ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Brugada Syndrome: 30 Years of Scientific Adventure

Brugada Sendromu: 30 Yıllık Bilimsel Macera

ABSTRACT

Thirty years ago, a distinct new clinical-electrocardiographic syndrome was described, now known as Brugada syndrome. Typical for this syndrome is EKG with ST elevation in the right precordial leads. The clinical presentation of the disease is highly variable: Patients may remain completely asymptomatic but may also develop episodes of syncope, atrial fibrillation, sick sinus syndrome, conduction disturbances, asystole, and ventricular fibrillation. The disease is caused by mutations in the genes responsible for the action potential of the heart cells. The most frequently involved gene is the SCN5A which controls the structure and function of the cardiac sodium channel. Describing this new syndrome has had very positive implications in all fields of medicine.

Keywords: Atrial fibrillation, Brugada syndrome, implantable cardioverter defibrillator, sodium channel gene, sudden death, syncope

ÖZET

Otuz yıl önce, şimdi Brugada sendromu olarak bilinen yeni bir klinik-elektrokardiyografik sendrom tanımlandı. Bu sendromun tipik özelliği, sağ prekordiyal derivasyonlarda ST yükselmesi olan EKG'dir. Hastalığın klinik görünümü oldukça değişkendir: Hastalar tamamen asemptomatik kalabilir, ancak aynı zamanda senkop, atriyal fibrilasyon, hasta sinüs sendromu, iletim bozuklukları, asistol ve ventriküler fibrilasyon atakları da geliştirebilirler. Hastalığa, kalp hücrelerinin aksiyon potansiyelinden sorumlu genlerdeki mutasyonlar neden olur. En sık dahil olan gen, kardiyak sodyum kanalının yapısını ve işlevini kontrol eden SCN5A'dır. Bu yeni sendromun tanımlanmasının tıbbın tüm alanlarında çok olumlu etkileri olmuştur.

Anahtar Kelimeler: Antiaritmikler, aritmi, Brugada sendromu, genetik, implante edilebilir kardiyoverter defibrilatör, ani kardiyak ölüm, senkop ventriküler taşikardi

REVIEW
DERLEME

In November, now 30 years ago, the *Journal of the American College of Cardiology* published an article entitled "Right bundle branch block, persistent ST segment elevation and sudden death: A distinct clinical and electrocardiographic syndrome: A multicenter report."[1] In that article, 8 patients were described with a history of resuscitated sudden death caused by ventricular fibrillation (VF). After extensive investigation, no cause for the arrhythmias was found in these patients. All 8 patients showed a very unusual electrocardiogram (EKG) with ST elevation in the right precordial leads and what appeared to be a right bundle branch block (Figure 1). Three of the patients were children. Two were young girls. Two of the children were brother and sister. Three patients also had features of sick sinus syndrom (SSS) and 3 were also diagnosed with atrial fibrillation (AF). Four patients had marked conduction disturbances and 4 also had a prolonged or borderline HV interval, and all patients had polymorphic ventricular tachycardia (VT) (sustained or not) inducible on electrophysiological examination. The causes of the syndrome were unknown at the time, but it was immediately clear that it was a purely electrical problem of the heart—the heart was structurally normal—and that it must be a hereditary problem. The very fast VF suggested a problem of dispersion of short or normal refractory periods, in contrast to the relatively slower VF (torsade de pointes) of long QT syndrome, where the ventricular refractory periods are prolonged due to prolonged repolarization. The publication was the beginning of a great adventure that is still ongoing.

It had taken 5 years to collect the first 4 patients. These 4 patients were presented in a poster in the North American Society of Pacing and Electrophysiology (NASPE)

Pedro Brugada, M.D.

Cardiology Heart Rhythm Management Centre, Brussel, Belgium

Corresponding author:
Pedro Brugada
✉ Pedro@brugada.org

Received: April 19, 2022
Accepted: May 16, 2022

Cite this article as: Brugada P. Brugada syndrome: 30 years of scientific adventure. *Turk Kardiyol Dern Ars.* 2022;50(6):452-458.

