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Propaedeutics of Internal Medicine and Physical Rehabilitation Department

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Scientific discussion

Brugada syndrome: solving the mystery of "Deadly dreams"syndrome

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Someone every hour of every day across the globe succumbs to SADS (sudden arrhythmia death syndrome).

SCD: sudden cardiac death

- Sudden cardiac death (SCD) is a leading cause of mortality worldwide with an estimated 15% to 20% of all deaths. SCD mostly occurs in older adults with acquired structural heart disease
- One of SCD type is SUNDS (sudden unexplained nocturnal death syndrome (SUNDS))
- SUNDS occurs predominantly in Southeast Asia and has different terms but similar definitions in different countries

The numerous denominations of the Sudden unexplained death syndrome

- 1.Lai-Tai (in Thailand and Laos): meaning "death during sleep". Sudden unexplained death syndrome (SUDS) was noted in 1977 among southeast Asian Hmong refugees in the United States and Canada. Between 1981 and 1988, the Centers for Disease Control and Prevention reported a very high incidence of sudden death among young male Southeast Asians who died unexpectedly during sleep.
- The victims (all males) were aged 21-54 (median 34). All the victims were apparently healthy before going to bed.

http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S0104-12822020000300018

The numerous denominations of the Sudden unexplained death syndrome

2. Bangungot is the Tagalog word for "nightmare". Also known in Ilocano (a Philippine ethnolinguistic group) as **batibat**, it appears in the shape of an overweight man (bangungot) or overweight Botero-like woman (batibat) who sits on the chest or head of the victim (always male) and suffocates him to death. It is useless to try to push away the bangungot or batibat.

3. The Japanese call it **pok-kuri.** "Pokkuri" means suddenly and unexpectedly in Japanese. According to folklore, these mysterious deaths are caused by a malicious visiting spirit that kills men in their sleep.

Despite these multiple terms, the characteristics of these victims are common:

- sudden death of young healthy individuals
- the vast majority are males
- during nocturnal sleep
- postmortem routine autopsy cannot explain their deaths!

The history of Brugada syndrome

- In 1986 a Polish engineer named Andrea Wockeczek barged into by Pedro Brugada office, carrying his 3-year-old son.
- The boy, Lech, had been experiencing frequent fainting attacks. On several occasions, Wockeczek had performed chest compressions and mouth-to-mouth breathing to resuscitate him
- Wockeczek was tragically familiar with these attacks. His 2-year-old daughter, Eva, had died several months before under similar circumstances. Doctors at his local hospital in Poland were unable to explain why she had died, and they were similarly stumped by Lech's symptoms.
- Desperate to save his son, Wockeczek snuck him out of the country.

The history of Brugada syndrome

- Brugada's first impression was that Lech was perfectly healthy. He was large for his age, with deep-blue eyes and curly blond locks. His heartbeat sounded normal, too, but when Brugada examined his ECG, he saw a pattern that he had never seen before
- Lech was admitted to the coronary care unit at the Maastricht University. For the first two days, he was fine. On the third day, however, he developed a sore throat and a mild fever.
- That night, telemetry alarms sounded. When a nurse got to his bedside, Lech was unconscious, and a monitor showed his heart was fibrillating. The nurse started CPR, and an external defibrillator shock was applied, restarting the tiny heart.

The history of Brugada syndrome

- After the arrhythmia, all manner of tests were performed. A catheter snaked into the boy's heart revealed no coronary anomalies. X-rays and an echocardiogram were normal.
Even tiny biopsies taken of his heart were negative.
- Lech stayed in the hospital for several weeks.
He had more episodes of cardiac arrest that were treated with cocktails of anti-arrhythmic drugs. In the end, a pacemaker was used to maintain a constant minimum heartbeat, because doctors observed that his arrhythmias often started during sleep, when his heartbeat slowed. (Implantable defibrillators were not yet widely available.)

- Despite the prolonged investigation, the cause of the ventricular fibrillation remained undiagnosed. Father and son returned to Poland with a follow-up appointment with Brugada. When they returned to see Brugada, Wockeczek brought the EKG of his deceased daughter, Eva. It was identical to Lech's.

The history of Brugada syndrome

- Over the next few years, Brugada searched for this electrical pattern in other victims of cardiac arrest.
- "I looked everywhere for this ECG but I found nothing," he told.

He collected a few more of these unusual EKGs and continue this work with his brother, Josep.
It was soon dubbed Brugada syndrome, and it and SUDS, from Southeast Asia, were essentially shown by cardiologists and epidemiologists to be the same disease.

- Sad conclusion: **Once patients develop symptoms — unexplained fainting is most common — there is a 50-50 chance they will die within 10 years**.

Brugada syndrome was initially described by brothers-cardiac electrophysiolo-gists Pedro and Joseph Brugada in 1992. It is the last "new clinical-cardiologic syndrome" described in the 20th century!

Brugada syndrome: definition and epidemiology

- The Brugada syndrome (BrS) is a hereditary arrhythmia syndrome manifesting as recurrent syncope or sudden cardiac death (SCD) due to polymorphic ventricular tachucardia (VT) or fibrillation (VF) in the absence of overt structural heart disease or myocardial ischemia.
- The prevalence of the syndrome is estimated at around 15 per 10,000 in South East Asia including Japan and around 2 per 10,000 in the Western countries.
- The BrS may be responsible for up to 4 % of all sudden cardiac deaths (SCD) and at least 20 % of SCDs in patients with structurally normal hearts. It is 8–10 times more prevalent in males than in females and males are at considerably higher risk of dying suddenly.
- The severity of symptoms varies from person to person. There are some known triggers for Brugada syndrome like fever and sodium blocking drugs.

MILESTONES IN OUR UNDERSTANDING OF BRUGADA SYNDROME

- It has been 100 years since the first description of SUNDS in 1917 in the Philippines.
- As a disorder mainly prevalent in Southeast Asia, SUNDS did not attract worldwide attention until 1981, when its first report was submitted to the Centers for Disease Control and Prevention.
- A report is detailing sudden, unexpected deaths during sleep among mostly young, male, Southeast Asian refugees in the United States. Thirty-three of those who died were from Laos, four were from Vietnam, and one was from Cambodia.
- *1991* – Brugada and Brugada presented an abstract in the NASPE meeting of a new clinical-cardiologic syndrome, characterized by the association of RBBB, persistent ST segment elevation, normal QT interval, and SCD
- *2002* – Genetic studies showed that unexplained nocturnal SCD syndrome, known as sudden unexplained nocturnal death syndrome, and Brugada disease are phenotypically, genetically, and functionally identical and allelic since both affect the same gene: SCN5A.

