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Catecholaminergic Polymorphic ventricular Tachycardia

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Agenda

- Introduction
- Clinical manifestations and prognosis
- Diagnosis of CPVT
- Mechanism of CPVT
- Subtypes of CPVT
- Therapy for the CPVT
- Conclusion



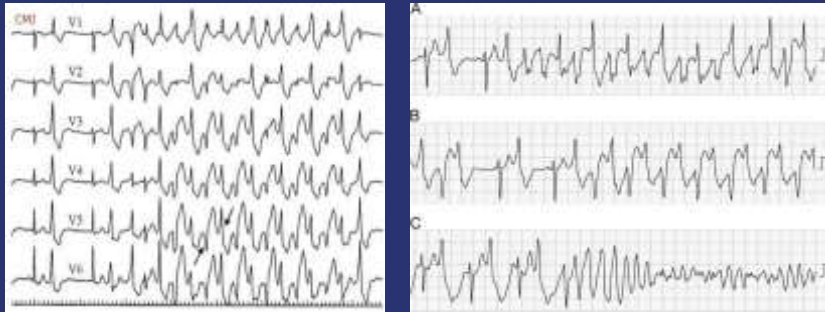
Introduction



- Catecholaminergic polymorphic (AKA: bidirectional) ventricular tachycardia (CPVT) is a highly malignant inheritable cardiac channelopathy.
- As implied by its name, CPVT is associated with the occurrence of potentially life-threatening catecholamine-mediated ventricular arrhythmias (VAs) triggered by stress or exertion.



- May be polymorphic or bidirectional



- A case of a 6-year-old girl with no cardiac structural abnormality presenting with bidirectional VT, apparently induced by effort and emotional stress, was first described in 1975
- The entity of CPVT was delineated in a longitudinal case series in 1995
- At the time, it was assumed to be a possible variant of long QT syndrome with a normal baseline electrocardiogram (ECG).



- Uncommon condition (one in 10,000), accounting for about 12% of autopsy-negative sudden deaths and 1.5% of sudden infant deaths



Clinical manifestations and prognosis



- Syncope or aborted sudden cardiac death during exercise or emotional stress and appear during the first or second decade of life
- Almost all syncopal events are associated with physical activity or emotional stress and do not occur during a resting state



- The untreated mortality rate for children with CPVT was approximately 50%
- 33-38% of patients presented with cardiac arrest
- Even with treatment, the incidence of cardiac events is close to 30%

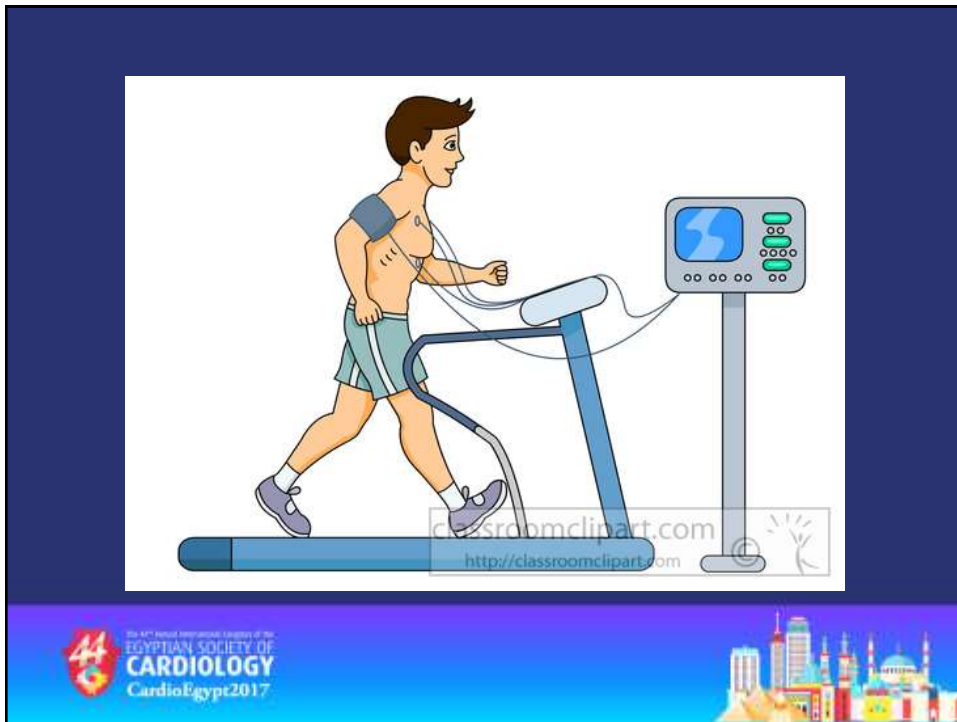


- The prognosis of CPVT is very poor. About 40% patients die within 10 years of diagnosis



