rugada syndrome (BS) is an inherited form of cardiac arrhythmia and sudden death presenting with a typical electrocardiographic pattern of ST segment elevation in leads V1 to V3, and incomplete or complete right bundle branch block1. ST segment elevation in the absence of acute myocardial necrosis had been reported in the literature several decades ago2,3, but only recently it has been systematically described4,5.

Syncope, typically occurring at rest or during sleep is a common presentation of BS6, and it is caused by fast short-coupled polymorphic ventricular tachycardia that may easily degenerate into ventricular fibrillation. Anecdotal cases BS presenting with monomorphic VT have been also reported7.

In their initial report on 8 patients, Brugada et al emphasized the lack of structural cardiac abnormalities in these patients and the high recurrence rate of life threatening cardiac events1. After the first reports an increasing number of clinical studies characterizing the clinical features of the disease and attempting evidence-based risk stratification have been published with an exponential increase in the last few years. The reason for such remarkable interest of the scientific community is not only justified by the novelty of the disease but also by the fact that, being a purely electrical disease, BS constitute a “human model” useful to investigate the basic mechanisms of cardiac electrical activity. Cardiac sodium channel (SCN5A) mutations in BS patients have been firstly shown in 19988. These findings has remarkable contributed to the understanding of the disease but it has also opened several still unresolved issues. Indeed, despite the initial reports rather consistently indicated that BS mutations bear a loss of SCN5A function, more recent data show that they may also be associated with a more heterogeneous phenotype. ST segment elevation, QT interval prolongation and progressive conduction defect have been identified at the same time in families with a single SCN5A mutation9-11 and in vitro expression of such genetic defects was (and still is) not able to gather data fully explaining the link with the clinical phenotypes.

In this article we will summarize the current knowledge of the pathophysiology and clinical features of BS in the attempt of pointing out the spectrum of possible manifestation of this disease and the current perspectives for clinical management and risk stratification.

Pathophysiology of Brugada syndrome: how many diseases for one gene?

When SCN5A mutations were first identified in BS patients3, it was already known
that the same gene was also involved in the LQT3 variant of long QT syndrome (LQTS). Therefore, the working pathophysiological model was that considering BS and LQT3 as allelic diseases with a common genetic substrate but with differential functional consequences of the associated mutations. According to this view in vitro expression of BS and LQT3 mutant channels initially brought to light substantial differences, with BS mutations causing a loss of sodium channel function and an excess of sodium inward current in the LQT3 defects. More recently, with the increasing number of patients with known SCN5A mutations, the overall spectrum of related phenotypes is becoming more complex than previously anticipated, and phenotypic overlap between BS and LQT3 has been repeatedly observed.

Several experimental and clinical evidences support the concept of such clinical overlapping. From this standpoint it has been shown that two different amino acidic substitutions at the same position in SCN5A protein may be associated with different clinical and cellular phenotypes. Furthermore, it is known that sodium channel blockers administration may represent a diagnostic test for BS and LQT3, respectively. However, when intravenous flecainide is administrated to LQT3 patients, beside a significant QT interval shortening, a clear-cut ST segment elevation in leads V1-V3 resembling the BS pattern is also induced in several patients. Coexistence of ST segment elevation and QT interval prolongation has been shown also within the same family carrying the SCN5A 1795insD mutation. Interestingly, while in vitro expression of this mutation did not provide a full explanation of this apparently paradoxical coexistence of the two syndromes at clinical level, a computer simulation of the effect of this mutation both on transmembrane currents and action potential pointed out a potential mechanism. In this paper Clancy & Rudy showed that 1795insD induces a loss of action potential dome in epicardial cells consistent with BS, but also a prolongation of the action potential at slow heart rates, which is consistent with LQTS. Although, computer simulation models may not perfectly resemble reality, this paper provides evidences on how a single genetic defect may manifest with phenotypes that, at clinical level, were classified as two distinct entities.

The realization of the blurred border between BS and LQTS is not only scientifically appealing but it has tangible implication as it brings in the decision of how to treat these “transitional” patients and it challenges the concept of a differential therapeutic approach for LQTS, usually treated with beta blockers and BS patients in whom the only proven effective treatment is ICD in higher risk subjects.