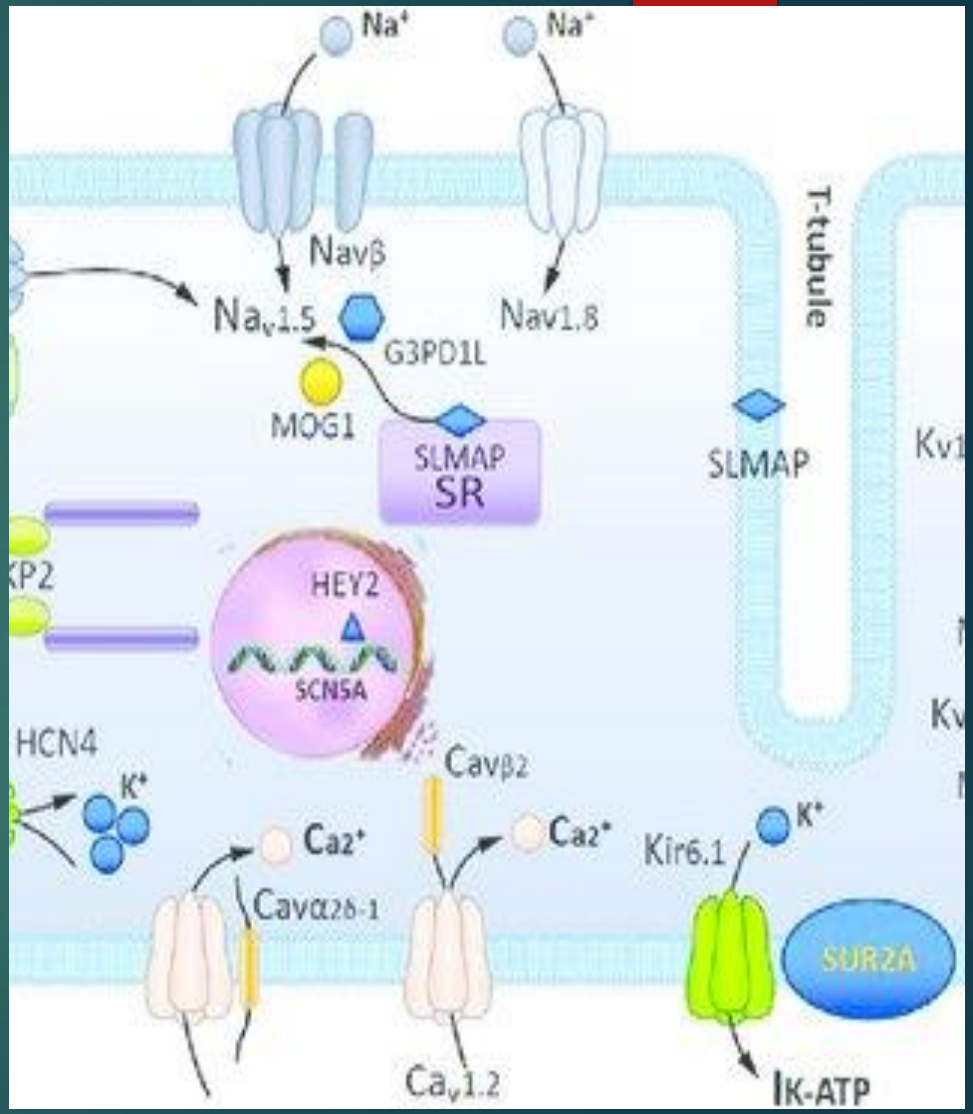
Causes of Brugada syndrome

- The primary gene known to be associated with Brugada syndrome is located on chromosome 3 and has been termed the *SCN5A* gene. Approximately 15%-30% of individuals with Brugada syndrome have a *SCN5A* gene mutation. This gene is responsible for the production of a protein that allows movement of sodium atoms into heart muscle cells through a channel called the sodium channel.

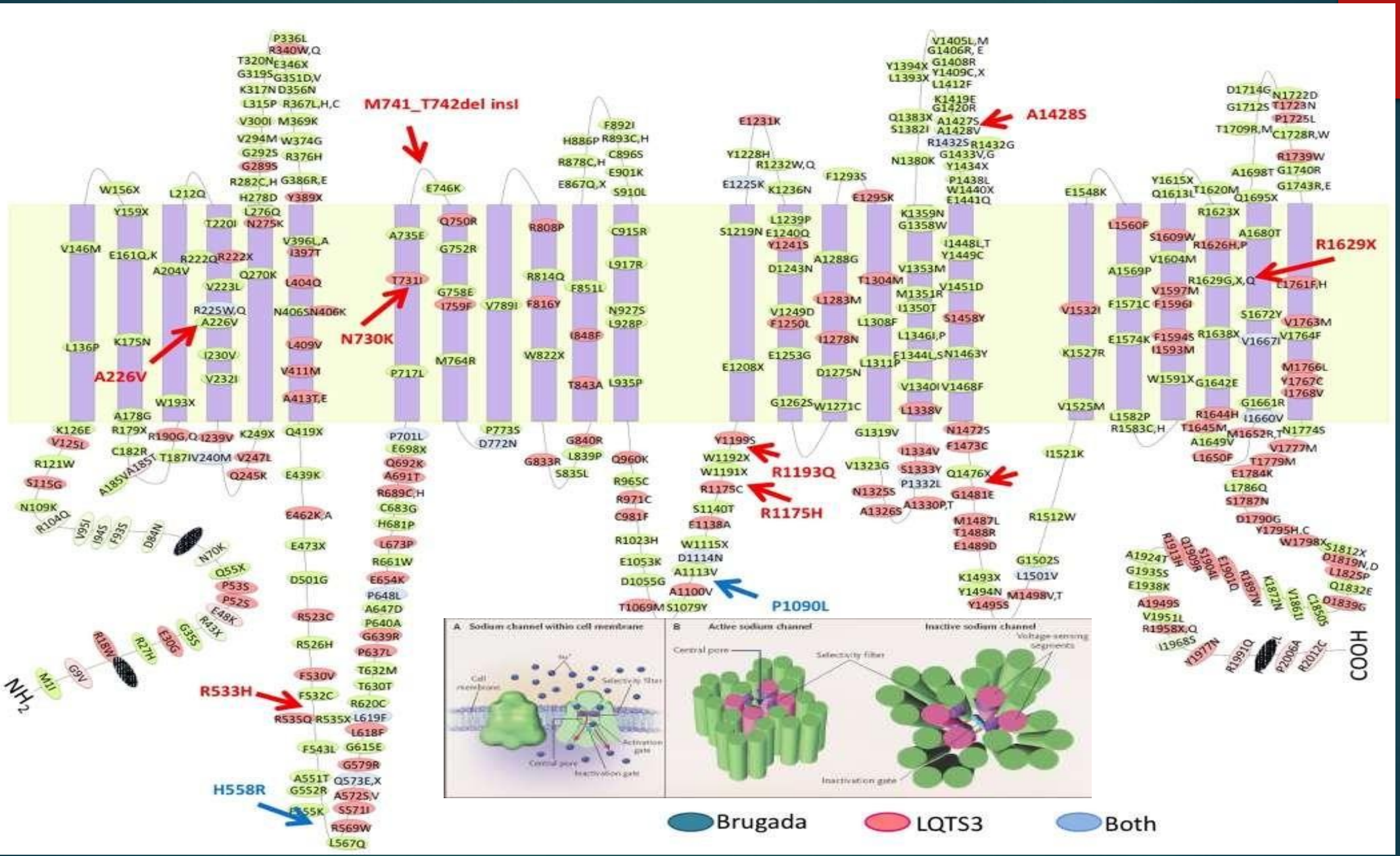
- Abnormalities in the *SCN5A* gene change the structure or function of the sodium channel and result in a reduction of sodium into the heart cells. Reduced sodium can lead to an abnormal heart rhythm that can lead to sudden death.

- The *SCN5A* gene mutations are also associated with the long QT syndrome type 3 (LQT3), which is one form of a heart rhythm abnormality called Romano-Ward syndrome. Some families have been reported that have relatives with Brugada syndrome and LQT3, suggesting that these conditions may be different types of the same disorder.