DOI:10.5543/tkda.2022.22444

meeting in 1991. After the presentation, and thanks to international collaboration, a large number of potentially equal patients was collected. Ultimately, 4 new patients were selected with identical characteristics to the first 4. This spontaneous international collaboration (without funding, without protocols, and no committees or councils) resulted in one of the most cited original publications in cardiology. What the authors initially regarded as a kind of curiosity later turned out to be a true scientific revolution. This revolution is felt in the positive implications that the discovery of this syndrome has had in multiple aspects of medicine.

Implications of the Brugada syndrome

For Clinical Cardiology

Describing this new syndrome has done tremendous justice to the value of the EKG as a simple, inexpensive, yet very valuable diagnosis method, The diagnosis of the Brugada syndrome (BrS) relies on the abnormal EKG. The so-called "type 1" EKG (Figure 1) is the only condition for the diagnosis after other possible causes (phenocopies, Table 1) have been excluded. The BrS has again made it clear how dangerous it is to classify unclear EKGs as "normal variants." The EKG of BrS was considered a normal variant for years, with no diagnostic or prognostic significance.[2] We had to realize our naivety in a very hard way. There

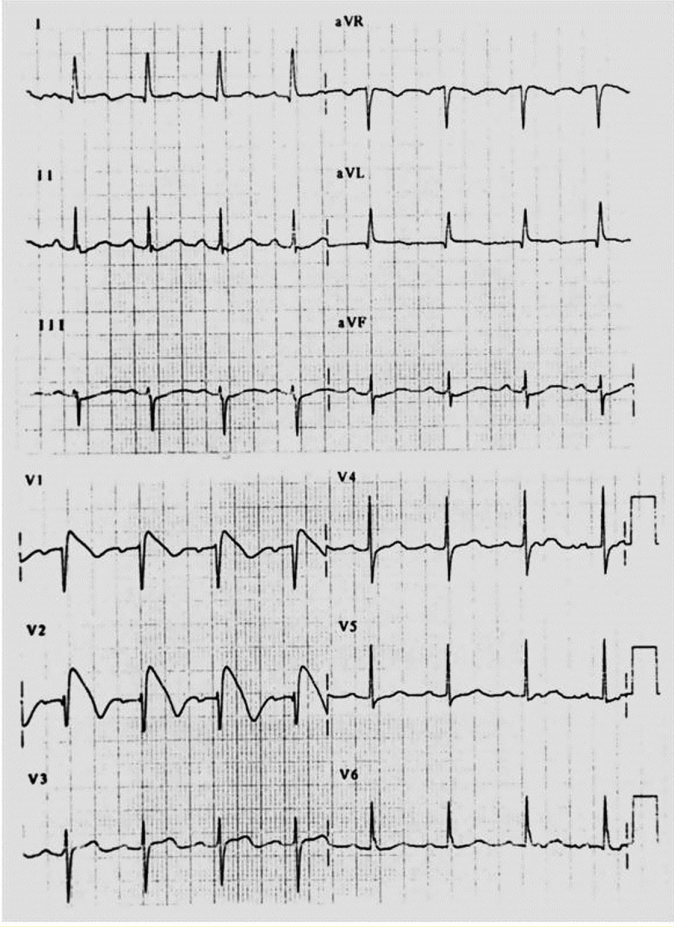

Figure 1. Typical 12 lead EKG of BrS. There is ST elevation in the right precordial leads V1 and V2, with a morphology that looks like the fin of a dolphin. BrS, Brugada syndrome.

Table 1. Phenocopies That Can Simulate BrS

Drugs
Antiarrhythmic drugs
• Class 1C sodium channel blockers (e.g., flecainide, pilsicainide, propafenone) • Class 1A sodium channel blockers (e.g., procainamide, disopyramide, cibenzoline) • Verapamil (L-type calcium channel blocker) • β-Blockers (inhibit ICaL)
Antianginal drugs
• Nitrates • Calcium channel blockers (e.g., nifedipine, diltiazem)
• Psychotropic agents
• Tricyclic antidepressants (e.g., amitriptyline, desipramine, clomipramine, nortriptyline) • Tetracyclic antidepressants (e.g., maprotiline) • Phenothiazines (e.g., perphenazine, cyamemazine) • Selective serotonin uptake inhibitors (e.g., fluoxetine) • Cocaine intoxication
Antiallergic agents
• Histamine H1 antihistaminics.
Acute ischemia in RVOT
Electrolyte disturbances
• Hyperkalemia • Hypercalcemia
Hyperthermia and hypothermia
Elevated insulin level
Mechanical compression of RVOT