Diagnosis of CPVT





- Normal resting ECG, or just a lower heart rate than is normal for their age
- During exercise in these patients, monomorphic premature ventricular contractions (PVCs) increase, then polymorphic, or bidirectional PVC bigeminy appear, followed by bidirectional or polymorphic VT.
- Exercise induced supraventricular arrhythmias (atrial fibrillation, premature atrial contraction, and atrial tachycardia) are also common in the patients with CPVT



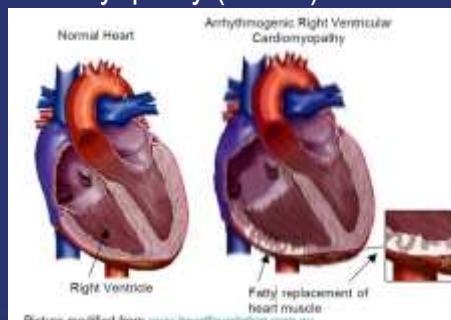
The diagnostic criteria of CPVT

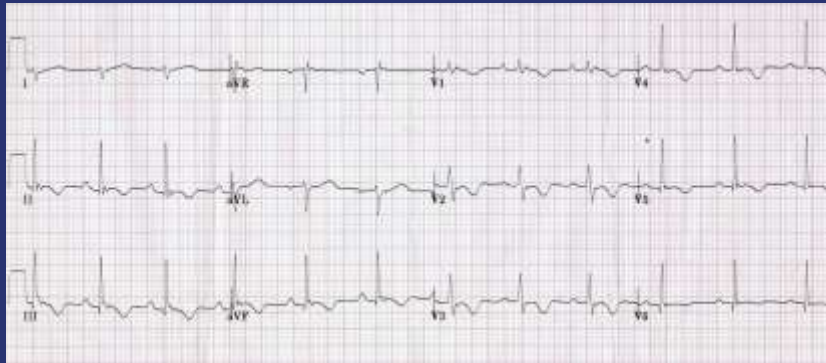
- Presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine- induced bidirectional, polymorphic ventricular premature beats or VT in individuals <40 years of age (possible diagnosis in patients >40 years with normal coronaries)
- Patients who have a pathogenic mutation
- Family members of a CPVT index case with a normal heart who manifests exercise-induced PVCs or bidirectional/polymorphic VT



Differential Diagnosis

- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC)





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- Short-coupled ventricular tachycardia (SC-torsade de pointes [TdP])



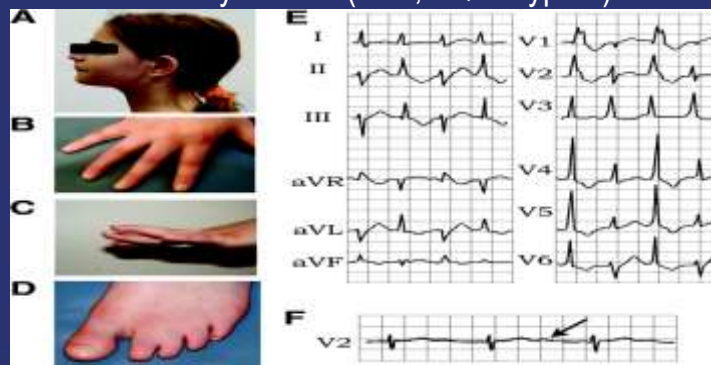
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- Long QT syndrome (LQTS)



- Andersen-Tawil syndrome (ATS, LQTS type 7)



