ICD in Children and Adolescentes with Brugada Syndrome - 2020

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Introduction

Brugada syndrome is an inherited disease characterized by a coved-type ST-segment elevation in the right precordial leads and increased risk of sudden cardiac death (1). The disease typically manifests in the fourth decade of life, but severe cases have clinical expression during childhood and can lead to life-threatening arrhythmias (2-4).

The placement of an implantable cardioverter defibrillator remains the only therapy with proven efficacy for the management of ventricular arrhythmias and prevention of sudden cardiac death in young patients with Brugada syndrome. Young patients who have experienced aborted sudden cardiac death represent a small group but are at a very high risk of recurrence of potentially lethal events during follow-up (4), and thus have clear class I indication for cardioverter defibrillator implantation (5). A less well studied group comprehends the children who manifest some degree of phenotypic expression of the disease but without experiences yet potentially lethal events. This group requires evaluation through a risk stratification methodology to decide on an indication of ICD implantation as primary

prevention. Our group has developed an algorithm for risk evaluation that is at present the single tool in this age group but is still pending of validation at a large scale (4). In the following chapter we will share with you the basis of risk stratification for ICD implantation and the different strategies to implant this device in children and adolescents.

ICD indication in young patients with Brugada Syndrome

The medical decision to indicate an ICD in a young patient with Brugada syndrome remains a challenge. The Consensus Statement on Brugada Syndrome offers some recommendations to guide management in the adult population (5). As this chapter is being written, specific guidelines for ICD recommendation in children with Brugada Syndrome are been made from an expert group within the Pediatric and Congenital Electrophysiology Society (PACES).

A publication by the author summarises a single centre experience with the largest cohort of patients < 20 years with Brugada syndrome that received an ICD (6). During a mean follow-up of 7 years, this therapy was effective to treat potentially lethal arrhythmias in > 25% of these patients. However, ICD placement is frequently associated with complication and inappropriate shocks (14% and 20% respectively in our series) (6).

In general, symptomatic patients presenting with sudden cardiac death, and a diagnostic type I electrocardiographic findings (either spontaneous or drug induced) are in the category of secondary prevention and have a clear indication for an ICD implantation. However, only around 10% of pediatric patients with Brugada syndrome present with a spontaneous or fever-induced type I electrocardiographic pattern. Moreover, our group reported that 75% of patients presenting with SCD had an abnormal baseline electrocardiogram but only half of them had a spontaneous type I ECG (4).

On the other extreme of the spectrum, asymptomatic patients with no phenotypic expression of the disease, irrespective of their genetic background have a very low risk, and thus have no indication for an ICD implantation. Future research may open some subsets of risks within this group, allowing us to make a difference between genotypic negative and genotype positive individuals.

The situation is yet more unclear in the asymptomatic young patient that manifest with the phenotypic expression of a spontaneous type I electrocardiogram, with or without concomitant fever. In the adult guidelines, these patients are recommended to undergo programmed electrical ventricular stimulation to complete the risk stratification (5). The finding of inducible ventricular arrhythmias warrants an ICD implantation. There is no expert consensus up to date on the benefits of using programmed electrical stimulation as a means of risk stratification in children. On the other hand, there is at present no robust data to support its use in this age group. Current practice in most centres around the globe do not include invasive stratification as standard of care for the pediatric age. There is thus a gap within the recommendations in terms of indications for ICD implantation in the young. In other words, there is no evidence to support or discourage an ICD implantation in young patients with phenotypical expression of the disease, but who had not suffered from sudden cardiac death. This remains an important caveat in a disease that can result lethal from the onset of the clinical expression. The main question remains: how to evaluate the individual risk of these young patients? And how to correlate this risk with unambiguous class II recommendations for ICD implantation? In an attempt to give an answer to this dilemma, our group has proposed a clinical risk stratification model for young patients with Brugada Syndrome.

Risk Stratification of Young Patients with Brugada Syndrome

Risk stratification in young patients with Brugada syndrome is complex but necessary to guide the indications for and ICD implantation. We have proposed a clinical model supported by data-based evidence. This model can be used by any clinician as it does not include genetic or invasive studies (4). The model is based 4 clinical variables that have shown a statistical relation with the occurrence of potentially lethal events (C statistics 0.93). **Table I** shows the variables and the related pointing system for the model. Patients with a punctuation of 0-3 are at a very low risk, representing mostly asymptomatic patients evaluated for screening in the setting of a family member with Brugada syndrome. Symptomatic patients in a high -risk category with a punctuation of 4 to 5 usually present with syncope with or without electrical anomalies. Patients with and score ≥ 6 correspond to a very high risk, presenting with aborted sudden cardiac death and/or multiple conduction abnormalities. Life threatening events present in at least half of this patients during follow-up, setting a clear indication for an ICD. **Figure I** shows the Kaplan-Meier event probability according to the score; the chronology of events is given in patients' age in years. Interestingly, in the very high-risk group 40% of patients present with a potentially lethal event before the age of 20 years compared to 10% in the high-risk group.