BrS, Brugada syndrome; RVOT, right ventricular outflow region.

have been attempts to structure the diagnosis of BrS through a point system.[3] Unfortunately, this score turns out to be of no value in practice, because up to 40% of patients with proven BrS would not have sufficient criteria to make the diagnosis through this system.[4] One may speak of a patient with a Brugada EKG if there are no other findings to speak of a syndrome, such as syncope, resuscitated sudden death, AF, conduction disorders, or pathological mutations. The moment one or more of these findings is established, one can speak of a BrS. The question is whether one can talk about a Brugada disease at the moment that also a genetic cause of the syndrome is found.

For Physiology

The BrS has discovered new mechanisms of arrhythmias, in particular, the phenomenon of "Phase 2 re-entry" (P2R) (Figure 2).[5] The correct mechanism of VF in BrS is still under debate. Besides the classical re-entry based on abnormal conduction (panel A in Figure 2), P2R and the neural crest theory are 2 alternatives to explain the arrhythmias. Classical re-entry into the right ventricular outflow region (RVOT) is considered the most important mechanism for VF by the group at Universitair Medisch Centrum (UMC) in Amsterdam. But Utica's group sticks to the theory of P2R. While in the first mechanism, the action potentials would be normal and the electrical gradient would be due to the slow conduction with out-of-phase action potentials, in P2R, the

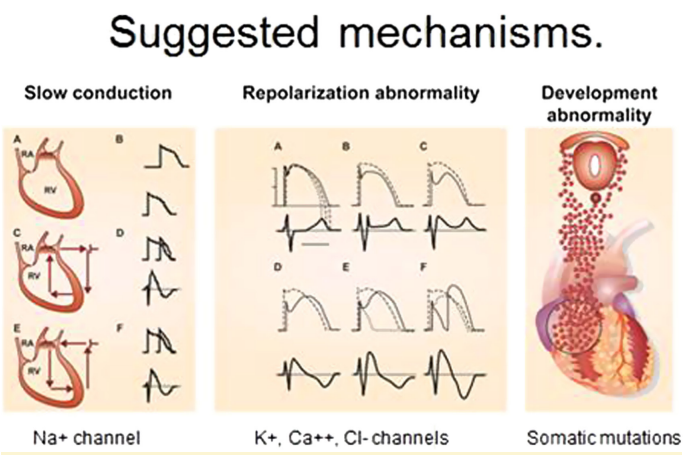

Figure 2. Illustration of the 3 possible mechanisms of BrS. Panel A shows the depolarization theory, where conduction disturbances in the RVOT could represent the most important phenomenon. Panel B shows the mechanism of P2R, where a shortening of the epicardial action potential in the RVOT operative would be. Panel C shows the theory by Elizari, based on embryonic abnormalities in the neural crest. Abnormal development of the cells reponsible for the formation of the RVOT with possible somatic mutations would be the most significant problem leading to BrS. BrS, Brugada syndrome; RVOT, right ventricular outflow region; P2R, phase 2 re-entry.

electrical gradient is caused by a shortening of the duration of the action potential in the epicardium of the RVOT (panel B). While in the first mechanism, the leading problem would reside in mutations that reduce sodium flow in the heart cell, P2R relies on an exaggerated flow of potassium (Ito). Interestingly enough, mutations in BrS have been found in many different genes with a very extensive range of functions. It is better to say that the BrS is just 1 phenotype with possibly many different causes. Similar to long QT syndrome (LQT), the EKG shows a long QT interval, but the causes can vary enormously (sodium channel ion in LQT type 3 and potassium channels in type 1 and 2). Elizari's group, in Buenos Aires, suggests that the basis for the BrS rests on mutations in the cells of the neural crest which would be somatic mutations. For them, the BrS is a problem of heart development in the embryonic stage. Interestingly enough, mutations in the germinal cells are found in up to 40% of families with BrS. Indeed, it is possible that the other patients have somatic mutations which would only be detectable through a biopsy of the RVOT and not through the usual techniques such as blood samples. This possibility was demonstrated long ago in patients with idiopathic VT, where a biopsy of the RV revealed somatic mutations.[6] This possibility of somatic mutations in BrS is also supported by the fact that about half of patients are isolated and non-familial cases as if these patients cannot transmit the disease via the germinal cells.

