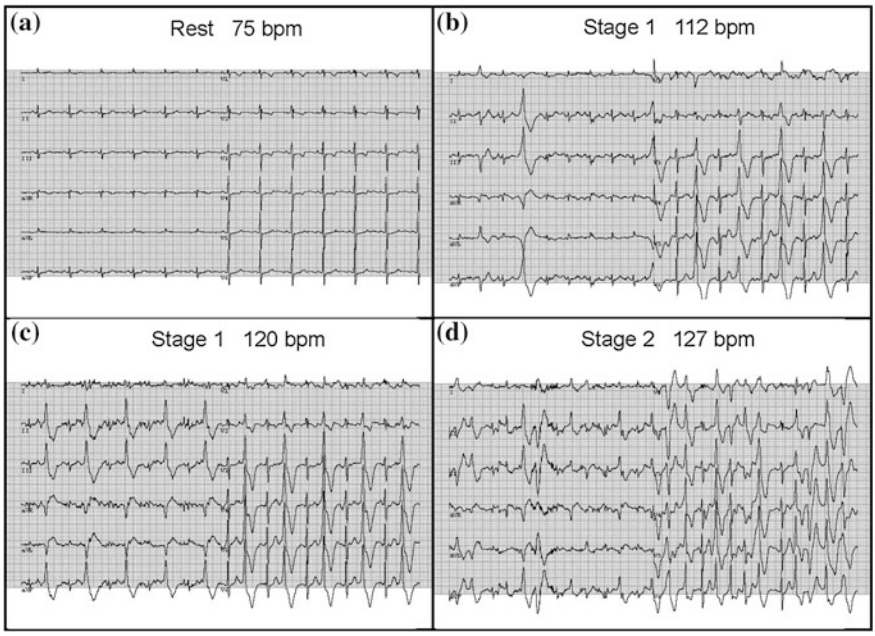

Fig. 29.3 Ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia. Polymorphic ventricular arrhythmias during an treadmill exercise test of *RyR2* mutation-associated catecholaminergic polymorphic ventricular tachycardia patient. **a** Normal resting ECG (**b**–**d**) ECGs during exercise, showing an increasing polymorphic ventricular arrhythmia burden, starting with isolated and bigeminal ventricular premature beats, and ending with bidirectional and polymorphic couplets and non-sustained ventricular tachycardia (Reproduced with permission from van der Werf and Wilde 2013. Heart 99(7):497–504)

numbers of patients. Because arrhythmic events may also occur in silent mutation-carrier, the therapeutic approach to these individuals should nowadays probably be similar to patients with a CPVT phenotype (van der Werf et al. 2012b).

29.2.4 Diagnosis of CPVT

29.2.4.1 Clinical Diagnosis and Differential Diagnosis

The clinical diagnosis of CPVT is made in case of documented exercise- or catecholamine-induced bidirectional of polymorphic VT in the absence of resting ECG abnormalities, structural heart disease, and coronary artery disease, particularly in patients under the age of 40 years. Older patients or patients with polymorphic ventricular arrhythmias, but not VT, who meet all criteria have a possible diagnosis of CPVT.

The gold standard for diagnosis is incremental exercise testing. In a study including 67 asymptomatic relatives of seven probands, the sensitivity and specificity of the exercise testing for predicting carriership of a *RYR2* or *CASQ2* mutation was 50 and 97 %, respectively (Hayashi et al. 2012). Alternatively, epinephrine infusion may be used as a diagnostic tool. A study in 36 CPVT patients and 45 unaffected relatives concluded that epinephrine infusion has low sensitivity as compared to exercise testing (Marjamaa et al. 2012). Maximum heart rate achieved upon epinephrine challenge was markedly lower as compared to exercise testing. Among 25 CPVT patients with a positive exercise test, seven had a positive epinephrine test (sensitivity of 28 %). The specificity of epinephrine infusion in the entire study population was 98 %. On the contrary, provocation of ventricular arrhythmias in CPVT patients who did not have any ventricular arrhythmia on Holter monitoring or exercise testing, have also been reported (Sy et al. 2011). In resuscitated patients who are not able to exercise, epinephrine testing is the test of choice to reach a diagnosis.

Holter or implantable loop recorder monitoring can be useful in young children or other patients who are unable to perform an adequate exercise test or in patients with adrenergically triggered unexplained syncope who have an unremarkable exercise test.

Programmed electrical stimulation has not proven to be effective in provoking arrhythmia in CPVT (Leenhardt et al. 1995). However, recently prominent postpacing changes of the QT-interval in mutation-carriers from one family with the M4109R *RYR2* mutation were reported (Nof et al. 2011).

The differential diagnosis of CPVT includes long QT syndrome (LQTS), in particular type 1, in patients with ventricular arrhythmias of symptoms under conditions of increased sympathetic activity. In case of an inconclusive resting ECG, incremental exercise testing may help in discriminating between these two channelopathies. Ventricular arrhythmia beyond single VPBs is far more common in CPVT compared to LQTS (Horner and Ackerman 2008). Another alternate diagnosis is Andersen-Tawil syndrome, which may very much mimic the CPVT phenotype, including the presence of bidirectional VT (Tristani-Firouzi and Etheridge 2010). Careful inspection of the resting ECG, focused on mild prolongation of the QT-interval or the presence of prominent U-waves, may help in distinguishing between both entities.