ICD Strategies in the Young

After covering the basis related to the complexities of risk stratification and ICD indication in the young patient with Brugada Syndrome, we proceed to share some aspects of ICD implantation.

At present, only 1% of ICDs are implanted before the age of 20 years (7). As a result, available resources including devices and leads as well as human technical expertise are

scarce in the pediatric field. Even if it is inappropriate to extrapolate adult-based strategies into the younger recipients, the pediatric electrophysiology community has no other option than to use the available technology and adapt it to its peculiar population. Keeping in mind that young ICD patients are a "unique subset" who face challenges specific to their body size and anatomy characteristic linked to their stage of development, we aim to present in the next sections different approaches to ICD implantation in this age group.

ICD Strategies in Infants

We start by acknowledging that these are extreme but very rare circumstances. However, every specialist who has faced the complexity of a toddler presenting with sudden cardiac death and a clear evidence of a phenotype for Brugada syndrome knows the difficulties this scenario represents. There is no ideal choice, and most times we need to agree to the strategy with the most acceptable balance of protection vs. risks and complications. During the first year of life, the option of a transvenous system is still unpalatable. We present below the different strategies that have been applied in these cases by different groups around the world. These may not be the only options but are the ones that we or our close colleagues have experienced with relative success. As sinus node dysfunction and atrial tachycardias are common findings in young patients with Brugada syndrome, we will only include those techniques that include the possibility of direct sensing and pacing of the ventricular myocardium. In the same line, completely leadless ICD systems currently in early clinical use and investigation in adults are not suitable in Brugada syndrome as they do not have the capability for chronic anti-bradycardia pacing or anti-tachycardia pacing, which may be indicated in a substantially higher proportion of this population (8).

Pure epicardial strategy

Figure II A depicts a pure epicardial system in an infant with extreme presentation of SCD associated to Brugada syndrome in the first months of life. This approach combines the implantation of a transvenous design ICD lead within the pericardium sac in the posterior region of the heart by a sternotomy approach. After full sternotomy, the pericardium is opened and the coil is attached by sutures to the posterior aspect of the left ventricular parietal pericardium by a couple of separate stiches. The implanting surgeons needs to take special care not to traverse any major coronary artery branch within the coil trajectory, to avoid coronary compression or discharge in the proximity of the heart blood supply in the case of shock delivery. This procedure may be also performed via a less invasive videoscopic technique. A bipolar sensing-pacing lead is implanted in the usual position in the anterior aspect of the left ventricle aiming the septal portion of the apex (9). A subxiphoid location is chosen for placement of the generator so that the vector between the shocking lead and the device box encompasses the main portion of the ventricular myocardium. It is advisable to confirm the position by fluoroscopy or flat-plane radiography during the operation.

Because this approach is exceptional and relies on technology conceived for transvenous utilisation, we prefer to test defibrillation threshold (DFT) immediately after implantation. In a series of combined non-transvenous strategies, the result was unacceptably high in 18% of these patients, with another 18% in which arrhythmia could not be induced (10).

The most feared complications from this approach are coronary compression and lead strangulation. In a series from Boston, patients with epicardial devices were evaluated by cardiac computed tomography (CT), with evidence of coronary compression in 5% of patients with a mean age of 11 years (11). Interestingly, the chest radiography had a sensitivity of only 57% for identifying the compression. Even if the study concludes that

chest radiography can serve as a good surveillance tool on general annual basis, they advocate for CT in those patients with suspicious radiography imaging or symptoms of chest pain and include coronary artery angiogram before a surgical intervention. Cardiac strangulation from epicardial leads and/or coils in children is a rare but potentially lethal complication (12, 13) that needs to be monitored and rued-out with yearly assessment by antero-posterior chest radiographies. Given the increased risk with growth during the first years of life, we propose this strategy as a temporary solution that requires close follow-up, a high degree of awareness and suspicion for the mentioned complications, and switch to more conventional techniques as soon as the patients body size allows it.