To make the issue even more complicated a third phenotype has been associated with SCN5A, the progressive cardiac conduction defect, or Lencrge syndrome. In 1999 Schott et al reported a large French kindred presenting with atrioventricular and intraventricular conduction block. This evidence was subsequently confirmed in other studies and by recent data showing that prolonged QT interval, ST segment elevation and conduction abnormalities may concomitantly present in the same family with SCN5A mutation.

Taken together these data support the idea that the spectrum of the possible effects of SCN5A mutations is much wider than that predictable upon the “simple” assessment of their effect on I_{Na}. Indeed, the mechanisms of onset of a progressive cardiac block may not be completely explained by the electrophysiological consequence of mutations, but it is likely to involve also some sort of structural abnormality that may evolve overtime. So far the pathways that may lead from a cardiac transmembrane ion channel dysfunction to a structural abnormality of the heart have not been experimentally investigated but indications that these mechanisms could be clinically relevant may be found in the literature. Martini and Nava reported the clinical and pathologic evaluation of individuals presenting with, ST segment elevation, incomplete right bundle branch block, and “minor” structural abnormalities of the right ventricle, thus suggesting that the Brugada-like ECG may also be present in patients with a “mild” from of right ventricular cardiomyopathy. A similar finding has also been reported by Corrado et al in a single family with ARVC. From a pathophysiological standpoint, the association of these two clinical variables may be purely casual since so far SCN5A mutations have never been reported in full co-segregation with ARVC, but it is tempting to speculate that some of such genetic defects could alter the intracellular trafficking of the SCN5A protein that would be no longer be integrated in the membrane but, conversely, remain confined in the intracellular space resulting in a toxic effect for the myocytes. As a consequence, SCN5A mutations could be associated with pro-
gressive structural defects as conduction block and myocardial degenerative abnormalities even if they do not fulfill the diagnostic criteria for ARVC.

Finally, it is important to consider that the pathophysiology and the genotype-phenotype correlation of BS are even more complex than may be perceived based on the available data. Indeed, SCN5A mutations account for only a minority of BS patients since only approximately 20% of them are successfully genotyped. At present time the search for the remaining BS is based on scanty clues. Only an additional locus on chromosome 3p22-25, has been very recently identified by linkage analysis in a single large family, but, despite the screening of several candidates in the region, the corresponding gene has not been found.

Brugada syndrome: epidemiology, clinical features and management

The wide spectrum of phenotypes possibly associated with SCN5A mutations has to be taken into account in the clinical evaluation of patients presenting with the typical BS ECG and a complete set of diagnostic procedures has to be undertaken, including accurate imaging assessment to exclude the presence of structural abnormalities.

However, given the relatively low prevalence of SCN5A mutations among BS patients, the overall clinical picture of the disease overshadows the border of genotyped patients and guidelines for risk stratification and management have to be applicable to wider groups of patients than those with a known genetic defect. This concept is further strengthened by the evidence, obtained in the largest series of genotyped BS patients so far reported, showing that the genetic defect may not be an independent predictor of the outcome.

Prevalence of Brugada syndrome

At the present time two major factors hinder the definition of the prevalence of BS: the lack of definitive electrocardiographic diagnostic criteria and the impossibility of determining the genetic defect in the majority of patients. As pointed out earlier, there is a general agreement that only a minority of clinically affected patients carry SCN5A mutations. Until the entire picture of the genetic determinants of BS will remain incomplete, the only feasible way to attempt an estimate of the prevalence of BS is to assess the frequency of the electrocardiographic pattern in the population. To this regard, the first challenging issue is the transitory nature of the ECG pattern that may significantly impair its diagnostic sensitivity and the evidence of the incomplete penetrance of the disease. Provocative testing with intravenous administration of sodium channel blockers (flecainide or ajamaine), may help unmasking the ECG abnormalities in suspected cases, but obviously it may not be applied to large group of subjects in studies targeted to the assessment of the prevalence of the disease. Furthermore, the morphology of ST elevation in BS has also represented a matter of debate in the last few years. In the earlier reports, BS patients were considered both those with a “coved” ECG and those with a “saddle back” pattern. More recently, only “coved” type ECG (either spontaneous or after challenge with intravenous sodium channel blocker administration) has been reported as diagnostic for the disease. Obviously the prevalence of BS varies depending upon the diagnostic criteria. The prevalence of a “coved” ST segment elevation >0.1mV is in the range of 0.02% to 0.27% in the different reports, while it is higher when considering both “coved” and “saddle-back” types. Only the availability of large groups of patients with known genetic defect will allow the assessment of the specificity of the ST segment elevation morphology for the diagnosis of BS. To this regard available data suggest that clinical manifestation of the disease are not different according to the electrocardiographic presentation.