For the Genetics

The 1998 description of the first gene associated with the BrS marked a true historic point in the relationships between genetics and cardiology. Genetic studies in cardiology were therefore very limited and almost exclusively focused on the search for mutations in patients with LQT or hypertrophic cardiomyopathy. The results were seen more as a curiosity than a potential contribution to understanding mechanisms and, who knows, perhaps developing a treatment in the future. But now, we could begin to understand. The sodium channel remains open with certain mutations, the repolarization is prolonged, and the patient suffers from LQT (type 3). But if the sodium current decreases as a result of other mutations in the same gene, then we get conduction disturbances and the BrS. Suddenly, a whole new world opened up. No surprise then that the number of published mutations in all cardiac hereditary disorders increased very rapidly. But not only with the old, long-known ailments. Discovering the gene responsible for short QT syndrome took only 3 years. With the new techniques for genetic research (genome wide analysis [GWAS]), the entire diagnostic process has been accelerated exponentially. Unfortunately, all this new information comes with a problem of interpretation: Do all mutations and all genes really matter? Are they the cause of the disease? What is the real importance of the polymorphisms? Unfortunately, we do not have the resources, time, and sufficient number and variety of patients to functionally study each mutation and to show that the expected effects of a particular mutation correspond to what we expect as manifesting as disease. There are models to help us, but the results of the models always come with a degree of probability and uncertainty about the value of the result. Nevertheless, these results are important for the treatment of families with BrS.

For Fertility

With all the limitations one can think of, preimplant genetic diagnosis (PGD) has become an obvious option to treat hereditary diseases. Opponents of the technique argue that almost no disease, especially BrS, is monogenetic. According to them, in addition to the main gene considered responsible for the disease, you must have a number of other mutations and variations, including polymorphisms, that pile up until a certain "genetic risk score" is reached. Thus, implanting an embryo selected based, for example, on the absence of a mutation in the sodium channel, would have no value in preventing BrS. Proponents of PGD say, with the same arguments, that just selecting an embryo without the mutation lowers that genetic risk score, and thus we can counteract the manifestation of the disease. Preimplant genetic diagnosis has been offered in our hospital for years for more than 200 different diseases that are considered monogenetic, including BrS. Given the young age of the children born after PGD, we are not yet able to draw any conclusions about whether or not they develop the disease. These children and young adults are closely monitored.

Another aspect of fertility concerns spontaneous miscarriages in families with BrS. While it is possible that embryos and fetuses died "in utero" from arrhythmias, or even from the heart never beating, it has been impossible to draw any conclusions.[7] There are far too many miscarriages that happen completely unnoticed in fertile women to study this phenomenon.

For Gynecology

Given the serious consequences of BrS, it is no surprise that people have wondered what the consequences of the disease could be for pregnant women. The information collected shows

that pregnancy and childbirth do not present any particular risks[7] in women with BrS.

For Pediatrics

The BrS is a cause of sudden death in children and also one of several possible causes of sudden infant death syndrome (SIDS). Few diseases have been speculated for so long and so esoterically as in the case of SIDS. From the baby's posture while sleeping, smoking in the baby's bedroom, using or not using pillows, and more, the most diverse unscientific explanations were constantly sought. Now, we know that the range of causes of SIDS is very wide and that indeed infant suffocation, murder, and hidden accidents can play a part in death. But now, we also know that most of these sudden deaths are due to arrhythmias, including the BrS.[8]

We encounter a similar problem in the diagnosis of epilepsy and syncope of unknown cause in children. Not only LQT but also short QT syndrome and BrS should be included in the differential diagnosis and even more so if the child has "difficult to treat" syncopes or epilepsy. We should also not forget that patients can also suffer from more than 1 disease: epilepsy and BrS together[9] and also vaso-vagal and simultaneously arrhythmic syncope.

