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When Brugada syndrome is at risk of sudden death: clinical and anatomical aspects

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The current prognostic stratification of asymptomatic patients with Brugada syndrome is suboptimal. The so-called 'Brugada burden' concept is certainly emerging: the more extensive are the electrocardiographic alterations of the syndrome in space (peripheral as well as precordial derivations) and in time (persistence in the follow-up of electrocardiographic alterations), the greater the probability of arrhythmic events. Numerous clinical and electrocardiographic markers have been considered risk factors, but none of them alone is able to guide the choice of whether or not to implant a defibrillator, the only therapy so far proved effective in preventing SD (sudden death) in these patients. The prognostic value of the electrophysiology study also gradually decreased over time. Therapeutic decisions must therefore be taken, at the moment, considering a large number of variables, possibly included in risk scores to be validated prospectively and in large series. Magnetic resonance and the study of electro-anatomical alterations of the right ventricular outflow tract will most likely improve our prognostic stratification capacity in the future.

Brugada syndrome (BrS) is an inherited condition characterized by coved-type ST segment elevation in right precordial leads in the absence of structural heart disease. On the last part of the previous sentence, the absence, that is, of structural cardiac alterations, we will actually return later as it is no longer unanimously shared concept. The syndrome was first described in the 90 s of the last century by the Brugada brothers and since then has represented a considerable challenge for the cardiologist due to the variability of its clinical manifestations. Patients who present it, in fact, can remain asymptomatic for life and be recognized only occasionally or they can suffer sudden death, passing through the intermediate forms of syncope or agonal nocturnal breathing. The challenge for the cardiologist is therefore to be able to identify which of the affected patients will present future events and which, instead, will die of peaceful old age. The only therapy that has so far proved to be certainly effective is the implantable cardioverter-defibrillator (ICD) whose use, however, also in consideration of the often young age of subjects with this clinical condition, is burdened by a rate of unwanted events not negligible. In a recent study,[1] for example, compared with an appropriate shock rate of 18.5% in 82 months, there was a similar number (18.1%) of inappropriate device interventions. To these must be added the complications of the implant: fracture or malfunction of the lead (5.4%), perforation by the catheter (0.7%), dislocation of the catheter (1.7%), infection (3, 9%), implant site pain (0.4%), succlavian vein thrombosis (0.3%), pericardial effusion (0.1%), endocarditis (0.1%), pneumothorax (0.7%) and, finally, psychiatric problems (1.5%). It is therefore obvious in the light of these data, also considering the economic reasons, that the use of the ICD system must be as well calibrated as possible to avoid excessive inconvenience to the individual and abnormal costs to society. An ICD is generally considered indicated if the risk of sudden death (SD) is > 1.2% per year and > 6% at 5 years.[2] Patients with BrS who have already presented a SD,

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fortunately aborted, and, albeit to a lesser extent, those who have already presented a syncope with proved arrhythmic genesis, undoubtedly place themselves in a risk range of SD above this threshold (respectively 8 and 2% per year) and therefore are unquestionably candidates to receive the ICD. On the other hand, asymptomatic patients are more difficult to manage. In the various series their total mortality (0.5% per year in the FINGER study, 0.9% in the Delise study, even 0.08% in subjects with drug-induced Brugada) did not differ significantly from that (0.5%) of the general population and therefore does not justify the implantation of the ICD. In compliance with what has been said so far, the guidelines provide specifically for the ICD in patients with previous aborted SD (Class I) and in patients with spontaneous Type 1 BrS and syncope (Class IIa). The indication of Class IIb reserved for subjects with spontaneous BrS 1 and inducibility of life-threatening arrhythmias during the electrophysiological study is more controversial. The low mortality of asymptomatic subjects, however, hides (as the Trilussa chickens teach), a non-negligible share of subjects who in any case experience SD. And the coarseness of the current indications is highlighted by the data from the SABRUS study[3] in which 25% of patients with ICD who experienced arrhythmic events (AEs) did not actually have a recognized indication at the time of implantation. The arduous task of the cardiologist is therefore, as mentioned, the recognition of who among asymptomatic patients still has a future risk of SD to justify the costs and complications of the ICD implant.