Overall, consistently with the vast majority of genetic diseases, BS appears to be a relatively uncommon condition, and a prevalence of 1-10/10.000 appears a realistic estimate. A higher prevalence may exist in eastern countries where BS is the suspected major cause of sudden death in young individuals and of SUNDS, Sudden Unexplained Nocturnal Death Syndrome. SCN5A mutations have been identified in patients diagnosed with this disorder, thus confirming that SUNDS and BS are the same clinical entity.

Nonetheless since BS affects young otherwise healthy individuals (see below), it is of remarkable clinical and social impact to undertake all the possible countermeasures to limit the burden of this disorder.

Cardiac events in Brugada syndrome

BS manifests with syncope and cardiac arrest typically occurring in the third and fourth decade of
life, and usually at rest or during sleep. In the earlier reports a remarkably high rate of events was shown. In 1998 Brugada et al presented data on 63 patients, in whom, after a mean follow up of 34±32 months, 34% of previously symptomatic (syncope and/or cardiac arrest) patients had recurrence, while a first cardiac event occurred in 27% of the asymptomatic individuals. This picture called for an aggressive therapeutic strategy in all patients with BS and, since no pharmacological treatments of proven efficacy were (and still are) available, it led to the ICD implant in several young asymptomatic individuals. However, more recent reports have brought to the attention of the scientific community new epidemiological data that depict a different figure. In 2000 Priori et al showed a 16% incidence of recurrence of a cardiac arrest in symptomatic patients while none of the asymptomatic individuals at enrollment had a cardiac event after three years of follow up. The very low incidence of events in asymptomatic patients has been subsequently confirmed by Atarashi et al, 1.5%, Takenaka et al, 0%, and in the large groups recently reported by Brugada et al, 8%. From these clinical studies it appears evident that the majority of subjects with a BS electrocardiographic pattern, is likely to remain asymptomatic and have a relatively low risk of events. Nonetheless, it is also true that in these individuals life-threatening events may sometimes occur, thus prompting the need of an effective risk stratification algorithm. This latter issue still represents a matter of vigorous debate. Indeed, although there is consensus in indicating the ICD implant in a BS patient presenting with documented cardiac arrest, no general agreement has been achieved concerning the approach to other subgroups.

The role of programmed electrical stimulation

Since BS is caused by a genetically determined substrate leading to cardiac electrical instability, programmed electrical stimulation (PES) has been as considered a rational approach to risk stratification in BS. The available evidences rather reproducibly show that ventricular fibrillation is inducible in the majority of patients. However, the prognostic significance of this finding is less clear. Indeed, while in the series by Brugada et al PES inducibility has been significantly associated with unfavorable clinical outcome, no difference of inducibility between symptomatic and asymptomatic patients, have been observed by Priori et al and by Eckardt et al. Recently, Brugada et al reported VF inducibility at PES in 83%, 68% and 33% of patients with a history of cardiac arrest, syncope and asymptomatic, respectively, thus pointing to the possibility of using PES inducibility as a risk stratifier. However, the study by Priori et al failed to confirm the role of PES that, in this study had a 66% sensitivity and 34% specificity in detecting symptomatic patients, and no significant association with cardiac events was found in multivariate analysis. These conflicting evidences on the role of PES may have several explanations. Obviously, a low level of standardization of the stimulation protocols in terms of number of extrastimuli and sites of stimulation used may have bias data analysis. However, it has to be considered that in BS the risk of experiencing a cardiac event is not stable throughout life (as it could be expected in a genetic disease), but it could be influenced by several, mostly still unknown, environmental factors (e.g. autonomic tone, blood electrolyte, drug assumption), that may increase the electrical instability of the heart in specific circumstances. Therefore, PES inducibility could also vary depending on the same “transitory” factors, thus being intrinsically poorly related with the life long risk of cardiac events. In conclusion, at the present time there are no sufficient information to confirm or dismiss the role of PES in BS and specifically designed protocols with longer follow up are needed.