- Currently, more than 250 mutations associated with BrS have been reported in 18 different genes Despite the identification of 18 associated genes, 65%–70% of clinically diagnosed cases remain without an identifiable genetic cause.



https://rarediseases.org/rare-diseases/brugada-syndrome/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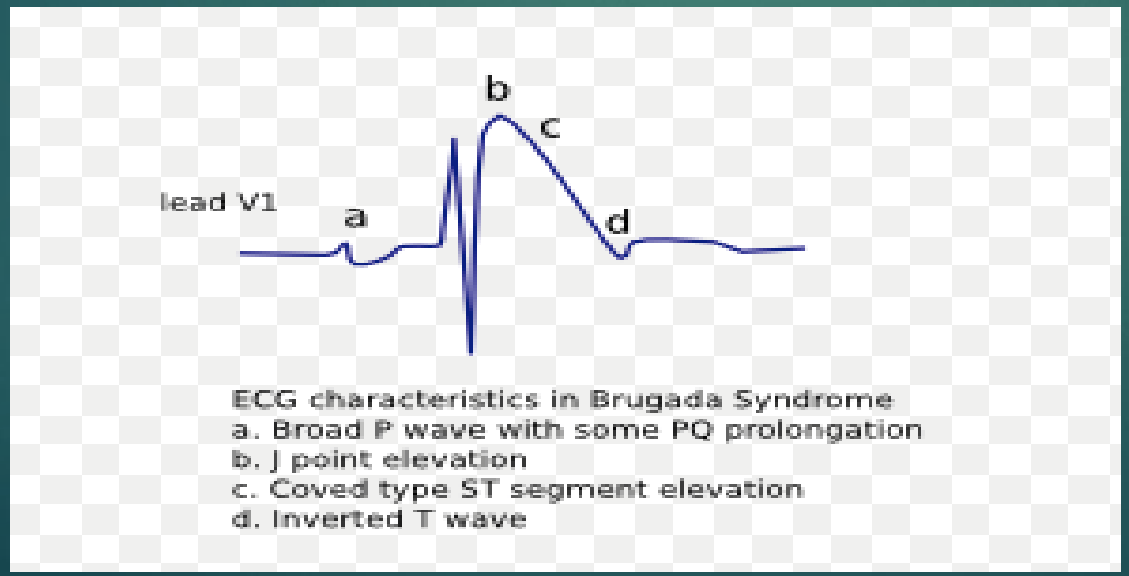
A226V
N730K
R533H
H558R
A1428S
R1629X
R1193Q
R1175H
P1090L
NH2
COOH
Brugada
LQTS3
Both
A Sodium channel within cell membrane
B Active sodium channel
Inactive sodium channel
Central pore
Selectivity filter
Voltage-sensing segments
Activation gate
Inactivation gate
Cell membrane

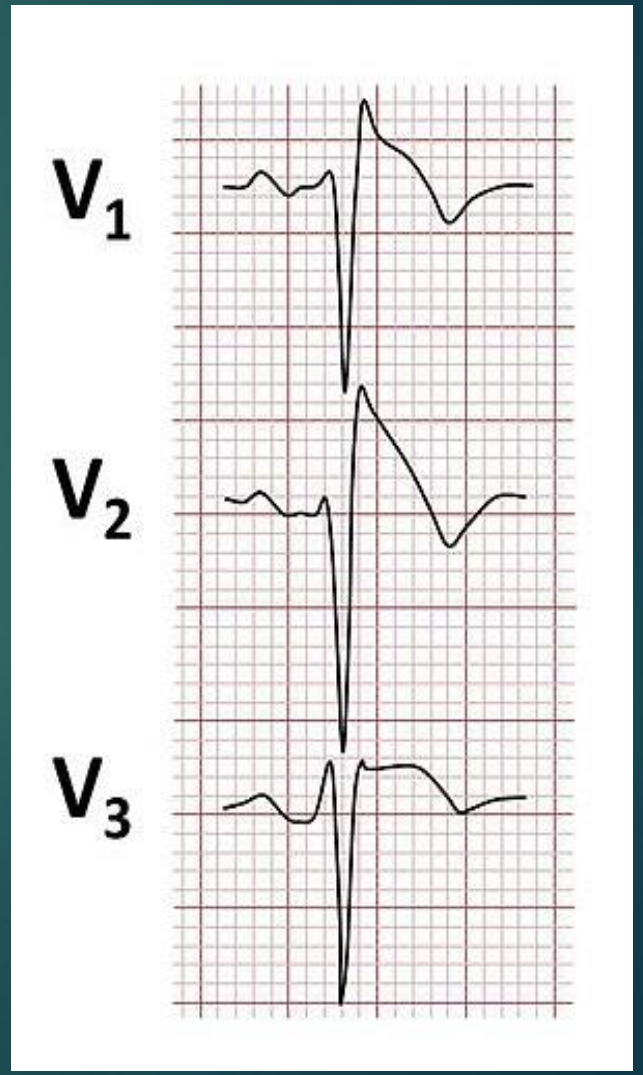
Diagnosis: the ECG is a key to the diagnosis of the brugada syndrome

- **Type 1** Brugada ECG pattern (so-called "coved")

– is the diagnostic hallmark of BrS. It characterized by J-point elevation with slowly descending or concave ST segment elevation merging into a negative or reaching the isoelectric line symmetric T wave.

The type 1 Brugada ECG pattern is observed most frequently in leads V1 and V2, much less frequently in lead V3.





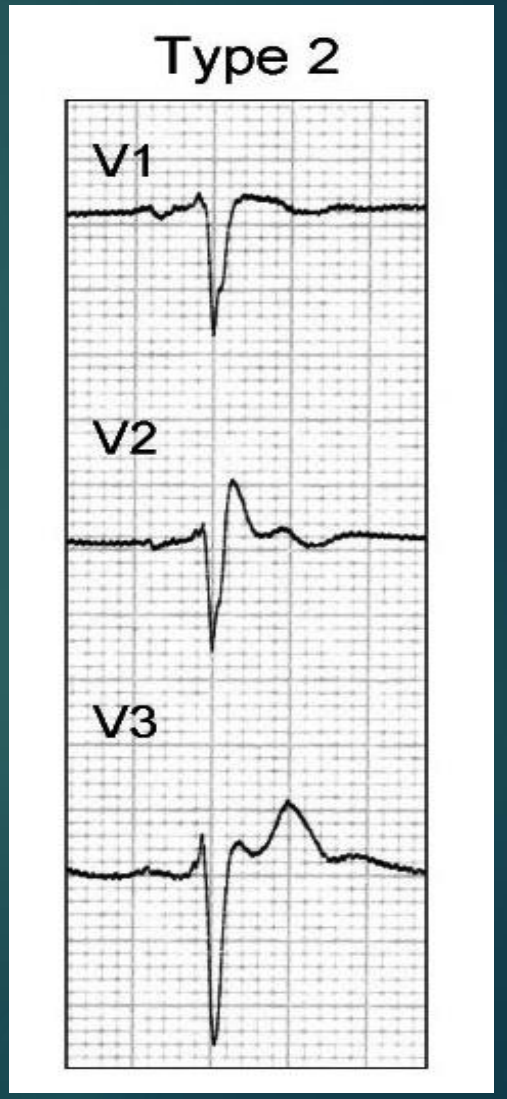
Diagnosis: the ECG is a key to the diagnosis of the Brugada syndrome