Electrophysiological study

The first aid used in the prognostic stratification of BrS was the electrophysiology study (EPS) whose usefulness, however, is still the subject of bitter academic contention and which alone, despite the indication of Class IIb of the guidelines mentioned above, it does not seem capable of justifying an implant. In the PRELUDE study,[4] for example, the 3-year risk of ventricular fibrillation (VF) or appropriate ICD interventions was 3.9% in inducible patients and 4.9% in non-inducible patients. This result is also confirmed in other studies, even with non-aggressive protocols with up to two extra stimuli, such as, for example, that of Shinohara[5] in which the annual incidence of AE did not significantly differ between inducible and non-inducible: 0.4 vs. 0.5%, respectively. However, other studies, both previous and contemporary, have instead shown conflicting results. Sroubek, for example,[6] found that inducibility to EPS was associated with a 2.7-fold increase in the risk of AE, especially if the induction occurred with only one or two extra stimuli. There are multiple possible explanations of the heterogeneity of the results available in the literature: (i) differences in stimulation protocols; (ii) secondary statistical limitations to the limited number of asymptomatic patients, inducible to the EPS and with subsequent AEs; (iii) difficulty in assessing the predictive power of the EPS as inducibility generally leads to the implantation of the ICD whose interventions, even for arrhythmias otherwise spontaneously terminated, can overestimate the risk; this may also account for the loss of predictive significance of the EPS in some studies, passing from the univariate to the multivariate analysis; (iv) the extensive variability of the result of the EPS even in the single patient with a reproducibility rate that does not exceed 35%. In light of the foregoing, therefore, the inducibility of arrhythmias alone in the EPS does not seem sufficient to justify the implantation of an ICD and the routine use of this procedure therefore does not seem recommendable. This does not preclude that the EPS may still be an element of the prognostic stratification of patients, for example, being able to function as a 'tie-breaker' in particular circumstances, such as young subjects with spontaneous Brugada and syncope of uncertain origin, in which the easy arrhythmic inducibility could favour the implantation of the ICD.

Clinical markers

Gender and age

Although women are less likely to have AEs than men, and the elderly have a better prognosis than younger people, with a risk in those > 55 years old that is comparable with that of the general population, none of these groups can be considered zero risk and therefore these parameters alone do not allow a reliable prognostic stratification. It should be noted that in women the presence of atrial fibrillation (AF) and the positivity of the genetic test for alterations in the SCN5A gene seem to have greater prognostic value than in men.

Familiarity with sudden death

Numerous studies have evaluated the prognostic significance of a family history of SD which, although with a wide heterogeneity of results, did not prove to be able to predict AEs in a statistically significant manner. However, a recent meta-analysis[7,8] has shown that considering only deaths that occur before the age of 35, thus reducing the causal role of ischaemic heart disease and other heart diseases that is present in the death of older subjects, familiarity becomes prognostically significant. The predictive value is greater the lower the age at which SD occurs.

Non-arrhythmic syncope

The negative prognostic meaning provided by the occurrence of a syncope is valid only if this event is of arrhythmic origin. Patients, in fact, who present syncopal episodes of another nature, usually vagal, do not present an increased future risk. However, the differentiation between arrhythmic and non-arrhythmic syncope is often impossible and subjects with doubtful syncope have an intermediate risk, which reflects, in fact, the presence in this group of a part of subjects with arrhythmic syncope and therefore at greater risk and a part of subjects, however, with other syncopal aetiologies and therefore at low risk. The tilt test in this context is of no use as vagal hypertonus is frequent in patients with

BrS, remember that most AEs occur at rest, and therefore the positivity of tilt test does not exclude that syncope can still be arrhythmic. In case of doubtful syncope, recourse to the EPS may be justified. Finally, there are reports that subjects with arrhythmic syncope have a wider QRS than those with vagal syncope.

Genetics

The stratification of genetic risk in BrS is constantly evolving and some studies have indicated that the presence of mutations in the SCN5A gene may be predictive of future events, at least in Asians population. The data, on the other hand, did not find confirmation in the European population covered by the FINGER study.[9] Also a 2019 meta-analysis[10] that included seven studies with a total of 1 049 patients (302 with SCN5A mutation and 747 without) found only a non-statistically significant ($P = 0.10$) increase in risk [risk ratio (RR): 1.5] in carriers of the mutation. At present, therefore, the mere presence of genetic mutations is not sufficient to indicate the implantation of the ICD.

Electrocardiographic markers

Spontaneous Type 1

Individuals with spontaneous Brugada Type 1 have an increased arrhythmic risk. In the Rattanawong study,[11] for example, the annual incidence of AE was 2.4% in subjects (symptomatic and asymptomatic) with spontaneous Brugada Type 1 vs. 0.65% of subjects with Brugada induced by drug testing with sodium channel blockers. In patients with syncope alone, the annual risk of AE was 2.3–3.7% in case of spontaneous Type 1 vs. 2.0% for drug-induced Brugada. In asymptomatic patients the risk of AE was 0.8–1.2% in the presence of spontaneous Brugada and 0.3% in the case of induced Brugada.