For Pharmacology

For years, a lot of research has been done in connection with the changes of the QT interval on the EKG due to drugs. An international working group is making an almost weekly update of drugs that can prolong the QT interval.[10] A QT prolongation can result in the development of "torsade de pointes" and sudden death. Now we know, thanks to the effects of drugs in the BrS, that other drugs can also cause sudden death through their effects in the sodium channel. A list of these medications is also kept active by an international consortium.[11]

For Sports Medicine

Nothing affects our imagination more than the sudden death of a "perfectly healthy" athlete. We consider these people to be the healthiest in our society, and it is almost impossible to comprehend that they can die unexpectedly. And it also happens to professional athletes who are screened annually for cardiovascular disease. Not all sudden death in athletes occurs during exercise. Actually, the opposite is true.[12] Most die suddenly after exertion, immediately or later, in complete rest. It has been known for a long time that the LQT syndrome and the cathecolamine-dependent polymorphic VT were a cause. But now, after detailed examination of the relatives of the deceased, it appears that the most frequent cause is BrS.[12] The fact that BrS can present with a completely normal EKG makes it extremely difficult to detect these patients.

For Medico-Legal Medicine

There are no good rules in many country regarding performing autopsies. In the case of the sudden death of a young person, this research is hardly taken into account. The autopsy will only become mandatory if it could be an unnatural death. The results of these autopsies vary enormously from study to study, as well as according to the expertise of the doctors and their "stamina." One doctor searches longer and deeper for the cause of death than another. But even after what is called an "expert autopsy," a very large group of patients remains undiagnosed.[12] This is where the study of the family members and the "molecular autopsy" come into play. The study by Papadakis et al[12] showed that the most frequent cause of sudden death—when a cause is found—is BrS. This was shown by them through the results of ajmaline test on the family members. Post-mortem genetic testing may also reveal a possible causative mutation in 20%-40% of cases.[13]

For Preventive Medicine

Screening people who appear healthy is one of the best ways to discover hidden diseases. But of course, the value of screening is very much related to the researcher and the studies being conducted. We all accept screening women for breast cancer or detecting potential carriers of colon tumors that have not yet manifested itself. But when it comes to cardiovascular screening, opinions differ. Unfortunately, the arguments for and against screening do not appear to be so hard. If one looks at the results of colorectal cancer prevention in the Netherlands, it appears that 95% of the positive—suspicious—tests are false positives. So, 95% of "patients" get a colonoscopy for nothing.[14] The same goes for breast cancer screening. The results are so controversial that medical authorities in Switzerland have stopped screening for breast cancer. As for the heart, the conclusions depend on the research we believe for screening, as the Italian studies suggest,[15] or against screening, as American studies suggest. There is, in any case, a big difference in the arguments for or against. While the Italians base their arguments on a reduction in the incidence of sudden death thanks to screening, the American arguments against screening are purely financial. But, what price do we give to a young person's life?

For Occupational Medicine

Perhaps the most extraordinary contribution to describing the BrS is in understanding some of the medical "mysteries." Take, for example, the high incidence in the 1970s of sudden death in America of workers from South Asia. There was no way to understand why these asymptomatic, healthy-looking young men suddenly died overnight. Given the near-endemic presence of the BrS in South Asia, and after the investigations of Nademannee,[16] we now know that the BrS was the cause of death. This has been proven not only by clinical studies but also by genetic studies.[17]

Before Anesthesia

In the list of drugs that can cause sudden death in patients with BrS, we also find anesthetics.[10] One of these is propofol, responsible for the so-called propofol syndrome.[18] This syndrome is also related to the BrS.[19] Curiously, in one of our studies, we were not able to experience any drawbacks with the use of propofol in patients with proven BrS.[20] The manifestations of propofol syndrome may depend on the dose and the sensitivity of the patient, but other underlying pathologies certainly play a role as well. The propofol syndrome manifests with the very bizarre widening of the QRS complex on the EKG with the typical ST elevations consistent with BrS and with ventricular arrhythmias that can cause sudden death of the patient.

For Emergency Medicine

The BrS is a mandatory part of the differential diagnosis of several medical problems such as syncope, trauma and traffic accidents caused by a possible arrhythmia or temporary impaired

consciousness, epilepsy, all forms of cardiac arrest and ventricular arrhythmias, and conduction disorders. A group that should be discussed separately are young patients with AF or atrial flutter. Before injecting intravenous drugs to stop these arrhythmias, one should always ask oneself whether this could not be BrS. The administration of intravenous flecainide in such a patent can lead to death.