Combined pleural strategy

An alternative strategy consists an ICD system implant technique with a subpleural defibrillation coil electrode, epicardial sensing/pacing leads, and abdominal or intrathoracic device placement (14, 15). The epicardial leads are placed through a left axillary muscle sparing thoracotomy through the 4th intercostal space. The shock electrode is placed in an extrapleural pocket between the thoracic wall and the parietal pleura, ensuring that the maximum ventricular myocardial mass is exposed to the shock vector between the shock electrode and the defibrillator. The bipolar epicardial electrodes and the shock electrode can be extruded through a small subxiphoid incision and connected to an ICD device, placed in a pocket created between the diaphragm and the parietal pericardium abutting it, fixed to the diaphragm to prevent migration **(Figure 2B).** A completely intrathoracic placement of leads and generator protects the leads from tension and ensures a good and durable functional status, and avoids the risks related to coronary injury by an epicardial coil.

Combined subcutaneous strategy

This approach places a transvenous design ICD lead in the subcutaneous space in a high left para-scapular position (4^{th}-5^{th} intercostal space), using a tunnel device . The sensing/pacing leads on a standard epicardial position, and the battery in a classical abdominal sub-xifoid location. In these non-classical approaches, it has been our practice to confirm the lead position and shocking vector by fluoroscopy immediately after implantation and to test defibrillation thresholds.

Transvenous ICD

Transvenous ICD systems are not usually indicated in small children, as they carry unacceptable high risks of venous occlusion and vessel and heart damage. Technological advances such as biphasic defibrillation waveform and active generators, combined with a progressive reduction of generator size and lead dimensions, have allowed transvenous ICD systems in adolescent patients (16).

Risk and Complications related to ICD implantation

A large pediatric cohort coming from ICD implantation in children in USA showed that young patient had the same frequency of complications (2.5%) and mortality (0.3%) than adults (17). Epicardial ICD systems are inherently more invasive procedures, have a higher incidence of lead failure, and a possibility of developing constrictive pericarditis and coronary artery compression. Interestingly, when non-transvenous ICD systems were retrospectively evaluated, it turned out that they had poorer longevity than traditional transvenous ICD systems in children (18). Therefore, non-transvenous ICD systems are not ready to supplant standard ICDs in the majority of pediatric patients but still have an

important role for those patients with limited alternatives. Non- standard systems might be used as the initial device until the child reaches a larger size and can potentially accommodate a transvenous standard ICD system. Finally, implanting an ICD in a child necessitates the consideration of potential quality of life and emotional and psychosocial development issues which need to be addressed with an appropriate team of mental health professionals.

Conclusions

Identifying appropriate candidates for an ICD within the pediatric patients with Brugada syndrome involves protocols for risk stratification to evaluate the cumulative risk for sudden cardiac death. An analysis of the potential risks for lethal arrhythmias has to be balanced against the risk of complications from this therapy. Secondary prevention recommendations, even if clear, have been taken up to present by the adult guidelines. The proposal for risk stratification on primary prevention indication in young patients with Brugada syndrome still needs validation. It is thus a priority to gather evidence on our young patients in the form of a multicentric international database, task on which our group is now focusing its efforts. Until this data can be built into a robust body of evidence, we choose to guide our practice by the means of the small but solid research introduced in the previous sections. Finally, we conclude that it is extremely important to evaluate each patient on individual basis and discuss with the patient and the family the benefits and potential risks associated with this therapy.

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Table I- Score system punctuation

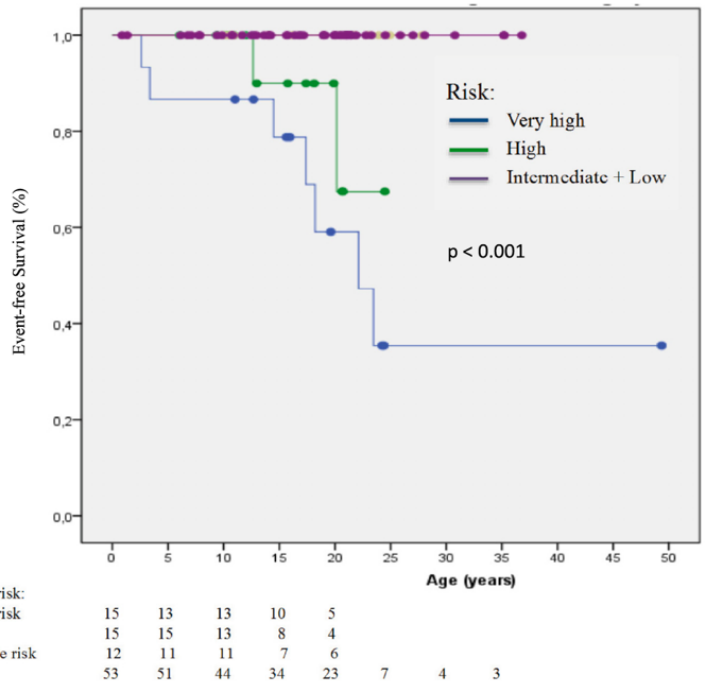
Risk Factor	Points
ASCD/ Syncope	4
Spontaneous type I ECG	3
SND/ AT	2
Conduction abnormalities	1