- **Type 2 and 3**

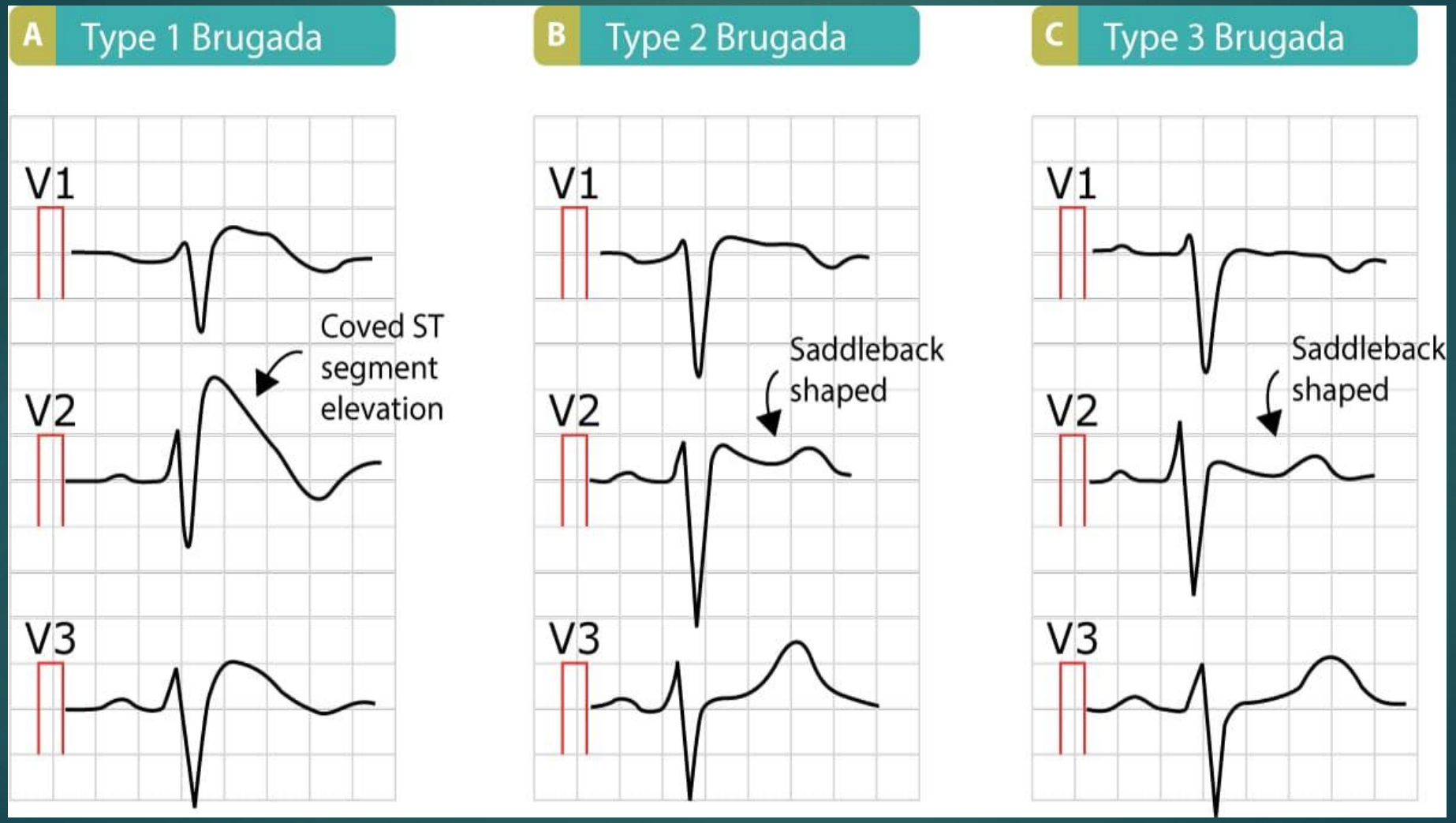
Type 2 and 3 are defined as the "saddle-back pattern," which is defined as an incomplete right bundle branch block (IRBBB) with ST-segment elevation (type 2 with ≥0.1 mV and type 3

- Although type 1 is the hallmark of patients with BrS, types 2 and 3 patterns should be distinguished from incomplete RBBB, present in 3% of the population
- To diagnose Brugada types 2 or 3, patients undergo antiarrhythmic drug challenge (AAD) to unmasked the Na/K channel dysfunction and convert to type 1.

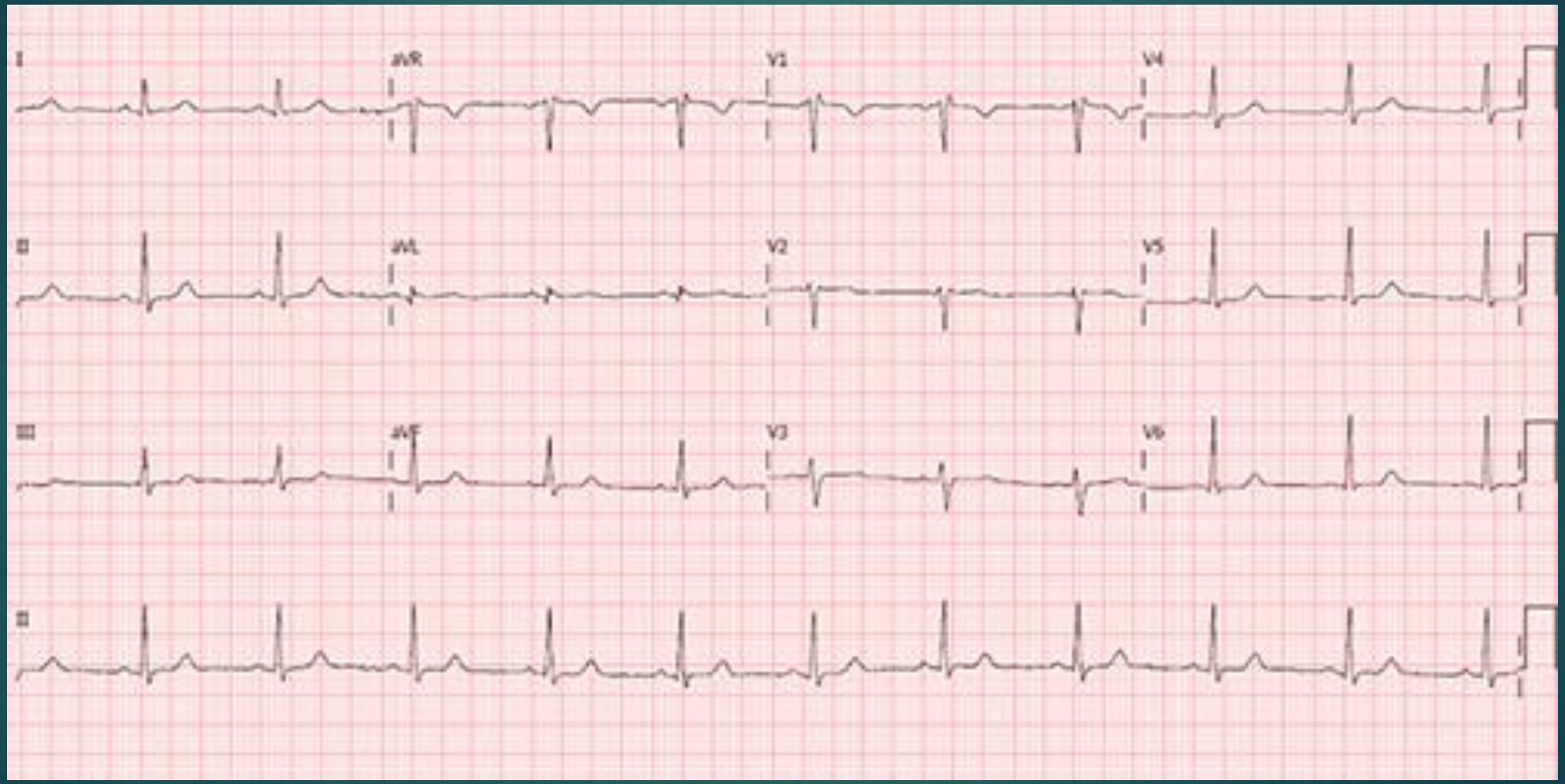
- If the patient does not convert to type 1, then it is presumed an IRBBB and not Brudaga pattern.