For the Cardiac Electronic Devices and Ablation of the Right Ventricular Outflow Region

Brugada syndrome is a disease of young people. It can only be controlled (in terms of sudden death) by implanting an internal defibrillator (ICD). It is no surprise then that the techniques of implantation have been adapted to children. For example, a subcostal abdominal implant is much more comfortable than a prepectoral implant, especially with regard to sports practice. With the necessary training, the implantation can be done with epicardial wires, so that the patient's venous system is completely spared (Figure 3). In experienced centers, this epicardial implantation can be combined with an epicardial ablation of the RVOT, where the substrate for the BrS is located.[21] This combination is our current protocol for treating BrS. It should be clear that we do not yet have sufficient data regarding the long-term effects of ablation. Currently, ablation is not an alternative to the ICD.

The World of Sudden Death Reimagined

We have entered a new world of causes of sudden death in people with structurally normal hearts, from long QT after BrS as the leading cause.[12]

Gender Aspects

Many publications on BrS have always emphasized that men with this disease do worse than women. While these thoughts seem to hold true in adults, they do not before puberty. No difference has been found in symptoms and mortality between prepubescent boys and girls.[22] It is very clear that testosterone plays a role in BrS. Male castration has itself been shown to improve the manifestations of the disease.[23]

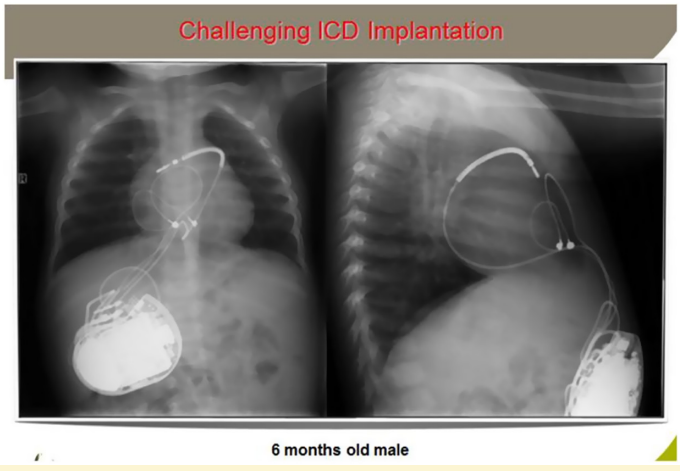

Figure 3. Thorax x-ray of the abdominal implantation of a defibrilator (ICD) in a 6month-old baby. The shock lead is located in the sinus transversus with the distal electrode screwd in the right atrium. Two epicardial electrodes are placed for sensing and pacing in the right ventricular free wall. The system is completely extravascular with all the benefits of a DDD ICD. Discrimination algorithms, DDD sensing, and pacing and antitachycardia pacing are in conrast with the subcutaneous ICD fully available.

For Understanding Certain Folk Traditions

Languageless traditions are now much better understood after describing the BrS. In Thailand, for example, the men dress like women after getting married when they go to bed with their bride. Tradition has it that a witch becomes jealous when a young woman gets married and as a punishment she comes to suffocate the groom at night. Lai tai is the name given to this sudden death in Thailand because the victim begins to snore before death. Pokkuri in Japan and Bangungut in the Philippines refer to the same phenomenon.

For the History

There are countless cases of sudden death in history that like Lai Tai and Pokkuri have gone unexplained. Of course, it is impossible to be sure whether the BrS played a role in that, but it is at least interesting to speculate about this. Take the case of Tommy Morris, arguably one of the best golfers of his time (he won the Open at the age of 17). Tommy was found dead in his bed in the morning at age 24. He had no complaints before death. On the contrary, he had just spelled and won a 200-hole (!) golf game in the snow. Two possible causes for the death were suggested: an internal hemorrhage and a "broken heart" as his wife had died during childbirth with the child a few months earlier. A sudden death at night at the age of 24 must certainly remind us of a possible BrS.

A second interesting case is the well-known singer Michael Jackson. He passed away suddenly at the age of 50 years after a propofol injection. A BrS in the differential diagnosis is more than appropriate.

For Animal Medicine

Sudden death is no stranger to the animal world.[24] A systematic search for the possible causes has never been done. It is only recently, after intensive analysis of this phenomenon, that the BrS has been included in the list of possible causes.