(Gonzalez Corcia, 2016)

ASCD represents aborted sudden cardiac death; ECG, electrocardiogram; SND, sinus node dysfunction; AT, atrial tachycardia.

Conduction abnormalities encompass first degree atrio-ventricular according PR measurement for age, second or third degree atrio-ventricular block; or any delay in intraventricular conduction according to standardized QRS length per age.

Figure I- Freedom from potentially lethal events



(Gonzalez Corcia 2016)

Figure I- Freedom from potentially lethal events according to age (in years) as per the Kaplan-Meier method.

Intermediate and low risk correspond to a punctuation of 0-3 in the score, high risk to 4-5 and very high risk to a punctuation ≥ 6.

Figure II- Pure epicardial ICD in an infant with Brugada Sydrome.

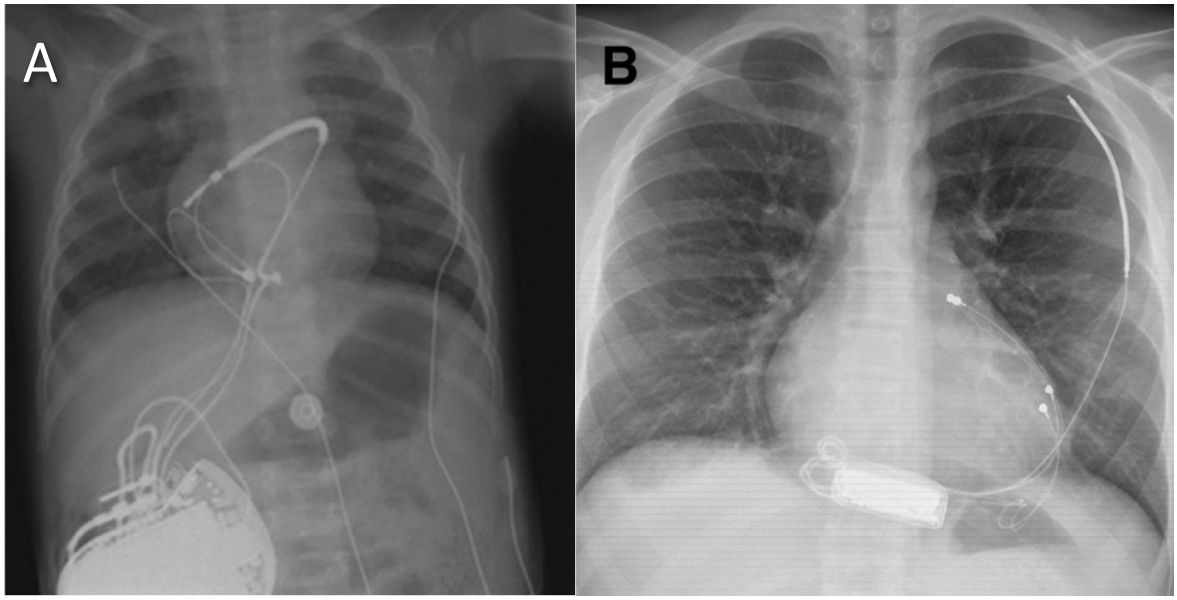


Figure II A- Antero-posterior projection of chest and upper abdomen radiography showing a pure epicardial ICD system in an infant. Note that the coil is placed in the high posterior epicardium, with a bipolar sensing/pacing lead in the apex and the generator placed in the right side of the abdomen. B- Antero-posterior projection of chest radiography showing a combined pleural system with the coil placed in a high left pleural position, the bipolar sensing/pacing lead in the epicardium and the generator in a pocket between the inferior parietal pericardium and the diaphragm.