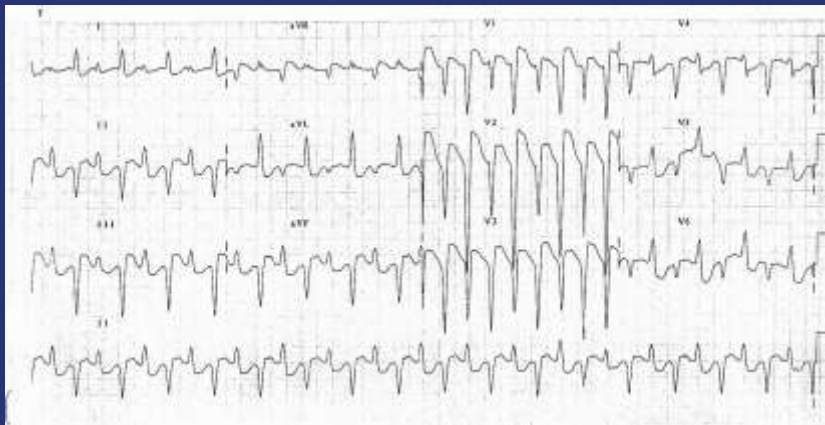
Mechanism of CPVT

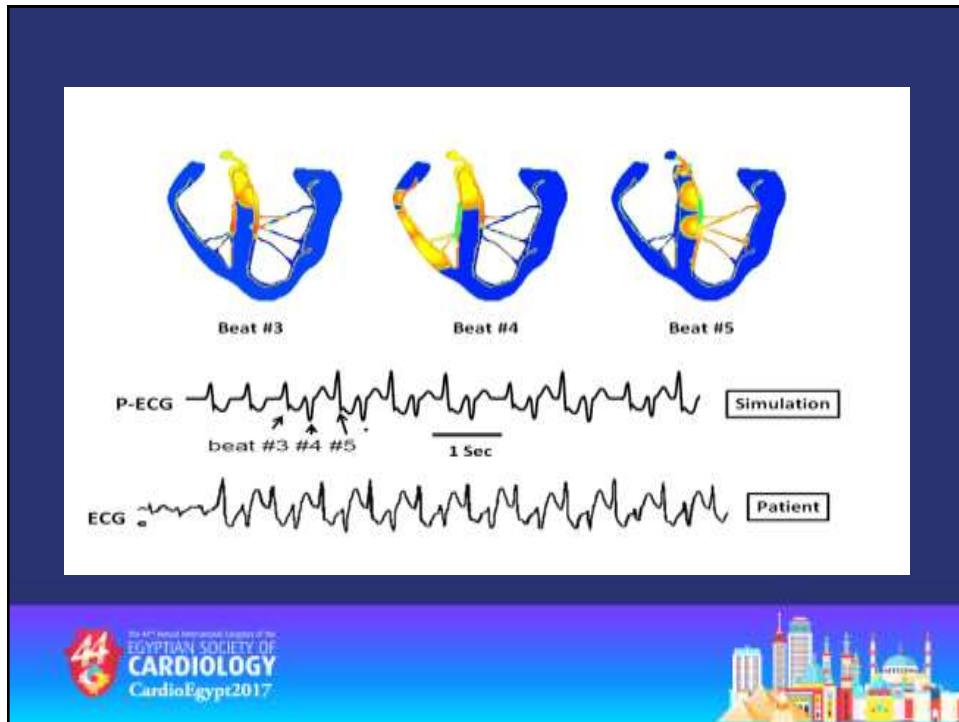


- The key feature underlying pathogenesis of CPVT is the aberrant release of Ca^{2+} into the SR during diastole (termed a transient inward current) leading to diastolic Ca^{2+} leak, which provides a substrate for delayed afterdepolarizations (DADs), specifically in the setting of β -adrenergic stimulation during stress or exercise
- Different hypotheses have been put forth to explain why mutations in the RyR2 gene cause abnormal gating of the ryanodine receptor. The result of these mutations is a gain-of-function in the ryanodine receptor leading to diastolic Ca^{2+} leak

