Ageing and Brugada syndrome: considerations and recommendations

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Abstract

Brugada syndrome is an inherited disease associated with an increased risk of lethal ventricular arrhythmias. Such arrhythmias stem from innate disruptions in cardiac electrophysiology. Typically, such arrhythmias occur in the third or fourth decade of life. However, Brugada syndrome may also affect geriatric patients. In this paper, we focus on the ageing patient with Brugada syndrome, and specifically, on the interaction between Brugada syndrome and the more usually acquired clinical problems that may occur with increasing age, such as the use of cardiovascular and non-cardiovascular drugs, or the need for surgery. Such common conditions may also disrupt cardiac electrophysiology, thereby conferring added risk for Brugada syndrome patients. We present some considerations and recommendations that may serve as guidance to address these complexities.

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1 Introduction

In 1992, Pedro Brugada and Josep Brugada described several patients with a peculiar electrocardiograph (ECG)-pattern, familial segregation and a propensity for ventricular arrhythmias and sudden cardiac arrest.[1] This report has been the start of the recognition of a new arrhythmia entity, which was labeled Brugada syndrome in the late nineties. The ECG-pattern consists of right-precordial ST elevation with a coved aspect which is followed by a negative T-wave and was named ‘type-1 Brugada ECG’ in the first consensus report in 2002 (example in Figure 1).[2] A type-2 or type-3 ECG can also be encountered, but these are not diagnostic for Brugada syndrome. Moreover, it is important to recognize that neither right precordial ST abnormalities nor this type-1 ECG-pattern are unique to Brugada syndrome, as they can be caused by many different etiologies (Table 1). Therefore, with the documentation of a clear type-1 ECG, one needs to clarify one or more of several other criteria suggestive of arrhythmias, or familial occurrence, before the diagnosis of Brugada syndrome can be made. These criteria include: documented ventricular tachycardia or fibrillation (VT/VF), a family history of sudden cardiac death < 45 years of age, coved-type ECGs in family members, inducibility of VT/VF during electrophysiological study, unexplained syncope or nocturnal agonal respiration. The type-1 ECG may also be uncovered by the administration of potent sodium channel blocking drugs such as ajmaline, flecainide, pilsicainide or procainamide.[3,4]

The pathophysiology underlying Brugada syndrome is still unresolved, but there are two leading hypotheses: the depolarization hypothesis and the repolarization hypothesis.[5] The former revolves around conduction slowing in the right ventricular outflow tract, with or without microscopic structural abnormalities,[6–8] and the latter involves dispersion of repolarization between the right ventricular outflow tract epicardium and endocardium.[9] The recently reported successful ablation of very late potentials on the right ventricular epicardium for the treatment of recurrent arrhythmias in a series of Brugada syndrome patients is in support of the depolarization hypothesis, but the final verdict on its pathophysiology has still to be made.[10] It might also be that both mechanisms are operative.

Our knowledge about the genetic underpinning of Brugada syndrome is also still developing. It seems to be clear that a substantial part can be explained by loss-of-function mutations of the alpha and beta subunits (and other modifying proteins) of the cardiac sodium and calcium channel. This implies that drugs that have either sodium or calcium channel blocking effects can be potentially troublesome in
Figure 1. Example of the development of a type-1 Brugada ECG during an ajmaline provocation test. Please note the absence of abnormal STT segments at baseline and the development of typical type-1, coved type, STT segments in the right precordial leads in concert with clear conduction delay upon ajmaline provocation. Please also note that the V3 lead is placed one intercostal space above V1 (V1 ic3) and V5 is placed one intercostal space above V2 (V2 ic3) to increase sensitivity.

Brugada syndrome patients. Of interest, there are also overlap syndromes with conduction disease and Long QT syndrome based on single sodium channel mutations.[11,12]

2 Prevalence

It is estimated that Brugada syndrome has a prevalence of 1 in 2000 persons.[13] This estimation is based on retrospective studies into the prevalence of the Brugada ECG pattern (i.e., the type-1 ECG) which, as explained above, does not equal a diagnosis of Brugada syndrome.[14] Still, there seem to be differences in the prevalence of Brugada syndrome in different countries. It is believed that Brugada syndrome is most prevalent in south east Asia, where it may, in part, underlie the Sudden Unexpected (Nocturnal) Death Syndrome (SU(N)DS).[15] In western societies, however, Brugada syndrome appears to be less prevalent than 1:2000.[14]