29.2.4.2 Genetic Testing

Comprehensive CPVT genetic testing is recommended in index patients in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion (Ackerman et al. 2011). In addition, mutations in *RYR2* may be regarded as a cause of adrenergically mediated idiopathic VF, which may justify genetic testing in such instances (Ackerman et al. 2011). Genetic testing in

CPVT is particularly important to identify asymptomatic relatives following identification of a CPVT-causative mutation in the index patient. This allows initiating prophylactic treatment in mutation-carriers, as SCD may be the first phenotypic manifestation. In addition, genetic testing may be useful to confirm the diagnosis in patients with a possible clinical diagnosis of CPVT.

In patients with a strong CPVT phenotype in whom *RYR2* genetic testing is negative, genetic testing of the other CPVT-associated genes may be considered: *CALM* (autosomal-dominant inheritance pattern) (Nyegaard et al. 2012), *CASQ2* (autosomal recessive) (Lahat et al. 2001), *TRDN* (autosomal recessive) (Roux-Buisson et al. 2012), and *KCNJ2* (underlying Andersen-Tawil syndrome, autosomal dominant). At present, the yield of mutational analysis of these genes in CPVT is unknown, but seems to be low.

29.2.5 Management of CPVT

Because very little is known on risk stratification in patients with CPVT, the current consensus is to have a similar therapeutic approach to every patient with a CPVT phenotype or to every patient with a pathogenic CPVT-associated mutation (van der Werf et al. 2012b). All patients are advised to avoid competitive sports and strenuous exercise.

As CPVT is induced under conditions of increased sympathetic activity, β-blockers are the cornerstone of therapy. Nadolol is probably the most effective and should therefore be the first choice (Hayashi et al. 2009). In countries where nadolol is not available, propranolol is presumably the preferred choice, although studies comparing different ß-blockers are not available to date. Unfortunately, β-blocker therapy does not completely prevent arrhythmic events. The pooled 8-year overall, near-fatal, and fatal event rates of 354 CPVT patients on β-blocker therapy were 35.9, 14.3, and 6.4 %, respectively (van der Werf et al. 2012b). Importantly, a significant proportion of events is probably due to non-compliance rather than true therapy failure.

The class 1c antiarrhythmic drug flecainide has proven to be effective in reducing ventricular arrhythmias in CVPT mouse models as well as in human CPVT patients, possibly through direct inhibition of RyR2-mediated calcium release as well as to the well-known I_{Na} blocking effect (van der Werf et al. 2011; Watanabe et al. 2009). The precise antiarrhythmic effect of flecainide in this setting is, however, disputed (Liu et al. 2011). In patients who are symptomatic despite β-blocker therapy, flecainide can be effective and is recommended. In addition, flecainide may be used in ventricular arrhythmia storms in CPVT patients (Hong et al. 2012).

Left cardiac sympathetic denervation appears to be an effective therapy for CPVT patients who are not adequately controlled by pharmacological treatment (Collura et al. 2009; Wilde et al. 2008). The anti-arrhythmic effect may not be

achieved immediately after the procedure, but it might take up to a couple of months before maximal response is reached (Gopinathannair et al. 2010).

Current guidelines recommend implantable cardioverter-defibrillator (ICD) in patients with aborted cardiac arrest or patients with resistant ventricular arrhythmia despite β-blocker therapy (Zipes et al. 2006). Given the adrenergic nature of arrhythmias in CPVT, catecholamine release as a result of pain or fear following an appropriate or inappropriate discharge of the ICD may be followed by ventricular arrhythmias and subsequent shocks, which may result in an arrhythmic storm. Several cases of this potentially proarrhythmic effect of ICDs in CPVT patients have been reported (Makanjee et al. 2009; Mohamed et al. 2006; Palanca et al. 2006, 2008), turning ICDs into an unattractive option in patients with CPVT. Even if ICD implantation is considered indicated in a CPVT patient, optimal drug therapy and/or LCSD is crucial to reduce the number of appropriate and inappropriate discharges.

29.3 Atrial Fibrillation and Heart Failure

Susceptibility to spontaneous diastolic calcium release from the SR through *RYR2* appears higher in AF and might trigger of maintain AF (Dobrev et al. 2011). This is most probably caused by altered RyR2 function (Vest et al. 2005). In addition, an increase in NCX expression and function has been observed in AF patients (Neef et al. 2010). DADs, caused by a mechanism similar to the mechanism underlying CPVT, may lead to triggered activity that contributes to AF maintenance.

VT in heart failure appears to be due to triggered activity primarily from DADs that arise from altered cellular calcium handling (Pogwizd and Bers 2004). HF is a chronic hyperadrenergic state, and it has been suggested that ß-adrenergic activation of PKA destabilized RyR2, contributing to SR calcium leak and consequent systolic dysfunction and arrhythmogenesis (Marx et al. 2000). In addition, CaMKII, which is upregulated and more active in heart failure, CaMKII-dependent *RYR2* phosphorylation may be a critical mediator of arrhythmias in heart failure (van Oort et al. 2010). New drugs specifically targeting diastolic calcium SR leak are being developed to reduce atrial and ventricular arrhythmogenesis in these settings.

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