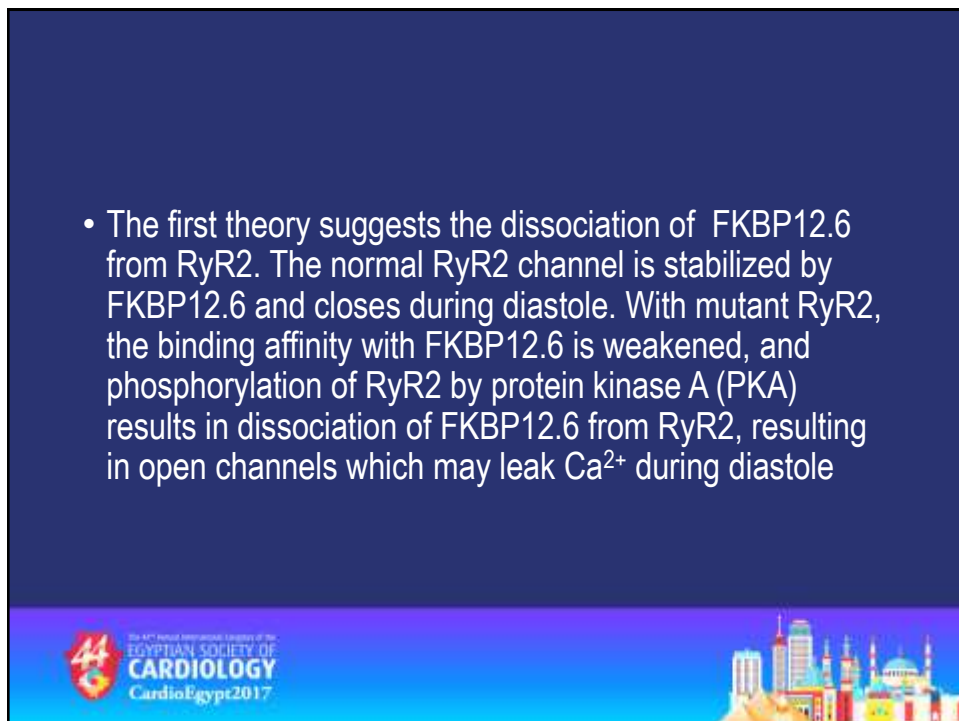


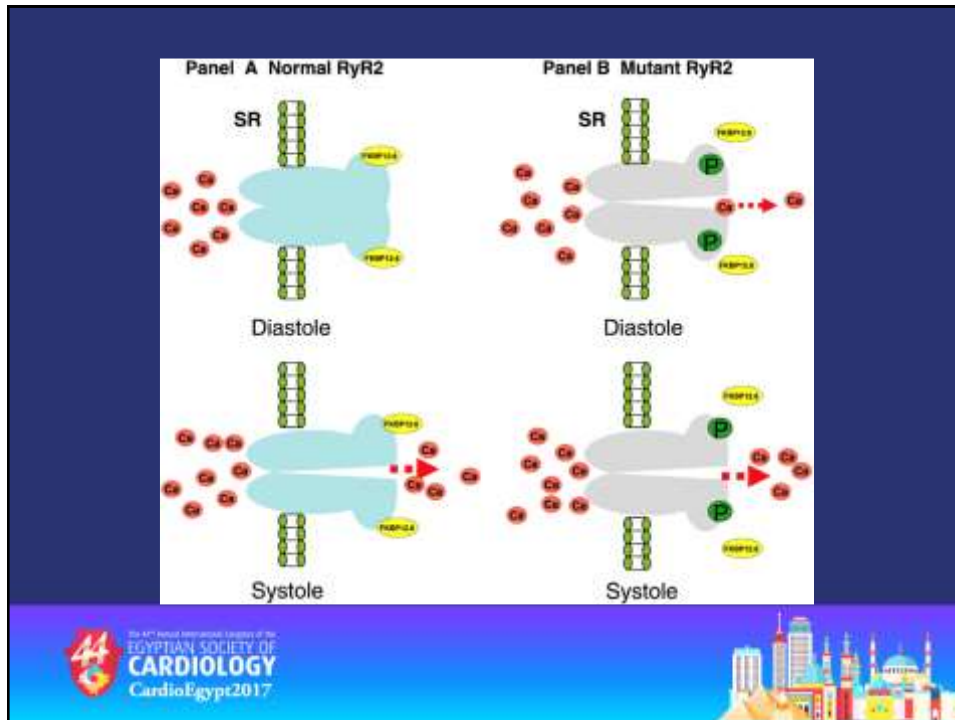
- Similarly, mutations in the gene encoding calsequestrin may lead to defective protein-protein interactions at the SR membrane complex
- One of the characteristic electrocardiographic findings in CPVT is BDVT. This is thought to occur due to alternating foci of triggered activity in the right and left ventricles, specifically in the area of the Purkinje system