For Philosophy Paradoxes and the Brugada syndrome

A very interesting aspect of the BrS concerns the assessment of the risk of sudden death. As reported in the introduction, the BrS has a very wide range of clinical presentation. The diagnosis can be made after an episode of resuscitated sudden death, but there are more and more patients who are diagnosed and are completely asymptomatic. Syncope, AF, SSS, and conduction disturbances are all symptoms and findings with an impact on the prognosis. But the question is who should get an ICD preventively. Half of the patients who experienced sudden death had no symptoms before the sudden death. The other half had experienced a syncope or presyncope at some point. Only after extensive research did Prof. Sieira come up with a "score" to estimate the risk of sudden death.[25] (Figure 4). The more points the patient gets, the greater the risk of cardiac arrest in the future. This risk stratification system is very valuable, but it carries a huge paradox. By classifying patients into low, medium, and high risk groups, we can make the mistake of assuming low risk as if it

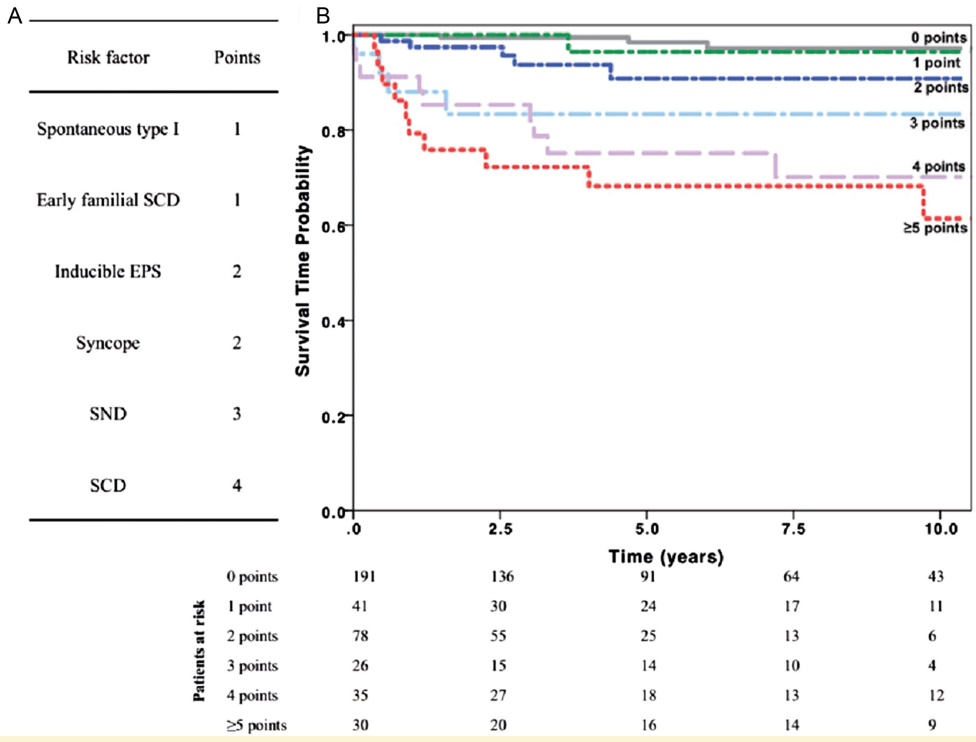

Figure 4. Score system by Sieira et al.[25] On the left, the risk factors are shown with the points of value for each parameter. The graph shows the risk of (resuscitated) sudden death during a 10-year follow-up period depending on the points.

The physician as a risk factor

1 Risk assessment	2 Physician's appreciation of risk	3 Action by physician	4 Result in case of event
Low		Do nothing, passive attitude	Death
Intermediate		Protect?	Death if not protected
High		Protect!	Alive

Figure 5. The paradox of risk stratification.

meant no risk. Patients with a low score, therefore, are not considered candidates for protection with an ICD. On the contrary, patients with a high score are systematically protected. The result, paradoxically, is that patients with a high risk and protection by the ICD survive the attacks of arrhythmias, thanks to the protection of the ICD, while the low-risk group, if an arrhythmia occurs, will die due to lack of protection with an ICD. Thus, although the incidence of arrhythmias is much lower in the low-risk category, the true mortality is the highest due to lack of protection. This paradox is illustrated in Figure 5.

Conclusion

In 30 years, we have learned a lot not only about the BrS but also about other related diseases. It is clear that with the description of the BrS, the whole world of rhythmology has entered a new dimension.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author declares that he has no competing interest.