ECG types of Brugada syndrome



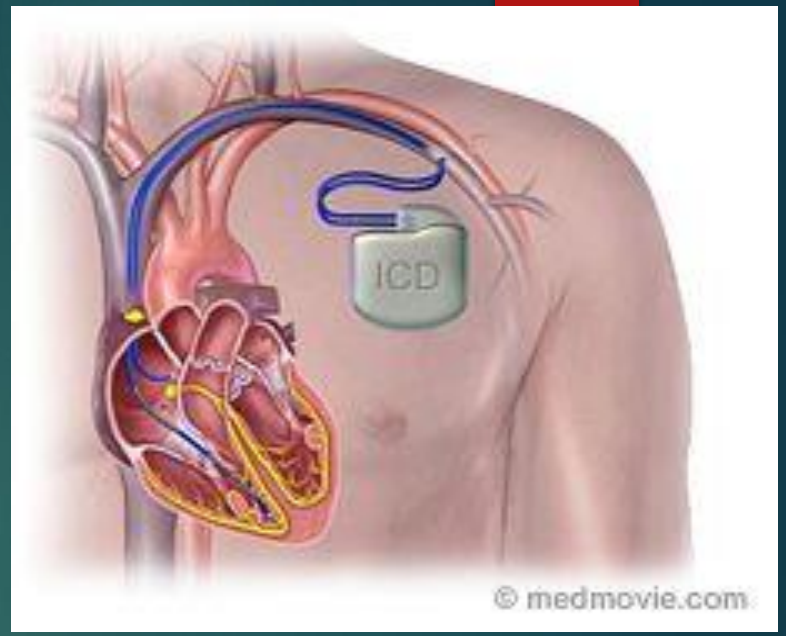
Incomplete Right bundle branch block



For establishing diagnosis BrS patient must have 1of:

- Documented ventricular fibrillation (VF) or polymorphic ventricular tachycardia (VT).
- Family history of sudden cardiac death at <45 years old .
- Coved-type ECGs in family members.
- Inducibility of VT with programmed electrical stimulation .
- Syncope.
- Nocturnal atonal respiration (abnormal pattern of breathing and brainstem reflex characterized by gasping, labored breathing, accompanied by strange vocalizations and myoclonus).
- Genetics is not currently used to make a diagnosis, but it can be used for family screening, in the case of a clinical diagnosis of Brugada and the finding of the genetic mutation in the proband.

TREATMENT



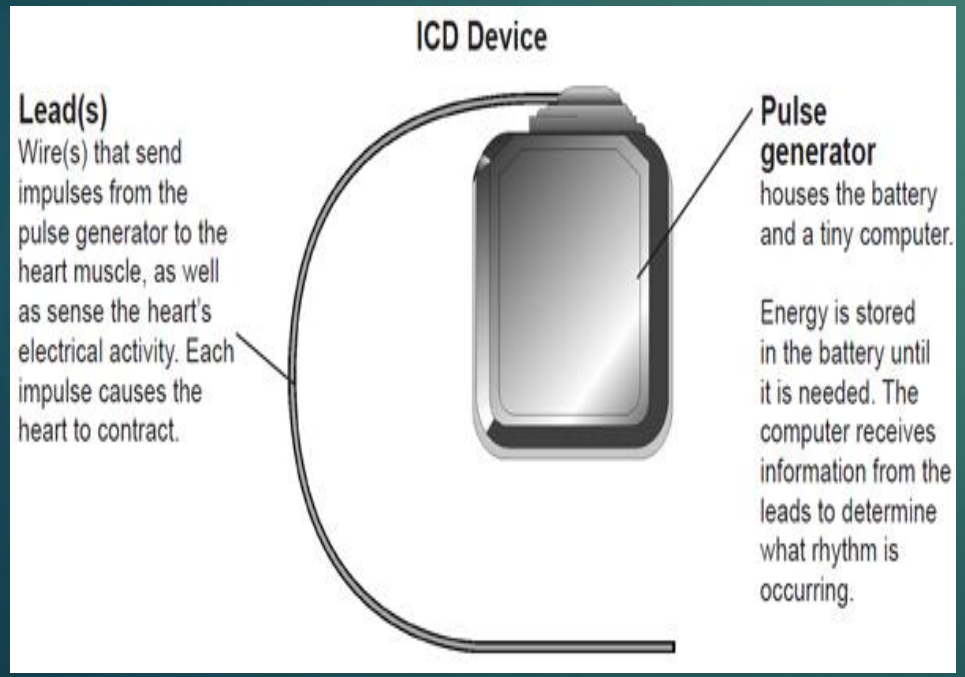
- No specific cure for Brugada syndrome exists, so far. Recommendations for treatment of asymptomatic individuals are controversial.