Atrial fibrillation

Various studies have evaluated the prognostic significance of AF in asymptomatic patients with BrS. The results were heterogeneous. A 2019 meta-analysis[12] comprising six studies with a total of 1703 patients, in which the prevalence of AF ranged from 5.2% to 17.9% and major arrhythmic events (MAEs) occurred between 2.3 and 10%, however, showed a significant association between the presence of AF and the risk of MAE [odd ratio (OR): 2.37, $P = 0.002$].

Fractional QRS

Another electrocardiographic parameter taken into consideration was the presence of a fractionated QRS (fQRS) in the precordial leads. A meta-analysis[13] evaluated nine studies, four retrospective and five prospective, comparing 550 subjects with Brugada and fQRS and 1 810 individuals with Brugada but without fQRS. In all studies, an increased risk of MAE (VF, sVT, ACS, and SD) was observed in subjects with fQRS, although in two of these studies the increase was not statistically significant. In the meta-analysis, however, the presence of fQRS induced an increased risk of MAE (RR: 3.36, $P < 0.001$).

Early repolarization

The electrocardiographic picture of early repolarization (ER) is common in patients with BrS. The presence of ER increases the risk of AE, especially if located inferior-laterally. A picture of global ER confers the maximum risk probably because it indicates a greater area of myocardium that may have re-entry circuits, thus confirming the importance of the 'Brugada pattern' in determining a person's arrhythmic risk. In a recent meta-analysis[14] the presence of ER in asymptomatic patients with Brugada showed an increased arrhythmic risk (OR 3.29, $P < 0.00001$) compared with its absence. The increase in risk was greater in the case of inferior-lateral ER (OR: 4.87, $P < 0.00001$) vs. inferior ER (OR 1.95, $P = 0.39$) vs. lateral ER (OR 0.43, $P = 0.42$).

QRS duration

A QRS duration > 120 msec, a possible consequence of reduced sodium channel function, has resulted in some studies, as prognostic factor for future AEs, especially in subjects with symptomatic Brugada. However, this result was not consistently reproducible. Yet another meta-analysis, however,[15] showed a significant association between QRS enlargement and an increased risk of MAE (RR: 1.55 $P = 0.03$).

ECG in the recovery of the ergometric test

The appearance of ventricular extrasystoles (PVCs) in the first (1.5–3) minutes of recovery after an ergometric test[16] is more frequent in patients with BrS who develop VF than in those without events, underlining the role of vagal stimulation in the arrhythmic genesis in this pathology.

Other electrocardiographic parameters that in some studies have shown some ability to predict future AEs in asymptomatic subjects include the extension of the Brugada alterations also in the peripheral leads, the presence of the so-called 'aVR sign' (R wave ≥ 0.3 mV or $R/q \geq 0.75$), the finding of S wave in the DI lead (expression of a delayed activation of the right ventricular outflow tract) (RVOT) and, finally, the concomitant presence of sinus node disease.

Risk scores

As we have seen, numerous electrocardiographic markers have been proposed for the risk stratification of asymptomatic patients with BrS but generally they are all derived from single-center studies not subsequently validated in other cohorts. No study has provided a comprehensive assessment of all proposed markers in a multi-centre international cohort. Furthermore, risk factors have good negative predictive power but low positive predictive power. The usefulness of these markers taken individually is, therefore, limited in clinical practice. Many authors have however tried to combine these risk factors with each other with the aim of

developing risk scores capable of helping the management of these patients.

In the Letsas study,[17] for example, the univariate analysis showed six significantly predictive elements of future AEs: spontaneous Type 1, history of syncope, inducibility to the EPS, family history of SD, presence of fQRS and duration of QRS. Combining them together, the authors found that the presence of at least 4 of these markers led to a significantly higher future risk than those with fewer than 4.

The Shanghai score,[5] initially created for diagnostic purposes, has been shown to have predictive capabilities. The algorithm considers four issues: (i) Ecg (spontaneous Type 1, fever-induced Type 1 and drug-induced Type 1), (ii) clinical history (cardiac arrest or documented VF, agonal nocturnal breathing, syncope of suspected arrhythmic origin, syncope of unclear aetiology, AF or atrial flutter in subjects under the age of 30), (iii) family history (first- or second-degree relatives with BrS, SD in first or second-degree relatives, SD of uncertain origin in first-degree relatives or second-degree and less than 45 years of age), (iv) probable genetic mutation. A score is assigned to each of these parameters. A total of less than 3.5 points would exclude future EAs which would instead be proportionally more probable as the score increases.