Funding: This study received no funding.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol*. 1992;20(6):1391-1396. [CrossRef]
2. Osher HL, Wolff L. Electrocardiographic pattern simulating acute myocardial injury. *Am J Med Sci*. 1953;226(5):541-545. [CrossRef]
3. Antzelevitch C, Yan GX, Ackerman MJ, et al. J-wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. *Heart Rhythm*. 2016;13(10):e295-e324. [CrossRef]
4. Probst V, Goronflot T, Anys S, et al. Robustness and relevance of predictive score in sudden cardiac death for patients with Brugada syndrome. *Eur Heart J*. 2021;42(17):1687-1695. [CrossRef]
5. Antzelevitch C. In vivo human demonstration of phase 2 reentry. *Heart Rhythm*. 2005;2(8):804-806. [CrossRef]
6. Lerman BB, Dong B, Stein KM, Markowitz SM, Linden J, Catanzaro DF. Right ventricular outflow tract tachycardia due to a somatic cell mutation in G protein subunitalphai2. *J Clin Invest*. 1998;101(12):2862-2868. [CrossRef]
7. Rodríguez-Mañero M, Casado-Arroyo R, Sarkozy A, et al. The clinical significance of pregnancy in Brugada syndrome. *Rev Esp Cardiol (Engl Ed)*. 2014;67(3):176-180. [CrossRef]
8. Priori SQ, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden death in children. *Lancet*. 2000;355(9206):808-809. [CrossRef]
9. Abdelghani MS, Chapra A, Asaad N, Hayat SA. Epilepsy and Brugada syndrome: association or uncommon presentation? *Heart Views*. 2020;21(2):114-117. [CrossRef]
10. Available at: www.crediblemeds.org.

11. Available at: www.brugadadrugs.org.
12. Papadakis M, Papatheodorou E, Mellor G, et al. The diagnostic yield of Brugada syndrome After sudden death With normal autopsy. *J Am Coll Cardiol*. 2018;71(11):1204-1214. [CrossRef]
13. Semsarian C, Ingles J. Molecular autopsy in victims of inherited arrhythmias. *J Arrhythm*. 2016;32(5):359-365. [CrossRef]
14. Available at: https://www.rivm.nl › bevolkingsonderzoek-darmkanker.
15. Sarto P, Zorzi A, Merlo L, et al. Serial Versus single cardiovascular screening of adolescent athletes. *Circulation*. 2021;143(17):1729-1731. [CrossRef]
16. Veerakul G, Nademanee K. What is the sudden death syndrome in South-East Asia males? *Cardiol Rev*. 2000;8(2):90-95. [CrossRef]
17. Makarawate P, Glinge C, Khongphatthanayothin A, et al. Common and rare susceptibility genetic variants predisposing to Brugada syndrome in Thailand. *Heart Rhythm*. 2020;17(12):2145-2153. [CrossRef]
18. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM. Propofol infusion syndrome in adults: a clinical update. *Crit Care Res Pract*. 2015;2015:260385. [CrossRef]
19. Shimizu W, Antzelevitch C, Suyama K, et al. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. *J Cardiovasc Electrophysiol*. 2000;11(12):1320-1329. [CrossRef]
20. Flamée P, De Asmundis C, Bhutia JT, et al. Safe single-dose administration of propofol in patients with established Brugada syndrome: a retrospective database analysis. *Pacing Clin Electrophysiol*. 2013;36(12):1516-1521. [CrossRef]
21. Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation*. 2011;123(12):1270-1279. [CrossRef]
22. Conte G, de Asmundis C, Ciconte G, et al. Follow-up From childhood to adulthood of individuals with family history of Brugada syndrome and normal electrocardiograms. *JAMA*. 2014;312(19):2039-2041. [CrossRef]
23. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing Clin Electrophysiol*. 2003;26(7 Pt 1):1551-1553. [CrossRef]
24. Brugada-Terradellas C, Hellemans A, Brugada P, Smets P. Sudden cardiac death: a comparative review of humans, dogs and cats. *Vet J*. 2021;274:105696. [CrossRef]
25. Sieira J, Conte G, Ciconte G, et al. A score model to predict risk of events in patients with Brugada syndrome. *Eur Heart J*. 2017;38(22):1756-1763. [CrossRef]