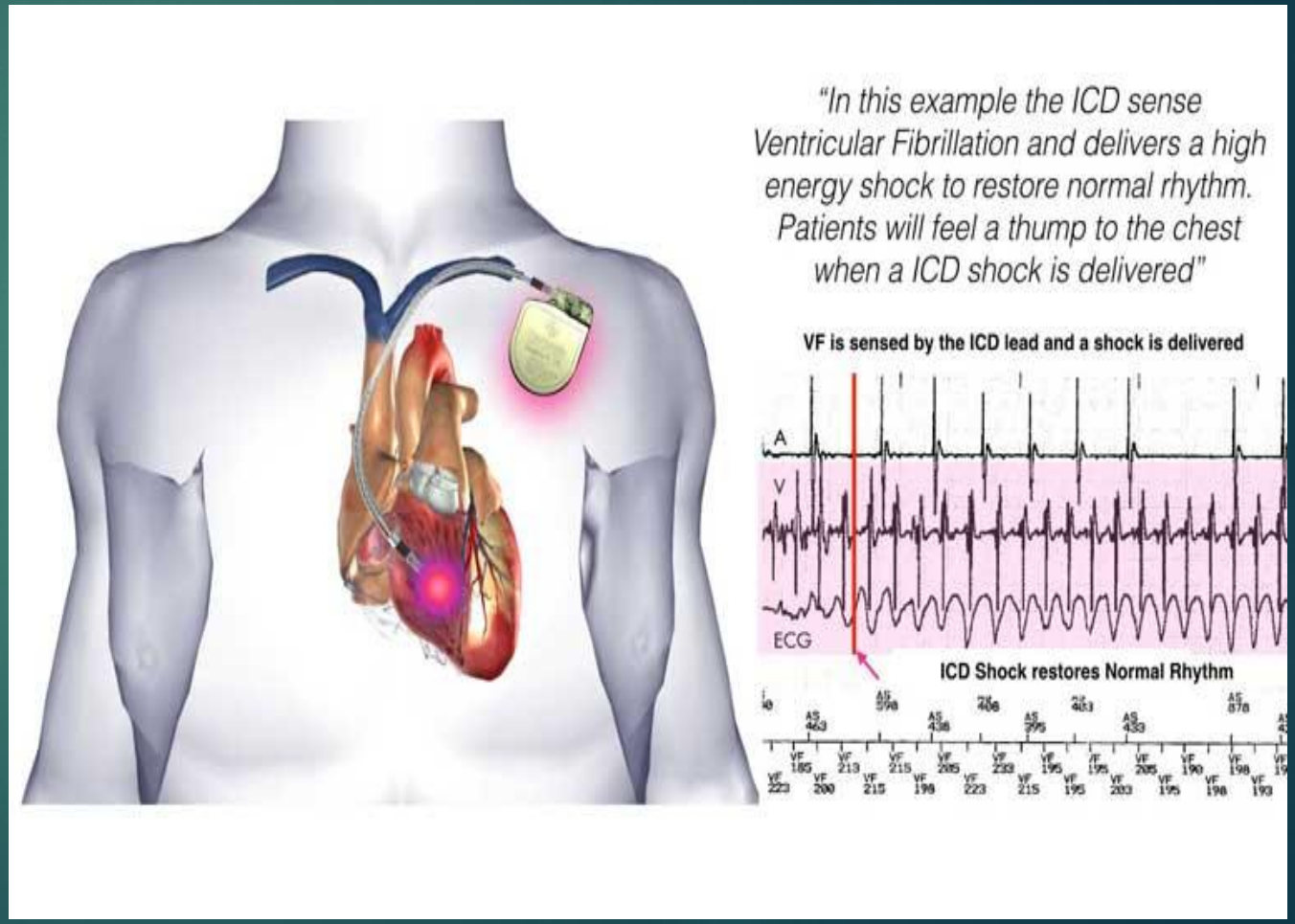
- Individuals at a high risk of ventricular fibrillation are treated with an implantable cardioverter defibrillator (ICD). This device detects the abnormal heartbeat automatically and selectively delivers an electrical impulse to the heart restoring normally rhythm.

- Drug therapy in BrS has several utilities: first, in the acute management of arrhythmic storm; second, in prevention of arrhythmic events in patients with implanted ICD who require many shocks; and third, as an alternative to ICD implantation when the latter is contraindicated, not feasible (infants and young children), unaffordable, or refused by the patient.

- Other treatment is symptomatic and supportive.

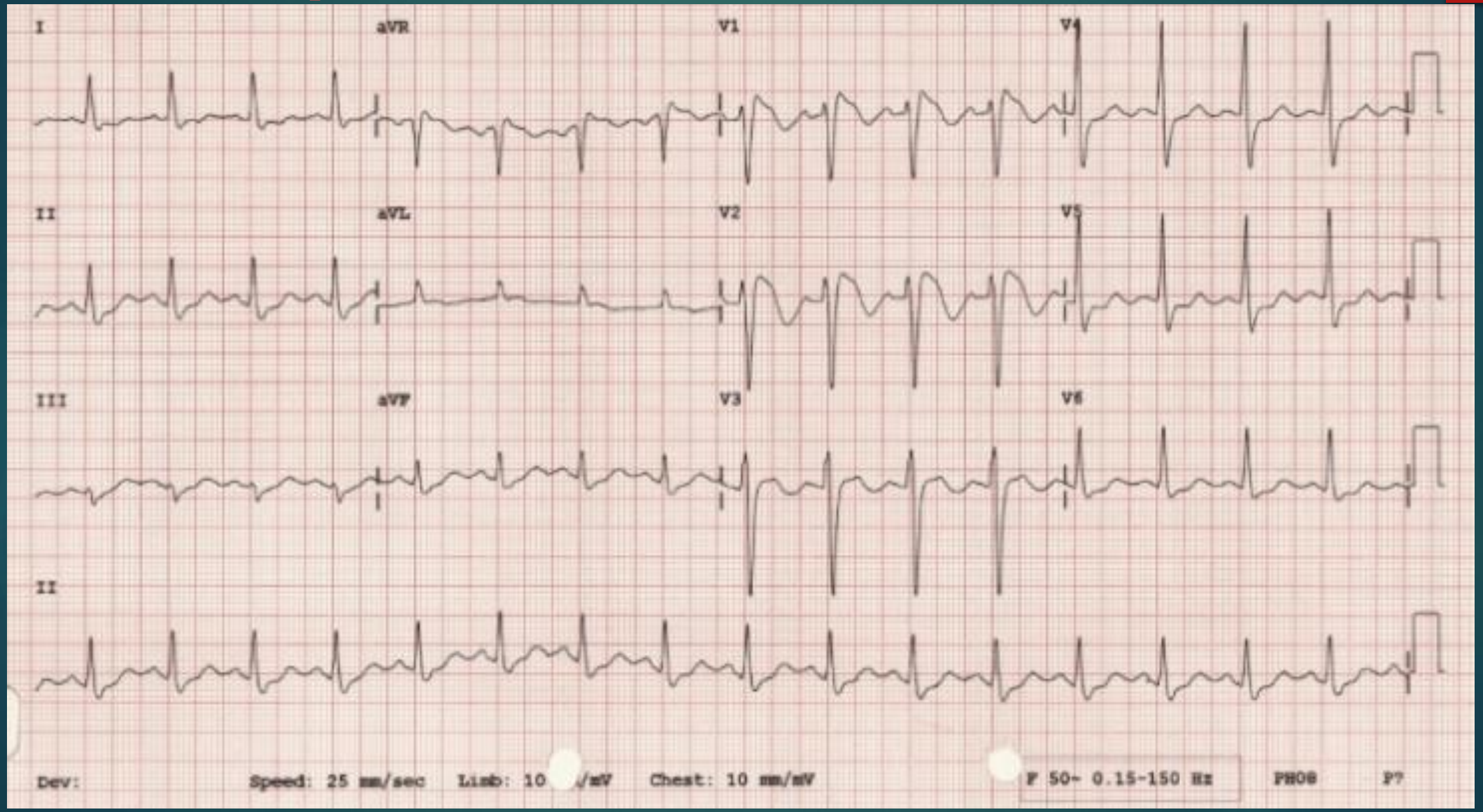
Implantable Cardioverter Defibrillator (ICD)-an ICD, is a device implanted in the body that can detect and terminate ventricular tachyarrhythmias.