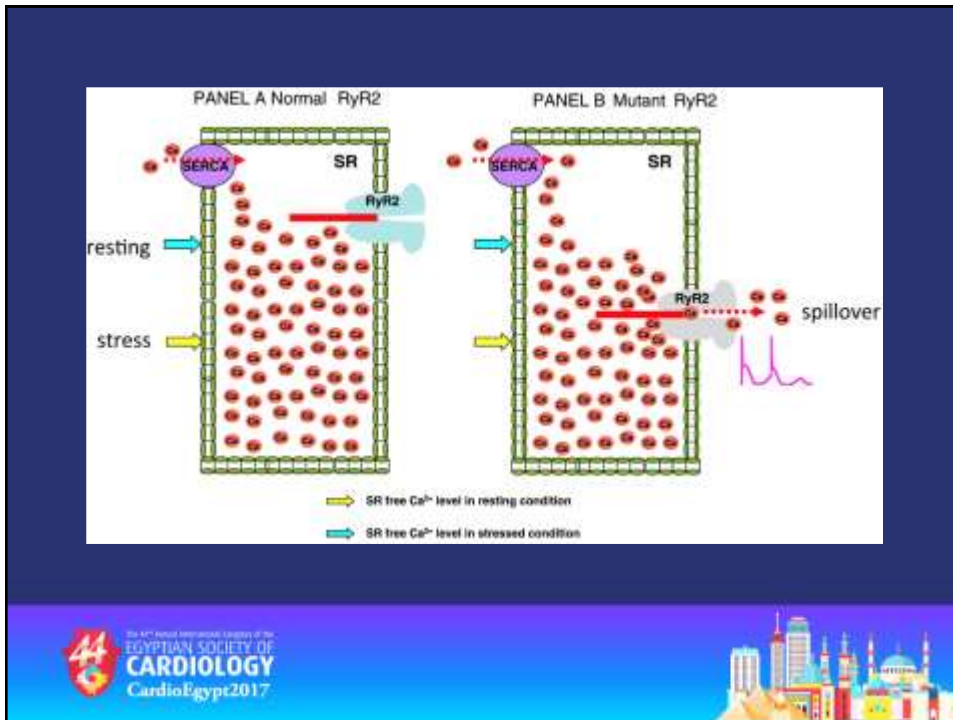
- The first theory suggests the dissociation of FKBP12.6 from RyR2. The normal RyR2 channel is stabilized by FKBP12.6 and closes during diastole. With mutant RyR2, the binding affinity with FKBP12.6 is weakened, and phosphorylation of RyR2 by protein kinase A (PKA) results in dissociation of FKBP12.6 from RyR2, resulting in open channels which may leak Ca^{2+} during diastole





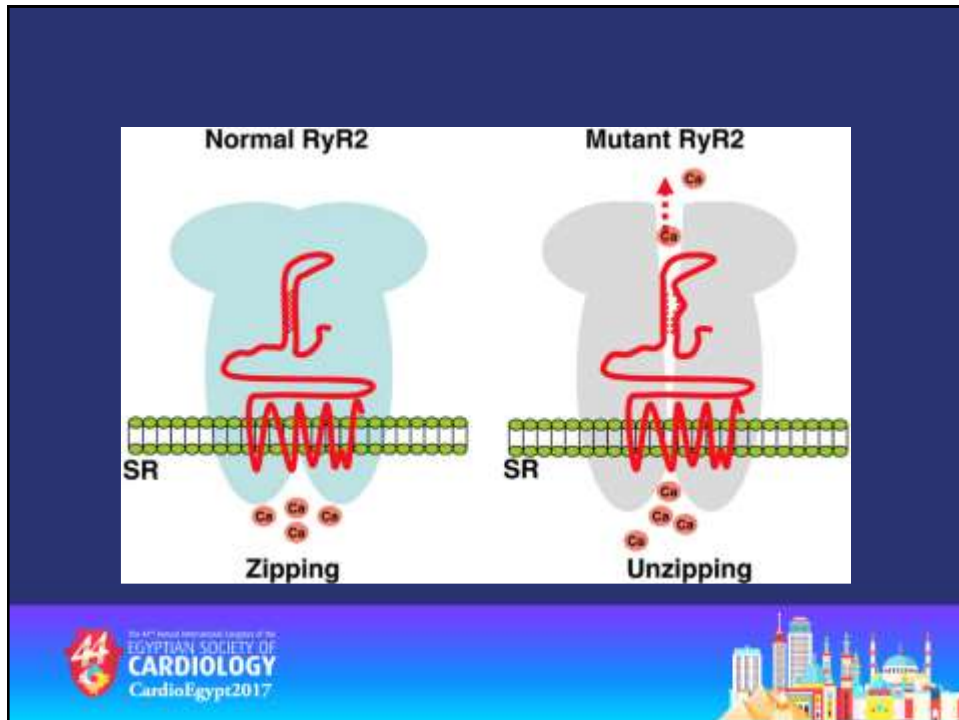
- The second hypothesis is a store overload-induced Ca^{2+} release (SOICR) theory. With normal RyR2, the resting and stress levels of free Ca^{2+} are below the SOICR level. However, with mutant RyR2, the SOICR threshold drops below the level of free Ca^{2+} in the SR. This may cause a spill over of Ca^{2+} from the SR