Clinical management of Brugada Syndrome: what can be learned from the epidemiological studies?

Thus, the approach to risk stratification of BS based upon the outcome of programmed electrical stimulation have limitation that may not be overcome using the available evidences. Being affected by a genetically determined disease, BS patients are exposed to a life long risk of events. Therefore it is rationale to attempt dissecting the natural history of the disease since birth in order to gather information useful for clinical management. This is still possible in the case of BS since a treatment effective in reducing the occurrence of cardiac events, thus changing the natural history of the disease, is not yet available. In a recent observational study by Priori et al the evaluation of cardiac events since birth in 200 patients with a mean observation time of 41 years showed that 11% of patients had a cardiac arrest and 17% experienced syncopeal episodes. By means of multivariate survivorship analysis a significant increase of risk of cardiac arrest
(HR 6.1) was identified in those BS patients presenting with history of syncope and a spontaneously abnormal ECG (i.e. patients in whom the ECG was diagnostic for BS independently from the provocative test with intravenous sodium channel blockers). In these patients the implant of an ICD may be indicated. The presence of only spontaneous ST segment elevation was associated with a moderate risk of life-threatening events (HR 2.1), while the history of syncope alone was not an independent predictor of outcome. These latter patients, as well as the silent gene carriers belong to a low risk group. Our current approach is to undertake a long term monitoring with implantable loop recorders in order to detect the potential occurrence of asymptomatic arrhythmias that could be the marker indicating the subjects in whom more aggressive therapy is advisable.

Overall these data suggest that risk stratification in BS based upon simple clinical parameters is feasible and that the use of this scheme may overcome the limitations inherent to the use of programmed electrical stimulation and allows the identification the higher risk subgroup of patients in whom the ICD implant is indicated.

An additional promising approach for risk stratification in BS could be represented by the signal averaging electrocardiogram. Intraventricular conduction abnormalities and late potentials are a relatively frequent finding among BS patients and preliminary clinical evidences suggest that they are more frequently detected in symptomatic patients. However, so far it is unknown whether this variable may represent an independent risk factor for sudden cardiac death in BS.

The role and prospective of molecular diagnosis in the management of Brugada syndrome

Establishing a diagnosis of BS in an asymptomatic individual based on the electrocardiographic phenotype is a big responsibility for the clinician as it implies informing a young “healthy” subject of being at risk of sudden death and to have a chance of procreating children at risk of sudden death. Molecular genetics may free the cardiologist from the burden of defining his diagnosis on a parameter that may sometime be difficult to quantify, allowing the diagnosis in all individuals. This may be particularly important in conditions such as BS that may present incomplete penetrance. In this case the detection of a genetic defect within a family may represent the only tool for the identification of all the subjects that may be at risk of cardiac events and may transmit the disease to the offspring. These information derived from the molecular genetic laboratory have a direct crucial impact for clinical management. However, the genetic testing of BS is so far limited by the evidence that only one fifth of patients may be genotyped and by the recent data showing that the presence or absence of SCN5A mutation is not a predictor of outcome. These limitations are likely to be overcome in the future with the increasing knowledge on the genetic basis of this disease.

Conclusions

The building up data on the pathophysiology and clinical features of BS have led to remarkable increase of our knowledge and to a better understanding to the overall clinical picture of the disease and to the delineation of novel risk stratification schemes. On the other hand the detailed evaluation of BS manifestation both at in vivo and in vitro level brought the evidence of a unexpected degree of complexity. Indeed, 5 years after the identification of a SCN5A defect in BS patients, along with the undisputable progression of knowledge, the number of unanswered questions is also increased. The evidence that multiple cardiac phenotypes may be associated with cardiac sodium channel gene mutations has been only recently brought to the attention of the scientific community.

In the future, only a close collaboration between the clinical cardiologists and the basic scientists will allow to fill the gap and to take the full advantage from molecular genetics and pathophysiological findings for the diagnosis and management of BS.

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