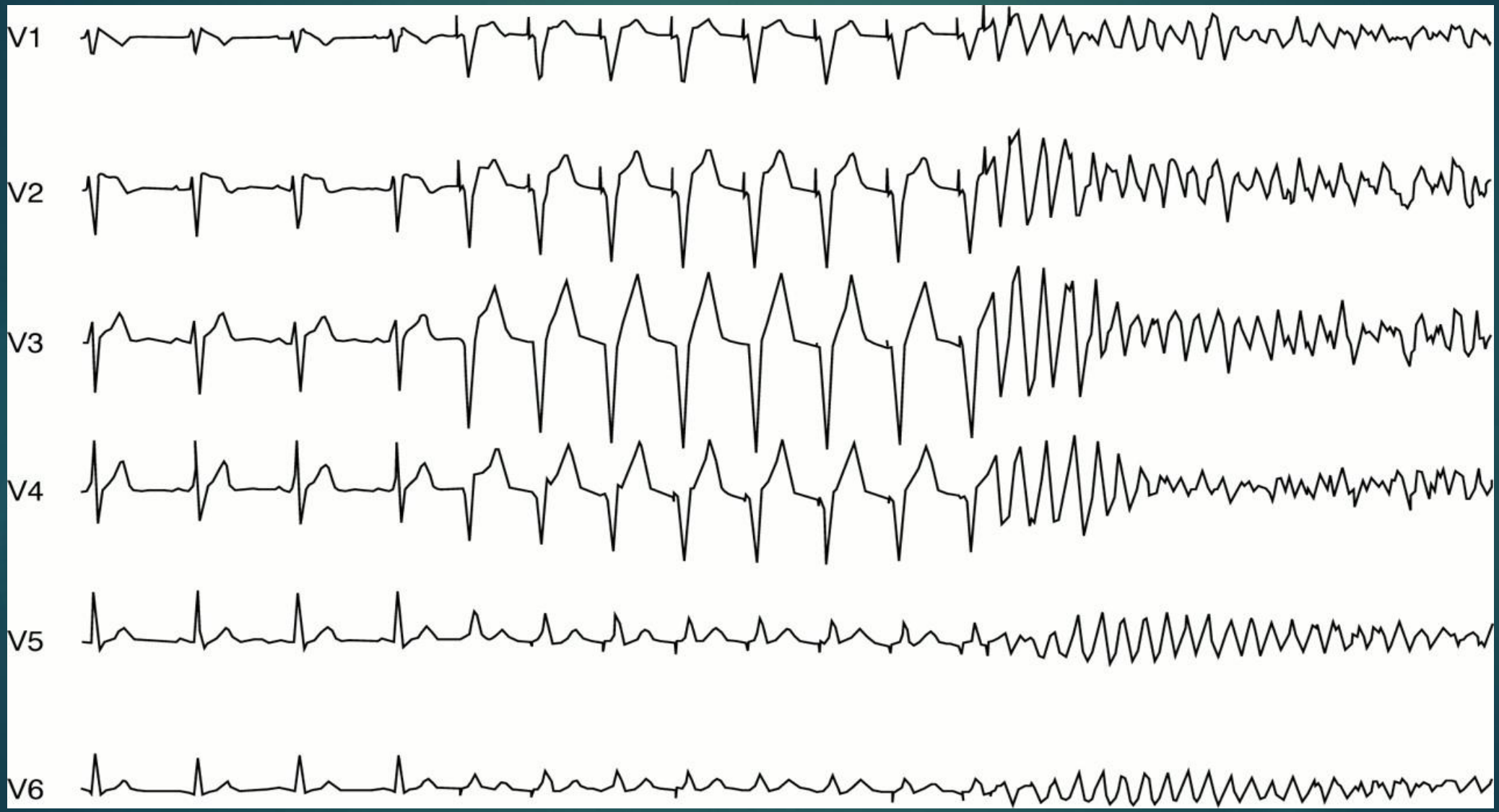


Evolution of ICD

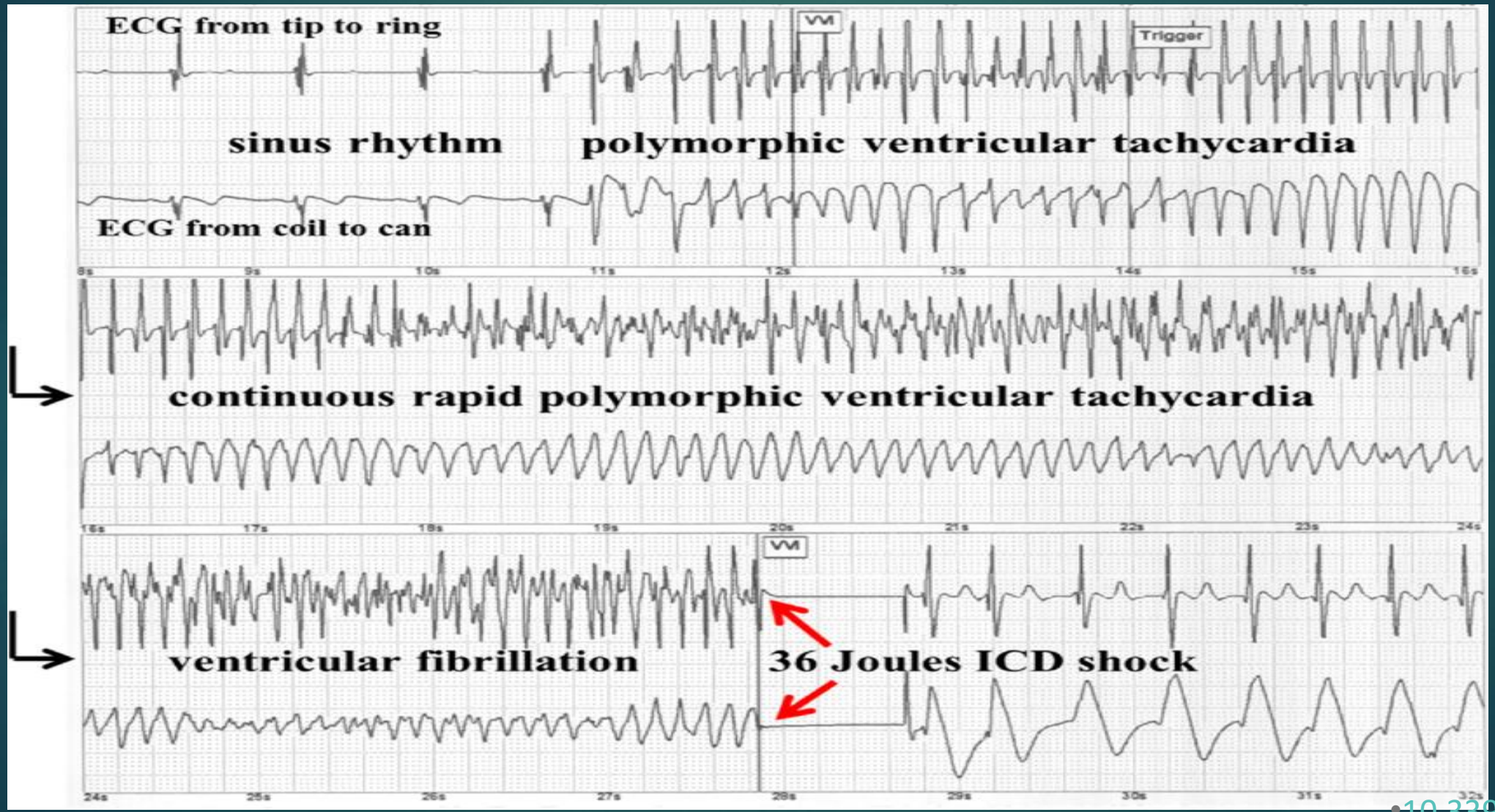
ECG of patient with BrS



The beginning of VF in patient with BrS

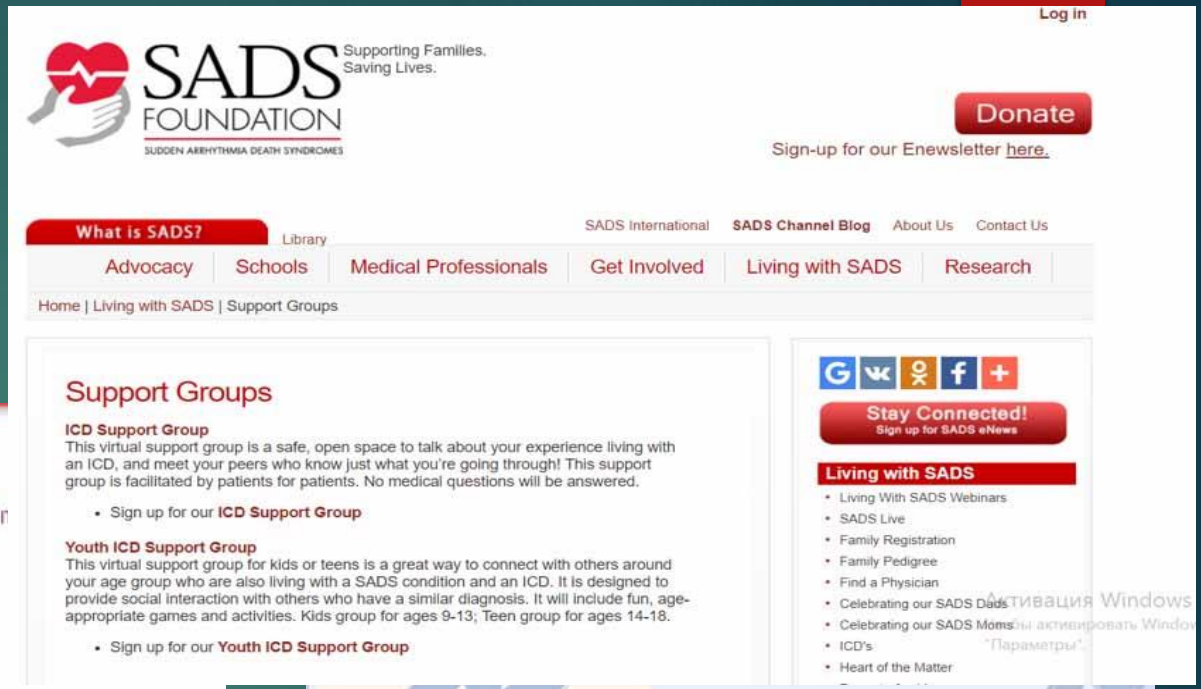


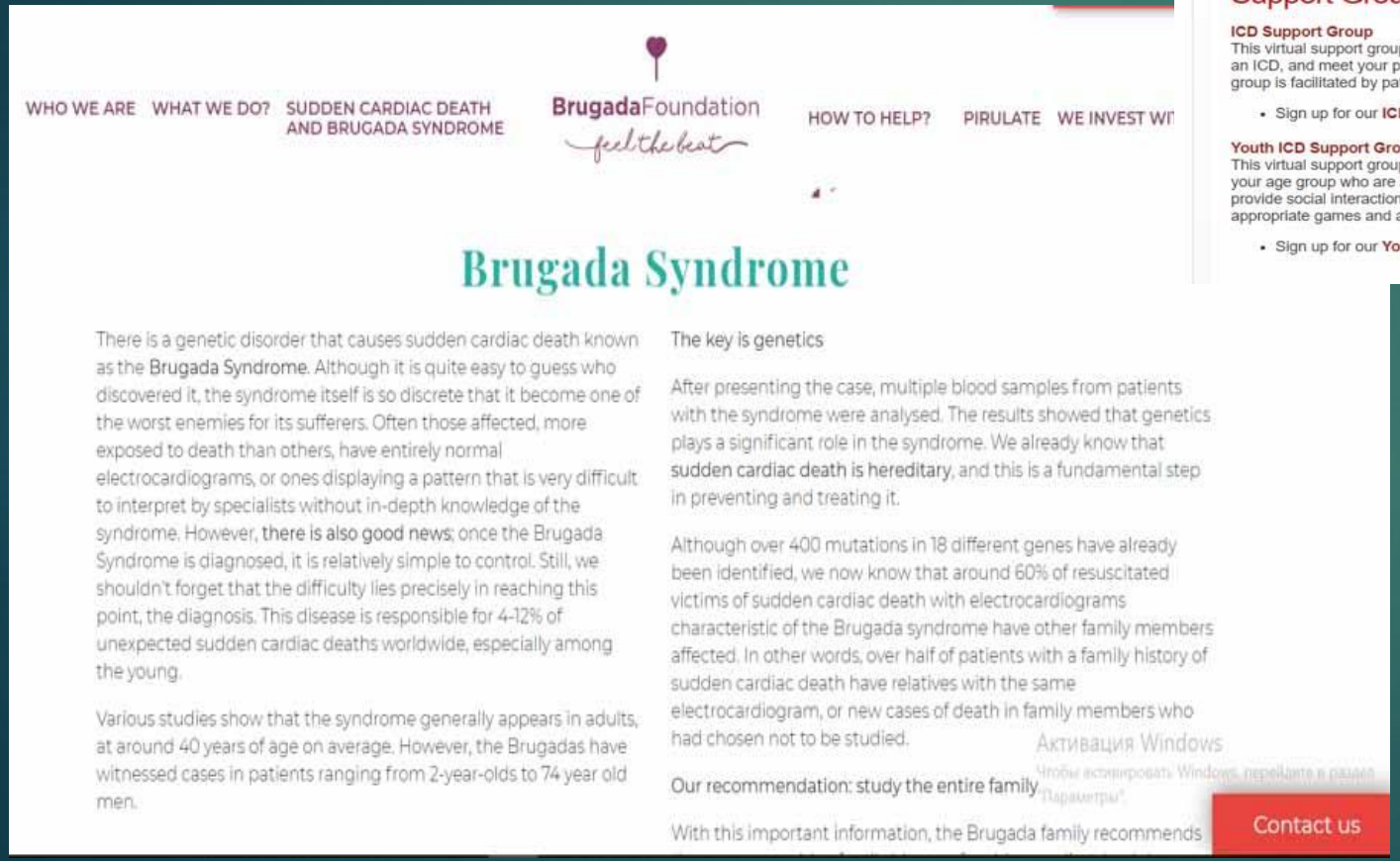
How does ICD work



•DOI:
•10.3390/ijms151018693

Support groups for patients with BrS





Key messages about Brugada syndrome

- Brugada syndrome is now believed to be responsible for as many as 20 percent of deaths in patients with structurally normal hearts.
- Typical ECG patterns are the key in BrS diagnosis
- For now, the only effective treatment remains an implantable defibrillator.
- Since its introduction as a clinical entity in 1992, the Brugada syndrome has progressed from being a rare disease to one that is second only to automobile accidents as a cause of death among young adults in some countries.

Sudden and unexplained death in sleep (SUDS) is a leading cause of death of young men in several Asian populations.

The photo shows Hmong men in Huay Nam Khao refugee camp, praying for a peaceful life.

From the Bangkok Post.

Thank you for your attention!

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