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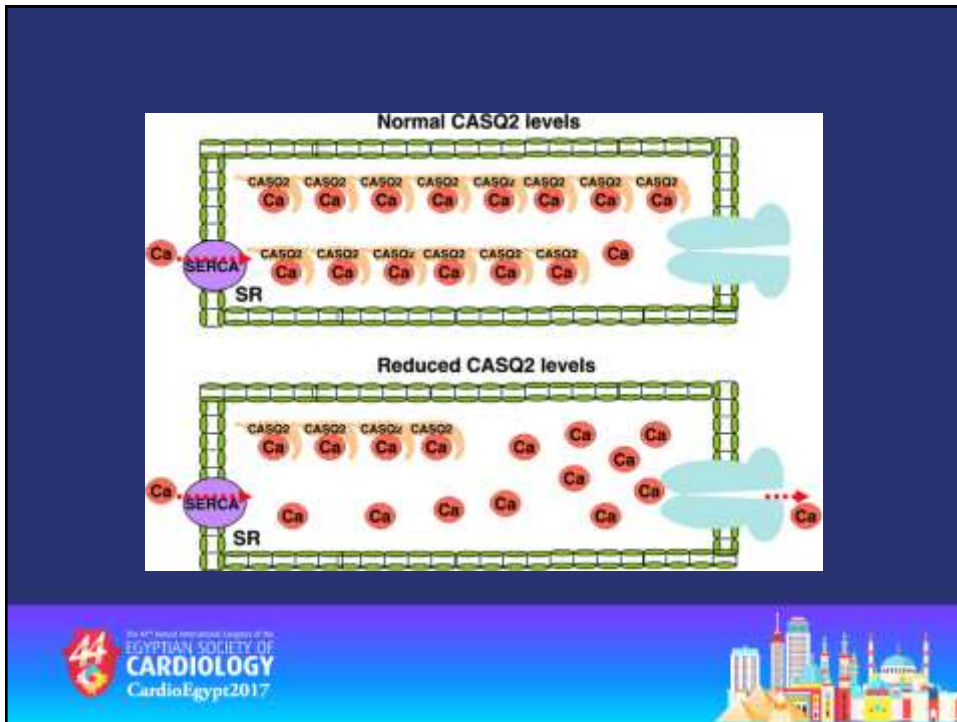
- The third hypothesis considers defective intramolecular domain interaction. RyR2 is stabilized by a tight zipping of the intramolecular structure. If a mutation interferes with this zipping structure, the intramolecular domain interaction is weakened, causing an unzipping of the interdomain structure and resulting in leaking of Ca^{2+} From the SR

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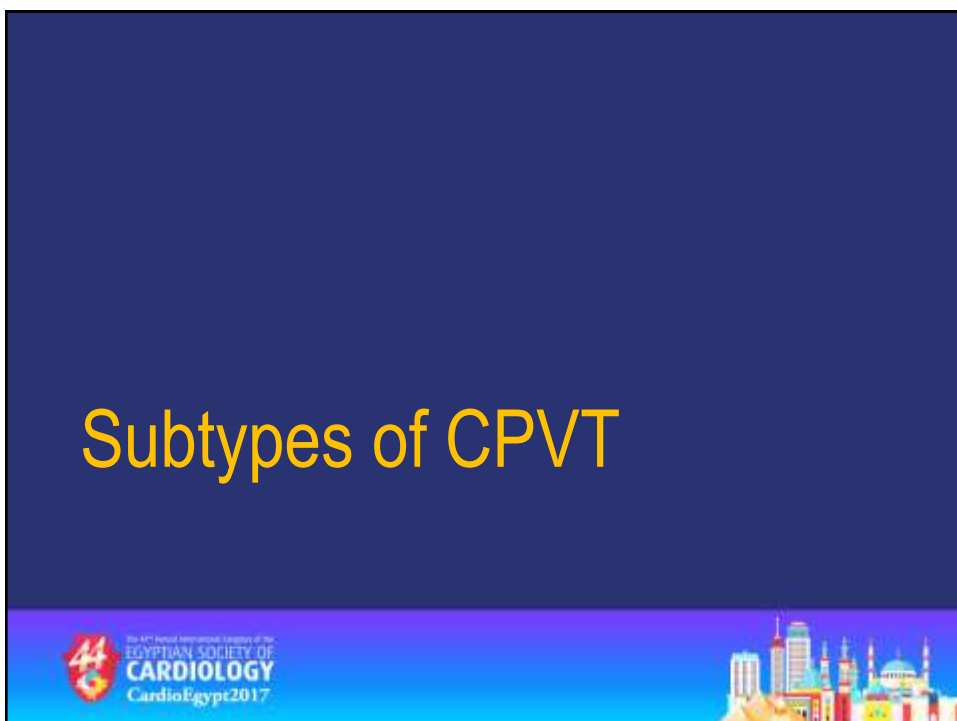


- The fourth hypothesis suggests that the molecular and functional abnormalities are related to mutations in the CASQ2 gene. CASQ2 is a Ca²⁺ storage protein inside the SR. The functional storage capacity of CASQ2 or its reduced levels, may lead to increased levels of free Ca²⁺ inside the SR, leading to a Ca²⁺ leak during diastole. It is also known that CASQ2 stabilizes binding of RyR2 with TRD and the junction.