3 Risk stratification

3.1 High risk

To consider someone who had an aborted cardiac arrest and who fulfills the criteria for Brugada syndrome to be at a high risk for another cardiac arrest seems prudent. Many physicians around the world will, therefore, advise an implantable cardioverter defibrillator (ICD) to these patients. However, one should still consider that when there are clear triggering factors such as the use of certain drugs or fever, and when there are important arguments to withhold ICD
Table 1. Differential diagnosis for ST segment abnormalities in the right precordial ECG leads.

| Abnormalities                                                                 |
|-------------------------------------------------------------------------------|
| Right or left bundle branch block, left ventricular hypertrophy               |
| Acute myocardial ischemia or infarction                                      |
| Acute myocarditis                                                             |
| Pericarditis                                                                  |
| Right ventricular ischemia or infarction                                      |
| Dissecting aortic aneurysm                                                    |
| Acute pulmonary embolism                                                      |
| Various central and autonomic nervous system abnormalities                    |
| Heterocyclic antidepressant overdose                                          |
| Duchenne muscular dystrophy                                                   |
| Friedreich’s ataxia                                                           |
| Thiamine deficiency                                                           |
| Hypercalcaemia                                                                |
| Hyperkalemia                                                                  |
| Cocaine intoxication                                                          |
| Mediastinal tumor compressing right ventricular outflow tract                 |
| Arrhythmogenic right ventricular dysplasia/cardio-myopathy                    |
| Long QT syndrome type 3                                                       |
| Other conditions                                                              |
| Early repolarization syndrome                                                  |
| Other normal variants (particularly in men)                                   |

Adapted from Reference [2].

Implantation (such as in children),[16] implantation may not be the wisest option. The most important argument in this matter is the young age of many of these patients that results in a very long exposure to device related problems such as infections, lead malfunction and a low appropriate/inappropriate shock-ratio.[17,18] In Long QT syndrome it is also often considered to not implant an ICD in patients with a clear and avoidable trigger (such as drugs), but to start with beta-blockers instead. In Brugada syndrome, beta-blockers do not seem to protect against VT/VF and may even be pro-arrhythmic in some patients.[4] The experience with (hydro) quinidine for Brugada syndrome is increasing,[19,20] but the final results of prospective studies have not yet emerged.[21,22] Nevertheless, the use of quinidine for the treatment of ventricular arrhythmias in Brugada syndrome patients has received a class I indication in the consensus report.[4] In the acute phase of arrhythmias, isoproterenol is also provided with a class I indication.[4] There are many more drugs that have been suggested to have anti-arrhythmic effects (see www.BrugadaDrugs.org), but most of those have not yet gathered enough supporting evidence.

3.2 Intermediate and low risk

The majority of patients with Brugada syndrome will not present with aborted cardiac arrest. In these patients, other signs that may be used to identify patients at increased risk for cardiac arrest are being sought. Documentation of arrhythmias on Holter monitoring, or unexplained malignant syncope are probably signs of a higher risk for sudden death. Also patients with a spontaneous type-1 ECG and/or with extreme QRS fragmentation may be at higher risk.[23,24] Patients who do fulfill the criteria for Brugada syndrome, but who do not have the above mentioned risk parameters, can often be considered to be at low risk. How low this risk actually is, is uncertain at this moment as the registries only have a median follow-up of several years. So whether a yearly risk for arrhythmic events (mainly appropriate shocks) of 0.5% increases to become 10% at 20 years of follow-up is not known at this moment.[14] However, in older patients this uncertainty may become even less relevant. In most studies, it was clear that the presence of the familial occurrence of sudden death does not seem to indicate higher risk,[23–25] although its psychological impact may be enormous. The value of the inducibility of arrhythmias during electrophysiological studies (EPS) to enhance risk stratification of this intermediate/low risk group has been a matter of large debate.[26,27] However, the recent study from Italy is in favor of a low value of EPS in risk stratification.[24]