In the study by Shinohara,[18] moreover, four risk factors were combined: spontaneous Type 1, family history of SD, QRS duration $>$ 90 msec and presence of J wave in inferior-lateral leads. Patients with none or only one of these parameters did not incur AE while the risk significantly increased in those who had three or four (3 vs. 1 marker $P=0.02$; 4 vs. 1 marker $P=0.04$).

Honarbakhsh[19] instead evaluated 16 clinical and electrocardiographic markers on a large multi-centre cohort of 1 110 patients. From these 16, he extrapolated four (presumably arrhythmic syncope, spontaneous Type 1, ER in peripherals, Brugada Type 1 pattern in peripherals) predictive of future events and with these four he built a risk score able, according to the authors, to discriminate the arrhythmic risk patients high enough to warrant the preventive implantation of an ICD.

Finally, Sieira[20] proposed a risk stratification algorithm including six parameters: (i) spontaneous Type 1 (1 point), (ii) early familiarity for SD (1 point), (iii) arrhythmic inducibility at EPS (2 points), (iv) syncope (2 points), (v) sinus node disease (3 points), (vi) previous aborted SD (4 points). A total score greater than 2 points confers a significantly ($P=0.02$) higher probability of EA than a total less than two.

Although risk scores may be promising in the stratification of the risk of patients with BrS, however, they need to be validated prospectively in large series. Furthermore, most of the proposed algorithms include the syncope parameter and therefore are scarcely applicable to the asymptomatic population. Finally, their greater efficacy is expressed in low or high risk patients while they are less performing in intermediate risk patients who constitute the subgroup in which they would be most needed.

Magnetic resonance

We said at the beginning of the text that classically BrS was considered free of structural alterations. However, this concept is currently heavily questioned. Cardiac magnetic resonance imaging (MRI)[21] has in fact highlighted in patients with the syndrome the frequent presence of anomalies such as: enlargement of the volumes of the right ventricle (RV), increase in the RVOT area, presence of slight kinetic anomalies of the RV, especially at the level of the inferior wall and biventricular fibrosis localized mainly at the level of the epicardium of the RVOT. In addition, MRI also showed a correlation between the maximum ST elevation and the maximum RVOT area in subjects with spontaneous Brugada Type 1. At the moment there are no data of correlation between these findings of MRI and prognosis, but there are many hopes that cardiac MRI may improve the prognostic stratification of patients with BrS in the future.

Electro-anatomical alterations of the RVOT

Lastly, recent evidence has highlighted how BrS is actually a combination of electrical and structural disease. Patients with the syndrome, in fact, present, at the RVOT level, extensive electro-anatomical anomalies linked to the presence of fibrosis and the reduction of connexin. These alterations are the cause of the presence of slow-conduction regions of the RVOT in turn responsible for the electrocardiographic alterations and arrhythmias present in the syndrome. Although the prognostic significance of these anomalies has yet to be validated prospectively in the context of multiparametric risk stratification models, there are correlation data between the extent of the alterations and the inducibility of VF during EPS.[22] Furthermore, patients with aborted SD show significantly larger areas of anomalies than asymptomatic subjects. These data give hope that the study of the electro-anatomical alterations of the RVOT could become in the future a valid tool for the prognostic stratification of these patients.[22]

Conclusions

The current prognostic stratification of asymptomatic patients with BrS is suboptimal. The so-called 'Brugada burden' concept is certainly emerging: the more extensive are the electrocardiographic alterations of the syndrome in space (peripheral derivations beyond precordial) and in time (persistence in the follow-up of electrocardiographic alterations), the greater the probability of AEs. Numerous clinical and electrocardiographic markers have been evaluated as predictors of arrhythmic risk but none of them alone is able to guide the choice of whether or not to implant a defibrillator, the only therapy so far proved effective in preventing SD in these patients. The prognostic value of the EPS also gradually decreased over time. Therapeutic decisions must therefore be taken, at the moment, considering a large number of variables, possibly included in risk scores to be validated prospectively and in large series. MRI and the study of the electro-anatomical alterations

of the RVOT will most likely improve our capacity for prognostic stratification in the future.

Conflict of interest: None declared.

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