Subtypes of CPVT



Subtypes of CPVT

Subtypes	Juvenile type						Adult type	
	CPVT1	CPVT2	CPVT3	CPVT4	CPVT5	CPVT related diseases		
						AIS	LQT4	
Incidence (%)	50-60	1	<1	<1	≈1	<1	<1	≈30
Inheritance	AD	AR	AR	AD	Sporadic	AD	AD	Sporadic
Onset of symptoms	10 years	7 years	10 years	4 years	2, 26 years	14, 9, 17 years	?	> 20 years (40 years)
Sex	M:F=1:1	M:F=1:1	M:F=1:1	M:F=1:1	M=3	F>M?	?	F=M
Chromosome locus	1q43	1p13.1	7p22-p14	14q32.11	6q22.31	7q24.3	4q25-26	
Gene	RyR2	CAC1Q2	?	CALM1	TRD	KCNJ2	ANK2	RyR2 ≈ 30%
Protein				CaM		K _v 2.3 _α	Ankyrin-B	
Sudden death (%)	≈10	≈42	≈75	≈18	≈25	?	?	0



Therapy for the CPVT



β Blockers

- β blockers can not completely suppress the arrhythmic events in CPVT patients
- The long acting β blocker, nadolol, is preferred for prophylactic treatment of CPVT
- Propranolol is also an effective medication.
- Only carvedilol inhibits RyR2 activity. Thus, carvedilol may be an effective β blocker for CPVT, but its β blocking effect may be weak in comparison to the other β blockers. Therefore, the efficacy of carvedilol needs to be further investigated



CCBs

- Verapamil has also shown beneficial effects in some CPVT patients. However, the long-term efficacy of verapamil is still controversial



Flecainide

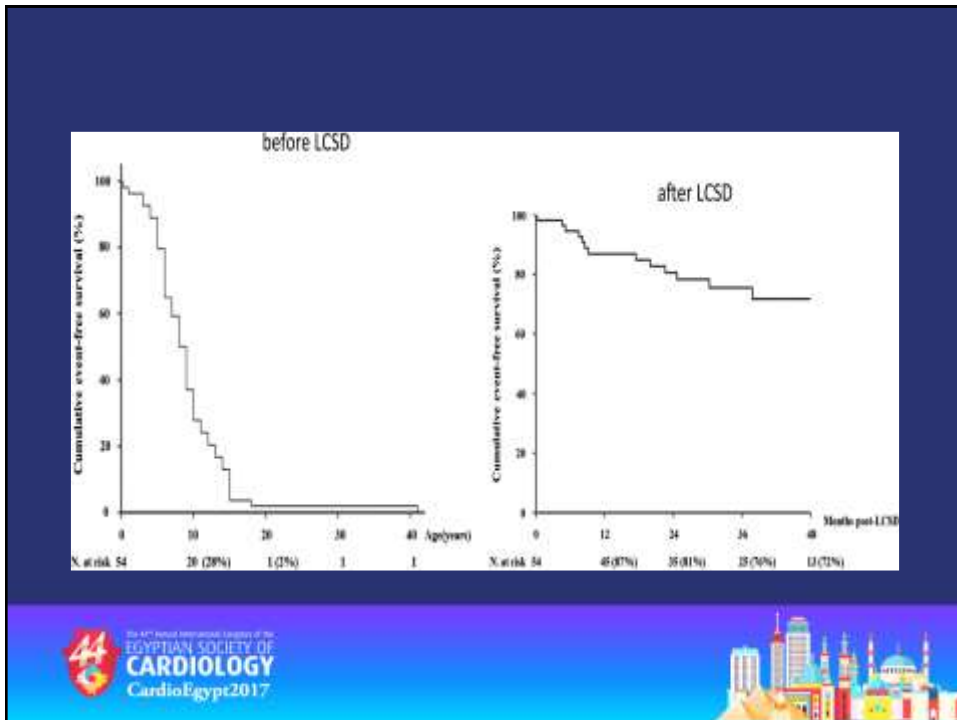
- Flecainide is an effective medication for CPVT . Flecainide treatment shows improvement of ventricular arrhythmias in 74% of the genotype positive CPVT cases , and in 92% of the genotype negative CPVT cases.
- Flecainide is thought to function by direct suppression of the RyR2 receptor. Among the Class I anti-arrhythmic medications, only flecainide and propafenone inhibit RyR2 activity. However, recent report denies the direct suppression of RyR2 by flecainide. That may suggest another mechanism of flecainide, such as inhibition of NCX.