4 Treatment

The decision to treat patients with Brugada syndrome with an ICD should not be taken lightly, as the risk-benefit ratio may be very disappointing.[17,18] This approach is very different from 10–20 years ago when most patients with Brugada syndrome seemed to be highly symptomatic, while currently the vast majority is, and remains, asymptomatic.[14,28] Therefore, non-invasive treatment modalities deserve the most attention. The first sensible thing to do is to advise against the use of many drugs (such as certain anti-arrhythmic drugs, anti-depressant drugs, anesthetics, etc.) which may provoke the type-1 ECG and/or arrhythmias; see www.BrugadaDrugs.org.[4] Still, one should take into account that these lists of drugs to avoid are not without limitations (see also next paragraph ‘Ageing and Brugada syndrome’). Secondly, some patients (particularly those with a mutation in SCN5A, the gene that encodes the major subunit of the cardiac sodium channel) may have a fever-sensitive form of Brugada syndrome.[30] Therefore, we advise all such patients with fever to come into the hospital at least once to establish whether they have a fever-sensitive form by studying how their ECG changes during fever. If so,
these patients should probably be admitted for monitoring and/or treatment of fever. We also advise patients to use antipyretics when fever commences. Importantly, when arrhythmias occur during fever, fever has to be treated, in addition to administration of general (yet Brugada syndrome-specific) antiarrhythmic treatments, such as the administration of isoproterenol and/or quinidine. Although beyond the scope of this paper, an extremely important issue in this respect is the possible pro-arrhythmic effect of isoproterenol in young patients (often babies or children) who have a loss-of-function SCN5A mutation that, in their particular case and at that age, does not present with a Brugada phenotype, but a conduction phenotype. This may give rise to a double hit with a decrease of sodium inward current due to the combination of fever and tachycardia dependent conduction slowing which then results in malignant ventricular arrhythmias. In these patients, isoproterenol may actually have devastating effects (due to the increase of the heart rate) as opposed to the anti-arrhythmic effects of beta-blockers (due to the decrease of the heart rate).[30] This notwithstanding, reaching a normal core temperature can be achieved through antipyretics or, ultimately, active cooling. Of note, when antibiotics are deemed necessary, one has to know that local anesthetics for intramuscular administration of the antibiotic, such as procaine or lidocaine, are contra-indicated (see www.BrugadaDrugs.org).[4,31] Otherwise, there are no untoward effects from antibiotics to be expected (in distinction to Long QT syndrome).

When ICD-implantation is decided upon, one needs to be aware of specific problems that may occur in Brugada syndrome patients. Particularly, T-wave oversensing, high physiologic heart rates (up to 200 beats/min) and lead problems due to physical exercise are known to occur in these young patients. Therefore, care should be taken to limit T-wave oversensing, one needs to consider programming only a VF zone at higher frequencies (e.g., from 210–220 beats/min) and one should consider home monitoring.[17,32] Also sub-cutaneous ICDs might be worthwhile in this young population who will probably need many generator and/or lead replacements.[33]

An interesting issue in Brugada syndrome is the influence of testosterone; two Brugada syndrome patients with type-1 ECG who had a surgical castration for prostrate cancer ceased to display the type-1 ECG after the procedure.[34] However, whether intentionally induced lower testosterone levels would be beneficial in Brugada syndrome patients is currently unknown. Still, as for ageing Brugada syndrome patients, there is no clear evidence that testosterone levels spontaneously decrease during ageing, although decreasing levels of testosterone are associated with co-morbidities.[35]

5 Ageing and Brugada syndrome

The first patients described with Brugada syndrome have now aged by 20 years since the diagnosis was made, while most patients will first be diagnosed between 40 and 50 years of age. It is understandable that the older patients will develop, or will already have, co-morbidities. There are several issues with the treatment of these co-morbidities as there are many drugs to (preferably) avoid in Brugada syndrome (see www.BrugadaDrugs.org).[4]

The first issue to address when one considers medical treatment of co-morbidities in Brugada syndrome is their risk profile. Of course, a 37-year-old male patient who was resuscitated and appeared to have a spontaneous Brugada ECG is at much higher risk than a 70-year-old female patient without any significant medical history who received flecainide for recently uncovered atrial fibrillation and developed a Brugada ECG. In the former patient, one will be much more aggressive in the avoidance of potentially pro-arrhythmic drugs than in the latter patient (although the flecainide needs to be replaced). Furthermore, one should realize that the experience of most drugs which have been associated with the development of a type-1 ECG and/or arrhythmias in Brugada syndrome patients is based only on one or two case reports.[4,29] This implies that there are probably several provoking factors (e.g., fever, mutation, overdosing, multiple drugs, etc.) that contributed in these patients, as the literature would otherwise have been much more extensive. Conceivably, these factors may not be present in the individual patient under consideration. So, while patients and physicians frequently use the www.BrugadaDrugs.org website and stop or discontinue drugs accordingly,[29] this may result in unjustified under-treatment.

Unfortunately, there are almost no reports on the safe use of drugs in Brugada syndrome patients. There is only one report of the group from Brussels, Belgium, who safely administered an anti-epileptic drug to a child with both epilepsy and Brugada syndrome.[36] The precautions that these authors took to decide whether this drug in this particular patient was safe is sensible, as it included hospital admission and close monitoring during the first administrations of the drug. Of course, one should be extra aware of overdosing and other provoking issues, such as fever or diminishing renal and/or liver function (e.g., because of the administration of other drugs). When a patient already has an ICD, one can probably accept more easily the use of drugs to preferentially avoid, as the patient will be protected. The occurrence of arrhythmias upon the administration of this drug or a clear change in the appearance of the ECG would indicate that this drug should be discontinued and not be used again.
5.1 Co-morbidities requiring surgery

Many patients with Brugada syndrome have had successful and uneventful surgery.[37,38] However, there are also reports of serious adverse events during the use of anesthetics.[39–41] Given that most surgery is necessary, one would need to discuss with the anesthetic team how to approach the surgery. Risk stratification at that point is paramount and will include prior symptoms, previous surgery/anesthesia, previous problems with drug administration and the presence or absence of a spontaneous type-1 ECG. The papers by Kloesel, et al.[37] and by Inamura, et al.[38] may serve as guidance. During surgery, we would recommend the use of continuous ECG monitoring with additional leads positioned over the right ventricular outflow tract (i.e., cranially from V1 and V2), and the direct availability of a defibrillator and pharmacologic agents to decrease vagal tone such as isoproterenol and adrenaline.

5.2 Cardiovascular co-morbidities: atrial fibrillation, ischemic heart disease and hypertension

Supraventricular arrhythmias, mainly atrial fibrillation, are frequently present in Brugada syndrome patients.[42] However, the use of flecainide in these patients is absolutely contra-indicated.[43] There is currently no evidence that sotalol would be inappropriate in Brugada patients.[44] In contrast, the use of beta-blockers or amiodarone is disputed. There have been reports of the development of the type-1 ECG in Brugada syndrome patients using amiodarone or propranolol, while these agents do not seem to protect against ventricular arrhythmias.[43,44] The use of verapamil is also disputed, since there have been case reports on the development of a type-1 ECG on verapamil. However, Chinushi, et al.[45] have extensively tested the short-term effects of verapamil in several Brugada syndrome patients and found no clear pro-arrhythmic effects. Careful use of these agents is thus warranted. Interestingly, Bepridil, a long-acting calcium-blocking agent has been used by several authors to treat Brugada patients with ventricular arrhythmias.[46,47] Whether quinidine also results in less supraventricular arrhythmias is currently unknown, but is certainly conceivable. We currently also use ivabradine as a beta-blocker substitute for long-term management of atrial fibrillation. Whether catheter ablation for atrial fibrillation in Brugada syndrome is safe and successful is also not yet established.[48] As it is more likely that the intrinsic defect that causes Brugada syndrome in these patients will also cause the susceptibility to atrial fibrillation, it is less likely that pulmonary vein isolation, for example, will be beneficial in these patients. However, there is a need for more experience with ablation for atrial fibrillation in patients with Brugada syndrome.

As for hypertension and ischemic heart disease, there are four types of drugs that need extra consideration. The first two are the beta-blockers and (non-dihydropyridine) calcium channel blockers that have been discussed above. Thirdly, one should be cautious with the use of diuretics. There is probably no direct pro-arrhythmic effect of diuretics, but severe electrolyte disturbances may cause the development of the type-1 ECG and arrhythmias.[49] Finally, nitrates have also been disputed because of their possible calcium channel blocking effects.[13] However, there are currently no reports that nitrates cause untoward events in Brugada syndrome patients.[44] Again, the long-acting calcium-blocker Bepridil has even been used to treat ventricular arrhythmias.[46,47] Importantly, it is conceivable that the under-treatment of ischemic heart disease and/or hypertension may also promote arrhythmias in Brugada patients (or patients with other inheritable arrhythmia syndromes), as the electrophysiological effects of untreated ischemic heart disease and/or hypertension may conspire with those of Brugada syndrome to result in increased arrhythmia risk. Probably, the use of angiotensin converting enzyme inhibitors or aldosterone antagonists is safe and preferable. Again, as a beta-blocker substitute, ivabradine, may be considered.

5.3 Psychiatric co-morbidities

Many anti-depressant and anti-psychotic drugs will cause cardiac sodium channel blockade. Accordingly, many case reports indicate that these drugs can be troublesome in Brugada syndrome patients.[44] Therefore, one should more heavily rely on non-drug therapies in these patients. Of note, there are examples that psychotherapy in depressive or anxiety disorders may be very helpful in patients with concomitant Brugada syndrome.[50]

6 Conclusions

Cardiovascular and non-cardiovascular co-morbidities are inevitable when the patients with Brugada syndrome grow older. However, there are several important pitfalls in the treatment of these co-morbidities, which should be addressed. In this paper, we provide considerations and recommendations for the treatment of these co-morbidities.

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