Left cardiac sympathetic denervation

- Left cardiac sympathetic denervation is reported to be a useful therapeutic method for suppressing ventricular arrhythmias in CPVT patients. In patients with uncontrollable ventricular arrhythmias, left cardiac sympathetic denervation is highly useful in controlling ventricular tachyarrhythmias. The rate of complications involving Horner syndrome is very low if denervation is performed in the lower half of the T1 sympathetic ganglion through the T4 ganglion.

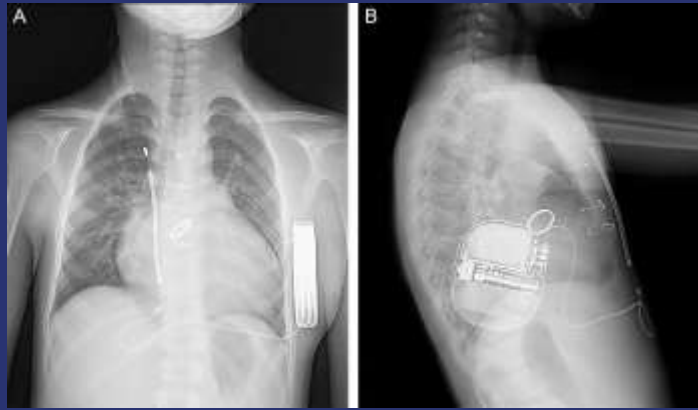




ICD

- Implantation of an ICD should be considered in patients in the absence of controlled optimal therapy. However, implantation of an ICD in children still has a number of technical problems. Moreover, inappropriate or painful shocks may increase the risk of further ventricular arrhythmias, and electrical storms that may result in lethal events.





Catheter ablation

- Pulmonary vein isolation is reported to be effective in some CPVT patients with atrial fibrillation. Purkinje cells are reported to be more arrhythmogenic than ventricular myocytes in a mutant knockout mouse model of CPVT. The onset of CPVT may be initiated from Purkinje cells. Successful catheter ablation has been reported at the site of Purkinje potentials or discrete prepotentials .



Gene therapy



Gene therapy

- The homozygous R33Q knock-in mouse has a dysfunctional CASQ2, which may cause CPVT. In this mouse model, isoproterenol induced DADs, which were markedly reduced after 12 months following infection with an adenoviral vector (serotype 9), that carried the normal CASQ2 gene. This report suggested the possible use of gene therapy for some types of CPVT in the future.



Exercise therapy

- A recent study demonstrated that patients with CPVT1 who underwent a 12-week high intensity ergometer bicycle exercise therapy (ET) program had higher threshold heart rates for VA (compared to pre-ET baseline) in comparison to a control group that did not undergo similar ET. This suggests a role for ET as an adjunctive treatment.



Sports participation



- Previously symptomatic athletes with CPVT or an asymptomatic CPVT athlete with exercise induced premature ventricular contractions in bigeminy, couplets, or non-sustained ventricular tachycardia should not participate in competitive sports except for class I a sports (low dynamic and low static sports such as bowling, cricket, curling, golf, and yoga).



- As our knowledge of CPVT continues to grow, further studies will yield a better understanding of the efficacy and pitfalls of established diagnostic approaches and therapies as well as help shape newer diagnostic and treatment strategies.



- Asymptomatic athletes who are genotype-positive for CPVT may participate in all competitive sports with appropriate precautionary measures including electrolyte replenishment, avoidance of dehydration for all, and acquisition of a personal automatic external defibrillator as part of the athlete's personal sports safety gear and establishment of an emergency action plan with the appropriate school or team officials
- An ICD should not be placed just to allow an individual with CPVT to participate in sports



Conclusion



Take Home Message

- CPVT is a highly malignant inheritable VT
- It is associated with the occurrence of lethal catecholamine-mediated ventricular arrhythmias (VAs)
- Triggered by stress or exertion
- Diagnosed by presence of structurally normal heart, normal resting ECG, exercise induced polymorphic or bidirectional PVCs or VT
- Management include B blockers, verapamile, flecainide and ICD



- Lastly; as our knowledge of CPVT continues to grow, further studies will yield a better understanding of the efficacy and pitfalls of established diagnostic approaches and therapies as well as help shape newer diagnostic and treatment strategies.





**Thank
You!!!**

